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Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial

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Running header: Cost-effectiveness of ranibizumab and bevacizumab for AMD

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Neovascular age-related macular degeneration (nAMD); vascular endothelial growth factor (VEGF) inhibitors; trial-based economic evaluation; cost-utility analysis; cost-minimisation analysis; cost-effectiveness.

Abstract

Objective: To assess the incremental cost and cost-effectiveness of continuous and discontinuous regimens of bevacizumab (Avastin®) and ranibizumab (Lucentis®) for neovascular age-related macular degeneration (nAMD) from a UK National Health Service perspective.

Design: A within-trial cost-utility analysis with two-year time horizon, based on a multi-centre factorial, non-inferiority randomised controlled trial.

Setting: 23 hospital ophthalmology clinics.

Participants: 610 patients aged ≥50 years with untreated nAMD in the study eye.

Interventions: 0.5 mg ranibizumab or 1.25 mg bevacizumab given continuous (monthly) or discontinuous (as-needed) for two years.

Main Outcome Measures: Quality-adjusted life-years (QALYs).

Results: Total two-year costs ranged from £3,002/patient ($4,700; 95% CI: £2,601 to £3,403) for discontinuous bevacizumab to £18,590/patient ($29,106; 95% CI: £18,258 to £18,922) for continuous ranibizumab. Ranibizumab was significantly more costly than bevacizumab for both continuous treatment (+£14,989/patient [$23,468; 95% CI: £14,522 to £15,456; p<0.001) and discontinuous treatment (+£8,498 [$13,305]; 95% CI: £7,700 to £9,295; p<0.001), with negligible difference in QALYs. Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay £3.5 million ($5.5 million) per additional QALY gained. Patients receiving continuous bevacizumab accrued higher total costs (+£599 [$938] 95% CI: £91 to £1,107; p=0.021) than those receiving discontinuous bevacizumab, but also accrued non-significantly more QALYs (+0.020; 95% CI: -0.032 to 0.071; p=0.452). Continuous bevacizumab therefore cost £30,220 ($47,316) per QALY gained compared with discontinuous bevacizumab. However, bootstrapping demonstrated that if the NHS is willing to pay £20,000/QALY gained, there is a 37% chance that continuous bevacizumab is cost-effective compared with discontinuous bevacizumab.

Conclusions: Ranibizumab is not cost-effective compared with bevacizumab, being substantially more costly and producing little/no QALY gain. Discontinuous bevacizumab is likely to be the most cost-effective of the four treatment strategies evaluated in IVAN, although there is a 37% chance that continuous bevacizumab is cost-effective.

Trial registration: ISRCTN92166560

Article summary: Strengths and limitations of this study

- We conducted a trial-based economic evaluation based on high-quality data on costs and quality of life prospectively collected within a randomised trial.
- This demonstrated that bevacizumab would achieve substantial cost-savings over ranibizumab with negligible differences in quality of life. In England, switching patients to bevacizumab could save at least £102 ($160) million per year. However, bevacizumab is not currently licensed for neovascular age-related macular degeneration (nAMD).
- Our study is the first to evaluate the cost-effectiveness of alternative treatment regimens for nAMD.
- Of the strategies for the treatment of nAMD evaluated in this trial, we found discontinuous (as needed) bevacizumab to be the least costly and most cost-effective. However, there was substantial uncertainty around this finding and sensitivity analyses suggested that the cost-effectiveness of using continuous (monthly) treatment rather than discontinuous treatment may vary between centres.

Introduction

Neovascular age-related macular degeneration (nAMD) is a common disorder of the ageing eye and if left untreated leads to severe central visual impairment. The current standard of care is treatment with biologicals that bind to or inhibit vascular endothelial growth factor (VEGF). Biologicals need to be injected into the vitreous cavity of the eye at 4-8 week intervals. However, the first treatment convincingly shown to be effective in preventing vision loss (ranibizumab, Lucentis®[2 3]) is expensive (£742/dose[4]). Another anti-VEGF biological, bevacizumab (Avastin®), is licensed to treat bowel cancer and has been used to treat nAMD, using smaller doses that cost much less than ranibizumab. Small non-randomised studies on bevacizumab have reported outcomes that were as good as those achievable with ranibizumab.[5] Comparative effectiveness randomised controlled trials (RCTs) of ranibizumab versus bevacizumab were therefore needed to provide unbiased estimates of relative efficacy and safety. The UK Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial[1 6] and the US Comparison of Age-related macular degeneration Treatments Trials (CATT)[7 8] were amongst the first such trials to report findings.

Two-year IVAN results demonstrated that ranibizumab and bevacizumab produced similar improvements in visual function, with no significant difference in arteriothrombotic events or hospital admissions for heart failure, which have previously been linked with anti-VEGF therapy.[6] IVAN also compared discontinuous (as-needed) treatment against continuous monthly injections. Continuous and discontinuous treatment produced similar improvements in visual function, although mortality was significantly lower with continuous treatment (p=0.05).

Given the rising demands for healthcare and limited budgets, it is important to assess cost-effectiveness as well as the clinical effectiveness and safety of medical interventions. Evidence on incremental cost and cost-effectiveness is of particular importance in nAMD, owing to the potential savings and health implications of either reducing treatment frequency or substituting a much cheaper alternative (bevacizumab) for a more expensive drug (ranibizumab). Although ranibizumab costs many times more than bevacizumab, it is important to consider all relevant costs and assess cost-effectiveness to determine whether the more expensive therapy has added

health benefits that justify the additional costs or lead to savings that offset the price difference.

A recent systematic review[9] identified nine economic evaluations of ranibizumab and three of bevacizumab. Six further studies evaluating ranibizumab[10-15] and one evaluating bevacizumab[11] have since been published. Most studies found ranibizumab to be cost-effective versus other treatments, such as pegaptanib. Four studies concluded that bevacizumab was likely to be cost-effective compared with ranibizumab, but relied on observational data[11 15] or assumptions about relative efficacy.[16 17] We are unaware of any other RCT that has estimated the cost-effectiveness of bevacizumab or any study that evaluated the cost-effectiveness of continuous versus discontinuous treatment.

A key objective of the IVAN trial was to assess the incremental cost and incremental cost-effectiveness of continuous and discontinuous regimens of bevacizumab and ranibizumab in nAMD from the perspective of the UK National Health Service (NHS). The results of these analyses are reported here.

Methods

The study was based on the two-year results from the IVAN trial (ISRCTN92166560), which provided high-quality data on resource use and outcomes and comprises the only UK trial directly comparing these interventions. Trial design and methods have been described previously[1 6]; in brief this was a factorial, multi-centre non-inferiority trial in which 610 patients not previously treated for nAMD in their study eyes were randomised to either bevacizumab (0.5 mg/dose) or ranibizumab (1.25 mg/dose) and to either discontinuous treatment or continuous monthly injections for two years. Discontinuous treatment comprised an initial course of three monthly injections, followed by further courses of three injections given monthly if pre-specified clinical and optical coherence tomography (OCT) re-treatment criteria were met. The economic evaluation took a two-year time horizon to estimate within-trial cost-effectiveness. Following UK guidelines,[18] we took the perspective of the UK NHS, which excludes costs incurred by patients and their families or employers.

Detailed methods and additional results will be published as a monograph in *Health Technology Assessment*.

Since IVAN was factorial, it was important to consider the likelihood of interactions: that is, whether the differences in costs and/or quality of life between bevacizumab and ranibizumab differ between treatment regimens. Although no interactions were anticipated for visual acuity,[1] large interactions between drug and treatment regimen were expected for costs and cost-effectiveness, since reducing the number of injections would have a proportionately greater effect on drug costs for ranibizumab than for less expensive bevacizumab. Interactions for quality of life or costs are also possible if the number of injections required for discontinuous treatment differed between drugs. We therefore estimate the mean costs and mean quality-adjusted life-years (QALYs) for each of the four treatment combinations and interpret the results based on four pair-wise comparisons:

- Continuous ranibizumab versus discontinuous ranibizumab;
- Continuous bevacizumab versus discontinuous bevacizumab;
- Continuous ranibizumab versus continuous bevacizumab;
- Discontinuous ranibizumab versus discontinuous bevacizumab.

We report two forms of economic evaluation. Comparisons between drugs were based on cost-minimisation analysis, which compares costs between treatments that are assumed to have identical health effects.[19] Cost-minimisation analysis is appropriate only if the difference in cost is so large that no plausible difference in efficacy could cause the more costly treatment to be cost-effective.[20 21] This approach is justified for the comparisons between drugs because the large difference in drug costs was inevitably going to be the main influence on the incremental cost-effectiveness of ranibizumab versus bevacizumab. We therefore pre-specified that ranibizumab and bevacizumab would be compared using cost-minimisation analysis unless ranibizumab-treated patients accrued ≥0.05 more QALYs than those receiving bevacizumab. By contrast, we used cost-utility analysis, in which health outcomes are measured in QALYs, to compare continuous and discontinuous treatment, where incremental costs are smaller.

Measurement and valuation of resource use

Our base case analysis also focused on resource use associated with the study eye or associated with adverse events (AEs) or serious adverse events (SAEs) that were "*expected*": i.e. previously linked to anti-VEGF treatment (Appendix). Concomitant medications, hospitalisations and ambulatory consultations that were neither associated with the study eye nor attributable to expected AEs or expected SAEs were excluded to avoid including episodes of high healthcare resource use unrelated to treatment (e.g. renal failure or cancer), which might otherwise have swamped the main effect of treatment on costs.[22]

After enrolment, participants were monitored for disease activity on a monthly basis with visual acuity assessments, colour fundus imaging and OCT. Fundus fluorescein angiography (FFA) was undertaken at specified visits and when OCT was insufficient to reach a decision on disease activity. A pre-specified algorithm was used to determine the need for re-treatment. Patients allocated to discontinuous treatment began a new course of three monthly injections whenever they met re-treatment criteria. However, costing analyses excluded protocol-driven resource use; in particular, we assumed that patients would not require colour fundus photography, OCT or FFA unless this would affect treatment decisions. As such, patients on discontinuous treatment were assumed not to require these investigations at the second or third visit in a course of three injections, when treatment was mandated (Figure 1). Similarly, patients on continuous treatment were assumed to require monitoring consultations only once every three months, on the grounds that ophthalmologists would want information about disease progression periodically, irrespective of whether treatment decisions are required.

Micro-costing was used to estimate the cost of injection and monitoring consultations since the available national average costs[23 24] are not nAMD-specific and do not differentiate between consultations for monitoring and intravitreal drug delivery. Staff at 13 of the 23 IVAN centres completed questionnaires on overheads, the cost of setting up clinic facilities and equipment and/or the staff required to run injection and monitoring clinics.

The drug acquisition cost for ranibizumab was the NHS list price (£742.17[4]) and that for bevacizumab was the price typically charged by the not-for-profit NHS provider used in the trial (£49/prefilled syringe). All concomitant medications, contacts with medical professionals and hospitalisations were recorded at each monthly clinic visit. Concomitant medications applied to the study eye or indicated for any expected SAE/AE were valued using list prices.[4] Costs of other medications, including those applied to the fellow eye, were excluded from the analysis. Unit costs for consultations with general practitioners, district or general practice nurses and hospital staff outside IVAN clinics were obtained from routine sources.[24 25] These costs were applied to ambulatory consultations that were either related to the eye or that occurred within 30 days of an expected SAE/AE. Hospital stays linked to expected SAEs were valued using the mean cost per bed-day for associated HRGs.[24]

Resource use data and unit costs were combined to estimate quarterly costs of: bevacizumab/ranibizumab; drug administration and monitoring consultations; and hospitalisations, ambulatory consultations and medication changes for expected SAEs/AEs. Value added tax (VAT) was excluded from the economic evaluation and included in budget impact estimates, following guidelines.[18] Costs are reported in 2011 pounds sterling, accompanied by equivalents in US dollars (exchange rate: $1.57/pound).

Measurement and valuation of health benefits

The three-level EQ-5D questionnaire[26] was administered at baseline, 3, 12 and 24 months, and (if the patient was willing and able to do so) at study exit, after any SAE and after a drop in visual acuity in the study eye of ≥15 letters on the Early Treatment Diabetic Retinopathy Study vision chart between two consecutive visits (referred to subsequently as a 'reduction in visual acuity'). The Health Utilities Index questionnaire version 3 (HUI3) was administered at the same timepoints and used in sensitivity analyses; EQ-5D comprised the utility primary measure following UK guidelines.[18] Patients self-completed large-print EQ-5D questionnaires, with assistance from study nurses where necessary; responses were valued using the UK time-trade-off tariff to give "utilities".[26]

Missing utility data were imputed using multiple imputation,[27] which avoids bias and enables analysis of the whole sample. Multiple imputation was conducted using the ice command[28] (version 1.9.4) in Stata Version 12 (StataCorp, College Station, TX).

QALYs for each participant were calculated as the area under the curve. We assumed that utility changed linearly between consecutive EQ-5D measurements in the absence of SAEs. Since linear changes are unlikely for patients with SAEs, we assumed that SAEs and reductions in visual acuity caused a sudden drop in utility on the day of onset, followed by a linear rise as the patient recovered; the rate of this linear rise was estimated using mixed models (Appendix).

Statistical methods

Linear regression models were used to estimate the effect of drug and treatment regimen on QALYs, drug costs, administration/monitoring costs and medication/medical service use in each three-month period or "quarter" (Appendix). Interactions between drug and treatment regimen were included in the models for quarters 2-8 if they were either statistically significant or were larger than the main effect for drug or for treatment regimen. The analysis of QALYs, drug costs and medication/medical service use in quarters 2-8 therefore took account of interactions, while drug and treatment regimen were assumed to have additive effects on administration/monitoring costs. A variant on Kaplan-Meier sample averaging[29 30] was used to account for patients withdrawing early from the trial and exclude differences in mortality unrelated to treatment; regression predictions of quarterly costs and QALYs were weighted by the proportion of patients alive at the start of each quarter. Costs accrued in Year 2 were discounted at 3.5% to allow for time preference (i.e. the tendency to prefer benefits sooner and costs later).[18] Uncertainty around quarterly costs and QALYs was quantified by estimating models separately for 130 nonparametric bootstrap draws on each of 100 datasets generated in multiple imputation to capture the uncertainty around imputed utilities. The appendix gives further details of the statistical methodology.

Presentation of results and uncertainty

Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in cost between two study arms by the difference in QALYs. Results were interpreted assuming that the UK NHS would be willing to pay £20,000 to gain one QALY (a £20,000/QALY "ceiling ratio").[31] We also present net benefits for each of the four treatment arms: net benefit equals total QALYs multiplied by the ceiling ratio, minus total costs. Uncertainty around ICERs is presented as cost-effectiveness acceptability curves, which plot the probability of each of the four treatment groups having the highest net benefits (i.e. being most cost-effective) at a range of ceiling ratios.

Sensitivity analyses evaluated the impact of changing the costs (e.g. halving the cost of ranibizumab), methods (e.g. taking a one-year time horizon) and assumptions (e.g. including the costs of all SAEs, not just 'expected' SAEs).

Results

QALYs and quality of life

The number of QALYs accrued over the two-year trial period did not differ significantly between bevacizumab and ranibizumab, or between continuous and discontinuous treatment ($p \geq 0.381$; Table 1). Patients randomised to continuous treatment accrued non-significantly more QALYs than those randomised to discontinuous treatment (mean difference: 0.020 [95% CI: -0.032, 0.071] for bevacizumab, p=0.452 and 0.026 [95% CI: -0.032, 0.085] for ranibizumab, p=0.381), while differences between ranibizumab and bevacizumab were negligible.

Resource use and costs

Patients receiving continuous treatment received a mean of 22 injections, while those on discontinuous treatment received 13. Consequently, drug costs differed substantially between continuous and discontinuous treatment (Table 1; $p<0.001$), as well as between ranibizumab and bevacizumab ($p<0.001$). Since reducing treatment frequency produces larger savings for ranibizumab than for bevacizumab, there were significant interactions between drug and treatment regimen for drug cost ($p<0.001$).

Administration of bevacizumab or ranibizumab cost £61 ($96; standard deviation, SD: £14) per injection, while each consultation for monitoring cost £72 ($113; SD: £41), plus £39 ($61; SD: £16) for each FFA. Administering intravitreal injections and monitoring disease progression/remission cost between £1,825 and £1,970 per patient over the two-year trial period (Table 1). Discontinuous treatment reduced the number of injections required, but increased the number of monitoring consultations needed to assess disease status against retreatment criteria, since we assumed that OCT would only be done when it would inform treatment decisions. Since continuous treatment requires, on average, nine more injections ($p<0.001$), but avoids only six monitoring visits ($p<0.001$), drug administration and monitoring costs were higher with continuous treatment than discontinuous treatment (mean difference: £130 per patient ($204); 95% CI: £20, £239; $p=0.021$), with no significant difference between bevacizumab and ranibizumab ($p=0.80$).

The cost of medication changes, hospitalisations and ambulatory consultations associated with expected SAEs and expected AEs was relatively small (mean: £469 [$735] per patient), but varied substantially between patients (95 percentile range: £0, £1,401). There was no significant difference in such costs between drugs or treatment regimens ($p\geq0.163$).

Taking account of the drug cost, drug administration/monitoring and medication/medical service use, the mean total cost per patient over the two-year trial ranged from £18,590 ($29,119) for continuous ranibizumab to £3,002 ($4,702) for discontinuous bevacizumab (Table 1). Drug cost accounted for 80-88% of the total cost for patients randomised to ranibizumab and 21-30% of the cost for patients randomised to bevacizumab. Drug administration and monitoring accounted for 54-61% of the costs accrued by patients randomised to bevacizumab and 10-15% of costs for those randomised to ranibizumab.

Base case comparison between ranibizumab and bevacizumab

Since the difference in mean QALYs between ranibizumab and bevacizumab was less than the pre-specified non-inferiority margin (0.05 QALYs), cost-minimisation analysis was used to compare the two drugs on the basis of cost alone. Overall,

continuous ranibizumab cost £14,989 more per patient ($23,476 [95% CI: £14,522, £15,456], Table 1) than continuous bevacizumab over the two-year trial period (p<0.001). Discontinuous ranibizumab cost £8,498 more per patient ($13,308 [95% CI: £7,700, £9,295], p<0.001) compared with discontinuous bevacizumab. Bootstrapping analyses estimated the probability that switching from ranibizumab to bevacizumab would save money and found that this exceeds 99.9%.

Base case comparison between continuous and discontinuous treatment

Overall, using continuous rather than discontinuous treatment increased costs by £7,090 ($11,102 [95% CI: £6,337, £7,844], p<0.001) for ranibizumab and £599 ($938 [95% CI: £91, £1,107], p=0.021) for bevacizumab.

However, patients randomised to continuous bevacizumab also accrued non-significantly more QALYs than those randomised to discontinuous bevacizumab (Table 1; p=0.452). In line with best practice,[19] we took account of the non-significant differences in QALYs and allowed for the joint distribution of costs and QALYs, since assuming no difference in health outcomes can introduce bias and give misleading conclusions.[20 21] Dividing the difference in cost by the difference in QALYs suggests that continuous bevacizumab costs £30,220 ($47,316) per additional QALY gained compared with discontinuous bevacizumab. This ICER is somewhat higher than the £20,000 ($31,000) per QALY "ceiling ratio" below which the NHS generally considers treatments to be cost-effective.[31] However, the imprecision around QALY differences means that there is substantial uncertainty around this ICER. Bootstrapping demonstrated that there is a 37% chance that continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at a £20,000/QALY ceiling ratio, which increases to 50% at £30,000/QALY.

Continuous ranibizumab cost £270,217 ($423,074) per QALY gained compared with discontinuous ranibizumab. Due to the substantial savings possible by giving ranibizumab less frequently, we can be >99.99% confident that continuous ranibizumab is poor value for money compared with discontinuous ranibizumab at a £20,000/QALY ceiling ratio.

Base case four-way comparison

It is also informative to consider the four trial treatment groups as four mutually-exclusive alternative strategies for managing nAMD. Framing the decision in this way demonstrates that discontinuous bevacizumab is the most cost-effective treatment strategy evaluated in IVAN, generating higher net benefits than the other three treatment strategies (Table 1), where net benefit equals QALYs multiplied by ceiling ratio (in this case £20,000/QALY) minus costs. Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay £3.5 million ($5.5 million) per additional QALY gained. Discontinuous ranibizumab is not cost-effective at any ceiling ratio, as it is more costly and less effective than continuous or discontinuous bevacizumab.

However, there remains substantial uncertainty around incremental QALY gains. This is illustrated by the cost-effectiveness acceptability curves plotting the probability of each treatment being the most cost-effective of the four strategies at different ceiling ratios (Figure 2). This demonstrates that, although we can be 98% confident that discontinuous bevacizumab is less costly than continuous bevacizumab, our confidence in the conclusion that discontinuous bevacizumab has highest net benefits decreases rapidly as the value we place on the small, non-significant QALY gains increases. At a £20,000/QALY ceiling ratio, there is a 63% probability that discontinuous bevacizumab is the most cost-effective strategy considered in IVAN and a 37% probability that continuous bevacizumab is the most cost-effective. By contrast, the probability of either continuous or discontinuous ranibizumab being the most cost-effective strategy for managing nAMD is <1% unless the NHS were willing to pay more than £100,000/QALY gained.

Sensitivity analyses

Sensitivity analyses demonstrated that the conclusions are very robust to changes in the assumptions and methods used to measure costs and utilities and conduct the analysis (Figure 3). Notably, no sensitivity analysis changed the conclusion that ranibizumab is not cost-effective compared with bevacizumab. However, three sensitivity analyses changed the conclusion that continuous bevacizumab is not cost-effective compared with discontinuous bevacizumab: assuming that FFA is only conducted at baseline, not at any subsequent monitoring consultation; measuring

quality of life using HUI3 rather than EQ-5D; and using unadjusted Kaplan-Meier estimates of the probability of surviving at any point in time to account for censoring, rather than excluding differences in deaths that were unrelated to study medication (see Appendix).

Threshold analyses demonstrated that the price of ranibizumab would need to be reduced to £63.46 per dose (a 91% price reduction) in order for continuous ranibizumab to be cost-effective compared with continuous bevacizumab at a £20,000/QALY ceiling ratio.

Discussion

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.[31] Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay >£3.5 ($5.5) million/QALY gained. Furthermore, our analysis also shows that giving discontinuous bevacizumab, rather than discontinuous ranibizumab could save the UK NHS £8,498 ($13,341) per patient treated, with little or no impact on the health gains from treatment. If the 17,295 eyes requiring anti-VEGF therapy each year in England[32] were switched from discontinuous ranibizumab to discontinuous bevacizumab, the NHS could save at least £102 ($160) million per year (including 20% VAT) based on the treatment regimens evaluated in IVAN. It remains controversial as to whether a drug (bevacizumab) that has not been approved and licensed for nAMD by regulatory agencies should be used when a licensed drug (ranibizumab) is available. In the UK, clinicians may prescribe unlicensed medications within approved research projects, when no suitable medicine is licensed, or when the licensed alternative is unavailable,[33] although prescribing on cost grounds is not mentioned. By contrast, in the US, ophthalmologists use bevacizumab freely.[34] National guidance (rather than local hospital/clinician policies) is therefore needed in the UK to direct the choice between bevacizumab and ranibizumab. 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.

The base case analysis found that continuous bevacizumab cost £30,220 ($47,445) per QALY gained compared with discontinuous bevacizumab, suggesting that discontinuous bevacizumab is the most cost-effective strategy evaluated in IVAN if the NHS is willing to pay up to £20,000/QALY gained. However, there remains substantial uncertainty around this conclusion and there is a 37% chance that continuous bevacizumab is cost-effective. The finding of non-significantly higher QALYs with continuous treatment contradicts our prior hypothesis that avoiding monthly injections might improve quality of life, although the observed difference could be due to chance. Nonetheless, discontinuous bevacizumab would remain the most cost-effective strategy even if there were no difference in quality of life between treatment regimens. Other considerations may affect the choice of anti-VEGF delivery model. In particular, since discontinuous treatment requires regular clinical review and access to retinal imaging, it may be more practical to provide treatment every month, with monitoring restricted to specified points in time (e.g. six or 12 months after initiation of therapy). Indeed the label for the newest anti-VEGF (aflibercept) incorporates a limited clinical monitoring regime.[35] The discontinuous treatment regimen evaluated in the IVAN trial was chosen partly to minimise the possibility of disadvantage to participants in these groups and partly to minimise the number of retreatment decisions required. Neither monthly treatment nor treatments given as blocks of three are used widely in routine practice, although following publication of IVAN,[1 6] there appears to be increased interest in the "IVAN regimen". The cost-effectiveness of monthly versus intermittent treatment will therefore vary between treatment centres depending on local costs and clinical practice.

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. It therefore provides unequivocally-unbiased estimates of incremental costs and QALYs. Nevertheless, our analysis confirms the findings of previous economic evaluations, namely that ranibizumab is not cost-effective compared with bevacizumab.[11 17] We are also (to our knowledge) the first to evaluate the cost-effectiveness of alternative treatment

regimens. In addition to following best practice for trial-based economic evaluation, this study includes several novel aspects, such as measuring quality of life after SAEs, excluding chance differences in deaths unrelated to treatment and allowing for the factorial design by including only large or statistically significant interactions.

The study also estimates the cost of consultations to administer ranibizumab/bevacizumab and monitor outcomes, which could be used in other economic evaluations. Micro-costing shows the main drivers of consultation costs and highlighted substantial variation in costs between centres; this variation means that the cost-effectiveness of continuous versus discontinuous bevacizumab (but not ranibizumab versus bevacizumab) will vary between centres. It is important to note that the costs were calculated to assess incremental cost-effectiveness in IVAN and should not be used to set the prices at which hospitals are reimbursed. In particular, they are bottom-up estimates that exclude unpaid overtime and VAT and make assumptions about overheads and proportion of staff-time spent on patient contacts. In most settings it is likely that the costs to healthcare commissioners will be higher and subject to local negotiations with care providers.

The base case analysis focused on mortality attributable to study medication and the costs associated with "expected" SAEs/AEs and excluded other costs. This reduced the risk that chance differences in resource use not associated with study medication could distort our conclusions. However, it also means that the unanticipated increase in the incidence of other SAEs (e.g. gastrointestinal events) with bevacizumab[1 6] (which comprised the only difference in SAEs between drugs) is not taken into account in the costing analysis. However, sensitivity analyses including the cost of all SAEs/AEs gave the same conclusions.

Further research is needed to assess the extent to which the cost-effectiveness findings generalise to other countries with different relative prices and management of nAMD and SAEs/AEs. 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. The costs of the two drugs may vary between centres within the UK as hospitals may use different bevacizumab suppliers or have different discounts on ranibizumab. Nevertheless, because we collected very detailed

information on resource use, policy makers in other countries can review these data against their own to examine their similarity and, hence, the applicability of our findings to their setting. Future work combining data from IVAN with that from other trials, such as CATT,[7] may help reduce uncertainty and evaluate the extent to which the results can be generalised. However we believe that our primary finding of ranibizumab representing very poor value for money compared with bevacizumab does apply throughout the world.

Funding and role of study sponsors

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Competing interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). All authors had financial support from the NIHR for the submitted work. HD, SW, GA and JR have no financial or non-financial interests relevant to the submitted work. UC, SH, SD and AL are principal investigators of trials sponsored by Novartis, the manufacturers of ranibizumab. UC has attended and been remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and Bausch and Lomb; and her employing institution has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and Pfizer. SH has attended and been remunerated for attendance at advisory boards for and received travel support from Novartis and Allergan. CR has received an honorarium from Novartis for a lecture. SD's and AL's employing institutions have received payments from Novartis. SD and AL have received honoraria from Novartis for lectures. AL has attended and been remunerated for attendance at advisory boards for Novartis and Bayer; likewise SD for Bayer and Ely Lilly. BR has received a fee for teaching from Janssen-Cilag.

Authorship statement

SW, CR, JR, SH, AL, SD, BR and UC conceived, designed and conducted the IVAN trial. HD, SW, GA and JR conceived and designed the economic evaluation, with extensive input from CR, SH and BR. CR supervised collation/cleaning of trial data, while HD, SW and GA collected additional resource use data from centres. HD conducted the economic analysis with help from GA under the supervision of SW. HD drafted the manuscript. All authors edited the manuscript for important intellectual content and approved the final version.

Acknowledgements

The IVAN Study Investigators are listed in Appendix 1 of reference.[1]

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Transparency declaration

The manuscript's guarantor (HD) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

No additional data available

Ethics statement

Participants provided written informed consent. A UK National Health Service Research Ethics Committee approved the trial (07/NIR03/37).

References

1. The IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. Ophthalmology 2012;**119**(7):1399-411.
2. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009;**116**(1):57-65.e5.
3. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. The New England journal of medicine 2006;**355**(14):1419-31.
4. British Medical Association. *British National Formulary 62 (http://bnf.org/bnf/index.htm)*. London: Pharmaceutical Press, September 2011.
5. Mitchell P. 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. Current Medical Research & Opinion 2011;**27**(7):1465-75.
6. 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.
7. 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.
8. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;**364**(20):1897-908.
9. Mitchell P, Annemans L, White R, et al. Cost effectiveness of treatments for wet age-related macular degeneration. PharmacoEconomics 2011;**29**(2):107-31.
10. Yanagi Y, Aihara Y, Fukuda T, et al. [Cost-effectiveness of ranibizumab, photodynamic therapy and pegaptanib sodium in the treatment of neovascular

age-related macular degeneration in Japanese]. Nihon Ganka Gakkai Zasshi 2011;**115**(9):825-31.

11. 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**(2):247-55.
12. Gower EW, Cassard SD, Bass EB, et al. A cost-effectiveness analysis of three treatments for age-related macular degeneration. Retina 2010;**30**(2):212-21.
13. Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, et al. Cost-effectiveness of ranibizumab compared with pegaptanib in neovascular age-related macular degeneration. Graefes Archive for Clinical & Experimental Ophthalmology 2010;**248**(4):467-76.
14. Neubauer AS, Holz FG, Sauer S, et al. Cost-effectiveness of ranibizumab for the treatment of neovascular age-related macular degeneration in Germany: Model analysis from the perspective of Germany's statutory health insurance system. Clinical Therapeutics 2010;**32**(7):1343-56.
15. Smiddy WE. Economic implications of current age-related macular degeneration treatments. Ophthalmology 2009;**116**(3):481-7.
16. Fletcher EC, Lade RJ, Adewoyin T, et al. Computerized model of cost-utility analysis for treatment of age-related macular degeneration. Ophthalmology 2008;**115**(12):2192-8.
17. Raftery J, Clegg A, Jones J, et al. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol 2007;**91**(9):1244-6.
18. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Secondary Guide to the methods of technology appraisal 2013 2013. http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf.
19. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the economic evaluation of health care programmes*. 3rd ed. New York: Oxford University Press, 2005.
20. Dakin H, Wordsworth S. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. Health Econ 2013;**22**(1):22-34.
21. Briggs AH, O'Brien BJ. The death of cost-minimization analysis? Health Econ 2001;**10**(2):179-84.

22. Jonsson B, Weinstein MC. Economic evaluation alongside multinational clinical trials. Study considerations for GUSTO IIb. International journal of technology assessment in health care 1997;**13**(1):49-58.

23. Department of Health. PbR operational guidance and tariffs: 2011-12 tariff information spreadsheet. Secondary PbR operational guidance and tariffs: 2011-12 tariff information spreadsheet 2011. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_124356.

24. Department of Health. National Schedule of Reference Costs 2010-11 for NHS Trusts and PCTs combined. Secondary National Schedule of Reference Costs 2010-11 for NHS Trusts and PCTs combined November 2011. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131148.xls.

25. Curtis L. Unit Costs of Health and Social Care 2011. Pages 91, 129-150, 177-213. Secondary Unit Costs of Health and Social Care 2011. Pages 91, 129-150, 177-213 2011. http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf.

26. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;**35**(11):1095-108.

27. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;**30**(4):377-99.

28. Royston P. Multiple imputation of missing values: further update of ice, with an emphasis on interval censoring. Stata Journal 2007;**7**:445-64.

29. Hallstrom AP, Sullivan SD. On estimating costs for economic evaluation in failure time studies. Med Care 1998;**36**(3):433-6.

30. Gray A, Clarke P, Wolstenholme J, et al. *Applied Methods of Cost-Effectiveness Analysis in Health Care* Oxford: Oxford University Press, 2011.

31. National Institute for Health and Clinical Excellence. Social value judgements: Principles for the development of NICE guidance. Second Edition. Secondary Social value judgements: Principles for the development of NICE guidance. Second Edition 2008. http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf.

32. National Institute for Health and Clinical Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration TA155: Costing template and report. Secondary Ranibizumab and pegaptanib for the

treatment of age-related macular degeneration TA155: Costing template and report August 2008. (http://www.nice.org.uk/nicemedia/live/12057/41735/41735.xls).

33. General Medical Council. Good practice in prescribing and managing medicines and devices. Secondary Good practice in prescribing and managing medicines and devices 2013. http://www.gmc-uk.org/static/documents/content/Prescribing_guidance.pdf.

34. Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration.[Erratum appears in Arch Ophthalmol. 2010 Dec;128(12):1623]. Archives of Ophthalmology 2010;**128**(10):1273-9.

35. Bayer Plc. Summary of product characteristics for Eylea 40mg/ml solution for injection in a vial Secondary Summary of product characteristics for Eylea 40mg/ml solution for injection in a vial 2013. http://www.medicines.org.uk/emc/medicine/27224/SPC/Eylea+40mg+ml+solution+for+injection+in+a+vial/.

Table 1: Results of the economic evaluation

	Total QALYs (95% CI)‡	Mean (95% CI) drug cost‡	Mean (95% CI) administration & monitoring cost	Mean (95% CI) medication/medical service cost‡	Total cost (95% CI)‡	Total net benefits (95% CI)†‡
Discontinuous bevacizumab	1.584 (1.538, 1.630)	£651 (£605, £698)	£1,825 (£1,708, £1,941)	£526 (£144, £908)	£3,002 (£2,601, £3,403)	£28,683 (£27,707, £29,658)
Continuous bevacizumab	1.604 (1.563, 1.645)	£1,065 (£1,048, £1,081)	£1,952 (£1,860, £2,043)	£585 (£250, £919)	£3,601 (£3,259, £3,943)	£28,480 (£27,548, £29,412)
Discontinuous ranibizumab	1.582 (1.530, 1.634)	£9,229 (£8,584, £9,875)	£1,838 (£1,724, £1,952)	£432 (£253, £611)	£11,500 (£10,798, £12,202)	£20,142 (£18,963, £21,321)
Continuous ranibizumab	1.608 (1.565, 1.651)	£16,286 (£16,011, £16,562)	£1,970 (£1,883, £2,057)	£334 (£215, £452)	£18,590 (£18,258, £18,922)	£13,576 (£12,769, £14,383)
Difference: ranibizumab vs. bevacizumab	Continuous: 0.004 (-0.046, 0.054)	Continuous: £15,222 (£14,948, £15,495)*	£16 (-£109, £141)	Continuous: -£251 (-£604, £102)	Continuous: £14,989 (£14,522, £15,456)*	Continuous: -£14,904 (-£15,995, -£13,813)*
	Discontinuous: -0.002 (-0.064, 0.060)	Discontinuous: £8,578 (£7,932, £9,225)*		Discontinuous: -£94 (-£514, £326)	Discontinuous: £8,498 (£7,700, £9,295)*	Discontinuous: -£8,541 (-£9,939, -£7,144)*
Difference: continuous vs. discontinuous	Ranibizumab: 0.026 (-0.032, 0.085)	Ranibizumab: £7,057 (£6,364, £7,750)*	£130 (£20, £239)*	Ranibizumab: -£98 (-£310, £113)	Ranibizumab: £7,090 (£6,337, £7,844)*	Ranibizumab: -£6,566 (-£7,861, -£5,271)*
	Bevacizumab: 0.020 (-0.032, 0.071)	Bevacizumab: £413 (£365, £462)*		Bevacizumab: £59 (-£438, £556)	Bevacizumab: £599 (£91, £1,107)*	Bevacizumab: -£203 (-£1,372, £967)
Interaction	0.006 (-0.071, 0.084)	£6,643 (£5,949, £7,338)*	£5 (-£31, £42)	-£157 (-£696, £381)	£6,491 (£5,604, £7,379)*	-£6,363 (-£8,088, -£4,638)*

* Significantly different from zero ($p<0.05$).
† Net benefits equal QALYs multiplied by ceiling ratio minus costs; the net benefits shown in this table were calculated at a £20,000/QALY ceiling ratio.
‡ Analysis allowed for interactions.

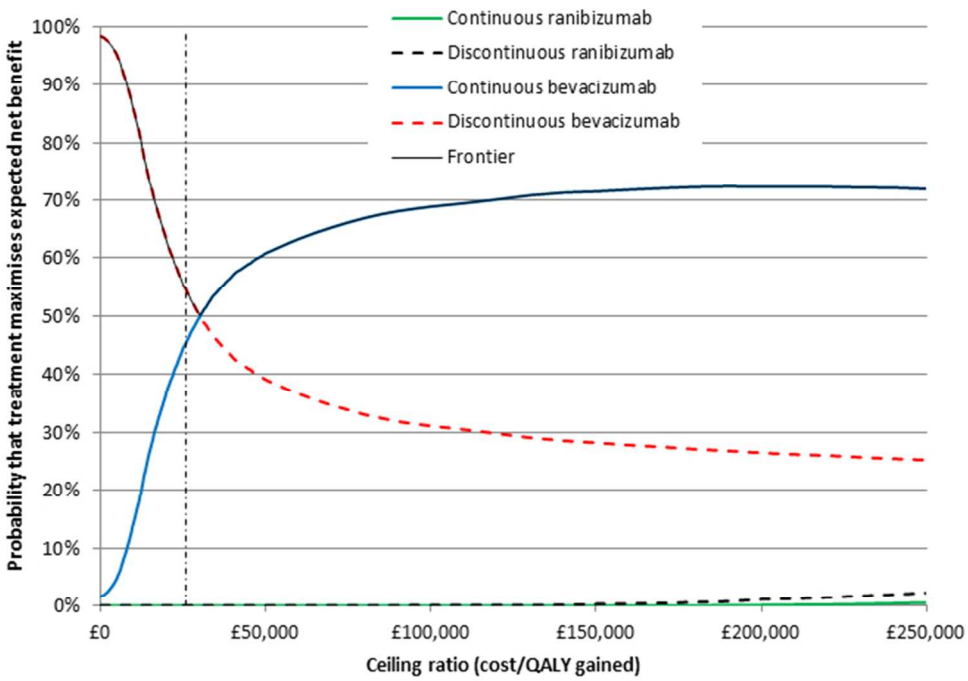
Figure 1: Schematic illustrating the assumptions made about the frequency of injection and monitoring consultations within the costing analysis. The consultations required by patients on discontinuous treatment will depend on when they met treatment failure criteria; Patient 2 met the re-treatment criteria at visits 0, 7 and 11.

	Visit	0	1	2	3	4	5	6	7	8	9	10	11
Patient 1: Continuous treatment	Injection	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
	Monitoring consult	✓			✓			X			✓		
	FFA	✓			?			X			?		
Patient 2: Discontinuous treatment	Injection	✓	✓	✓					✓	✓	✓		✓
	Monitoring consult	✓			✓	✓	X	✓	✓			✓	✓
	FFA	✓			?	?	X	?	?			?	?

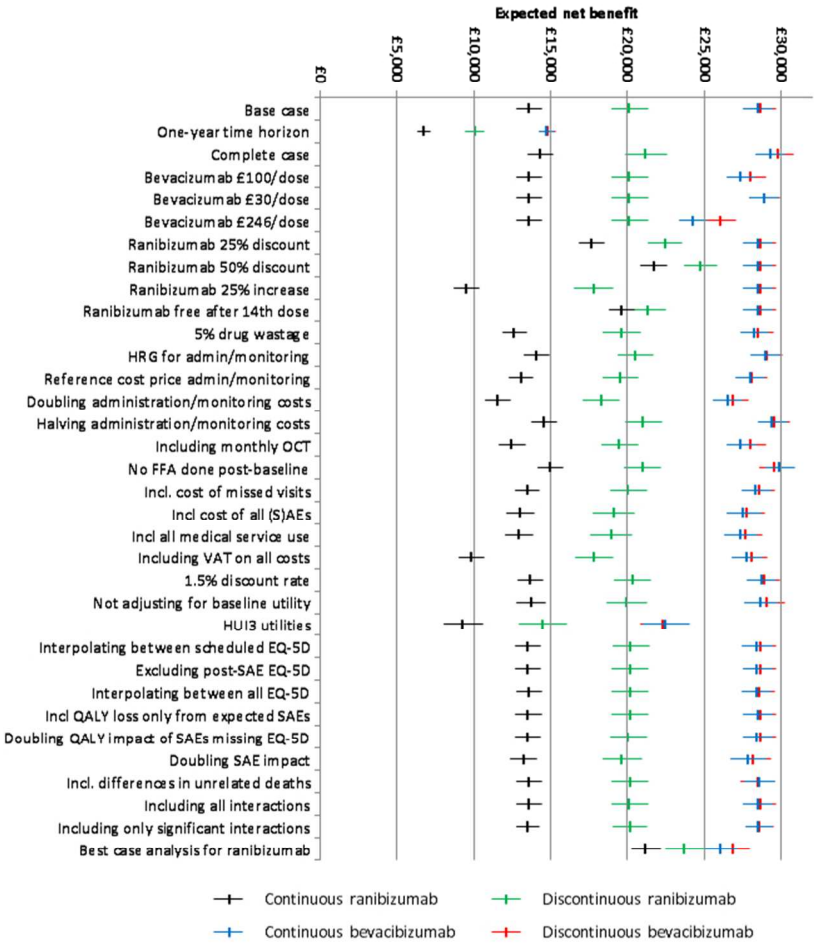
✓ Relevant consultation cost was applied.
? The cost of fundus fluorescein angiography (FFA) was applied if clinically indicated: for discontinuous patients, this was applied whenever the patient had FFA in the trial; for continuous patients, the proportion of patients having FFA was based on estimated use in routine clinical practice.
X No consultation cost was applied as the participant missed the visit.

Figure 2: Cost-effectiveness acceptability curve showing the probability that each treatment is the most cost-effective strategy evaluated in IVAN at a range of ceiling ratios. For example, at a ceiling ratio of £20,000/QALY gained (shown by the vertical dashed line), there is a 63% probability that discontinuous bevacizumab is best and a 37% probability that continuous bevacizumab is best, while the probability that either ranibizumab treatment regimen is best is approximately 0% (total = 100%).

Figure 3: Effect of sensitivity analyses on total net benefits for each of the four treatment arms, assuming a £20,000/QALY ceiling ratio. Treatments that are more cost-effective have higher net benefits; the treatment furthest to the right is therefore most cost-effective, while the treatment furthest to the left is the least cost-effective. Error bars represent 95% confidence intervals.



Cost-effectiveness acceptability curve showing the probability that each treatment is the most cost-effective strategy evaluated in IVAN at a range of ceiling ratios. For example, at a ceiling ratio of £20,000/QALY gained (shown by the vertical dashed line), there is a 63% probability that discontinuous bevacizumab is best and a 37% probability that continuous bevacizumab is best, while the probability that either ranibizumab treatment regimen is best is approximately 0% (total = 100%).
179x129mm (96 x 96 DPI)



Effect of sensitivity analyses on total net benefits for each of the four treatment arms, assuming a £20,000/QALY ceiling ratio. Treatments that are more cost-effective have higher net benefits; the treatment furthest to the right is therefore most cost-effective, while the treatment furthest to the left is the least cost-effective. Error bars represent 95% confidence intervals.
190x254mm (96 x 96 DPI)

Appendix: Additional details on the statistical analysis

Definition of expected AEs or SAEs

The base case analysis focused on resource use associated with the study eye or associated with adverse events (AEs) or serious adverse events (SAEs) that were "*expected*": i.e. previously linked to anti-VEGF treatment. The list of AEs and SAEs continued to be "expected" was based on the IVAN trial protocol.[1]

The following were considered to be expected SAEs within the economic evaluation: angina pectoris; arthralgia; cardiac arrest; cardiac failure; cardiovascular disorder; cataract traumatic; cerebrovascular accident; coronary artery bypass; deep vein thrombosis; endophthalmitis; haemorrhage; intraocular pressure increased; left ventricular failure; myocardial infarction; nausea; pulmonary embolism; retinal detachment; retinal pigment epithelial tear; retinal vein occlusion; transient ischaemic attack; upper respiratory tract infection; urinary tract infection; and uveitis.

The following AEs were considered to be expected: angina pectoris; arthralgia; bronchitis; cardiac disorder; cataract; cataract cortical; cataract nuclear; cataract operation; cataract traumatic; conjunctival haemorrhage; cough; eye inflammation; eye irritation; eye pain; haemorrhage; hallucination, visual; headache; hypertension; influenza; intraocular pressure increased; lacrimation increased; nasopharyngitis; nausea; pulmonary embolism; retinal detachment; retinal pigment epithelial tear; retinal vein occlusion; sinusitis; transient ischaemic attack; upper respiratory tract infection; urinary tract infection; uveitis; visual impairment; vitreous detachment; and vitreous floaters.

Measurement and valuation of health benefits

Mixed models were used to estimate the rate at which patients' EQ-5D utility improves after SAEs or reductions in visual acuity. For patients who experienced an SAE that reduced EQ-5D utility, models assumed that EQ-5D utility fell on the day of the SAE and rose linearly afterwards. Similar profiles have previously been used to model recovery from acute hepatitis[2] and chronic obstructive pulmonary disease exacerbations.[3] We focused on linear

recovery profiles to simplify subsequent QALY calculations and as models with quadratic recovery curves did not fit the data as well as those with linear profiles.

Mixed models were estimated on all post-baseline utility measurements using the xtmixed command in Stata. A basic model was defined and a pre-specified series of variations on this model were evaluated and included in the base case analysis if they reduced Akaike's information criterion (AIC). The final model divided SAEs into four categories:

- Ocular (including reductions in visual acuity, increased intraocular pressure and all SAEs in the "eye disorders" MedDRA category)
- Cardiovascular (including all SAEs classed as "cardiac disorders", plus cerebrovascular accident, coronary artery bypass, deep vein thrombosis, haemorrhage, pulmonary embolism and transient ischaemic attack)
- Cancer (comprising all events in the "Neoplasms benign, malignant and unspecified" MedDRA category)
- Other (all events not falling into one of the previous four categories)

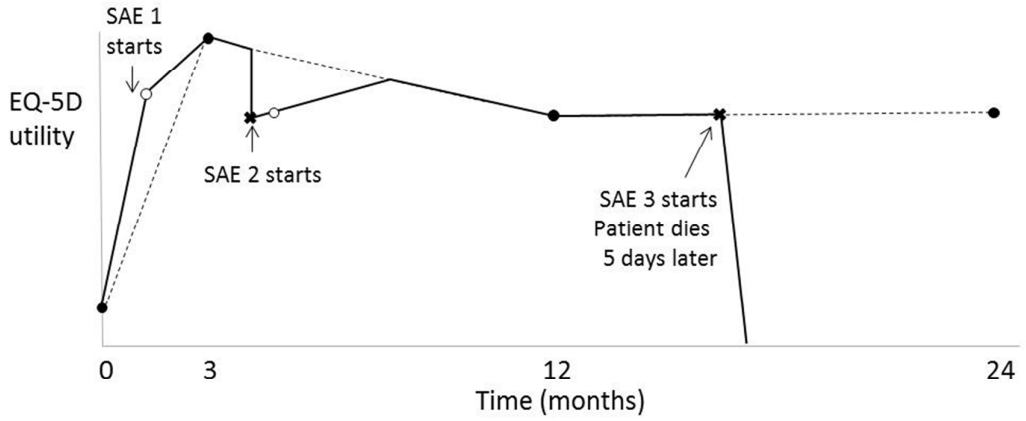
The model assumed that each type of SAE that patients had experienced reduced the EQ-5D utility of patient i at time j by $\beta_{Event,i}$, but that EQ-5D utility rose by a certain amount ($\beta_{EventRecovery}$) with each day that passed after each type of SAE. EQ-5D utility was also assumed to be a function of time since randomisation, treatment and baseline EQ-5D utility (centred by subtracting the mean baseline EQ-5D utility across all patients):

$$\begin{aligned}EQ\text{-}5D_{ij} = {} & Constant_i + \beta_{BL}.(BLEQ5D_{ij} - MeanBLEQ5D) + \beta_{Time,j}.Time_{ij} \\ & + \beta_{Bevacizumab}.Bevacizumab_i + \beta_{Discontinuous}.Discontinuous_i \\ & + \beta_{Interact}.Bevacizumab_i.Discontinuous_i \\ & + \beta_{CVD,i}.CVD_{ij} + \beta_{CVDRecovery}.TimeSinceCVD_{ij} \\ & + \beta_{Ocular,i}.Ocular_{ij} + \beta_{OcularRecovery}.TimeSinceOcular_{ij} \\ & + \beta_{Cancer,i}.Cancer_{ij} + \beta_{CancerRecovery}.TimeSinceCancer_{ij} \\ & + \beta_{Other,i}.Other_{ij} + \beta_{OtherRecovery}.TimeSinceOther_{ij}\end{aligned}$$

The slopes estimated in the mixed models (e.g. $\beta_{CVDRecovery}$) were used alongside the observed EQ-5D measurements for each patient to estimate EQ-5D utility on the day the SAE started and identify the point at which EQ-5D utility returned to the level that would be expected from the EQ-5D utility measurements that were not taken after SAEs (Figure A). However, some post-SAE measurements were higher than would have been expected from

the other measurements for that patient (e.g. Figure A); in these cases, we assumed that EQ-5D utility changed linearly between the routine measurements (Figure A). For patients dying 1-7 days after the latest SAE, EQ-5D utility was assumed to fall linearly to 0 between the date the SAE started and the date of death. Further details will be reported in *Health Technology Assessment*.

Figure A Illustration of the utility profile around SAEs. EQ-5D utility measurements after SAEs are shown in white circles, while scheduled measurements are shown in black circles. The EQ-5D utility measurement after this patient's first set of SAEs is higher than would be expected from the baseline and three-month measurements; we therefore assumed that EQ-5D utility rose linearly from baseline to the post-SAE measurement and from this onto the 3-month measurement. EQ-5D utility is lower after their second set of SAEs; here, we use the slope coefficients from the mixed model that show the rate of recovery after the categories of SAE that this patient has experienced to draw a line through the post-SAE 2 measurement and estimate EQ-5D utility on the day SAE 2 starts and the time and EQ-5D utility at which the patient is expected to have recovered from the SAE and returned to the EQ-5D utility trend between visits three and 12. The patient died five days after SAE 3; their EQ-5D utility was therefore assumed to follow the linear trend observed between visit 12 and the value imputed at visit 24 up until the day before SAE 3, and then fall linearly to zero between that date and the date of death.



Statistical methods

The economic evaluation used linear regression models with nonparametric bootstrapping, Kaplan-Meier sample averaging and Rubin's rule to combine the quarterly costs and QALYs accrued by each patient to estimate mean total costs and mean QALYs for each of the four study arms.

Thirty-two ordinary least squares regression analyses[1] were used to predict the drug costs, administration/monitoring costs, medication/medical service use costs and QALYs accrued in each quarter conditional on treatment regimen and drug. Interactions between drug and treatment regimen were included as additional independent variables for quarters 2-8 if they

[1] 32 = four variables multiplied by eight quarters.

were either statistically significant or larger than main effects.[2] Since all patients received monthly injections at visits 0-2, we assumed no interaction and no impact of treatment regimen during quarter 1. Analyses of QALYs also controlled for baseline utility to eliminate any bias that could result from imbalance in baseline utility.[4]

We used non-parametric bootstrapping to quantify the uncertainty around quarterly costs and QALYs, allowing for the skewed, heteroskedastic distributions and correlations between outcomes.[5] Bootstrapping involved sampling patients with replacement from each randomised group and estimating all regressions on each bootstrap sample. We also allowed for uncertainty around multiple imputation by generating 100 imputed datasets, each with different values drawn from the imputation model. Uncertainty around consultation costs and the rate of recovery from SAEs was taken into account by randomly sampling values from the relevant distributions for each imputed data set. Bootstrap samples were drawn 130 times for each of the 100 imputed datasets, generating 13,000 bootstrap estimates of mean quarterly costs and QALYs for each of the four study groups, which allow for uncertainty around imputed utilities, the rate of recovery from SAEs and consultation costs.

We also allowed for patients withdrawing early from the trial using Kaplan-Meier sample averaging, whereby costs and outcomes in each quarter are multiplied by Kaplan-Meier estimates of the probability of patients remaining alive at the start of each quarter and summed over all four quarters.[5 6] Kaplan-Meier estimates were adapted to prevent chance differences in numbers of deaths unrelated to treatment[3] affecting incremental QALYs by adding the overall probability of deaths unlikely/not related to study medication (averaged across all four arms) to the probability of potentially-drug related deaths that was observed in each arm. After weighting quarterly costs and QALYs by the Kaplan-Meier estimate of the proportion of patients alive at the start of the quarter and discounting costs incurred in Year 2 by 3.5%, quarterly costs and QALYs were added up to give the total cost and total QALYs accrued in each treatment group over the two-year trial period. The 100 imputed datasets

[2] Analyses were replicated with and without interactions for drug costs, administration/monitoring costs, medication/medical service use costs and QALYs to identify any interactions that were statistically significant or had an absolute magnitude larger than either the main effect for treatment regimen or the main effect for drug. Interactions that were either statistically significant or larger than either main effect were included in the base case analysis to ensure that the bias associated with omitting qualitative interactions did not change the conclusions.

[3] The five causality groups that study investigators classified all SAEs into were used to categorise deaths into those definitely/probably/possibly related to study medication (referred to as potentially drug-related deaths) and those unlikely to be/not related to study medication (referred to as unrelated deaths).

were combined using Rubin's rule[7] to estimate total and incremental costs, QALYs and net benefits and their standard errors (SE). Rubin's rule was implemented in Microsoft Excel, while all other statistical analyses were conducted in Stata version 12.

References

1. The IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. Ophthalmology 2012;**119**(7):1399-411.
2. Luyten J, Marais C, Hens N, et al. Imputing QALYs from single time point health state descriptions on the EQ-5D and the SF-6D: a comparison of methods for hepatitis a patients. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2011;**14**(2):282-90.
3. Spencer M, Briggs AH, Grossman RF, et al. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. PharmacoEconomics 2005;**23**(6):619-37.
4. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005;**14**(5):487-96.
5. Gray A, Clarke P, Wolstenholme J, et al. *Applied Methods of Cost-Effectiveness Analysis in Health Care* Oxford: Oxford University Press, 2011.
6. Hallstrom AP, Sullivan SD. On estimating costs for economic evaluation in failure time studies. Med Care 1998;**36**(3):433-6.
7. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;**30**(4):377-99.

The CHEERS Checklist is part of the CHEERS Statement.

The CHEERS Statement has been endorsed and co-published by the following journals: BJOG: An International Journal of Obstetrics and Gynaecology BMC Medicine 2013; 11:80 BMJ 2013;346:f1049 Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003) Cost Effectiveness and Resource Allocation 2013 11:6. The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print] International Journal of Technology Assessment in Health Care Journal of Medical Economics 2013 Mar 25. [Epub ahead of print] Pharmacoeconomics 2013 Mar 26. [Epub ahead of print] Value in Health 2013 March - April;16(2):e1-e5

Checklist taken from: http://www.equator-network.org/wp-content/uploads/2013/09/CHEERS-Checklist-PDF.pdf

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 6
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Pages 7-8
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 6 and 8
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pages 6 and 8
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 8
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 8
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 12
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 9

Section/item	Item No	Recommendation	Reported on page No/ line No
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 8
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 11
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pages 10-11
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 11
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 11-13 and Appendix

Section/item	Item No	Recommendation	Reported on page No/ line No
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 1, pages 13-16
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Figures 2 and 3, pages 15-16
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 17-20
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 3
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 3

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Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial

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Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial

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Running header: Cost-effectiveness of ranibizumab and bevacizumab for AMD

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Key words

Neovascular age-related macular degeneration (AMD); vascular endothelial growth factor (VEGF) inhibitors; trial-based economic evaluation; cost-utility analysis; cost-minimisation analysis; cost-effectiveness.

Abstract

Objective: To assess the incremental cost and cost-effectiveness of continuous and discontinuous regimens of bevacizumab (Avastin®) and ranibizumab (Lucentis®) for neovascular age-related macular degeneration (nAMD) from a UK National Health Service (NHS) perspective.

Design: A within-trial cost-utility analysis with two-year time horizon, based on a multi-centre factorial, non-inferiority randomised controlled trial.

Setting: 23 hospital ophthalmology clinics.

Participants: 610 patients aged ≥50 years with untreated nAMD in the study eye.

Interventions: 0.5 mg ranibizumab or 1.25 mg bevacizumab given continuous (monthly) or discontinuous (as-needed) for two years.

Main Outcome Measures: Quality-adjusted life-years (QALYs).

Results: Total two-year costs ranged from £3,002/patient ($4,700; 95% CI: £2,601 to £3,403) for discontinuous bevacizumab to £18,590/patient ($29,106; 95% CI: £18,258 to £18,922) for continuous ranibizumab. Ranibizumab was significantly more costly than bevacizumab for both continuous (+£14,989/patient [$23,468; 95% CI: £14,522 to £15,456; p<0.001) and discontinuous treatment (+£8,498 [$13,305]; 95% CI: £7,700 to £9,295; p<0.001), with negligible difference in QALYs. Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay £3.5 million ($5.5 million) per additional QALY gained. Patients receiving continuous bevacizumab accrued higher total costs (+£599 [$938] 95% CI: £91 to £1,107; p=0.021) than those receiving discontinuous bevacizumab, but also accrued non-significantly more QALYs (+0.020; 95% CI: -0.032 to 0.071; p=0.452). Continuous bevacizumab therefore cost £30,220 ($47,316) per QALY gained versus discontinuous bevacizumab. However, bootstrapping demonstrated that if the NHS is willing to pay £20,000/QALY gained, there is a 37% chance that continuous bevacizumab is cost-effective versus discontinuous bevacizumab.

Conclusions: Ranibizumab is not cost-effective compared with bevacizumab, being substantially more costly and producing little or no QALY gain. Discontinuous bevacizumab is likely to be the most cost-effective of the four treatment strategies evaluated in IVAN, although there is a 37% chance that continuous bevacizumab is cost-effective.

Trial registration: ISRCTN92166560

Article summary: Strengths and limitations of this study

- We conducted a trial-based economic evaluation based on high-quality data on costs and quality of life prospectively collected within a randomised trial.
- This demonstrated that bevacizumab would achieve substantial cost-savings over ranibizumab with negligible differences in quality of life. In England, switching patients to bevacizumab could save at least £102 ($160) million per year. However, bevacizumab is not currently licensed for neovascular age-related macular degeneration (nAMD).
- Our study is the first trial-based economic evaluation to evaluate the cost-effectiveness of alternative anti-VEGF treatments for nAMD.
- Of the strategies for the treatment of nAMD evaluated in this trial, we found discontinuous (as-needed) bevacizumab to be the least costly and most cost-effective. However, there was substantial uncertainty around this finding and sensitivity analyses suggested that the cost-effectiveness of using continuous (monthly) treatment rather than discontinuous treatment may vary between centres.

Introduction

Neovascular age-related macular degeneration (nAMD) is a common disorder of the ageing eye and if left untreated leads to severe central visual impairment. The current standard of care is treatment with biologicals that bind to or inhibit vascular endothelial growth factor (VEGF). Biologicals need to be injected into the vitreous cavity of the eye at 4-8 week intervals. However, the first treatment convincingly shown to be effective in preventing vision loss (ranibizumab, Lucentis®[1 2]) is expensive (£742/dose in the UK[3]). Another anti-VEGF biological, bevacizumab (Avastin®), is licensed to treat cancer and has been used to treat nAMD, using smaller doses that cost much less than ranibizumab. Small non-randomised studies on bevacizumab have reported outcomes that were as good as those achievable with ranibizumab.[4] Comparative effectiveness randomised controlled trials (RCTs) of ranibizumab versus bevacizumab were therefore needed to provide unbiased estimates of relative efficacy and safety. The UK Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial[5 6] and the US Comparison of Age-related macular degeneration Treatments Trials (CATT)[7 8] were amongst the first such trials to report findings.

Two-year IVAN results demonstrated that ranibizumab and bevacizumab produced similar improvements in visual function, with no significant difference in arteriothrombotic events or hospital admissions for heart failure, which have previously been linked with anti-VEGF therapy.[5] IVAN also compared discontinuous (as-needed) treatment against continuous monthly injections. Continuous and discontinuous treatment produced similar improvements in visual function, although mortality was significantly lower with continuous treatment (p=0.05).

Given the rising demands for healthcare and limited budgets, it is important to assess cost-effectiveness as well as the clinical effectiveness and safety of medical interventions. Evidence on incremental cost and cost-effectiveness is of particular importance in nAMD, owing to the potential savings and health implications of either reducing treatment frequency or substituting a much cheaper alternative (bevacizumab) for a more expensive drug (ranibizumab). Although ranibizumab costs many times more than bevacizumab, it is important to consider all relevant costs and

assess cost-effectiveness to determine whether the more expensive therapy has added health benefits that justify the additional costs or lead to savings that offset the price difference.

A recent systematic review[9] identified nine economic evaluations of ranibizumab and three of bevacizumab. Seven further studies evaluating ranibizumab[10-16] and two evaluating bevacizumab[11 16] have since been published. Most studies found ranibizumab to be cost-effective versus other treatments, such as pegaptanib. Five studies concluded that bevacizumab was likely to be cost-effective compared with ranibizumab, of which four relied on observational data[11 15] or assumptions about relative efficacy.[17 18] We are unaware of any other RCT-based economic evaluation that has estimated the cost-effectiveness of anti-VEGF treatment for nAMD.

A key objective of the IVAN trial was to assess the incremental cost and incremental cost-effectiveness of continuous and discontinuous regimens of bevacizumab and ranibizumab in nAMD from the perspective of the UK National Health Service (NHS). The results of these analyses are reported here.

Methods

The study was based on the two-year results from the IVAN trial (ISRCTN92166560), which provided high-quality data on resource use and outcomes and comprises the only UK trial directly comparing these interventions. Trial design and methods have been described previously[5 6]; in brief this was a factorial, multi-centre non-inferiority trial in which 610 patients not previously treated for nAMD in their study eyes were randomised to either bevacizumab (1.25 mg/dose) or ranibizumab (0.5 mg/dose) and to either discontinuous treatment or continuous monthly injections for two years. Discontinuous treatment comprised an initial course of three monthly injections, followed by further courses of three injections given monthly if pre-specified clinical and optical coherence tomography (OCT) re-treatment criteria were met. 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. Following UK guidelines,[19] we took the perspective of the UK NHS, which excludes costs incurred by patients and their families or

employers. Detailed methods and additional results will be published as a monograph in *Health Technology Assessment*.

Since IVAN was factorial, it was important to consider the likelihood of interactions: that is, whether the differences in costs and/or quality of life between bevacizumab and ranibizumab differ between treatment regimens. Although no interactions were anticipated for visual acuity,[6] large interactions between drug and treatment regimen were expected for costs and cost-effectiveness, since reducing the number of injections would have a proportionately greater effect on drug costs for ranibizumab than for less expensive bevacizumab. Interactions for quality of life or costs were also possible if the number of injections required for discontinuous treatment differed between drugs. We therefore estimated the mean costs and mean quality-adjusted life-years (QALYs) for each of the four treatment combinations and interpreted the results based on four pair-wise comparisons:

- Continuous ranibizumab versus discontinuous ranibizumab;
- Continuous bevacizumab versus discontinuous bevacizumab;
- Continuous ranibizumab versus continuous bevacizumab;
- Discontinuous ranibizumab versus discontinuous bevacizumab.

We report two forms of economic evaluation. Comparisons between drugs were based on cost-minimisation analysis, which compares costs between treatments that are assumed to have identical health effects.[20] Cost-minimisation analysis is appropriate only if the difference in cost is so large that no plausible difference in efficacy could cause the more costly treatment to be cost-effective.[21 22] This approach is justified for the comparisons between drugs because the large difference in drug costs was inevitably going to be the main influence on the incremental cost-effectiveness of ranibizumab versus bevacizumab. We therefore pre-specified that ranibizumab and bevacizumab would be compared using cost-minimisation analysis unless ranibizumab-treated patients accrued ≥0.05 more EQ-5D QALYs than those receiving bevacizumab. By contrast, we used cost-utility analysis, in which health outcomes are measured in QALYs, to compare continuous and discontinuous treatment, where incremental costs are smaller.

Measurement and valuation of resource use

Our base case analysis also focused on resource use associated with the study eye or associated with adverse events (AEs) or serious adverse events (SAEs) that were "*expected*": i.e. previously linked to anti-VEGF treatment (Appendix). Concomitant medications, hospitalisations and ambulatory consultations that were neither associated with the study eye nor attributable to expected AEs or expected SAEs were excluded to avoid including episodes of high healthcare resource use unrelated to treatment (e.g. renal failure or cancer), which might otherwise have swamped the main effect of treatment on costs.[23]

After enrolment, participants were monitored for disease activity on a monthly basis with visual acuity assessments, colour fundus imaging and OCT. Fundus fluorescein angiography (FFA) was undertaken at specified visits and when OCT was insufficient to reach a decision on disease activity. A pre-specified algorithm was used to determine the need for re-treatment. Patients allocated to discontinuous treatment began a new course of three monthly injections whenever they met re-treatment criteria. However, costing analyses excluded protocol-driven resource use; in particular, we assumed that patients would not require colour fundus photography, OCT or FFA unless this would affect treatment decisions. As such, patients on discontinuous treatment were assumed not to require these investigations at the second or third visit in a course of three injections, when treatment was mandated (Figure 1). Similarly, patients on continuous treatment were assumed to require monitoring consultations only once every three months, on the grounds that ophthalmologists would want information about disease progression periodically, irrespective of whether treatment decisions are required.

Micro-costing was used to estimate the cost of injection and monitoring consultations since the available national average costs[24 25] are not nAMD-specific and do not differentiate between consultations for monitoring and intravitreal drug delivery. Staff at 13 of the 23 IVAN centres completed questionnaires on overheads, the cost of setting up clinic facilities and equipment and/or the staff required to run injection and monitoring clinics.

The drug acquisition cost for ranibizumab was the NHS list price (£742.17[3]) and that for bevacizumab was the price typically charged by the not-for-profit NHS provider used in the trial (£49/prefilled syringe). All concomitant medications, contacts with medical professionals and hospitalisations were recorded at each monthly clinic visit. Concomitant medications applied to the study eye or indicated for any expected SAE/AE were valued using list prices.[3] Costs of other medications, including those applied to the fellow eye, were excluded from the analysis. Unit costs for consultations with general practitioners, district or general practice nurses and hospital staff outside IVAN clinics were obtained from routine sources.[25 26] These costs were applied to ambulatory consultations that were either related to the eye or that occurred within 30 days of an expected SAE/AE. Hospital stays linked to expected SAEs were valued using the mean cost per bed-day for associated HRGs.[25]

Resource use data and unit costs were combined to estimate quarterly costs of: bevacizumab/ranibizumab; drug administration and monitoring consultations; and hospitalisations, ambulatory consultations and medication changes for expected SAEs/AEs. Value added tax (VAT) was excluded from the economic evaluation and included in budget impact estimates, following guidelines.[19] Costs are reported in 2011 pounds sterling, accompanied by equivalents in US dollars (exchange rate: $1.57/pound).

Measurement and valuation of health benefits

The three-level EQ-5D questionnaire[27] was administered at baseline, 3, 12 and 24 months, and (if the patient was willing and able to do so) at study exit, after any SAE and after a drop in visual acuity in the study eye of ≥15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) vision chart between two consecutive visits (referred to subsequently as a 'reduction in visual acuity'). The Health Utilities Index questionnaire version 3 (HUI3) was administered at the same timepoints and used in sensitivity analysis; EQ-5D comprised the utility primary measure following UK guidelines.[19] Patients self-completed large-print EQ-5D questionnaires, with assistance from study nurses where necessary; responses were valued using the UK time-trade-off tariff to give "utilities".[27]

Missing utility data were imputed using multiple imputation,[28] which avoids bias and enables analysis of the whole sample. Multiple imputation was conducted using the `ice` command[29] (version 1.9.4) in Stata Version 12 (StataCorp, College Station, TX).

QALYs for each participant were calculated as the area under the curve. We assumed that utility changed linearly between consecutive EQ-5D measurements in the absence of SAEs. Since linear changes are unlikely for patients with SAEs, we assumed that SAEs and reductions in visual acuity caused a sudden drop in utility on the day of onset, followed by a linear rise as the patient recovered; the rate of this linear rise was estimated using mixed models (Appendix).

Statistical methods

Linear regression models were used to estimate the effect of drug and treatment regimen on QALYs, drug costs, administration/monitoring costs and medication/medical service use in each three-month period or "quarter" (Appendix). Interactions between drug and treatment regimen were included in the models for quarters 2-8 if they were either statistically significant or were larger than the main effect for drug or for treatment regimen. The analysis of QALYs, drug costs and medication/medical service use in quarters 2-8 therefore took account of interactions, while drug and treatment regimen were assumed to have additive effects on administration/monitoring costs. A variant on Kaplan-Meier sample averaging[30 31] was used to account for patients withdrawing early from the trial and exclude differences in mortality unrelated to treatment; regression predictions of quarterly costs and QALYs were weighted by the proportion of patients alive at the start of each quarter. Costs and QALYs accrued in Year 2 were discounted at 3.5% to allow for time preference (i.e. the tendency to prefer benefits sooner and costs later).[19] Uncertainty around quarterly costs and QALYs was quantified by estimating models separately for 130 nonparametric bootstrap draws on each of 100 datasets generated in multiple imputation to capture the uncertainty around imputed utilities. The appendix gives further details of the statistical methodology.

Presentation of results and uncertainty

Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in cost between two study arms by the difference in QALYs. Results were interpreted assuming that the UK NHS would be willing to pay £20,000 to gain one QALY (a £20,000/QALY "ceiling ratio").[32] We also present net benefits for each of the four treatment arms: net benefit equals total QALYs multiplied by the ceiling ratio, minus total costs. Uncertainty around ICERs is presented as cost-effectiveness acceptability curves, which plot the probability of each of the four treatment regimens having the highest net benefits (i.e. being most cost-effective) at a range of ceiling ratios.

Sensitivity analyses evaluated the impact of changing the costs (e.g. halving the cost of ranibizumab), methods (e.g. taking a one-year time horizon) and assumptions (e.g. including the costs of all SAEs, not just 'expected' SAEs).

Results

QALYs and quality of life

The number of QALYs accrued over the two-year trial period did not differ significantly between bevacizumab and ranibizumab, or between continuous and discontinuous treatment ($p \geq 0.381$; Table 1). Patients randomised to continuous treatment accrued non-significantly more QALYs than those randomised to discontinuous treatment (mean difference: 0.020 [95% CI: -0.032, 0.071] for bevacizumab, p=0.452 and 0.026 [95% CI: -0.032, 0.085] for ranibizumab, p=0.381), while differences between ranibizumab and bevacizumab were negligible.

Resource use and costs

Patients receiving continuous treatment received a mean of 22 injections, while those on discontinuous treatment received 13. Consequently, drug costs differed substantially between continuous and discontinuous treatment (Table 1; $p<0.001$), as well as between ranibizumab and bevacizumab ($p<0.001$). Since reducing treatment frequency produces larger savings for ranibizumab than for bevacizumab, there were significant interactions between drug and treatment regimen for drug cost ($p<0.001$).

Administration of bevacizumab or ranibizumab cost £61 ($96; standard deviation, SD: £14) per injection, while each consultation for monitoring cost £72 ($113; SD: £41), plus £39 ($61; SD: £16) for each FFA. Administering intravitreal injections and monitoring disease progression/remission cost between £1,825 and £1,970 per patient over the two-year trial period (Table 1). Discontinuous treatment reduced the number of injections required, but increased the number of monitoring consultations needed to assess disease status against retreatment criteria, since we assumed that OCT would only be done when it would inform treatment decisions. Since continuous treatment requires, on average, nine more injections ($p<0.001$), but avoids only six monitoring visits ($p<0.001$), drug administration and monitoring costs were higher with continuous treatment than discontinuous treatment (mean difference: £130 per patient ($204); 95% CI: £20, £239; $p=0.021$), with no significant difference between bevacizumab and ranibizumab ($p=0.80$).

The cost of medication changes, hospitalisations and ambulatory consultations associated with expected SAEs and expected AEs was relatively small (mean: £469 [$735] per patient), but varied substantially between patients (95 percentile range: £0, £1,401). There was no significant difference in such costs between drugs or treatment regimens ($p\geq0.163$).

Taking account of the drug cost, drug administration/monitoring and medication/medical service use, the mean total cost per patient over the two-year trial ranged from £18,590 ($29,119) for continuous ranibizumab to £3,002 ($4,702) for discontinuous bevacizumab (Table 1). Drug cost accounted for 80-88% of the total cost for patients randomised to ranibizumab and 21-30% of the cost for patients randomised to bevacizumab. Drug administration and monitoring accounted for 54-61% of the costs accrued by patients randomised to bevacizumab and 10-15% of costs for those randomised to ranibizumab.

Base case comparison between ranibizumab and bevacizumab

Since the difference in mean QALYs between ranibizumab and bevacizumab was less than the pre-specified non-inferiority margin (0.05 QALYs), cost-minimisation analysis was used to compare the two drugs on the basis of cost alone. Overall,

continuous ranibizumab cost £14,989 more per patient ($23,476 [95% CI: £14,522, £15,456], Table 1) than continuous bevacizumab over the two-year trial period (p<0.001). Discontinuous ranibizumab cost £8,498 more per patient ($13,308 [95% CI: £7,700, £9,295], p<0.001) compared with discontinuous bevacizumab. Bootstrapping analyses estimated the probability that switching from ranibizumab to bevacizumab would save money and found that this exceeds 99.9%.

Base case comparison between continuous and discontinuous treatment

Overall, using continuous rather than discontinuous treatment increased costs by £7,090 ($11,102 [95% CI: £6,337, £7,844], p<0.001) for ranibizumab and £599 ($938 [95% CI: £91, £1,107], p=0.021) for bevacizumab.

However, patients randomised to continuous bevacizumab also accrued non-significantly more QALYs than those randomised to discontinuous bevacizumab (Table 1; p=0.452). In line with best practice,[20] we took account of the non-significant differences in QALYs and allowed for the joint distribution of costs and QALYs, since assuming no difference in health outcomes can introduce bias and give misleading conclusions.[21 22] Dividing the difference in cost by the difference in QALYs suggests that continuous bevacizumab costs £30,220 ($47,316) per additional QALY gained compared with discontinuous bevacizumab. This ICER is somewhat higher than the £20,000 ($31,000) per QALY "ceiling ratio" below which the NHS generally considers treatments to be cost-effective.[32] However, the imprecision around QALY differences means that there is substantial uncertainty around this ICER. Bootstrapping demonstrated that there is a 37% chance that continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at a £20,000/QALY ceiling ratio, which increases to 50% at £30,000/QALY.

Continuous ranibizumab cost £270,217 ($423,074) per QALY gained compared with discontinuous ranibizumab. Due to the substantial savings possible by giving ranibizumab less frequently, we can be >99.99% confident that continuous ranibizumab is poor value for money compared with discontinuous ranibizumab at a £20,000/QALY ceiling ratio.

Base case four-way comparison

It is also informative to consider the four trial treatment groups as four mutually-exclusive alternative strategies for managing nAMD. Framing the decision in this way demonstrates that discontinuous bevacizumab is the most cost-effective treatment strategy evaluated in IVAN, generating higher net benefits than the other three treatment strategies (Table 1), where net benefit equals QALYs multiplied by ceiling ratio (in this case £20,000/QALY) minus costs. Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay £3.5 million ($5.5 million) per additional QALY gained. Discontinuous ranibizumab is not cost-effective at any ceiling ratio, as it is more costly and less effective than continuous or discontinuous bevacizumab.

However, there remains substantial uncertainty around incremental QALY gains. This is illustrated by the cost-effectiveness acceptability curves plotting the probability of each treatment being the most cost-effective of the four strategies at different ceiling ratios (Figure 2). This demonstrates that, although we can be 98% confident that discontinuous bevacizumab is less costly than continuous bevacizumab, our confidence in the conclusion that discontinuous bevacizumab has highest net benefits decreases rapidly as the value we place on the small, non-significant QALY gains increases. At a £20,000/QALY ceiling ratio, there is a 63% probability that discontinuous bevacizumab is the most cost-effective strategy considered in IVAN and a 37% probability that continuous bevacizumab is the most cost-effective. By contrast, the probability of either continuous or discontinuous ranibizumab being the most cost-effective strategy for managing nAMD is <1% unless the NHS were willing to pay more than £100,000/QALY gained.

Sensitivity analyses

Sensitivity analyses demonstrated that the conclusions are very robust to changes in the assumptions and methods used to measure costs and utilities and conduct the analysis (Figure 3). Notably, no sensitivity analysis changed the conclusion that ranibizumab is not cost-effective compared with bevacizumab, including analyses discounting the ranibizumab list price by 50%. However, three sensitivity analyses changed the conclusion that continuous bevacizumab is not cost-effective compared with discontinuous bevacizumab: assuming that FFA is only conducted at baseline,

not at any subsequent monitoring consultation; measuring quality of life using HUI3 rather than EQ-5D; and using unadjusted Kaplan-Meier estimates of the probability of surviving at any point in time to account for censoring, rather than excluding differences in deaths that were unrelated to study medication (see Appendix).

Threshold analyses demonstrated that the price of ranibizumab would need to be reduced to £63.46 per dose (a 91% price reduction) in order for continuous ranibizumab to be cost-effective compared with continuous bevacizumab at a £20,000/QALY ceiling ratio.

Discussion

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.[32] Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay >£3.5 ($5.5) million/QALY gained. Furthermore, our analysis also shows that giving discontinuous bevacizumab, rather than discontinuous ranibizumab could save the UK NHS £8,498 ($13,341) per patient treated, with little or no impact on the health gains from treatment. If the 17,295 eyes requiring anti-VEGF therapy each year in England[33] were switched from discontinuous ranibizumab to discontinuous bevacizumab, the NHS could save at least £102 ($160) million per year (including 20% VAT) based on the treatment regimens evaluated in IVAN. It remains controversial as to whether a drug (bevacizumab) that has not been approved and licensed for nAMD by regulatory agencies should be used when a licensed drug (ranibizumab) is available. In the UK, clinicians may prescribe unlicensed medications within approved research projects, when no suitable medicine is licensed, or when the licensed alternative is unavailable,[34] although prescribing on cost grounds is not mentioned. By contrast, in the US, ophthalmologists use bevacizumab freely.[35] National guidance (rather than local hospital/clinician policies) is therefore needed in the UK to direct the choice between bevacizumab and ranibizumab. 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,[5 7] but that (based on the current analysis of IVAN) ranibizumab costs £3.5 million per QALY compared with bevacizumab.

The base case analysis found that continuous bevacizumab cost £30,220 ($47,445) per QALY gained compared with discontinuous bevacizumab, suggesting that discontinuous bevacizumab is the most cost-effective strategy evaluated in IVAN if the NHS is willing to pay up to £20,000/QALY gained. However, there remains substantial uncertainty around this conclusion and there is a 37% chance that continuous bevacizumab is cost-effective. The finding of non-significantly higher QALYs with continuous treatment contradicts our prior hypothesis that avoiding monthly injections might improve quality of life, although the observed difference could be due to chance. Nonetheless, discontinuous bevacizumab would remain the most cost-effective strategy even if there were no difference in quality of life between treatment regimens. Other considerations may affect the choice of anti-VEGF delivery model. In particular, since discontinuous treatment requires regular clinical review and access to retinal imaging, it may be more practical to provide treatment every month, with monitoring restricted to specified points in time (e.g. six or 12 months after initiation of therapy). Indeed the label for the newest anti-VEGF (aflibercept) incorporates a limited clinical monitoring regime.[36] The discontinuous treatment regimen evaluated in the IVAN trial was chosen partly to minimise the possibility of disadvantage to participants in these groups and partly to minimise the number of retreatment decisions required. Neither monthly treatment nor treatments given as blocks of three are used widely in routine practice, although following publication of IVAN,[5 6] there appears to be increased interest in the "IVAN regimen". The cost-effectiveness of monthly versus intermittent treatment will therefore vary between treatment centres depending on local costs and clinical practice.

Unlike previous studies, our analysis is based on high-quality data from an RCT with prospective measurements of costs and quality of life, which was powered to exclude any clinically-meaningful difference in visual acuity. It therefore provides unequivocally-unbiased estimates of incremental costs and QALYs. Nevertheless, our analysis confirms the findings of previous economic evaluations, namely that ranibizumab is not cost-effective compared with bevacizumab.[11 16 18] We are also (to our knowledge) the first to evaluate the cost-effectiveness of the discontinuous

treatment regimen used in IVAN. In addition to following best practice for trial-based economic evaluation, this study includes several novel aspects, such as measuring quality of life after SAEs, excluding chance differences in deaths unrelated to treatment and allowing for the factorial design by including only large or statistically significant interactions.

The study also estimates the cost of consultations to administer ranibizumab/bevacizumab and monitor outcomes, which could be used in other economic evaluations. Micro-costing shows the main drivers of consultation costs and highlighted substantial variation in costs between centres; this variation means that the cost-effectiveness of continuous versus discontinuous bevacizumab (but not ranibizumab versus bevacizumab) will vary between centres. It is important to note that the costs were calculated to assess incremental cost-effectiveness in IVAN and should not be used to set the prices at which hospitals are reimbursed. In particular, they are bottom-up estimates that exclude unpaid overtime and VAT and make assumptions about overheads and proportion of staff-time spent on patient contacts. In most settings it is likely that the costs to healthcare commissioners will be higher and subject to local negotiations with care providers.

The base case analysis focused on mortality attributable to study medication and the costs associated with "expected" SAEs/AEs and excluded other costs. This reduced the risk that chance differences in resource use not associated with study medication could distort our conclusions. However, it also meant that the unanticipated increase in the incidence of other SAEs (e.g. gastrointestinal events) with bevacizumab[5 6] (which comprised the only difference in SAEs between drugs) was not taken into account in the costing analysis. However, sensitivity analyses including the cost of all SAEs/AEs gave the same conclusions. 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. 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. The analysis also uses data only from IVAN, rather than synthesising all available evidence.

Further research is needed to assess the extent to which the cost-effectiveness findings generalise to other countries with different relative prices and management of nAMD and SAEs/AEs. For example, the incidence of SAEs was substantially lower in IVAN than CATT,[5 7] although sensitivity analyses doubling the impact of SAEs on costs and QALYs suggested that this did not change the conclusions. The costs of the two drugs may vary between centres within the UK as hospitals may use different bevacizumab suppliers or have different discounts on ranibizumab. Nevertheless, because we collected very detailed information on resource use, policy makers in other countries can review these data against their own to examine their similarity and, hence, the applicability of our findings to their setting. Future work combining data from IVAN with that from other trials, such as CATT,[7] may help reduce uncertainty and evaluate the extent to which the results can be generalised. However we believe that our primary finding of ranibizumab representing very poor value for money compared with bevacizumab does apply throughout the world.

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Competing interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). All authors had financial support from the NIHR for the submitted work. HD, SW, GA and JR have no financial or non-financial interests relevant to the submitted

work. UC, SH, SD and AL are principal investigators of trials sponsored by Novartis, the manufacturers of ranibizumab. UC has attended and been remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and Bausch and Lomb; and her employing institution has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and Pfizer. SH has attended and been remunerated for attendance at advisory boards for and received travel support from Novartis and Allergan. CR has received an honorarium from Novartis for a lecture. SD's and AL's employing institutions have received payments from Novartis. SD and AL have received honoraria from Novartis for lectures. AL has attended and been remunerated for attendance at advisory boards for Novartis and Bayer; likewise SD for Bayer and Ely Lilly. BR has received a fee for teaching from Janssen-Cilag.

Authorship statement

SW, CR, JR, SH, AL, SD, BR and UC conceived, designed and conducted the IVAN trial. HD, SW, GA and JR conceived and designed the economic evaluation, with extensive input from CR, SH and BR. CR supervised collation/cleaning of trial data, while HD, SW and GA collected additional resource use data from centres. HD conducted the economic analysis with help from GA under the supervision of SW. HD drafted the manuscript. All authors edited the manuscript for important intellectual content and approved the final version.

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The IVAN Study Investigators are listed in Appendix 1 of reference.[6]

We would also like to thank the IVAN participants and the clinicians, nurses and clinic managers who completed resource use questionnaires.

Transparency declaration

The manuscript's guarantor (HD) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

No additional data available

Ethics statement

Participants provided written informed consent. A UK National Health Service Research Ethics Committee approved the trial (07/NIR03/37).

References

1. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009;**116**(1):57-65.e5.
2. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;**355**(14):1419-31.
3. British Medical Association. *British National Formulary 62 (http://bnf.org/bnf/index.htm)*. London: Pharmaceutical Press, September 2011.
4. Mitchell P. 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. Current Medical Research & Opinion 2011;**27**(7):1465-75.
5. 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.
6. The IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. Ophthalmology 2012;**119**(7):1399-411.
7. 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.
8. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;**364**(20):1897-908.
9. Mitchell P, Annemans L, White R, et al. Cost effectiveness of treatments for wet age-related macular degeneration. PharmacoEconomics 2011;**29**(2):107-31.
10. Yanagi Y, Aihara Y, Fukuda T, et al. [Cost-effectiveness of ranibizumab, photodynamic therapy and pegaptanib sodium in the treatment of neovascular age-related macular degeneration in Japanese]. Nihon Ganka Gakkai Zasshi 2011;**115**(9):825-31.
11. 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**(2):247-55.
12. Gower EW, Cassard SD, Bass EB, et al. A cost-effectiveness analysis of three treatments for age-related macular degeneration. Retina 2010;**30**(2):212-21.
13. Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, et al. Cost-effectiveness of ranibizumab compared with pegaptanib in neovascular age-related macular degeneration. Graefes Archive for Clinical & Experimental Ophthalmology 2010;**248**(4):467-76.
14. Neubauer AS, Holz FG, Sauer S, et al. Cost-effectiveness of ranibizumab for the treatment of neovascular age-related macular degeneration in Germany: Model analysis from the perspective of Germany's statutory health insurance system. Clinical Therapeutics 2010;**32**(7):1343-56.
15. Smiddy WE. Economic implications of current age-related macular degeneration treatments. Ophthalmology 2009;**116**(3):481-7.

16. Stein JD, Newman-Casey PA, Mrinalini T, et al. Cost-effectiveness of bevacizumab and ranibizumab for newly diagnosed neovascular macular degeneration. Ophthalmology 2014;**121**(4):936-45.
17. Fletcher EC, Lade RJ, Adewoyin T, et al. Computerized model of cost-utility analysis for treatment of age-related macular degeneration. Ophthalmology 2008;**115**(12):2192-8.
18. Raftery J, Clegg A, Jones J, et al. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol 2007;**91**(9):1244-6.
19. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Secondary Guide to the methods of technology appraisal 2013 2013. http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf.
20. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the economic evaluation of health care programmes*. 3rd ed. New York: Oxford University Press, 2005.
21. Dakin H, Wordsworth S. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. Health Econ 2013;**22**(1):22-34.
22. Briggs AH, O'Brien BJ. The death of cost-minimization analysis? Health Econ 2001;**10**(2):179-84.
23. Jonsson B, Weinstein MC. Economic evaluation alongside multinational clinical trials. Study considerations for GUSTO IIb. Int J Technol Assess Health Care 1997;**13**(1):49-58.
24. Department of Health. PbR operational guidance and tariffs: 2011-12 tariff information spreadsheet. Secondary PbR operational guidance and tariffs: 2011-12 tariff information spreadsheet 2011. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_124356.
25. Department of Health. National Schedule of Reference Costs 2010-11 for NHS Trusts and PCTs combined. Secondary National Schedule of Reference Costs 2010-11 for NHS Trusts and PCTs combined November 2011. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131148.xls.
26. Curtis L. Unit Costs of Health and Social Care 2011. Pages 91, 129-150, 177-213. Secondary Unit Costs of Health and Social Care 2011. Pages 91, 129-150, 177-213 2011. http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf.
27. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;**35**(11):1095-108.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;**30**(4):377-99.
29. Royston P. Multiple imputation of missing values: further update of ice, with an emphasis on interval censoring. Stata Journal 2007;**7**:445-64.
30. Hallstrom AP, Sullivan SD. On estimating costs for economic evaluation in failure time studies. Med Care 1998;**36**(3):433-6.
31. Gray A, Clarke P, Wolstenholme J, et al. *Applied Methods of Cost-Effectiveness Analysis in Health Care* Oxford: Oxford University Press, 2011.
32. National Institute for Health and Clinical Excellence. Social value judgements: Principles for the development of NICE guidance. Second Edition. Secondary Social value judgements: Principles for the development of NICE guidance.

Second Edition 2008. http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf.
33. National Institute for Health and Clinical Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration TA155: Costing template and report. Secondary Ranibizumab and pegaptanib for the treatment of age-related macular degeneration TA155: Costing template and report August 2008. (http://www.nice.org.uk/nicemedia/live/12057/41735/41735.xls).
34. General Medical Council. Good practice in prescribing and managing medicines and devices. Secondary Good practice in prescribing and managing medicines and devices 2013. http://www.gmc-uk.org/static/documents/content/Prescribing_guidance.pdf.
35. Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration.[Erratum appears in Arch Ophthalmol. 2010 Dec;128(12):1623]. Archives of Ophthalmology 2010;**128**(10):1273-9.
36. Bayer Plc. Summary of product characteristics for Eylea 40mg/ml solution for injection in a vial Secondary Summary of product characteristics for Eylea 40mg/ml solution for injection in a vial 2013. http://www.medicines.org.uk/emc/medicine/27224/SPC/Eylea+40mg+ml+solution+for+injection+in+a+vial/.

Table 1: Results of the economic evaluation

	Total QALYs (95% CI)‡	Mean (95% CI) drug cost‡	Mean (95% CI) administration & monitoring cost	Mean (95% CI) medication/medical service cost‡	Total cost (95% CI)‡	Total net benefits (95% CI)†‡
Discontinuous bevacizumab	1.584 (1.538, 1.630)	£651 (£605, £698)	£1,825 (£1,708, £1,941)	£526 (£144, £908)	£3,002 (£2,601, £3,403)	£28,683 (£27,707, £29,658)
Continuous bevacizumab	1.604 (1.563, 1.645)	£1,065 (£1,048, £1,081)	£1,952 (£1,860, £2,043)	£585 (£250, £919)	£3,601 (£3,259, £3,943)	£28,480 (£27,548, £29,412)
Discontinuous ranibizumab	1.582 (1.530, 1.634)	£9,229 (£8,584, £9,875)	£1,838 (£1,724, £1,952)	£432 (£253, £611)	£11,500 (£10,798, £12,202)	£20,142 (£18,963, £21,321)
Continuous ranibizumab	1.608 (1.565, 1.651)	£16,286 (£16,011, £16,562)	£1,970 (£1,883, £2,057)	£334 (£215, £452)	£18,590 (£18,258, £18,922)	£13,576 (£12,769, £14,383)
Difference: ranibizumab vs. bevacizumab	Continuous: 0.004 (-0.046, 0.054)	Continuous: £15,222 (£14,948, £15,495)*	£16 (-£109, £141)	Continuous: -£251 (-£604, £102)	Continuous: £14,989 (£14,522, £15,456)*	Continuous: -£14,904 (-£15,995, -£13,813)*
	Discontinuous: -0.002 (-0.064, 0.060)	Discontinuous: £8,578 (£7,932, £9,225)*		Discontinuous: -£94 (-£514, £326)	Discontinuous: £8,498 (£7,700, £9,295)*	Discontinuous: -£8,541 (-£9,939, -£7,144)*
Difference: continuous vs. discontinuous	Ranibizumab: 0.026 (-0.032, 0.085)	Ranibizumab: £7,057 (£6,364, £7,750)*	£130 (£20, £239)*	Ranibizumab: -£98 (-£310, £113)	Ranibizumab: £7,090 (£6,337, £7,844)*	Ranibizumab: -£6,566 (-£7,861, -£5,271)*
	Bevacizumab: 0.020 (-0.032, 0.071)	Bevacizumab: £413 (£365, £462)*		Bevacizumab: £59 (-£438, £556)	Bevacizumab: £599 (£91, £1,107)*	Bevacizumab: -£203 (-£1,372, £967)
Interaction	0.006 (-0.071, 0.084)	£6,643 (£5,949, £7,338)*	£5 (-£31, £42)	-£157 (-£696, £381)	£6,491 (£5,604, £7,379)*	-£6,363 (-£8,088, -£4,638)*

* Significantly different from zero ($p<0.05$).
† Net benefits equal QALYs multiplied by ceiling ratio minus costs; the net benefits shown in this table were calculated at a £20,000/QALY ceiling ratio.
‡ Analysis allowed for interactions

FIGURE LEGENDS

Figure 1: Schematic illustrating the assumptions made about the frequency of injection and monitoring consultations within the costing analysis. The consultations required by patients on discontinuous treatment will depend on when they met treatment failure criteria; Patient 2 met the re-treatment criteria at visits 0, 7 and 11.

✓ Relevant consultation cost was applied.
? The cost of FFA was applied if clinically indicated: for discontinuous patients, this was applied whenever the patient had FFA in the trial; for continuous patients, the proportion of patients having FFA was based on estimated use in routine clinical practice.
X No consultation cost was applied as the participant missed the visit.

Figure 2: Cost-effectiveness acceptability curve showing the probability that each treatment is the most cost-effective strategy evaluated in IVAN at a range of ceiling ratios. For example, at a ceiling ratio of £20,000/QALY gained (shown by the vertical dashed line), there is a 63% probability that discontinuous bevacizumab is best and a 37% probability that continuous bevacizumab is best, while the probability that either ranibizumab treatment regimen is best is approximately 0% (total = 100%).

Figure 3: Effect of sensitivity analyses on total net benefits for each of the four treatment arms, assuming a £20,000/QALY ceiling ratio. Treatments that are more cost-effective have higher net benefits; the treatment furthest to the right is therefore most cost-effective, while the treatment furthest to the left is the least cost-effective. Error bars represent 95% confidence intervals. In the analysis “doubling SAE impact”, both the medication/medical service use cost and the impact of SAEs on QALYs were doubled. The “best case” analysis simultaneously changed several assumptions in favour of ranibizumab: 50% discount off ranibizumab list price; assuming that 15.9% of bevacizumab (as occurred in the trial) but no ranibizumab is wasted; assuming that bevacizumab costs £100 per dose; and including medical service use costs associated with expected and unexpected AEs and SAEs.

Cost-effectiveness of ranibizumab and bevacizumab for age-related macular degeneration: 2-year findings from the IVAN randomised trial

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Running header: Cost-effectiveness of ranibizumab and bevacizumab for AMD

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~~**Competing interest statement**~~

~~All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author). All authors had financial support from the NIHR for the submitted work. HD, SW, GA and JR have no financial or non-financial interests relevant to the submitted work. UC, SH, SD and AL are principal investigators of trials sponsored by Novartis, the manufacturers of ranibizumab. UC has attended and been remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and Bausch and Lomb; and her employing institution has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and Pfizer. SH has attended and been remunerated for attendance at advisory boards for and received travel support from Novartis and Allergan. CR has received an honorarium from Novartis for a lecture. SD's and AL's employing institutions have received payments from Novartis. SD and AL have received honoraria from Novartis for lectures. AL has attended and been remunerated for attendance at advisory boards for Novartis and Bayer; likewise SD for Bayer and Ely Lilly. BR has received a fee for teaching from Janssen-Cilag.~~

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Authorship statement

SW, CR, JR, SH, AL, SD, BR and UC conceived, designed and conducted the IVAN trial. HD, SW, GA and JR conceived and designed the economic evaluation, with extensive input from CR, SH and BR. CR supervised collation/cleaning of trial data, while HD, SW and GA collected additional resource use data from centres. HD conducted the economic analysis with help from GA under the supervision of SW. HD drafted the manuscript. All authors edited the manuscript for important intellectual content and approved the final version.

Acknowledgements

The IVAN Study Investigators are listed in Appendix 1 of reference.[1]

We would also like to thank the IVAN participants and the clinicians, nurses and clinic managers who completed resource use questionnaires.

Transparency declaration

The manuscript's guarantor (HD) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

~~**Data sharing**~~

~~No additional data available~~

~~**Ethics statement**~~

~~Participants provided written informed consent. A UK National Health Service Research Ethics Committee approved the trial (07/NIR03/37).~~

Key words

Neovascular age-related macular degeneration (~~n~~AMD); vascular endothelial growth factor (VEGF) inhibitors; trial-based economic evaluation; cost-utility analysis; cost-minimisation analysis; cost-effectiveness.

Abstract

Objective: To assess the incremental cost and cost-effectiveness of continuous and discontinuous regimens of bevacizumab (Avastin®) and ranibizumab (Lucentis®) for neovascular age-related macular degeneration (nAMD) from a UK National Health Service (NHS) perspective.

Design: A within-trial cost-utility analysis with two-year time horizon, based on a multi-centre factorial, non-inferiority randomised controlled trial.

Setting: 23 hospital ophthalmology clinics.

Participants: 610 patients aged ≥50 years with untreated nAMD in the study eye.

Interventions: 0.5 mg ranibizumab or 1.25 mg bevacizumab given continuous (monthly) or discontinuous (as-needed) for two years.

Main Outcome Measures: Quality-adjusted life-years (QALYs).

Results: Total two-year costs ranged from £3,002/patient ($4,700; 95% CI: £2,601 to £3,403) for discontinuous bevacizumab to £18,590/patient ($29,106; 95% CI: £18,258 to £18,922) for continuous ranibizumab. Ranibizumab was significantly more costly than bevacizumab for both continuous ~~treatment~~ (+£14,989/patient [$23,468; 95% CI: £14,522 to £15,456; p<0.001) and discontinuous treatment (+£8,498 [$13,305]; 95% CI: £7,700 to £9,295; p<0.001), with negligible difference in QALYs. Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay £3.5 million ($5.5 million) per additional QALY gained. Patients receiving continuous bevacizumab accrued higher total costs (+£599 [$938] 95% CI: £91 to £1,107; p=0.021) than those receiving discontinuous bevacizumab, but also accrued non-significantly more QALYs (+0.020; 95% CI: -0.032 to 0.071; p=0.452). Continuous bevacizumab therefore cost £30,220 ($47,316) per QALY gained versus ~~compared with~~ discontinuous bevacizumab. However, bootstrapping demonstrated that if the NHS is willing to pay £20,000/QALY gained, there is a 37% chance that continuous bevacizumab is cost-effective versus ~~compared with~~ discontinuous bevacizumab.

Conclusions: Ranibizumab is not cost-effective compared with bevacizumab, being substantially more costly and producing little or~~/~~ no QALY gain. Discontinuous bevacizumab is likely to be the most cost-effective of the four treatment strategies evaluated in IVAN, although there is a 37% chance that continuous bevacizumab is cost-effective.

Trial registration: ISRCTN92166560

Article summary: Strengths and limitations of this study

- We conducted a trial-based economic evaluation based on high-quality data on costs and quality of life prospectively collected within a randomised trial.
- This demonstrated that bevacizumab would achieve substantial cost-savings over ranibizumab with negligible differences in quality of life. In England, switching patients to bevacizumab could save at least £102 ($160) million per year. However, bevacizumab is not currently licensed for neovascular age-related macular degeneration (nAMD).
- Our study is the first trial-based economic evaluation to evaluate the cost-effectiveness of alternative anti-VEGF ~~pharmacological~~ treatment ~~regimen~~s for nAMD.
- Of the strategies for the treatment of nAMD evaluated in this trial, we found discontinuous (~~as needed~~as-needed) bevacizumab to be the least costly and most cost-effective. However, there was substantial uncertainty around this finding and sensitivity analyses suggested that the cost-effectiveness of using continuous (monthly) treatment rather than discontinuous treatment may vary between centres.

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Introduction

Neovascular age-related macular degeneration (nAMD) is a common disorder of the ageing eye and if left untreated leads to severe central visual impairment. The current standard of care is treatment with biologicals that bind to or inhibit vascular endothelial growth factor (VEGF). Biologicals need to be injected into the vitreous cavity of the eye at 4-8 week intervals. However, the first treatment convincingly shown to be effective in preventing vision loss (ranibizumab, Lucentis®[2 3]) is expensive (£742/dose in the UK[4]). Another anti-VEGF biological, bevacizumab (Avastin®), is licensed to treat ~~bowel~~ cancer and has been used to treat nAMD, using smaller doses that cost much less than ranibizumab. Small non-randomised studies on bevacizumab have reported outcomes that were as good as those achievable with ranibizumab.[5] Comparative effectiveness randomised controlled trials (RCTs) of ranibizumab versus bevacizumab were therefore needed to provide unbiased estimates of relative efficacy and safety. The UK Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial[1 6] and the US Comparison of Age-related macular degeneration Treatments Trials (CATT)[7 8] were amongst the first such trials to report findings.

Two-year IVAN results demonstrated that ranibizumab and bevacizumab produced similar improvements in visual function, with no significant difference in arteriothrombotic events or hospital admissions for heart failure, which have previously been linked with anti-VEGF therapy.[6] IVAN also compared discontinuous (as-needed) treatment against continuous monthly injections. Continuous and discontinuous treatment produced similar improvements in visual function, although mortality was significantly lower with continuous treatment (p=0.05).

Given the rising demands for healthcare and limited budgets, it is important to assess cost-effectiveness as well as the clinical effectiveness and safety of medical interventions. Evidence on incremental cost and cost-effectiveness is of particular importance in nAMD, owing to the potential savings and health implications of either reducing treatment frequency or substituting a much cheaper alternative (bevacizumab) for a more expensive drug (ranibizumab). Although ranibizumab costs many times more than bevacizumab, it is important to consider all relevant costs and

assess cost-effectiveness to determine whether the more expensive therapy has added health benefits that justify the additional costs or lead to savings that offset the price difference.

A recent systematic review[9] identified nine economic evaluations of ranibizumab and three of bevacizumab. Seven~~ix~~ further studies evaluating ranibizumab[10-16] and two ~~one~~ evaluating bevacizumab[11 16] have since been published. Most studies found ranibizumab to be cost-effective versus other treatments, such as pegaptanib. Five ~~Four~~ studies concluded that bevacizumab was likely to be cost-effective compared with ranibizumab, of which four ~~but~~ relied on observational data[11 15] or assumptions about relative efficacy.[17 18] We are unaware of any other RCT-based economic evaluation that has estimated the cost-effectiveness of ~~bevacizumab or any study that evaluated the cost-effectiveness of continuous versus discontinuous~~anti-VEGF treatment for nAMD.

A key objective of the IVAN trial was to assess the incremental cost and incremental cost-effectiveness of continuous and discontinuous regimens of bevacizumab and ranibizumab in nAMD from the perspective of the UK National Health Service (NHS). The results of these analyses are reported here.

Methods

The study was based on the two-year results from the IVAN trial (ISRCTN92166560), which provided high-quality data on resource use and outcomes and comprises the only UK trial directly comparing these interventions. Trial design and methods have been described previously[1 6]; in brief this was a factorial, multi-centre non-inferiority trial in which 610 patients not previously treated for nAMD in their study eyes were randomised to either bevacizumab (~~0.5~~ 1.25 mg/dose) or ranibizumab (~~1.25~~ 0.5 mg/dose) and to either discontinuous treatment or continuous monthly injections for two years. Discontinuous treatment comprised an initial course of three monthly injections, followed by further courses of three injections given monthly if pre-specified clinical and optical coherence tomography (OCT) re-treatment criteria were met. 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. Following UK guidelines,[19] we took the perspective of the UK NHS, which excludes costs incurred by patients and their families or employers. Detailed methods and additional results will be published as a monograph in *Health Technology Assessment*.

Since IVAN was factorial, it was important to consider the likelihood of interactions: that is, whether the differences in costs and/or quality of life between bevacizumab and ranibizumab differ between treatment regimens. Although no interactions were anticipated for visual acuity,[1] large interactions between drug and treatment regimen were expected for costs and cost-effectiveness, since reducing the number of injections would have a proportionately greater effect on drug costs for ranibizumab than for less expensive bevacizumab. Interactions for quality of life or costs weare also possible if the number of injections required for discontinuous treatment differed between drugs. We therefore estimated the mean costs and mean quality-adjusted life-years (QALYs) for each of the four treatment combinations and interpreted the results based on four pair-wise comparisons:

- Continuous ranibizumab versus discontinuous ranibizumab;
- Continuous bevacizumab versus discontinuous bevacizumab;
- Continuous ranibizumab versus continuous bevacizumab;
- Discontinuous ranibizumab versus discontinuous bevacizumab.

We report two forms of economic evaluation. Comparisons between drugs were based on cost-minimisation analysis, which compares costs between treatments that are assumed to have identical health effects.[20] Cost-minimisation analysis is appropriate only if the difference in cost is so large that no plausible difference in efficacy could cause the more costly treatment to be cost-effective.[21 22] This approach is justified for the comparisons between drugs because the large difference in drug costs was inevitably going to be the main influence on the incremental cost-effectiveness of ranibizumab versus bevacizumab. We therefore pre-specified that ranibizumab and bevacizumab would be compared using cost-minimisation analysis unless ranibizumab-treated patients accrued ≥0.05 more EQ-5D QALYs than those receiving bevacizumab. By contrast, we used cost-utility analysis, in which health

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outcomes are measured in QALYs, to compare continuous and discontinuous treatment, where incremental costs are smaller.

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Measurement and valuation of resource use

Our base case analysis also focused on resource use associated with the study eye or associated with adverse events (AEs) or serious adverse events (SAEs) that were "*expected*": i.e. previously linked to anti-VEGF treatment (Appendix). Concomitant medications, hospitalisations and ambulatory consultations that were neither associated with the study eye nor attributable to expected AEs or expected SAEs were excluded to avoid including episodes of high healthcare resource use unrelated to treatment (e.g. renal failure or cancer), which might otherwise have swamped the main effect of treatment on costs.[23]

After enrolment, participants were monitored for disease activity on a monthly basis with visual acuity assessments, colour fundus imaging and OCT. Fundus fluorescein angiography (FFA) was undertaken at specified visits and when OCT was insufficient to reach a decision on disease activity. A pre-specified algorithm was used to determine the need for re-treatment. Patients allocated to discontinuous treatment began a new course of three monthly injections whenever they met re-treatment criteria. However, costing analyses excluded protocol-driven resource use; in particular, we assumed that patients would not require colour fundus photography, OCT or FFA unless this would affect treatment decisions. As such, patients on discontinuous treatment were assumed not to require these investigations at the second or third visit in a course of three injections, when treatment was mandated (Figure 1). Similarly, patients on continuous treatment were assumed to require monitoring consultations only once every three months, on the grounds that ophthalmologists would want information about disease progression periodically, irrespective of whether treatment decisions are required.

Micro-costing was used to estimate the cost of injection and monitoring consultations since the available national average costs[24 25] are not nAMD-specific and do not differentiate between consultations for monitoring and intravitreal drug delivery. Staff at 13 of the 23 IVAN centres completed questionnaires on overheads, the cost of setting up clinic facilities and equipment and/or the staff required to run injection and monitoring clinics.

The drug acquisition cost for ranibizumab was the NHS list price (£742.17[4]) and that for bevacizumab was the price typically charged by the not-for-profit NHS provider used in the trial (£49/prefilled syringe). All concomitant medications, contacts with medical professionals and hospitalisations were recorded at each monthly clinic visit. Concomitant medications applied to the study eye or indicated for any expected SAE/AE were valued using list prices.[4] Costs of other medications, including those applied to the fellow eye, were excluded from the analysis. Unit costs for consultations with general practitioners, district or general practice nurses and hospital staff outside IVAN clinics were obtained from routine sources.[25 26] These costs were applied to ambulatory consultations that were either related to the eye or that occurred within 30 days of an expected SAE/AE. Hospital stays linked to expected SAEs were valued using the mean cost per bed-day for associated HRGs.[25]

Resource use data and unit costs were combined to estimate quarterly costs of: bevacizumab/ranibizumab; drug administration and monitoring consultations; and hospitalisations, ambulatory consultations and medication changes for expected SAEs/AEs. Value added tax (VAT) was excluded from the economic evaluation and included in budget impact estimates, following guidelines.[19] Costs are reported in 2011 pounds sterling, accompanied by equivalents in US dollars (exchange rate: $1.57/pound).

Measurement and valuation of health benefits

The three-level EQ-5D questionnaire[27] was administered at baseline, 3, 12 and 24 months, and (if the patient was willing and able to do so) at study exit, after any SAE and after a drop in visual acuity in the study eye of ≥15 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) vision chart between two consecutive visits (referred to subsequently as a 'reduction in visual acuity'). The Health Utilities Index questionnaire version 3 (HUI3) was administered at the same timepoints and used in sensitivity analysies; EQ-5D comprised the utility primary measure following UK guidelines.[19] Patients self-completed large-print EQ-5D questionnaires, with assistance from study nurses where necessary; responses were valued using the UK time-trade-off tariff to give "utilities".[27]

Missing utility data were imputed using multiple imputation,[28] which avoids bias and enables analysis of the whole sample. Multiple imputation was conducted using the `ice` command[29] (version 1.9.4) in Stata Version 12 (StataCorp, College Station, TX).

QALYs for each participant were calculated as the area under the curve. We assumed that utility changed linearly between consecutive EQ-5D measurements in the absence of SAEs. Since linear changes are unlikely for patients with SAEs, we assumed that SAEs and reductions in visual acuity caused a sudden drop in utility on the day of onset, followed by a linear rise as the patient recovered; the rate of this linear rise was estimated using mixed models (Appendix).

Statistical methods

Linear regression models were used to estimate the effect of drug and treatment regimen on QALYs, drug costs, administration/monitoring costs and medication/medical service use in each three-month period or "quarter" (Appendix). Interactions between drug and treatment regimen were included in the models for quarters 2-8 if they were either statistically significant or were larger than the main effect for drug or for treatment regimen. The analysis of QALYs, drug costs and medication/medical service use in quarters 2-8 therefore took account of interactions, while drug and treatment regimen were assumed to have additive effects on administration/monitoring costs. A variant on Kaplan-Meier sample averaging[30 31] was used to account for patients withdrawing early from the trial and exclude differences in mortality unrelated to treatment; regression predictions of quarterly costs and QALYs were weighted by the proportion of patients alive at the start of each quarter. Costs and QALYs accrued in Year 2 were discounted at 3.5% to allow for time preference (i.e. the tendency to prefer benefits sooner and costs later).[19] Uncertainty around quarterly costs and QALYs was quantified by estimating models separately for 130 nonparametric bootstrap draws on each of 100 datasets generated in multiple imputation to capture the uncertainty around imputed utilities. The appendix gives further details of the statistical methodology.

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Presentation of results and uncertainty

Incremental cost-effectiveness ratios (ICERs) were calculated by dividing the difference in cost between two study arms by the difference in QALYs. Results were interpreted assuming that the UK NHS would be willing to pay £20,000 to gain one QALY (a £20,000/QALY "ceiling ratio").[32] We also present net benefits for each of the four treatment arms: net benefit equals total QALYs multiplied by the ceiling ratio, minus total costs. Uncertainty around ICERs is presented as cost-effectiveness acceptability curves, which plot the probability of each of the four treatment regimens ~~groups~~ having the highest net benefits (i.e. being most cost-effective) at a range of ceiling ratios.

Sensitivity analyses evaluated the impact of changing the costs (e.g. halving the cost of ranibizumab), methods (e.g. taking a one-year time horizon) and assumptions (e.g. including the costs of all SAEs, not just 'expected' SAEs).

Results

QALYs and quality of life

The number of QALYs accrued over the two-year trial period did not differ significantly between bevacizumab and ranibizumab, or between continuous and discontinuous treatment ($p \geq 0.381$; Table 1). Patients randomised to continuous treatment accrued non-significantly more QALYs than those randomised to discontinuous treatment (mean difference: 0.020 [95% CI: -0.032, 0.071] for bevacizumab, p=0.452 and 0.026 [95% CI: -0.032, 0.085] for ranibizumab, p=0.381), while differences between ranibizumab and bevacizumab were negligible.

Resource use and costs

Patients receiving continuous treatment received a mean of 22 injections, while those on discontinuous treatment received 13. Consequently, drug costs differed substantially between continuous and discontinuous treatment (Table 1; $p<0.001$), as well as between ranibizumab and bevacizumab ($p<0.001$). Since reducing treatment frequency produces larger savings for ranibizumab than for bevacizumab, there were significant interactions between drug and treatment regimen for drug cost ($p<0.001$).

Administration of bevacizumab or ranibizumab cost £61 ($96; standard deviation, SD: £14) per injection, while each consultation for monitoring cost £72 ($113; SD: £41), plus £39 ($61; SD: £16) for each FFA. Administering intravitreal injections and monitoring disease progression/remission cost between £1,825 and £1,970 per patient over the two-year trial period (Table 1). Discontinuous treatment reduced the number of injections required, but increased the number of monitoring consultations needed to assess disease status against retreatment criteria, since we assumed that OCT would only be done when it would inform treatment decisions. Since continuous treatment requires, on average, nine more injections ($p<0.001$), but avoids only six monitoring visits ($p<0.001$), drug administration and monitoring costs were higher with continuous treatment than discontinuous treatment (mean difference: £130 per patient ($204); 95% CI: £20, £239; $p=0.021$), with no significant difference between bevacizumab and ranibizumab ($p=0.80$).

The cost of medication changes, hospitalisations and ambulatory consultations associated with expected SAEs and expected AEs was relatively small (mean: £469 [$735] per patient), but varied substantially between patients (95 percentile range: £0, £1,401). There was no significant difference in such costs between drugs or treatment regimens ($p\geq0.163$).

Taking account of the drug cost, drug administration/monitoring and medication/medical service use, the mean total cost per patient over the two-year trial ranged from £18,590 ($29,119) for continuous ranibizumab to £3,002 ($4,702) for discontinuous bevacizumab (Table 1). Drug cost accounted for 80-88% of the total cost for patients randomised to ranibizumab and 21-30% of the cost for patients randomised to bevacizumab. Drug administration and monitoring accounted for 54-61% of the costs accrued by patients randomised to bevacizumab and 10-15% of costs for those randomised to ranibizumab.

Base case comparison between ranibizumab and bevacizumab

Since the difference in mean QALYs between ranibizumab and bevacizumab was less than the pre-specified non-inferiority margin (0.05 QALYs), cost-minimisation analysis was used to compare the two drugs on the basis of cost alone. Overall,

continuous ranibizumab cost £14,989 more per patient ($23,476 [95% CI: £14,522, £15,456], Table 1) than continuous bevacizumab over the two-year trial period (p<0.001). Discontinuous ranibizumab cost £8,498 more per patient ($13,308 [95% CI: £7,700, £9,295], p<0.001) compared with discontinuous bevacizumab. Bootstrapping analyses estimated the probability that switching from ranibizumab to bevacizumab would save money and found that this exceeds 99.9%.

Base case comparison between continuous and discontinuous treatment

Overall, using continuous rather than discontinuous treatment increased costs by £7,090 ($11,102 [95% CI: £6,337, £7,844], p<0.001) for ranibizumab and £599 ($938 [95% CI: £91, £1,107], p=0.021) for bevacizumab.

However, patients randomised to continuous bevacizumab also accrued non-significantly more QALYs than those randomised to discontinuous bevacizumab (Table 1; p=0.452). In line with best practice,[20] we took account of the non-significant differences in QALYs and allowed for the joint distribution of costs and QALYs, since assuming no difference in health outcomes can introduce bias and give misleading conclusions.[21 22] Dividing the difference in cost by the difference in QALYs suggests that continuous bevacizumab costs £30,220 ($47,316) per additional QALY gained compared with discontinuous bevacizumab. This ICER is somewhat higher than the £20,000 ($31,000) per QALY "ceiling ratio" below which the NHS generally considers treatments to be cost-effective.[32] However, the imprecision around QALY differences means that there is substantial uncertainty around this ICER. Bootstrapping demonstrated that there is a 37% chance that continuous bevacizumab is cost-effective compared with discontinuous bevacizumab at a £20,000/QALY ceiling ratio, which increases to 50% at £30,000/QALY.

Continuous ranibizumab cost £270,217 ($423,074) per QALY gained compared with discontinuous ranibizumab. Due to the substantial savings possible by giving ranibizumab less frequently, we can be >99.99% confident that continuous ranibizumab is poor value for money compared with discontinuous ranibizumab at a £20,000/QALY ceiling ratio.

Base case four-way comparison

It is also informative to consider the four trial treatment groups as four mutually-exclusive alternative strategies for managing nAMD. Framing the decision in this way demonstrates that discontinuous bevacizumab is the most cost-effective treatment strategy evaluated in IVAN, generating higher net benefits than the other three treatment strategies (Table 1), where net benefit equals QALYs multiplied by ceiling ratio (in this case £20,000/QALY) minus costs. Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay £3.5 million ($5.5 million) per additional QALY gained. Discontinuous ranibizumab is not cost-effective at any ceiling ratio, as it is more costly and less effective than continuous or discontinuous bevacizumab.

However, there remains substantial uncertainty around incremental QALY gains. This is illustrated by the cost-effectiveness acceptability curves plotting the probability of each treatment being the most cost-effective of the four strategies at different ceiling ratios (Figure 2). This demonstrates that, although we can be 98% confident that discontinuous bevacizumab is less costly than continuous bevacizumab, our confidence in the conclusion that discontinuous bevacizumab has highest net benefits decreases rapidly as the value we place on the small, non-significant QALY gains increases. At a £20,000/QALY ceiling ratio, there is a 63% probability that discontinuous bevacizumab is the most cost-effective strategy considered in IVAN and a 37% probability that continuous bevacizumab is the most cost-effective. By contrast, the probability of either continuous or discontinuous ranibizumab being the most cost-effective strategy for managing nAMD is <1% unless the NHS were willing to pay more than £100,000/QALY gained.

Sensitivity analyses

Sensitivity analyses demonstrated that the conclusions are very robust to changes in the assumptions and methods used to measure costs and utilities and conduct the analysis (Figure 3). Notably, no sensitivity analysis changed the conclusion that ranibizumab is not cost-effective compared with bevacizumab, including analyses discounting the ranibizumab list price by 50%. However, three sensitivity analyses changed the conclusion that continuous bevacizumab is not cost-effective compared with discontinuous bevacizumab: assuming that FFA is only conducted at baseline,

not at any subsequent monitoring consultation; measuring quality of life using HUI3 rather than EQ-5D; and using unadjusted Kaplan-Meier estimates of the probability of surviving at any point in time to account for censoring, rather than excluding differences in deaths that were unrelated to study medication (see Appendix).

Threshold analyses demonstrated that the price of ranibizumab would need to be reduced to £63.46 per dose (a 91% price reduction) in order for continuous ranibizumab to be cost-effective compared with continuous bevacizumab at a £20,000/QALY ceiling ratio.

Discussion

This study demonstrates that in the setting of the UK IVAN trial~~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.[32] Continuous ranibizumab would only be cost-effective compared with continuous bevacizumab if the NHS were willing to pay >£3.5 ($5.5) million/QALY gained. Furthermore, our analysis also shows that giving discontinuous bevacizumab, rather than discontinuous ranibizumab could save the UK NHS £8,498 ($13,341) per patient treated, with little or no impact on the health gains from treatment. If the 17,295 eyes requiring anti-VEGF therapy each year in England[33] were switched from discontinuous ranibizumab to discontinuous bevacizumab, the NHS could save at least £102 ($160) million per year (including 20% VAT) based on the treatment regimens evaluated in IVAN. It remains controversial as to whether a drug (bevacizumab) that has not been approved and licensed for nAMD by regulatory agencies should be used when a licensed drug (ranibizumab) is available. In the UK, clinicians may prescribe unlicensed medications within approved research projects, when no suitable medicine is licensed, or when the licensed alternative is unavailable,[34] although prescribing on cost grounds is not mentioned. By contrast, in the US, ophthalmologists use bevacizumab freely.[35] National guidance (rather than local hospital/clinician policies) is therefore needed in the UK to direct the choice between bevacizumab and ranibizumab. 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.

The base case analysis found that continuous bevacizumab cost £30,220 ($47,445) per QALY gained compared with discontinuous bevacizumab, suggesting that discontinuous bevacizumab is the most cost-effective strategy evaluated in IVAN if the NHS is willing to pay up to £20,000/QALY gained. However, there remains substantial uncertainty around this conclusion and there is a 37% chance that continuous bevacizumab is cost-effective. The finding of non-significantly higher QALYs with continuous treatment contradicts our prior hypothesis that avoiding monthly injections might improve quality of life, although the observed difference could be due to chance. Nonetheless, discontinuous bevacizumab would remain the most cost-effective strategy even if there were no difference in quality of life between treatment regimens. Other considerations may affect the choice of anti-VEGF delivery model. In particular, since discontinuous treatment requires regular clinical review and access to retinal imaging, it may be more practical to provide treatment every month, with monitoring restricted to specified points in time (e.g. six or 12 months after initiation of therapy). Indeed the label for the newest anti-VEGF (aflibercept) incorporates a limited clinical monitoring regime.[36] The discontinuous treatment regimen evaluated in the IVAN trial was chosen partly to minimise the possibility of disadvantage to participants in these groups and partly to minimise the number of retreatment decisions required. Neither monthly treatment nor treatments given as blocks of three are used widely in routine practice, although following publication of IVAN,[1 6] there appears to be increased interest in the "IVAN regimen". The cost-effectiveness of monthly versus intermittent treatment will therefore vary between treatment centres depending on local costs and clinical practice.

Unlike previous studies, our analysis is based on high-quality data from an RCT with prospective measurements of costs and quality of life, which was powered to exclude any clinically-meaningful difference in visual acuity ~~and with prospective measurements of costs and quality of life~~. It therefore provides unequivocally-unbiased estimates of incremental costs and QALYs. Nevertheless, our analysis confirms the findings of previous economic evaluations, namely that ranibizumab is not cost-effective compared with bevacizumab.[11 16 18] We are also (to our knowledge)

the first to evaluate the cost-effectiveness of the discontinuous ~~alternative~~ treatment regimen~~s~~ used in IVAN. In addition to following best practice for trial-based economic evaluation, this study includes several novel aspects, such as measuring quality of life after SAEs, excluding chance differences in deaths unrelated to treatment and allowing for the factorial design by including only large or statistically significant interactions.

The study also estimates the cost of consultations to administer ranibizumab/bevacizumab and monitor outcomes, which could be used in other economic evaluations. Micro-costing shows the main drivers of consultation costs and highlighted substantial variation in costs between centres; this variation means that the cost-effectiveness of continuous versus discontinuous bevacizumab (but not ranibizumab versus bevacizumab) will vary between centres. It is important to note that the costs were calculated to assess incremental cost-effectiveness in IVAN and should not be used to set the prices at which hospitals are reimbursed. In particular, they are bottom-up estimates that exclude unpaid overtime and VAT and make assumptions about overheads and proportion of staff-time spent on patient contacts. In most settings it is likely that the costs to healthcare commissioners will be higher and subject to local negotiations with care providers.

The base case analysis focused on mortality attributable to study medication and the costs associated with "expected" SAEs/AEs and excluded other costs. This reduced the risk that chance differences in resource use not associated with study medication could distort our conclusions. However, it also mean~~t~~s that the unanticipated increase in the incidence of other SAEs (e.g. gastrointestinal events) with bevacizumab[16] (which comprised the only difference in SAEs between drugs) wa~~i~~s not taken into account in the costing analysis. However, sensitivity analyses including the cost of all SAEs/AEs gave the same conclusions. 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. The study focused on the ~~randomised trial~~ 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. The analysis also uses data only from IVAN, rather than synthesising all available evidence.

Further research is needed to assess the extent to which the cost-effectiveness findings generalise to other countries with different relative prices and management of nAMD and SAEs/AEs. For example, the incidence of SAEs was substantially lower in IVAN than CATT,[6 7] although sensitivity analyses doubling the impact of SAEs on costs and QALYs suggested that this did not change the conclusions. The costs of the two drugs may vary between centres within the UK as hospitals may use different bevacizumab suppliers or have different discounts on ranibizumab. Nevertheless, because we collected very detailed information on resource use, policy makers in other countries can review these data against their own to examine their similarity and, hence, the applicability of our findings to their setting. Future work combining data from IVAN with that from other trials, such as CATT,[7] may help reduce uncertainty and evaluate the extent to which the results can be generalised. However we believe that our primary finding of ranibizumab representing very poor value for money compared with bevacizumab does apply throughout the world.

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Funding and role of study sponsors

The IVAN trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment (HTA) programme (project number 07/36/01) and a full report will be published in *Health Technology Assessment*. Visit the HTA programme website (www.hta.ac.uk) for further project information. The views and opinions expressed are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, the UK National Health Service or the Department of Health. The funder had no involvement in: the collection, analysis, and interpretation of data; in the writing of the report; and in the decision to submit the article for publication. The authors had full access to the data (including statistical reports and tables), can take responsibility for the integrity of the data and the accuracy of the data analysis and are responsible for submitting this paper.

Competing interest statement

All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding

author). All authors had financial support from the NIHR for the submitted work. HD, SW, GA and JR have no financial or non-financial interests relevant to the submitted work. UC, SH, SD and AL are principal investigators of trials sponsored by Novartis, the manufacturers of ranibizumab. UC has attended and been remunerated for attendance at advisory boards for Novartis, Bayer, Neovista, Oraya, Allergan, and Bausch and Lomb; and her employing institution has received payments from Novartis, Bayer, Neovista, Oraya, Alcon, and Pfizer. SH has attended and been remunerated for attendance at advisory boards for and received travel support from Novartis and Allergan. CR has received an honorarium from Novartis for a lecture. SD's and AL's employing institutions have received payments from Novartis. SD and AL have received honoraria from Novartis for lectures. AL has attended and been remunerated for attendance at advisory boards for Novartis and Bayer; likewise SD for Bayer and Ely Lilly. BR has received a fee for teaching from Janssen-Cilag.

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Authorship statement

SW, CR, JR, SH, AL, SD, BR and UC conceived, designed and conducted the IVAN trial. HD, SW, GA and JR conceived and designed the economic evaluation, with extensive input from CR, SH and BR. CR supervised collation/cleaning of trial data, while HD, SW and GA collected additional resource use data from centres. HD conducted the economic analysis with help from GA under the supervision of SW. HD drafted the manuscript. All authors edited the manuscript for important intellectual content and approved the final version.

Acknowledgements

The IVAN Study Investigators are listed in Appendix 1 of reference.[1]

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Transparency declaration

The manuscript's guarantor (HD) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Data sharing

No additional data available

Ethics statement

Participants provided written informed consent. A UK National Health Service Research Ethics Committee approved the trial (07/NIR03/37).

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References

1. The IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. Ophthalmology 2012;**119**(7):1399-411.
2. Brown DM, Michels M, Kaiser PK, et al. Ranibizumab versus verteporfin photodynamic therapy for neovascular age-related macular degeneration: Two-year results of the ANCHOR study. Ophthalmology 2009;**116**(1):57-65.e5.
3. Rosenfeld PJ, Brown DM, Heier JS, et al. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;**355**(14):1419-31.
4. British Medical Association. *British National Formulary 62 (http://bnf.org/bnf/index.htm)*. London: Pharmaceutical Press, September 2011.
5. Mitchell P. 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. Current Medical Research & Opinion 2011;**27**(7):1465-75.
6. 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.
7. 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.

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8. Martin DF, Maguire MG, Ying GS, et al. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;**364**(20):1897-908.
9. Mitchell P, Annemans L, White R, et al. Cost effectiveness of treatments for wet age-related macular degeneration. PharmacoEconomics 2011;**29**(2):107-31.
10. Yanagi Y, Aihara Y, Fukuda T, et al. [Cost-effectiveness of ranibizumab, photodynamic therapy and pegaptanib sodium in the treatment of neovascular age-related macular degeneration in Japanese]. Nihon Ganka Gakkai Zasshi 2011;**115**(9):825-31.
11. 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**(2):247-55.
12. Gower EW, Cassard SD, Bass EB, et al. A cost-effectiveness analysis of three treatments for age-related macular degeneration. Retina 2010;**30**(2):212-21.
13. Hernandez-Pastor LJ, Ortega A, Garcia-Layana A, et al. Cost-effectiveness of ranibizumab compared with pegaptanib in neovascular age-related macular degeneration. Graefes Archive for Clinical & Experimental Ophthalmology 2010;**248**(4):467-76.
14. Neubauer AS, Holz FG, Sauer S, et al. Cost-effectiveness of ranibizumab for the treatment of neovascular age-related macular degeneration in Germany: Model analysis from the perspective of Germany's statutory health insurance system. Clinical Therapeutics 2010;**32**(7):1343-56.
15. Smiddy WE. Economic implications of current age-related macular degeneration treatments. Ophthalmology 2009;**116**(3):481-7.
16. Stein JD, Newman-Casey PA, Mrinalini T, et al. Cost-effectiveness of bevacizumab and ranibizumab for newly diagnosed neovascular macular degeneration. Ophthalmology 2014;**121**(4):936-45.
17. Fletcher EC, Lade RJ, Adewoyin T, et al. Computerized model of cost-utility analysis for treatment of age-related macular degeneration. Ophthalmology 2008;**115**(12):2192-8.
18. Raftery J, Clegg A, Jones J, et al. Ranibizumab (Lucentis) versus bevacizumab (Avastin): modelling cost effectiveness. Br J Ophthalmol 2007;**91**(9):1244-6.
19. National Institute for Health and Care Excellence. Guide to the methods of technology appraisal 2013. Secondary Guide to the methods of technology

appraisal 2013 2013. http://www.nice.org.uk/media/D45/1E/GuideToMethodsTechnologyAppraisal2013.pdf.

20. Drummond MF, Sculpher MJ, Torrance GW, et al. *Methods for the economic evaluation of health care programmes*. 3rd ed. New York: Oxford University Press, 2005.
21. Dakin H, Wordsworth S. Cost-minimisation analysis versus cost-effectiveness analysis, revisited. Health Econ 2013;**22**(1):22-34.
22. Briggs AH, O'Brien BJ. The death of cost-minimization analysis? Health Econ 2001;**10**(2):179-84.
23. Jonsson B, Weinstein MC. Economic evaluation alongside multinational clinical trials. Study considerations for GUSTO IIb. Int J Technol Assess Health Care 1997;**13**(1):49-58.
24. Department of Health. PbR operational guidance and tariffs: 2011-12 tariff information spreadsheet. Secondary PbR operational guidance and tariffs: 2011-12 tariff information spreadsheet 2011. http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_124356.
25. Department of Health. National Schedule of Reference Costs 2010-11 for NHS Trusts and PCTs combined. Secondary National Schedule of Reference Costs 2010-11 for NHS Trusts and PCTs combined November 2011. http://www.dh.gov.uk/prod_consum_dh/groups/dh_digitalassets/documents/digitalasset/dh_131148.xls.
26. Curtis L. Unit Costs of Health and Social Care 2011. Pages 91, 129-150, 177-213. Secondary Unit Costs of Health and Social Care 2011. Pages 91, 129-150, 177-213 2011. http://www.pssru.ac.uk/archive/pdf/uc/uc2011/uc2011.pdf.
27. Dolan P. Modeling valuations for EuroQol health states. Med Care 1997;**35**(11):1095-108.
28. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;**30**(4):377-99.
29. Royston P. Multiple imputation of missing values: further update of ice, with an emphasis on interval censoring. Stata Journal 2007;**7**:445-64.
30. Hallstrom AP, Sullivan SD. On estimating costs for economic evaluation in failure time studies. Med Care 1998;**36**(3):433-6.

31. Gray A, Clarke P, Wolstenholme J, et al. *Applied Methods of Cost-Effectiveness Analysis in Health Care* Oxford: Oxford University Press, 2011.

32. National Institute for Health and Clinical Excellence. Social value judgements: Principles for the development of NICE guidance. Second Edition. Secondary Social value judgements: Principles for the development of NICE guidance. Second Edition 2008. http://www.nice.org.uk/media/C18/30/SVJ2PUBLICATION2008.pdf.

33. National Institute for Health and Clinical Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration TA155: Costing template and report. Secondary Ranibizumab and pegaptanib for the treatment of age-related macular degeneration TA155: Costing template and report August 2008. (http://www.nice.org.uk/nicemedia/live/12057/41735/41735.xls).

34. General Medical Council. Good practice in prescribing and managing medicines and devices. Secondary Good practice in prescribing and managing medicines and devices 2013. http://www.gmc-uk.org/static/documents/content/Prescribing_guidance.pdf.

35. Curtis LH, Hammill BG, Schulman KA, et al. Risks of mortality, myocardial infarction, bleeding, and stroke associated with therapies for age-related macular degeneration.[Erratum appears in Arch Ophthalmol. 2010 Dec;128(12):1623]. Archives of Ophthalmology 2010;**128**(10):1273-9.

36. Bayer Plc. Summary of product characteristics for Eylea 40mg/ml solution for injection in a vial Secondary Summary of product characteristics for Eylea 40mg/ml solution for injection in a vial 2013. http://www.medicines.org.uk/emc/medicine/27224/SPC/Eylea+40mg+ml+solution+for+injection+in+a+vial/.

Table 1: Results of the economic evaluation

	Total QALYs (95% CI)‡	Mean (95% CI) drug cost‡	Mean (95% CI) administration & monitoring cost	Mean (95% CI) medication/medical service cost‡	Total cost (95% CI)‡	Total net benefits (95% CI)†‡
Discontinuous bevacizumab	1.584 (1.538, 1.630)	£651 (£605, £698)	£1,825 (£1,708, £1,941)	£526 (£144, £908)	£3,002 (£2,601, £3,403)	£28,683 (£27,707, £29,658)
Continuous bevacizumab	1.604 (1.563, 1.645)	£1,065 (£1,048, £1,081)	£1,952 (£1,860, £2,043)	£585 (£250, £919)	£3,601 (£3,259, £3,943)	£28,480 (£27,548, £29,412)
Discontinuous ranibizumab	1.582 (1.530, 1.634)	£9,229 (£8,584, £9,875)	£1,838 (£1,724, £1,952)	£432 (£253, £611)	£11,500 (£10,798, £12,202)	£20,142 (£18,963, £21,321)
Continuous ranibizumab	1.608 (1.565, 1.651)	£16,286 (£16,011, £16,562)	£1,970 (£1,883, £2,057)	£334 (£215, £452)	£18,590 (£18,258, £18,922)	£13,576 (£12,769, £14,383)
Difference: ranibizumab vs. bevacizumab	Continuous: 0.004 (-0.046, 0.054)	Continuous: £15,222 (£14,948, £15,495)*	£16 (-£109, £141)	Continuous: -£251 (-£604, £102)	Continuous: £14,989 (£14,522, £15,456)*	Continuous: -£14,904 (-£15,995, -£13,813)*
	Discontinuous: -0.002 (-0.064, 0.060)	Discontinuous: £8,578 (£7,932, £9,225)*		Discontinuous: -£94 (-£514, £326)	Discontinuous: £8,498 (£7,700, £9,295)*	Discontinuous: -£8,541 (-£9,939, -£7,144)*
Difference: continuous vs. discontinuous	Ranibizumab: 0.026 (-0.032, 0.085)	Ranibizumab: £7,057 (£6,364, £7,750)*	£130 (£20, £239)*	Ranibizumab: -£98 (-£310, £113)	Ranibizumab: £7,090 (£6,337, £7,844)*	Ranibizumab: -£6,566 (-£7,861, -£5,271)*
	Bevacizumab: 0.020 (-0.032, 0.071)	Bevacizumab: £413 (£365, £462)*		Bevacizumab: £59 (-£438, £556)	Bevacizumab: £599 (£91, £1,107)*	Bevacizumab: -£203 (-£1,372, £967)
Interaction	0.006 (-0.071, 0.084)	£6,643 (£5,949, £7,338)*	£5 (-£31, £42)	-£157 (-£696, £381)	£6,491 (£5,604, £7,379)*	-£6,363 (-£8,088, -£4,638)*

* Significantly different from zero ($p<0.05$).
† Net benefits equal QALYs multiplied by ceiling ratio minus costs; the net benefits shown in this table were calculated at a £20,000/QALY ceiling ratio.
‡ Analysis allowed for interactions.

Figure 1: Schematic illustrating the assumptions made about the frequency of injection and monitoring consultations within the costing analysis. The consultations required by patients on discontinuous treatment will depend on when they met treatment failure criteria; Patient 2 met the re-treatment criteria at visits 0, 7 and 11.

	Visit	0	1	2	3	4	5	6	7	8	9	10	11
Patient 1: Continuous treatment	Injection	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
	Monitoring consult	✓			✓			X			✓		
	FFA	✓			?			X			?		
Patient 2: Discontinuous treatment	Injection	✓	✓	✓					✓	✓	✓		✓
	Monitoring consult	✓			✓	✓	X	✓	✓			✓	✓
	FFA	✓		?	?	X	?	?			?	?	

✓ Relevant consultation cost was applied.
? The cost of ~~fundus fluorescein angiography (~~FFA~~)~~ was applied if clinically indicated: for discontinuous patients, this was applied whenever the patient had FFA in the trial; for continuous patients, the proportion of patients having FFA was based on estimated use in routine clinical practice.
X No consultation cost was applied as the participant missed the visit.

Figure 2: Cost-effectiveness acceptability curve showing the probability that each treatment is the most cost-effective strategy evaluated in IVAN at a range of ceiling ratios. For example, at a ceiling ratio of £20,000/QALY gained (shown by the vertical dashed line), there is a 63% probability that discontinuous bevacizumab is best and a 37% probability that continuous bevacizumab is best, while the probability that either ranibizumab treatment regimen is best is approximately 0% (total = 100%).

Figure 3: Effect of sensitivity analyses on total net benefits for each of the four treatment arms, assuming a £20,000/QALY ceiling ratio. Treatments that are more cost-effective have higher net benefits; the treatment furthest to the right is therefore most cost-effective, while the treatment furthest to the left is the least cost-effective. Error bars represent 95% confidence intervals. In the analysis "doubling SAE impact", both the medication/medical service use cost ~~impact of each SAE on costs~~ and the impact of SAEs on QALYs were ~~was~~ doubled. The "best case" analysis simultaneously changed several assumptions in favour of ranibizumab: 50% discount off ranibizumab list price; assuming that 15.9% of bevacizumab (as occurred in the trial) but no ranibizumab is wasted; assuming that bevacizumab costs £100 per dose; and including medical service ~~resource~~ use costs associated with expected and unexpected AEs and SAEs.

	Visit	0	1	2	3	4	5	6	7	8	9	10	11
Patient 1: Continuous treatment	Injection	✓	✓	✓	✓	✓	✓	X	✓	✓	✓	✓	✓
	Monitoring consult	✓			✓			X			✓		
	FFA	✓			?			X			?		
Patient 2: Discontinuous treatment	Injection	✓	✓	✓					✓	✓	✓		✓
	Monitoring consult	✓			✓	✓	X	✓	✓			✓	✓
	FFA	✓			?	?	X	?	?			?	?

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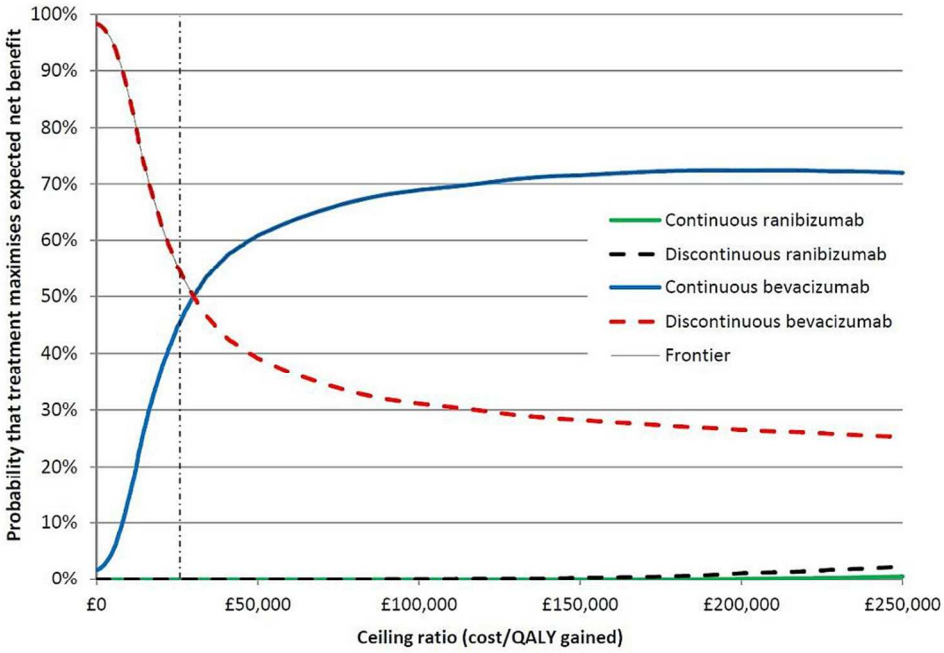

Cost-effectiveness acceptability curve showing the probability that each treatment is the most cost-effective strategy evaluated in IVAN at a range of ceiling ratios. For example, at a ceiling ratio of £20,000/QALY gained (shown by the vertical dashed line), there is a 63% probability that discontinuous bevacizumab is best and a 37% probability that continuous bevacizumab is best, while the probability that either ranibizumab treatment regimen is best is approximately 0% (total = 100%).
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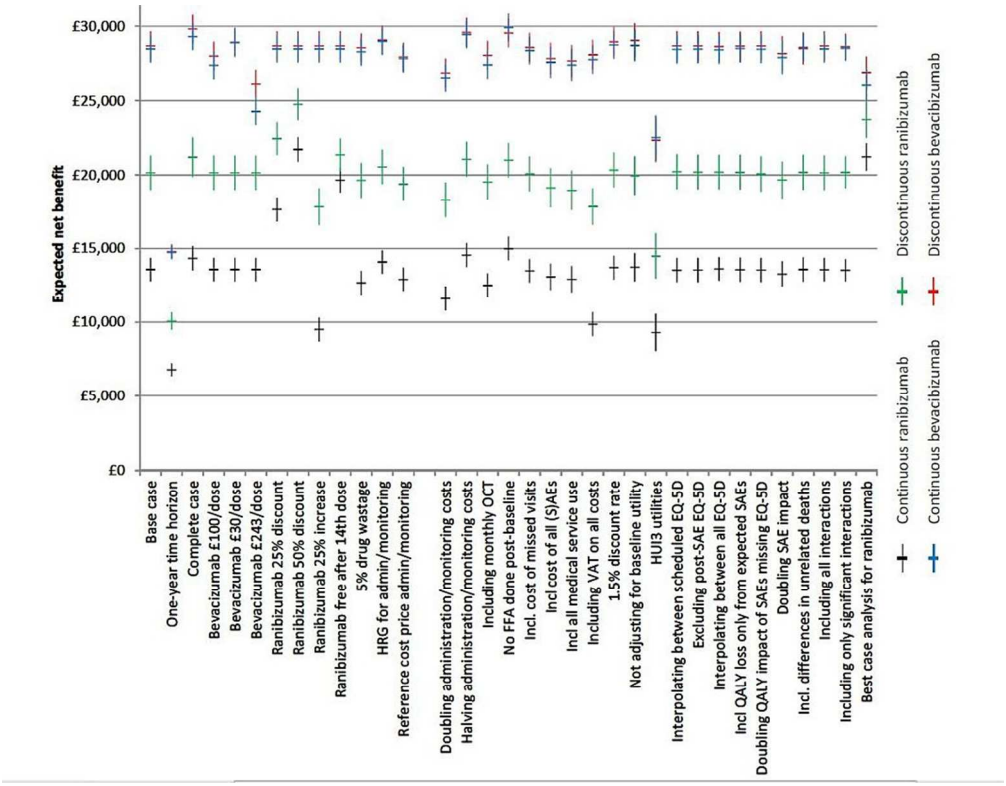

Effect of sensitivity analyses on total net benefits for each of the four treatment arms, assuming a £20,000/QALY ceiling ratio. Treatments that are more cost-effective have higher net benefits; the treatment furthest to the right is therefore most cost-effective, while the treatment furthest to the left is the least cost-effective. Error bars represent 95% confidence intervals. In the analysis "doubling SAE impact", both the medication/medical service use cost and the impact of SAEs on QALYs were doubled. The "best case" analysis simultaneously changed several assumptions in favour of ranibizumab: 50% discount off ranibizumab list price; assuming that 15.9% of bevacizumab (as occurred in the trial) but no ranibizumab is wasted; assuming that bevacizumab costs £100 per dose; and including medical service use costs associated with expected and unexpected AEs and SAEs.
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Appendix: Additional details on the statistical analysis

Definition of expected AEs or SAEs

The base case analysis focused on resource use associated with the study eye or associated with adverse events (AEs) or serious adverse events (SAEs) that were "*expected*": i.e. previously linked to anti-VEGF treatment. The list of AEs and SAEs continued to be "expected" was based on the IVAN trial protocol.[1]

The following were considered to be expected SAEs within the economic evaluation: angina pectoris; arthralgia; cardiac arrest; cardiac failure; cardiovascular disorder; cataract traumatic; cerebrovascular accident; coronary artery bypass; deep vein thrombosis; endophthalmitis; haemorrhage; intraocular pressure increased; left ventricular failure; myocardial infarction; nausea; pulmonary embolism; retinal detachment; retinal pigment epithelial tear; retinal vein occlusion; transient ischaemic attack; upper respiratory tract infection; urinary tract infection; and uveitis.

The following AEs were considered to be expected: angina pectoris; arthralgia; bronchitis; cardiac disorder; cataract; cataract cortical; cataract nuclear; cataract operation; cataract traumatic; conjunctival haemorrhage; cough; eye inflammation; eye irritation; eye pain; haemorrhage; hallucination, visual; headache; hypertension; influenza; intraocular pressure increased; lacrimation increased; nasopharyngitis; nausea; pulmonary embolism; retinal detachment; retinal pigment epithelial tear; retinal vein occlusion; sinusitis; transient ischaemic attack; upper respiratory tract infection; urinary tract infection; uveitis; visual impairment; vitreous detachment; and vitreous floaters.

Measurement and valuation of health benefits

Mixed models were used to estimate the rate at which patients' EQ-5D utility improves after SAEs or reductions in visual acuity. For patients who experienced an SAE that reduced EQ-5D utility, models assumed that EQ-5D utility fell on the day of the SAE and rose linearly afterwards. Similar profiles have previously been used to model recovery from acute hepatitis[2] and chronic obstructive pulmonary disease exacerbations.[3] We focused on linear recovery profiles to simplify subsequent QALY calculations and as models with quadratic recovery curves did not fit the data as well as those with linear profiles.

Mixed models were estimated on all post-baseline utility measurements using the xtmixed command in Stata. A basic model was defined and a pre-specified series of variations on this model were evaluated and included in the base case analysis if they reduced Akaike's information criterion (AIC). The final model divided SAEs into four categories:

- Ocular (including reductions in visual acuity, increased intraocular pressure and all SAEs in the "eye disorders" MedDRA category)
- Cardiovascular (including all SAEs classed as "cardiac disorders", plus cerebrovascular accident, coronary artery bypass, deep vein thrombosis, haemorrhage, pulmonary embolism and transient ischaemic attack)
- Cancer (comprising all events in the "Neoplasms benign, malignant and unspecified" MedDRA category)
- Other (all events not falling into one of the previous four categories)

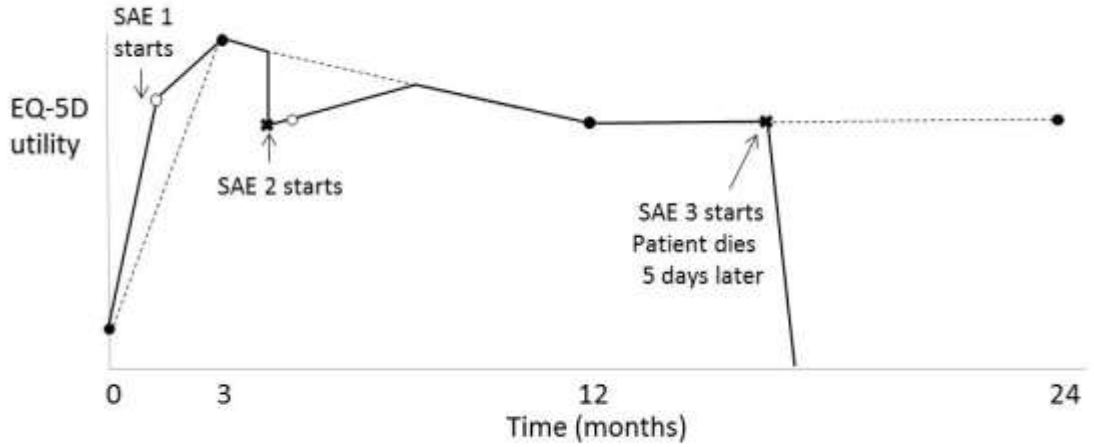
The model assumed that each type of SAE that patients had experienced reduced the EQ-5D utility of patient i at time j by $\beta_{Event,i}$, but that EQ-5D utility rose by a certain amount ($\beta_{EventRecovery}$) with each day that passed after each type of SAE. EQ-5D utility was also assumed to be a function of time since randomisation ($Time_{ij}$), treatment ($Bevacizumab_i$, $Discontinuous_i$) and baseline EQ-5D utility ($BLEQ5D_{ij}$, centred by subtracting the mean baseline EQ-5D utility across all patients [MeanBLEQ5D]):

$$\begin{aligned} EQ\text{-}5D_{ij} = {} & Constant_i + \beta_{BL}.(BLEQ5D_{ij} - MeanBLEQ5D) + \beta_{Time,j}.Time_{ij} \\ & + \beta_{Bevacizumab}.Bevacizumab_i + \beta_{Discontinuous}.Discontinuous_i \\ & + \beta_{Interact}.Bevacizumab_i.Discontinuous_i \\ & + \beta_{CVD,i}.CVD_{ij} + \beta_{CVDRecovery}.TimeSinceCVD_{ij} \\ & + \beta_{Ocular,i}.Ocular_{ij} + \beta_{OcularRecovery}.TimeSinceOcular_{ij} \\ & + \beta_{Cancer,i}.Cancer_{ij} + \beta_{CancerRecovery}.TimeSinceCancer_{ij} \\ & + \beta_{Other,i}.Other_{ij} + \beta_{OtherRecovery}.TimeSinceOther_{ij} \end{aligned}$$

The slopes estimated in the mixed models (e.g. $\beta_{CVDRecovery}$) were used alongside the observed EQ-5D measurements for each patient to estimate EQ-5D utility on the day the SAE started and identify the point at which EQ-5D utility returned to the level that would be expected from the EQ-5D utility measurements that were not taken after SAEs (Figure A). However, some post-SAE measurements were higher than would have been expected from the other measurements for that patient (e.g. Figure A); in these cases, we assumed that EQ-

5D utility changed linearly between the routine measurements (Figure A). For patients dying 1-7 days after the latest SAE, EQ-5D utility was assumed to fall linearly to 0 between the date the SAE started and the date of death. Further details will be reported in *Health Technology Assessment*.

Figure A Illustration of the utility profile around SAEs. EQ-5D utility measurements after SAEs are shown in white circles, while scheduled measurements are shown in black circles. The EQ-5D utility measurement after this patient's first set of SAEs is higher than would be expected from the baseline and three-month measurements; we therefore assumed that EQ-5D utility rose linearly from baseline to the post-SAE measurement and from this onto the 3-month measurement. EQ-5D utility is lower after their second set of SAEs; here, we use the slope coefficients from the mixed model that show the rate of recovery after the categories of SAE that this patient has experienced to draw a line through the post-SAE 2 measurement and estimate EQ-5D utility on the day SAE 2 starts and the time and EQ-5D utility at which the patient is expected to have recovered from the SAE and returned to the EQ-5D utility trend between visits three and 12. The patient died five days after SAE 3; their EQ-5D utility was therefore assumed to follow the linear trend observed between visit 12 and the value imputed at visit 24 up until the day before SAE 3, and then fall linearly to zero between that date and the date of death.



Statistical methods

The economic evaluation used linear regression models with nonparametric bootstrapping, Kaplan-Meier sample averaging and Rubin's rule to combine the quarterly costs and QALYs accrued by each patient to estimate mean total costs and mean QALYs for each of the four study arms.

Thirty-two ordinary least squares regression models[a] were used to predict the drug costs, administration/monitoring costs, medication/medical service use costs and QALYs accrued in each quarter conditional on treatment regimen and drug. Interactions between drug and treatment regimen were included as additional independent variables for quarters 2-8 if they

[a] 32 = four variables multiplied by eight quarters.

were either statistically significant or larger than main effects.[b] Since all patients received monthly injections at visits 0-2, we assumed no interaction and no impact of treatment regimen during quarter 1. Analyses of QALYs also controlled for baseline utility to eliminate any bias that could result from imbalance in baseline utility.[4]

We used non-parametric bootstrapping to quantify the uncertainty around quarterly costs and QALYs, allowing for the skewed, heteroskedastic distributions and correlations between outcomes.[5] Bootstrapping involved sampling patients with replacement from each randomised group and estimating all regressions on each bootstrap sample. We also allowed for uncertainty around multiple imputation by generating 100 imputed datasets, each with different values drawn from the imputation model. Uncertainty around consultation costs and the rate of recovery from SAEs was taken into account by randomly sampling values from the relevant distributions for each imputed data set. Bootstrap samples were drawn 130 times for each of the 100 imputed datasets, generating 13,000 bootstrap estimates of mean quarterly costs and QALYs for each of the four study groups, which allow for uncertainty around imputed utilities, the rate of recovery from SAEs and consultation costs.

We also allowed for patients withdrawing early from the trial using Kaplan-Meier sample averaging, whereby costs and outcomes in each quarter are multiplied by Kaplan-Meier estimates of the probability of patients remaining alive at the start of each quarter and summed over all four quarters.[5 6] Kaplan-Meier estimates were adapted to prevent chance differences in numbers of deaths unrelated to treatment[c] affecting incremental QALYs by adding the overall probability of deaths unlikely/not related to study medication (averaged across all four arms) to the probability of potentially-drug related deaths that was observed in each arm. After weighting quarterly costs and QALYs by the Kaplan-Meier estimate of the proportion of patients alive at the start of the quarter and discounting costs and QALYs incurred in Year 2 by 3.5%, quarterly costs and QALYs were added up to give the total cost and total QALYs accrued in each treatment group over the two-year trial period. The 100

[b] Analyses were replicated with and without interactions for drug costs, administration/monitoring costs, medication/medical service use costs and QALYs to identify any interactions that were statistically significant or had an absolute magnitude larger than either the main effect for treatment regimen or the main effect for drug. Interactions that were either statistically significant or larger than either main effect were included in the base case analysis to ensure that the bias associated with omitting qualitative interactions did not change the conclusions.

[c] The five causality groups that study investigators classified all SAEs into were used to categorise deaths into those definitely/probably/possibly related to study medication (referred to as potentially drug-related deaths) and those unlikely to be/not related to study medication (referred to as unrelated deaths).

imputed datasets were combined using Rubin's rule[7] to estimate total and incremental costs, QALYs and net benefits and their standard errors (SE). Rubin's rule was implemented in Microsoft Excel, while all other statistical analyses were conducted in Stata version 12.

References

1. The IVAN Study Investigators, Chakravarthy U, Harding SP, et al. Ranibizumab versus Bevacizumab to Treat Neovascular Age-related Macular Degeneration: One-Year Findings from the IVAN Randomized Trial. Ophthalmology 2012;**119**(7):1399-411.
2. Luyten J, Marais C, Hens N, et al. Imputing QALYs from single time point health state descriptions on the EQ-5D and the SF-6D: a comparison of methods for hepatitis a patients. Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research 2011;**14**(2):282-90.
3. Spencer M, Briggs AH, Grossman RF, et al. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. PharmacoEconomics 2005;**23**(6):619-37.
4. Manca A, Hawkins N, Sculpher MJ. Estimating mean QALYs in trial-based cost-effectiveness analysis: the importance of controlling for baseline utility. Health Econ 2005;**14**(5):487-96.
5. Gray A, Clarke P, Wolstenholme J, et al. *Applied Methods of Cost-Effectiveness Analysis in Health Care* Oxford: Oxford University Press, 2011.
6. Hallstrom AP, Sullivan SD. On estimating costs for economic evaluation in failure time studies. Med Care 1998;**36**(3):433-6.
7. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;**30**(4):377-99.

The CHEERS Checklist is part of the CHEERS Statement.

The CHEERS Statement has been endorsed and co-published by the following journals: BJOG: An International Journal of Obstetrics and Gynaecology BMC Medicine 2013; 11:80 BMJ 2013;346:f1049 Clinical Therapeutics 27 March 2013 (Article in Press DOI: 10.1016/j.clinthera.2013.03.003) Cost Effectiveness and Resource Allocation 2013 11:6. The European Journal of Health Economics 2013 Mar 26. [Epub ahead of print] International Journal of Technology Assessment in Health Care Journal of Medical Economics 2013 Mar 25. [Epub ahead of print] Pharmacoeconomics 2013 Mar 26. [Epub ahead of print] Value in Health 2013 March - April;16(2):e1-e5

Checklist taken from: http://www.equator-network.org/wp-content/uploads/2013/09/CHEERS-Checklist-PDF.pdf

CHEERS Checklist
Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Page 6
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study. Present the study question and its relevance for health policy or practice decisions.	Pages 7-8
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Pages 6 and 8
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pages 6 and 8
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Page 8
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Page 9
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Page 8
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 12
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Page 9

Section/item	Item No	Recommendation	Reported on page No/ line No
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Page 8
	11b	*Synthesis-based estimates:* Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	N/A
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	Page 11
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	Pages 10-11
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	N/A
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Page 11
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	N/A
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	N/A
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 11-13 and Appendix

Section/item	Item No	Recommendation	Reported on page No/ line No
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	N/A
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Table 1, pages 13-16
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	Figures 2 and 3, pages 15-16
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	N/A
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	N/A
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 17-20
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Page 3
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Page 3