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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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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 a 2-year time horizon, based on a multicentre 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 continuously (monthly) or discontinuously (as-needed) for 2 years.

Main outcome measures: Quality-adjusted life-years (QALYs).

Results: Total 2-year costs ranged from £3002/patient ($4700; 95% CI £2601 to £3403) 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 (+£8498 ($13 305); 95% CI £7700 to £9295; 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 £1107; 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 this UK trial, although there is a 37% chance that continuous bevacizumab is cost-effective.

Trial registration number: ISRCTN92166560.

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 vascular endothelial growth factor inhibitor 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, which 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 among 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 studies 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 studies 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 2-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, multicentre 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 2 years. Discontinuous treatment comprised an initial course of three monthly injections, followed by further courses of three injections given monthly if prespecified clinical and optical coherence tomography (OCT) retreatment criteria were met. The economic evaluation took a 2-year time horizon to estimate within-trial cost-effectiveness as incremental costs and quality-adjusted life-years (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*.

As 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, as 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 QALYs for each of the four treatment combinations and interpreted the results based on four pairwise 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 prespecified 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. In 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', that is, previously linked to anti-VEGF treatment (see online supplementary 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 (eg, 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 prespecified algorithm was used to determine the need for retreatment. Patients allocated to discontinuous treatment began a new course of three monthly injections whenever they met retreatment 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 3 months, on the grounds that ophthalmologists would want information about disease progression periodically, irrespective of whether treatment decisions are required.

Microcosting was used to estimate the cost of injection and monitoring consultations as 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

	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	?	?			?	?

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 retreatment criteria at visits 0, 7 and 11. ✓ 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.

SAEs were valued using the mean cost per bed-day for associated healthcare resource groups (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 vision chart between two consecutive visits (referred to subsequently as a 'reduction in visual acuity'). The Health Utilities Index questionnaire Mark 3 (HUI3) was administered at the same timepoints and used in sensitivity analysis; EQ-5D comprised the primary utility 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] (V.1.9.4) in Stata V.12 (StataCorp, College Station, Texas, USA).

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. As 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 (see online supplementary 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 3-month period or 'quarter' (see online supplementary 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 of Kaplan-Meier sample averaging[30 31] was used to account for patients withdrawing early from the trial and excludes 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 (ie, the tendency to prefer benefits sooner and costs later).[19] Uncertainty around quarterly costs and QALYs was quantified by estimating models separately for 130 non-parametric bootstrap draws on each of 100 data sets 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 (ie, being most cost-effective) at a range of ceiling ratios.

Sensitivity analyses evaluated the impact of changing the costs (eg, halving the cost of ranibizumab), methods (eg, taking a 1-year time horizon) and assumptions (eg, including the costs of all SAEs, not just 'expected' SAEs).

RESULTS

QALYs and quality of life

The number of QALYs accrued over the 2-year trial period did not differ significantly between bevacizumab and ranibizumab, or between continuous and discontinuous treatments ($p \geq 0.381$; 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 to 0.071) for bevacizumab, p=0.452 and 0.026 (95% CI −0.032 to 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 injections. Consequently, drug costs differed substantially between continuous and discontinuous treatments (table 1; $p<0.001$), as well as between ranibizumab and bevacizumab ($p<0.001$). As reducing treatment frequency produces larger savings for ranibizumab

Table 1 Results of the economic evaluation

	Total QALYs (95% CI)†	Mean (95% CI) drug cost†	Mean (95% CI) administration and monitoring cost	Mean (95% CI) medication/ medical service cost†	Total cost (95% CI)†	Total net benefits (95% CI)†‡
Discontinuous bevacizumab	1.584 (1.538 to 1.630)	£651 (£605 to £698)	£1825 (£1708 to £1941)	£526 (£144 to £908)	£3002 (£2601 to £3403)	£28 683 (£27 707 to £29 658)
Continuous bevacizumab	1.604 (1.563 to 1.645)	£1065 (£1048 to £1081)	£1952 (£1860 to £2043)	£585 (£250 to £919)	£3601 (£3259 to £3943)	£28 480 (£27 548 to £29 412)
Discontinuous ranibizumab	1.582 (1.530 to 1.634)	£9229 (£8584 to £9875)	£1838 (£1724 to £1952)	£432 (£253 to £611)	£11 500 (£10 798 to £12 202)	£20 142 (£18 963 to £21 321)
Continuous ranibizumab	1.608 (1.565 to 1.651)	£16 286 (£16 011 to £16 562)	£1970 (£1883 to £2057)	£334 (£215 to £452)	£18 590 (£18 258 to £18 922)	£13 576 (£12 769 to £14 383)
Difference: ranibizumab vs bevacizumab	Continuous: 0.004 (−0.046 to 0.054) Discontinuous: −0.002 (−0.064 to 0.060)	Continuous: £15 222 (£14 948 to £15 495)* Discontinuous: £8578 (£7932 to £9225)*	£16 (−£109 to £141)	Continuous: −£251 (−£604 to £102) Discontinuous: −£94 (−£514 to £326)	Continuous: £14 989 (£14 522 to £15 456)* Discontinuous: £8498 (£7700 to £9295)*	Continuous: −£14 904 (−£15 995 to −£13 813)* Discontinuous: −£8541 (−£9939 to −£7144)*
Difference: continuous vs discontinuous	Ranibizumab: 0.026 (−0.032 to 0.085) Bevacizumab: 0.020 (−0.032 to 0.071)	Ranibizumab: £7057 (£6364 to £7750)* Bevacizumab: £413 (£365 to £462)*	£130 (£20 to £239)*	Ranibizumab: −£98 (−£310 to £113) Bevacizumab: £59 (−£438 to £556)	Ranibizumab: £7090 (£6337 to £7844)* Bevacizumab: £599 (£91 to £1107)*	Ranibizumab: −£6566 (−£7861 to −£5271)* Bevacizumab: −£203 (−£1372 to £967)
Interaction	0.006 (−0.071 to 0.084)	£6643 (£5949 to £7338)*	£5 (−£31 to £42)	−£157 (−£696 to £381)	£6491 (£5604 to £7379)*	−£6363 (−£8088 to −£4638)*

*Significantly different from zero (p<0.05).
†Analysis allowed for interactions.
‡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.

than for bevacizumab, there were significant interactions between drug and treatment regimen for drug cost (p<0.001).

Administration of bevacizumab or ranibizumab costs £61 ($96; SD: £14) per injection, while each consultation for monitoring costs £72 ($113; SD: £41), plus £39 ($61; SD: £16) for each FFA. Administering intravitreal injections and monitoring disease progression/remission cost between £1825 and £1970 per patient over the 2-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, as we assumed that OCT would only be performed when it would inform treatment decisions. As 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 to £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 (95th centile range: £0, £1401). There was no significant difference in such costs between drugs or between treatment regimens (p≥0.163).

Taking account of the drug cost, drug administration/monitoring and medication/medical service use, the mean total cost per patient over the 2-year trial ranged from £18 590 ($29 119) for continuous ranibizumab to £3002 ($4702) 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 the costs for those randomised to ranibizumab.

Base case comparison between ranibizumab and bevacizumab

As the difference in mean QALYs between ranibizumab and bevacizumab was less than the prespecified 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 to £15 456), table 1) than continuous bevacizumab over the 2-year trial period (p<0.001). Discontinuous ranibizumab costs £8498 more per patient ($13 308 (95% CI £7700 to £9295), 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 £7090 ($11 102 (95% CI £6337 to £7844), p<0.001) for ranibizumab and £599 ($938 (95% CI £91 to £1107), 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, as 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 costs £270 217 ($423 074) per QALY gained compared with discontinuous ranibizumab. Owing 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

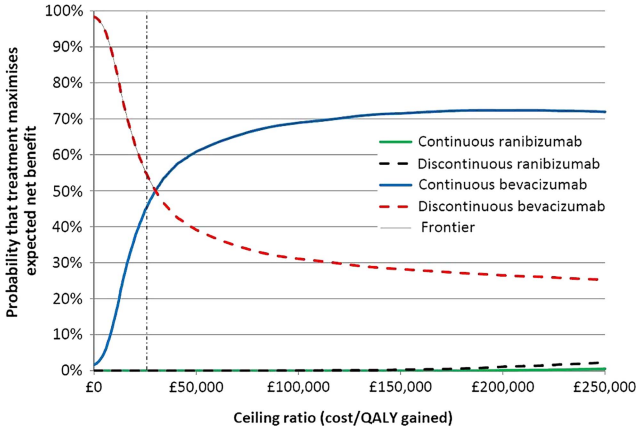

Figure 2 Cost-effectiveness acceptability curve showing the probability that each treatment is the most cost-effective strategy evaluated in the UK Inhibition of VEGF in Age-related choroidal Neovascularisation trial at a range of ceiling ratios. For example, at a ceiling ratio of £20 000/quality-adjusted life-year (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%).

continuous bevacizumab, our confidence in the conclusion that discontinuous bevacizumab has the 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. In 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). Of note, 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 online supplementary appendix).

Threshold analyses demonstrated that the price of ranibizumab would need to be reduced to £63.46 per

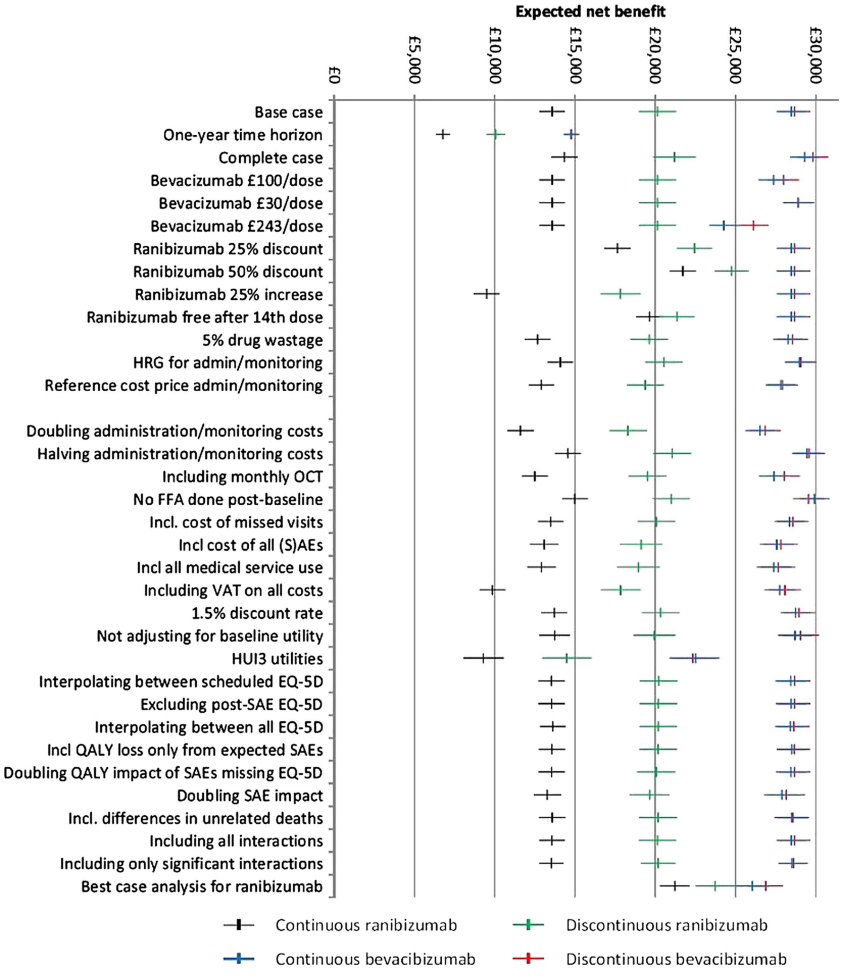

Figure 3 Effect of sensitivity analyses on total net benefits for each of the four treatment arms, assuming a £20 000/quality-adjusted life-year (QALY) ceiling ratio. Treatments that are more cost-effective have higher net benefits; the treatment furthest to the right is therefore most cost-effective, while the treatment furthest to the left is the least cost-effective. Error bars represent 95% CIs. In the analysis 'doubling SAE impact', both the medication/medical service use cost and the impact of serious adverse events (SAEs) on QALYs were doubled. The 'best case' analysis simultaneously changed several assumptions in favour of ranibizumab: 50% discount off the 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 adverse events (AEs) and SAEs.

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 £8498 ($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 USA, 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 costs £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. Nevertheless, 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 the anti-VEGF delivery model. In particular, as 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 (eg, 6 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 the publication of IVAN,[5 6] there appears to be increased interest in the 'IVAN regimen'. The cost-effectiveness of monthly treatment 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 the best of 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. Microcosting 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 vs 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 (eg, 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, as 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, as we collected very detailed information on resource use, policymakers 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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Collaborators The IVAN study investigators are listed online (available at http://aaojournal.org) in supplementary appendix 1 of ref. 6.

Contributors SW, CAR, JR, SPH, AJL, SMD, BCR and UC conceived, designed and conducted the IVAN trial. HAD, SW, GA and JR conceived and designed the economic evaluation, with extensive input from CAR, SPH and BCR. CAR supervised the collation/cleaning of trial data, while HAD, SW and GA collected additional resource use data from centres. HAD conducted the economic analysis with help from GA under the supervision of SW. HAD drafted the manuscript. All authors edited the manuscript for important intellectual content and approved the final version.

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Competing interests All authors had financial support from the NIHR for the submitted work. UC, SH, SMD and AJL 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. CAR has received an honorarium from Novartis for a lecture. SMD's and AJL's employing institutions have received payments from Novartis. SMD and AJL have received honoraria from Novartis for lectures. AJL has attended and been remunerated for attendance at advisory boards for Novartis and Bayer; likewise, SMD has been remunerated by Bayer and Ely Lilly. BCR has received a fee for teaching from Janssen-Cilag.

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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)

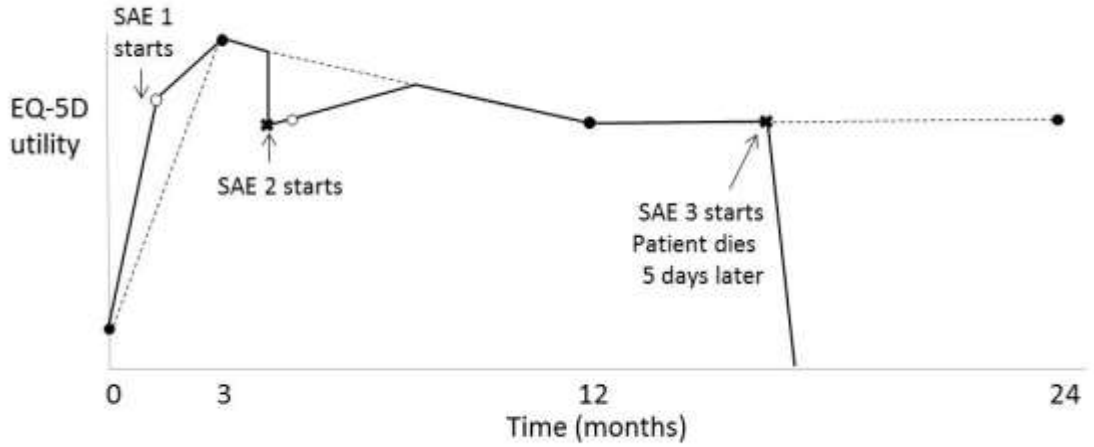
The model assumed that each type of SAE that patients had experienced reduced the EQ-5D utility of patient i at time j by $\beta_{Event,i}$, but that EQ-5D utility rose by a certain amount ($\beta_{EventRecovery}$) with each day that passed after each type of SAE. EQ-5D utility was also assumed to be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

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

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.

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