

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 hepatitis² 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)

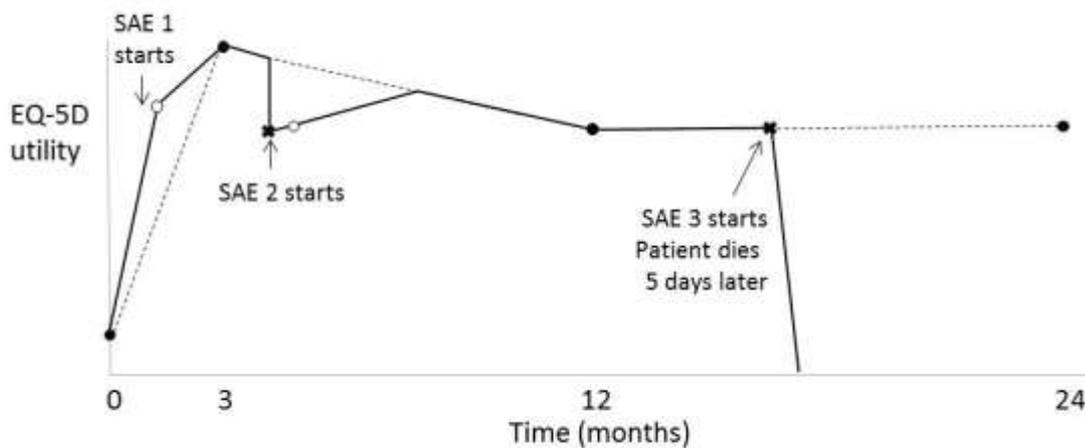
The model assumed that each type of SAE that patients had experienced reduced the EQ-5D utility of patient i at time j by $\beta_{\text{Event},i}$, but that EQ-5D utility rose by a certain amount ($\beta_{\text{EventRecovery}}$) with each day that passed after each type of SAE. EQ-5D utility was also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

$$\begin{aligned} \text{EQ-5D}_{ij} = & \text{Constant}_i + \beta_{\text{BL}} \cdot (\text{BLEQ5D}_{ij} - \text{MeanBLEQ5D}) + \beta_{\text{Time},j} \cdot \text{Time}_{ij} \\ & + \beta_{\text{Bevacizumab}} \cdot \text{Bevacizumab}_i + \beta_{\text{Discontinuous}} \cdot \text{Discontinuous}_i \\ & + \beta_{\text{Interact}} \cdot \text{Bevacizumab}_i \cdot \text{Discontinuous}_i \\ & + \beta_{\text{CVD},i} \cdot \text{CVD}_{ij} + \beta_{\text{CVDRecovery}} \cdot \text{TimeSinceCVD}_{ij} \\ & + \beta_{\text{Ocular},i} \cdot \text{Ocular}_{ij} + \beta_{\text{OcularRecovery}} \cdot \text{TimeSinceOcular}_{ij} \\ & + \beta_{\text{Cancer},i} \cdot \text{Cancer}_{ij} + \beta_{\text{CancerRecovery}} \cdot \text{TimeSinceCancer}_{ij} \\ & + \beta_{\text{Other},i} \cdot \text{Other}_{ij} + \beta_{\text{OtherRecovery}} \cdot \text{TimeSinceOther}_{ij} \end{aligned}$$

The slopes estimated in the mixed models (e.g. $\beta_{\text{CVDRecovery}}$) 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 rule⁷ 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.