Bevacizumab (Avastin®) in the management of neovascular age-related macular degeneration:

Updated Appraisal

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Summary

• NETAG did not recommend bevacizumab for AMD in April 2009 but did agree to reconsider their recommendation when evidence from a direct randomised study with ranibizumab, the current standard of care, is available. Bevacizumab is not licensed for any ophthalmic indication but has been extensively investigated in several eye conditions.

• The one-year interim results of the CATT study of bevacizumab vs. ranibizumab and monthly vs. PRN dosing in AMD have not demonstrated a significant difference between the drugs providing that regimens are the same.

• There were small and currently unexplained differences in the number of serious adverse events, with bevacizumab demonstrating a significantly greater burden than ranibizumab. In addition, bevacizumab PRN patients required a greater number of doses than ranibizumab PRN patients (~1 additional injection in the first 12 months).

• The relative safety profile of intravitreal bevacizumab has been established across numerous studies involving many patients in various indications and is generally considered acceptable and comparable to licensed treatments. Intravitreal bevacizumab is already used within several NHS North East treatment centres for indications other than ‘wet’ AMD.

• One area where there is a substantial difference between bevacizumab and ranibizumab is in the cost of therapy, with bevacizumab costing about £50 per dose and ranibizumab nearly £900. Given the substantial difference and relatively large number of doses administered annually for AMD within NHS North East, the potential savings from a switch to bevacizumab run into millions of pounds. For example a switch based on current use for new cases only is conservatively estimated to result in a saving of £4 million over 12 months for NHS North East.

• Issues regarding liability associated with prescribing an unlicensed treatment may need to be resolved. These issues extend to possibly obtaining patient consent and providing information for patients.
Introduction

In April 2009 NETAG conducted an appraisal on the use of bevacizumab (Avastin®) in an unlicensed indication for the treatment of age-related macular degeneration (AMD), essentially as an alternative to licensed treatment with ranibizumab (Lucentis®). The group did not recommend bevacizumab for AMD, principally due to absence of evidence of sufficient quality demonstrating that bevacizumab was at least as effective and safe as ranibizumab. The group gave an undertaking to the North East Specialised Commissioning Team (NESCT) that they would reconsider, or re-appraise, bevacizumab in AMD when evidence becomes available from direct randomised comparisons of the two treatments.

The NESCT has requested that NETAG re-appraise bevacizumab for AMD in light of the recent publication of results from a large randomised direct comparison of bevacizumab and ranibizumab in AMD.

This appraisal report should be considered in conjunction with the previous report published in April 2009.

Clinical evidence

A search for new evidence published since the previous literature search in 2009 identified a large volume of evidence relating to the use of bevacizumab in AMD. However, only two studies met the quality criteria of being direct randomised comparisons between bevacizumab and ranibizumab, both from American research teams and both with 12 month's follow-up. One involved only 22 patients whereas the other involved 1,208 patients and is the main focus of this appraisal.

The CATT study (Comparison of AMD Treatment Trials) is one of several large randomised studies currently underway comparing bevacizumab and ranibizumab in AMD. In common with other comparisons, the CATT study is not only investigating bevacizumab vs. ranibizumab but also a specified-dose regimen vs. a 'when required' (PRN) dose regimen. The specified-dose regimen in the CATT study involved monthly (target 28 day interval) dose intervals for 24 months. Patients were aged ≥ 50 years and had baseline visual acuity of between 20/25 and 20/320; equivalent to 40 to 95 letters respectively where ‘normal’ vision (20/20) would permit 100 letters; the mean was about 60 letters in all treatment groups. The study eye had a confirmed diagnosis of exudative or ‘wet’ AMD and was treatment-naïve. Patients were randomised to treatment with monthly ranibizumab (n = 301), monthly bevacizumab (n = 286), PRN ranibizumab (n = 298) or PRN bevacizumab (n = 300). One year follow-up results are available for most patients (95%) with the last observation carried forward for missing outcomes.
CATT was designed as a non-inferiority study with non-inferiority between groups defined as the mean difference and 99.2% confidence interval within a limit of ±5 letters.

The results demonstrated no significant differences between groups with respect to changes in, or actual, mean visual acuity. Other outcomes were also measured and these are summarised in table 1. Although between-group comparisons did not identify any significant differences the pre-specified non-inferiority end point was not demonstrated for all comparisons. Notably, non-inferiority was not demonstrated for bevacizumab PRN vs. monthly regimens. The smallest between-group mean differences were observed with identical treatment regimens and the only difference was in the drugs used. It should also be noted that the bevacizumab-monthly group used a mean of nearly one more injection per patient compared with the ranibizumab-monthly group.

**Table 1.** Summary 1-yr results from the CATT study

<table>
<thead>
<tr>
<th></th>
<th>Ranibizumab</th>
<th></th>
<th>Bevacizumab</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Monthly</td>
<td>PRN</td>
<td>Monthly</td>
<td>PRN</td>
</tr>
<tr>
<td>Number of patients</td>
<td>284</td>
<td>285</td>
<td>265</td>
<td>271</td>
</tr>
<tr>
<td>Mean number of treatments</td>
<td>11.7</td>
<td>6.9</td>
<td>11.9</td>
<td>7.7</td>
</tr>
<tr>
<td><strong>Visual acuity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(letters)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>60.1</td>
<td>61.5</td>
<td>60.2</td>
<td>60.4</td>
</tr>
<tr>
<td>Mean 1-yr</td>
<td>68.8</td>
<td>68.4</td>
<td>68.4</td>
<td>66.5</td>
</tr>
<tr>
<td>Mean gain</td>
<td>8.5</td>
<td>6.8</td>
<td>8.0</td>
<td>5.9</td>
</tr>
<tr>
<td>Gain ≥ 15</td>
<td>34.2%</td>
<td>31.3%</td>
<td>24.9%</td>
<td>28.0%</td>
</tr>
<tr>
<td>Gain 5 to 14</td>
<td>31.7%</td>
<td>36.1%</td>
<td>37.0%</td>
<td>33.2%</td>
</tr>
<tr>
<td>Change ≤ 4</td>
<td>21.8%</td>
<td>26.3%</td>
<td>18.9%</td>
<td>21.8%</td>
</tr>
<tr>
<td>Loss 5 to 14</td>
<td>6.7%</td>
<td>8.1%</td>
<td>6.8%</td>
<td>8.5%</td>
</tr>
<tr>
<td>Loss ≥ 15</td>
<td>5.6%</td>
<td>4.6%</td>
<td>6.0%</td>
<td>8.5%</td>
</tr>
<tr>
<td><strong>Foveal thickness</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(micrometers)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>458</td>
<td>458</td>
<td>463</td>
<td>461</td>
</tr>
<tr>
<td>Mean reduction</td>
<td>196</td>
<td>168</td>
<td>164</td>
<td>152</td>
</tr>
</tbody>
</table>
The other relevant study of bevacizumab and ranibizumab in AMD randomised only 22 patients with AMD in a 2:1 ratio to treatment with bevacizumab (n = 15) or ranibizumab (n = 7). The study was double-blind and the primary outcome measure was visual acuity measured using the ETDRS chart. The treatment regimen was three, monthly, loading doses followed by PRN dosing (i.e. the same regimen as is currently used in UK practice with Lucentis®). The main outcomes at 12 months are described in table 2.

**Table 2.** Summary 1-yr results of small randomised comparison of aVEGF treatments for AMD

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab</th>
<th>Ranibizumab</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>15</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>Mean number of treatments</td>
<td>8.0</td>
<td>4.0</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>Visual acuity (letters)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean baseline</td>
<td>34.9</td>
<td>32.7</td>
<td>not reported</td>
</tr>
<tr>
<td>Mean 1-yr</td>
<td>42.5</td>
<td>39.0</td>
<td>not reported</td>
</tr>
<tr>
<td>Difference (gain)</td>
<td>9.6</td>
<td>6.3</td>
<td>0.50</td>
</tr>
</tbody>
</table>

**Safety**

Safety results from the CATT study are summarised in table 3. The study was insufficiently powered to identify important differences in drug-related adverse events. 4,5

As can be seen from table 3, overall bevacizumab demonstrated a greater burden of adverse events compared with ranibizumab although only one category was significantly different; ≥ 1 serious systemic adverse event (p = 0.04). Within this category only the sub-categories of gastrointestinal disorders (p = 0.02) and ‘other’ (p = 0.04) were individually significant and both are characterised by small patient numbers. Although more patients receiving bevacizumab had multiple systemic serious adverse events and hospitalisations than those receiving ranibizumab, these events were not associated with organ systems typically identified with systemic aVEGF therapy. 5 There were only seven events in total relating to ocular complications, all in the monthly treatment groups and all relating to ophthalmitis. The total number of injections in the first year of the whole study was nearly 11,000 meaning that the overall incidence of ophthalmitis was very low (< 0.1%). 4
Table 3. Summary 1-yr safety results from the CATT study

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ranibizumab Monthly</th>
<th>PRN</th>
<th>Bevacizumab Monthly</th>
<th>PRN</th>
<th>P value (between drugs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>301</td>
<td>298</td>
<td>286</td>
<td>300</td>
<td></td>
</tr>
<tr>
<td>All cause mortality</td>
<td>4</td>
<td>4</td>
<td>5</td>
<td>11</td>
<td>0.22</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>2</td>
<td>3</td>
<td>2</td>
<td>1</td>
<td>0.73</td>
</tr>
<tr>
<td>Venous thrombosis</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>1</td>
<td>0.28</td>
</tr>
<tr>
<td>Non-fatal stroke</td>
<td>3</td>
<td>1</td>
<td>2</td>
<td>2</td>
<td>1.00</td>
</tr>
<tr>
<td>Transient ischaemic attack</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>3</td>
<td>1.00</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0.24</td>
</tr>
<tr>
<td>≥ 1 serious systemic event *</td>
<td>53</td>
<td>61</td>
<td>64</td>
<td>77</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**Ocular events in study eye**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Ranibizumab</th>
<th>PRN</th>
<th>Bevacizumab</th>
<th>PRN</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endophthalmitis</td>
<td>2</td>
<td>0</td>
<td>4</td>
<td>0</td>
<td>0.45</td>
</tr>
<tr>
<td>Pseudoendophthalmitis</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1.00</td>
</tr>
</tbody>
</table>

* : By default, any adverse event resulting in hospitalisation was classified as a serious adverse event. Consequently, hospitalisations accounted for the majority (80%) of this classification.

Adverse events in the smaller study did not demonstrate any significant differences between treatments or any particular pattern. No cases of endophthalmitis occurred.

The safety of intravitreal injections of either bevacizumab or ranibizumab has been established across numerous studies in various indications, particularly in the management of age-related macular degeneration, some with extensive follow-up and most relating to multiple repeat dosing.

Other recent safety reports on aVEGF drugs in ophthalmology have also been published.

A review of patient safety incidents relating to aVEGF medications (bevacizumab, ranibizumab and pegaptinib) reported to the National Patient Safety Agency covering England and Wales over the period 2003 to 2010 identified 166 incidents. Most incidents related to administrative and clinical processes (e.g. treatment delay, wrong medication, wrong eye, missing clinical records) as opposed to adverse effects directly related to the drug or mode of administration (n = 131; 79%). There were 16 incidents relating to endophthalmitis or inflammation, five relating to ‘treatment complications’ and 14 ‘other’. In total, 125 incidents involved ranibizumab, 40 bevacizumab and one pegaptinib. Of the endophthalmitis or inflammation reports, 14 were with ranibizumab and two with bevacizumab. There were no fatalities and most incidents were rated as presenting ‘low’ or ‘no’ harm. The number of reports has increased year on year since 2006 when the first incident report was made. However this report is unable to provide data relating to the relative safety of any
of the included drugs, for example bevacizumab compared with ranibizumab, as it is not matched against usage or patient volumes and the patient safety incident reporting scheme is voluntary with varying rates of participation.  

A retrospective report investigated the incidence of raised intra-ocular pressure (IOP) in 127 patients (155 eyes) treated with intravitreal aVEGF therapies (bevacizumab, pegaptinib or ranibizumab). The overall incidence of raised IOP was 9%, with 6% experiencing sustained raised IOP requiring IOP-lowering medication or surgery. No association was found between the drug used, injection frequency or cumulative number of injections.

Another US-based report investigated one-year mortality in patients treated with bevacizumab (n = 1,302) or ranibizumab (n = 1,719) or both (n = 189) and compared patient mortality rates with 117,364 patients with dry AMD not treated with these or similar drugs. The overall mortality rate was 3.9% in treated AMD patients and 4.5% in the control group (hazard ratio 0.89, p > 0.05). Differential analyses between the individual hazard ratios for each drug identified only small and statistically insignificant differences.

A recent US report described vascular and cardiac outcomes in nearly 40,000 patients treated with intravitreal bevacizumab and 19,000 patients treated with intravitreal ranibizumab for AMD. Some patients were counted in more than one group as therapies were switched during the course of the observation period. The overall rates of serious vascular and cardiac sequelae were low but were slightly higher in bevacizumab- compared with ranibizumab-treated patients. However numerous other factors could rationally have caused the apparent small increased risk and the report does not provide conclusive evidence that bevacizumab presents a greater safety risk than ranibizumab in ophthalmology.
Relevant guidance

In December 2010, after a robust consultation process, NICE published their report on the feasibility of appraising bevacizumab in eye conditions. NICE agreed that there is indeed a need for such an appraisal but that it could only proceed if:

\[12\]

\[12\] .... the safety and quality of intravitreal bevacizumab is assured by a regulatory body or through the involvement of regulatory expertise. Furthermore, arrangements for safety monitoring / pharmacovigilance will need to be explored.

To date NICE is not currently, nor planning to, conduct an appraisal of intravitreal bevacizumab for any indication. However NICE has considered intravitreal bevacizumab as a valid comparator treatment in other appraisals.

The Royal College of Ophthalmologists has issued guidance, both non-specific concerning the management of AMD \[13\] and also specifically concerning the use of bevacizumab in AMD \[14\].

\[13\] .... the College does not recommend the routine use of intravitreal bevacizumab for choroidal neovascularisation over anti-VEGFs which are already licensed for that indication, and recommended by NICE.

\[14\] Should intravitreal bevacizumab be used, the College advises such use must either be part of a research programme (as in the IVAN Study) or be documented by robust ongoing audit, with systematic prospective data collection.

A press statement released by the Royal College of Ophthalmologists in May 2011 stated: \[15\]

\[15\] Until the safety concerns [with bevacizumab] are properly addressed, ranibizumab remains the recommended treatment for wet AMD. The College however continues to support use of bevacizumab as part of research.
Licensing

Bevacizumab is a licensed drug although it is not licensed for any ophthalmic indications. Therefore use of bevacizumab in AMD would normally be described as ‘off-label’ or off-license as opposed to unlicensed use. However, due to the additional compounding of bevacizumab when used in ophthalmology, NICE consider this to be more akin to unlicensed use.

Either way, guidance regarding the use of un- and off-license treatments is essentially the same.

The Medicines and Healthcare Products Regulatory Agency advice for prescribers is:

- Before prescribing an unlicensed medicine, be satisfied that an alternative, licensed medicine would not meet the patient's needs
- Before prescribing a medicine off-label, be satisfied that such use would better serve the patient’s needs than an appropriately licensed alternative
- Before prescribing an unlicensed medicine or using a medicine off-label:
  - be satisfied that there is a sufficient evidence base and/or experience of using the medicine to show its safety and efficacy
  - take responsibility for prescribing the medicine and for overseeing the patient’s care, including monitoring and follow-up
  - record the medicine prescribed and, where common practice is not being followed, the reasons for prescribing this medicine; you may wish to record that you have discussed the issue with the patient

The General Medical Council has recently issued draft guidance which includes reference to unlicensed medicines:

- You should usually prescribe licensed medicines for their licensed uses; but you may prescribe off-label or unlicensed medicines outside an approved research protocol if:
  - there is no appropriately licensed alternative available or you are satisfied, on the basis of authoritative clinical guidance, that it is as safe and effective as an appropriately licensed alternative
  - you have adequate insurance or indemnity cover or are covered by an employer’s indemnity scheme to prescribe in this way
- You must make a clear record of all off-label and unlicensed medicines you prescribe, and your reasons for doing so.
- Some medicines are routinely used off-label. When this is the case and there is authoritative clinical guidance to support your prescribing decision, it may not be necessary to draw the patient’s attention to the licensing status of the medicine. You should, however, give patients the information they want or need when seeking consent to prescribe. If a patient is concerned, you should explain why the medicine you intend to prescribe is not licensed for the use you intend.

Current guidance from the General Medical Council is broadly similar to this draft guidance (see appendix 1).
Economic analysis

Following the previous appraisal, NETAG specified that the appropriate comparator for future appraisals involving bevacizumab in ophthalmic indications should be pre-filled syringes produced by a licensed compounding facility. This requirement is also supported by recent advice from the NHS West Midlands Specialised Commissioning Team in which NHS commissioners nationally were advised to ensure that bevacizumab for ophthalmic indications is purchased from licensed manufacturing facilities. Previously, this comparator has been based on supply from Moorfields Pharmaceuticals at about £120 per syringe (including VAT). However, an alternative supplier has recently been identified which is able to provide bevacizumab 5 mg in 200 microlitres pre-filled syringes with a shelf-life of 90 days from the date of compounding (manufacture). Syringes cost £48 each, do not attract VAT, and delivery is £30 per package irrespective of volume. Syringes must be stored in a refrigerator at all times. Therefore, for the purpose of this analysis, it will be estimated that each syringe will cost £50.

Ranibizumab (Lucentis®) is available in small single-use vials at £891 each (including VAT). The cost of admission for an intravitreal injection is defined by the payment-by-results tariff code ‘vitreous retinal procedures – category 1’ (BZ23Z), currently £619 per admission excluding the market forces factor uplift. However the North East Specialised Commissioning Team (NESCT) has agreed an ex-tariff price per admission for AMD cases with NHS North East acute trusts of about £480 per admission.

In the fiscal year 2009-10 the NESCT reimbursed North East acute trusts for 8,043 doses of Lucentis®. The corresponding figure for 2010-11 is estimated at 9,764, an increase of 1,721 (21%). Three methods have been used to estimate future volumes (table 4): the first is to assume that volumes have reached a plateau and remain stable at 9,764; the second is to assume a linear increase in volumes with the same actual increase in volume each year; and the third is to assume a geometric rate of increase so that the increase is 21.4% each year. Table 4 demonstrates the effect on volumes.

The most likely scenario of those presented in table 4 is somewhere between the plateau and the linear predictions as the current patient cohort is probably nearing maturation (with treatment having commenced in summer 2007) and few patients appear to remain in long-term treatment.
Table 4. Projected volumes of AMD treatment episodes for NHS North East

<table>
<thead>
<tr>
<th>Volume growth model</th>
<th>Fiscal year (April to March)</th>
<th>2010-11</th>
<th>2011-12</th>
<th>2012-13</th>
<th>2013-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plateau</td>
<td></td>
<td>9,764</td>
<td>9,764</td>
<td>9,764</td>
<td></td>
</tr>
<tr>
<td>Linear</td>
<td></td>
<td>11,485</td>
<td>13,206</td>
<td>14,927</td>
<td></td>
</tr>
<tr>
<td>Geometric</td>
<td></td>
<td>11,853</td>
<td>14,390</td>
<td>17,469</td>
<td></td>
</tr>
</tbody>
</table>

If Lucentis® is reimbursed at the current price and VAT rate then the value of the 2010-11 volume is £8.485 million. The value of this volume based on the price of Avastin® doses (1.25 mg) is £488,000, a difference of just under £8 million. Table 5 demonstrates the costs based on the two most liberal volume growth models.

Table 5. Projected AMD treatment costs (£ million)

<table>
<thead>
<tr>
<th>Volume growth model</th>
<th>Fiscal year (April to March)</th>
<th>2011-12</th>
<th>2012-13</th>
<th>2013-14</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear</td>
<td>Bevacizumab</td>
<td>£0.574</td>
<td>£0.660</td>
<td>£0.746</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab</td>
<td>£9.981</td>
<td>£11.467</td>
<td>£12.972</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>£9.406</td>
<td>£10.816</td>
<td>£12.225</td>
</tr>
<tr>
<td>Geometric</td>
<td>Bevacizumab</td>
<td>£0.593</td>
<td>£0.719</td>
<td>£0.873</td>
</tr>
<tr>
<td></td>
<td>Ranibizumab</td>
<td>£10.301</td>
<td>£12.505</td>
<td>£15.180</td>
</tr>
<tr>
<td></td>
<td>Difference</td>
<td>£9.708</td>
<td>£11.785</td>
<td>£14.307</td>
</tr>
</tbody>
</table>

Whichever model is used the difference in drug costs runs into several million pounds. However, there are two caveats to these predictions. The first is an assumption that all existing and future use of ranibizumab is switched to bevacizumab. Instead, a policy of using bevacizumab only for new cases might be implemented. The cost impact of such a policy is difficult to predict as there is no data concerning the annual incidence of treated AMD cases within the North East. The issue is further compounded by the ranibizumab dose regimen, which is for three, monthly loading doses followed by PRN dosing. Therefore it is not straightforward to infer the annual incidence of cases from the current annual ranibizumab usage figures. The NICE costing template, which accompanied the NICE guidance for ranibizumab in AMD, leads to an estimate of 914 cases (eyes) per annum within NHS North East.
The drug cost of treating all cases with ranibizumab at current prices, and assuming six doses in the first year, is £4.766 million per annum. If bevacizumab was used instead the cost would be £274,200, a saving of £4.491 million.

The second issue with the predicted values in tables 4 and 5 is an assumption that ranibizumab can be substituted directly for an equal number of bevacizumab doses. Evidence from the CATT study, and supported by evidence from the smaller RCT, shows that where PRN dosing is used a greater number of bevacizumab treatments are required compared with ranibizumab. The current regimen of ranibizumab used within the UK does not match any of the regimens which have been used in direct randomised comparisons of the two aVEGF treatments. The UK regimen requires three, monthly, ‘loading dose’ injections followed by PRN management. Therefore, after the first year of treatment, UK patients will have had three months of regular monthly dosing and nine months of PRN dosing. The difference observed after 12 months in the PRN groups of the CATT study was almost one additional bevacizumab injection compared with ranibizumab (i.e. about 8 vs. 7). The additional drug cost with bevacizumab is only £50 yet the additional admission cost is £480. However, even with an additional admission in the first year, or even if the difference recurs in subsequent treatment years, bevacizumab will still remain substantially less costly than ranibizumab given the large difference in drug costs. Based on an assumption of 914 new cases per year and a mean of six doses per case, the total number of injections of ranibizumab is estimated at 5,484 (drug cost £4.766 million, admission cost £2.632 million, total cost £7.398 million). If one extra injection per annum is required with bevacizumab then it is estimated that 6,398 injections will be required for new cases per annum (drug cost £320,000, admission cost £3.071 million, total cost £3.391 million) which will still cost £4.007 million less than using ranibizumab.

Another financial consideration is the ‘volume cap’ patient access scheme with ranibizumab in AMD whereby every dose per case (eye) after the 14th is provided at nil cost. Such a scheme would not be in place with bevacizumab. To date there are only a small number of cases which have qualified for the scheme although the patient cohort is far from mature in this respect. The scheme would only begin to be cost-saving compared with bevacizumab after the 249th dose of bevacizumab which represents more than 20 years of monthly therapy at current prices.
**Points to consider**

The efficacy and safety of bevacizumab in AMD has now been compared directly in a large randomised study with ranibizumab. The evidence indicates that, where treatment regimens are identical, there is no significant difference between them.

The safety profile of intravitreal bevacizumab has been established in a large number of studies for numerous indications. In direct comparisons with ranibizumab there is no evidence of an increased risk of ophthalmological adverse effects with bevacizumab. There are concerns regarding the exophthalmo logical safety of intravitreal bevacizumab although the pattern of adverse effects observed is diverse; longer term data should provide a clearer picture.

The effects can be distinguished between those relating to the drug, which are often limited due to the localised nature of administration and very small doses, or due to the intravitreal technique of administration which carries some inherent risks regardless of which drug is used. The safety profile of intravitreal bevacizumab is generally considered acceptable and comparable to ranibizumab.

Bevacizumab used in the CATT study was repackaged into glass vials for each study centre. Known UK suppliers of intravitreal bevacizumab provide single-use pre-filled plastic syringes with at least one able to assign a shelf-life of ninety days. At least one supplier has ‘extensive stability/sterility/particulate data to meet all MHRA requirements for bevacizumab for eyes’. However the properties of bevacizumab stored in plastic vesicles have been found to be potentially clinically detrimental.

The use of bevacizumab in AMD is not licensed and is considered by NICE to be unlicensed use, as opposed to off-license. Consequently, there are implications for prescribing clinicians with regards to liability in the event of adverse treatment consequences. Guidance from recognised and authoritative bodies states a clear preference for licensed treatments in licensed indications as is provided by ranibizumab in AMD. However, the use of unlicensed treatments, such as bevacizumab in AMD, is not absolutely precluded by these bodies providing specific governance issues are properly adhered to. Indeed, bevacizumab, which is not licensed for any ophthalmological indication, is already used within regional ophthalmological clinics for various other indications. Ranibizumab (Lucentis®) is licensed for AMD, recommended by NICE, and has evidence in AMD from three large randomised studies.
The financial consequences of using bevacizumab instead of ranibizumab for AMD cases are substantial. This is due to a combination of the size of the patient cohort and the vast difference in unit drug prices, with ranibizumab being about 18 times more costly per dose than bevacizumab. It is difficult to accurately predict the actual savings from a change in policy however it is likely they savings will run into several million pounds per annum.

A major component of the cost of treating AMD is the cost per admission and this will not be affected by a change in drug use. Indeed, the clinical evidence indicates that the frequency of drug admission might be greater for the same clinical effect with bevacizumab compared with ranibizumab. However, any such effect on admission rates is likely to be small and more than compensated for by the differential drug costs.

There are three potential positions which the group could consider:

1. Not to recommend bevacizumab and retain ranibizumab for all AMD cases.

2. Recommend bevacizumab for all new AMD cases and retain ranibizumab for all AMD cases which have already commenced treatment with at least one dose of ranibizumab.

3. Recommend bevacizumab for all new and existing AMD cases henceforth.

Option 1 may not be considered acceptable to commissioning organisations due to the substantial financial implications in light of the CATT study evidence.

Option 2, whilst supported by clinical evidence and complimentary to usual practice, where existing treatment decisions are maintained until the treatment course is completed, may present practical difficulties with different patients within the same clinic requiring different drugs depending on the timing of treatment commencement. In addition, the situation might arise where a patient is receiving treatment with ranibizumab in one eye and bevacizumab in the other. UK-derived safety data already indicates a number of incidences of the wrong drug being given in intravitreal ophthalmological clinics and this problem might only be compounded if clinicians were to use different drugs for different cases. These issues are not insurmountable if best practice is achieved at all times.

Option 3 offers the greatest financial benefit to commissioners and may be the easiest to manage practically in the long-term. However, a switch from ranibizumab to bevacizumab is not strictly supported by any robust clinical evidence and in the short-term could present practical issues as patient consent might be required.
When NETAG previously considered bevacizumab in AMD in 2009 the group issued a negative recommendation. However the group did stipulate that the supply of bevacizumab for ophthalmological indications should always be via the purchase of pre-filled syringes from a licensed compounding facility as opposed to in-house aseptic compounding. This stance is supported by a national communication from the West Midlands Specialised Commissioning Team which has requested that all NHS organisations use bevacizumab purchased from a licensed compounding facility so that potential treatment risks are minimised and avoiding any detrimental impact on the use of intravitreal bevacizumab. 

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Author’s declaration: The author has participated in several advisory boards and similar, and non-promotional educational events, either directly or indirectly on behalf of Novartis Pharmaceuticals, including one specifically regarding Lucentis®.
Appendix 1. Current General Medical Council guidance for prescribers

Prescribing unlicensed medicines
You can prescribe unlicensed medicines but, if you decide to do so, you must:

• Be satisfied that an alternative, licensed medicine would not meet the patient’s needs
• Be satisfied that there is a sufficient evidence base and/or experience of using the medicine to demonstrate its safety and efficacy
• Take responsibility for prescribing the unlicensed medicine and for overseeing the patient’s care, including monitoring and any follow up treatment
• Record the medicine prescribed and, where you are not following common practice, the reasons for choosing this medicine in the patient’s notes.

Prescribing medicines for use outside the terms of their licence (off-label)
You may prescribe medicines for purposes for which they are not licensed. Although there are a number of circumstances in which this may arise, it is likely to occur most frequently in prescribing for children. […].

When prescribing a medicine for use outside the terms of its licence you must:

• Be satisfied that it would better serve the patient’s needs than an appropriately licensed alternative
• Be satisfied that there is a sufficient evidence base or experience of using the medicine to demonstrate its safety and efficacy; the manufacturer’s information may be of limited help, in which case the necessary information must be sought from other sources take responsibility for prescribing the medicine and for overseeing the patient’s care, monitoring and any follow up treatment, or arrange for another doctor to do so
• Make a clear, accurate and legible record of all medicines prescribed and, where you are not following common practice, your reasons for prescribing the medicine in the patient’s notes.

Information for patients about the licence for their medicines
You must give patients, or those authorising treatment on their behalf, sufficient information about the proposed course of treatment, including any known serious or common side effects or adverse reactions. This is to enable them to make an informed decision

Some medicines are routinely used outside the scope of their licence, […] Where current practice supports the use of a medicine in this way it may not be necessary to draw attention to the licence when seeking consent. However, it is good practice to give as much information as patients, or those authorising treatment on their behalf, require or which they may see as significant. If patients or their carers express concern, you should also explain, in broad terms, the reasons why medicines are not licensed for their proposed use. Such explanations may be supported by written information, […]

However, you must explain the reasons for prescribing a medicine that is unlicensed or being used outside the scope of its licence where there is little research or other evidence of current practice to support its use, or the use of the medicine is innovative.