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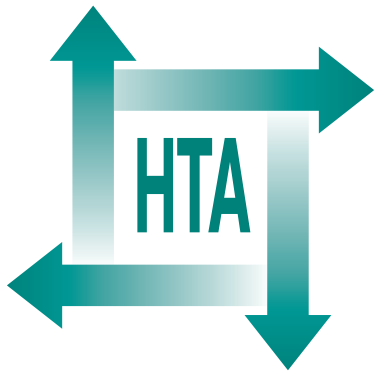

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Abstract

Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation

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Objectives: To assess the clinical effectiveness and cost-effectiveness of ranibizumab and pegaptanib for subfoveal choroidal neovascularisation (CNV) associated with wet age-related macular degeneration (AMD).

Data sources: Electronic databases were searched from inception to September 2006. Experts in the field were consulted and manufacturers' submissions were examined.

Review methods: The quality of included studies was assessed using standard methods and the clinical effectiveness data were synthesised through a narrative review with full tabulation of results. A model was developed to estimate the cost-effectiveness of ranibizumab and of pegaptanib (separately), compared with current practice or best supportive care, from the perspective of the NHS and Personal Social Services. Two time horizons were adopted for each model. The first adopted time horizons determined by the available trial data. The second analysis extrapolated effects of treatment beyond the clinical trials, adopting a time horizon of 10 years.

Results: The combined analysis of two randomised controlled trials (RCTs) of pegaptanib [0.3 mg (licensed dose), 1.0 mg and 3.0 mg] versus sham injection in patients with all lesion types was reported by three publications (the VISION study). Three published RCTs of ranibizumab were identified (MARINA, ANCHOR, FOCUS), and an additional unpublished RCT was provided by the manufacturer (PIER). Significantly more patients lost less than 15 letters of visual acuity at 12 months when taking pegaptanib (0.3 mg: 70% of patients; 1.0 mg: 71% of patients; 3.0 mg: 65% of patients) or ranibizumab (0.3 mg: 94.3–94.5%; 0.5 mg: 94.6–96.4%) than sham injection patients (55% versus pegaptanib and 62.2% versus ranibizumab) or, in the case of ranibizumab, photodynamic therapy (PDT) (64.3%). The proportion of patients gaining 15 letters or more (a clinically important outcome having a significant impact on quality of life) was statistically significantly greater in the pegaptanib group for doses of 0.3 and 1.0 mg but not for 3.0 mg, and for all ranibizumab groups compared to the sham injection groups or PDT. This was also statistically significant for patients receiving 0.5 mg ranibizumab plus PDT compared with PDT plus sham injection. Pegaptanib patients lost statistically significantly fewer letters after 12 months of treatment than the sham group [mean letters lost: 7.5 (0.3 mg), 6.5 (1.0 mg) or 10 (3.0 mg) vs 14.5 (sham)]. In the MARINA and ANCHOR trials, ranibizumab patients gained letters of visual acuity at 12 months whereas patients with sham injection or PDT lost about 10 letters ($p < 0.001$) and in the PIER study, ranibizumab patients lost significantly fewer than the sham injection group. Significantly fewer patients receiving pegaptanib or ranibizumab deteriorated to legal blindness compared with the control groups. Adverse events were common for both pegaptanib and ranibizumab but most were mild to moderate. Drug costs for 1 year of treatment were estimated as £4626 for pegaptanib and £9134 for ranibizumab. Non-drug costs accounted for an additional £2614 for pegaptanib and £3120 for ranibizumab. Further costs are associated with the management of injection-related adverse events, from £1200 to £2100. For pegaptanib compared with usual care, the incremental cost-effectiveness ratio (ICER) ranged from £163,603 for the 2-year model to £30,986 for the 10-year model. Similarly, the ICERs for ranibizumab for patients with minimally classic and occult no classic lesions, compared with usual care, ranged from £152,464 for the 2-year model to £25,098 for the 10-year model.

Conclusions: Patients with AMD of any lesion type benefit from treatment with pegaptanib or ranibizumab on measures of visual acuity when compared with sham injection and/or PDT. Patients who continued

treatment with either drug appeared to maintain benefits after 2 years of follow-up. When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison through head-to-head trials and the lack of opportunity for indirect statistical comparison due to heterogeneity. The cost-effectiveness analysis showed that the two drugs offered additional benefit over the comparators of usual care and PDT but at increased cost. Future research should encompass trials to compare pegaptanib with ranibizumab and bevacizumab, and to investigate the role of verteporfin PDT in combination with these drugs. Studies are also needed to assess adverse events outside the proposed RCTs, to consider the optimal dosing regimes of these drugs and the benefits of re-treatment after initial treatment, and to review costing in more detail. Health state utilities and their relationship with visual acuity and contrast sensitivity, the relationship between duration of vision loss and the quality of life and functional impact of vision loss, behavioural studies of those genetically at risk are other topics requiring further research.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Vascular endothelial growth factor (VEGF, VEGF-A) This is a protein that plays a critical role in angiogenesis (development of new blood vessels) and serves as one of the contributors to physiological or pathological conditions that can stimulate the formation of new blood vessels.

List of abbreviations

ACD	Appraisal Consultation Document
AMD	age-related macular degeneration
AREDS	Age-related Eye Disease Study
ARM	age-related maculopathy
ARMD	age-related macular degeneration
BNF	British National Formulary
CI	confidence interval
CIC	commercial-in-confidence
CNV	choroidal neovascularisation
CRD	Centre for Reviews and Dissemination
CVI	Certificate of Vision Impairment
DA	optic disc area (measurement of lesion size: DA = 2.54 mm^2)
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fluorescein angiography
FDA	Food and Drug Administration
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
ITT	intention-to-treat
IVI	Impact of Vision Impairment
MAR	minimum angle of resolution
MLRM	multinomial logistic regression model
NEI-VFQ	National Eye Institute Visual Function Questionnaire
NICE	National Institute for Health and Clinical Excellence
OCT	optical coherence tomography
PDT	photodynamic therapy

continued

List of abbreviations *continued*

POMS	Profile of Mood States
PSS	Personal Social Services
QALY	quality-adjusted life-year
QWB	Quality of Well-Being
RCT	randomised controlled trial
RNIB	Royal National Institute for the Blind
RPE	retinal pigment epithelium
SD	standard deviation
SG	standard gamble
SF-12	Short Form with 12 Items
SF-36	Short Form with 36 Items
SPC	Summary of Product Characteristics
TAP	Treatment of Age-related Macular Degeneration with Photodynamic Therapy
TTO	time trade-off
VAR	visual acuity rating
VEGF, VEGF-A	vascular endothelial growth factor (-A).
VIP	Verteporfin in Photodynamic Therapy

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Age-related macular degeneration (AMD) causes loss of central vision and is one of the leading causes of irreversible sight loss among adults registered blind. The decrease in vision is associated with a loss of independence, an increased risk of depression, falls and fractures and a decrease in health-related quality of life. There are different types of AMD, which have different manifestations, prognoses and treatment strategies. Neovascular or wet AMD has a more variable course than other types and can progress much more quickly. Neovascular AMD is due to choroidal neovascularisation (CNV), which can be subdivided into different disease types according to its appearance on fluorescein angiography: 100% classic, predominantly classic (>50% classic), minimally classic (<50% classic) or occult with no classic. AMD lesions can also be classified according to where they occur in relation to the fovea: subfoveal, juxtafoveal or extrafoveal. Geographic atrophy (or dry AMD) is associated with gradual, progressive loss of visual function, and is not considered in this report.

Treatment options for AMD are limited. Photocoagulation therapy may be used for those with extrafoveal CNV, but only a small proportion of patients have extrafoveal lesions. Photodynamic therapy (PDT) with verteporfin has been recommended by the National Institute for Health and Clinical Excellence (NICE) for those with classic no occult subfoveal CNV and may be used in patients with predominantly classic lesions as part of clinical studies. Although these treatments may be effective in treating established lesions, they do not prevent new CNV formation and are limited to certain subgroups of patients. Ranibizumab and pegaptanib aim to alter the progression of vision loss in patients with subfoveal CNV, and may improve vision in some patients.

Objectives

The objectives of the study were to assess the clinical effectiveness and cost-effectiveness of ranibizumab and pegaptanib for subfoveal CNV associated with wet AMD.

Methods

Data sources

Electronic databases, including MEDLINE, EMBASE, The Cochrane Database of Systematic Reviews and 10 others, were searched from inception to September 2006. Bibliographies of included studies and related papers were checked for relevant studies. Experts were contacted for advice and peer review and to identify additional studies. Manufacturers' submissions to NICE were reviewed.

Study selection

Titles and abstracts were screened for eligibility by two reviewers. Inclusion criteria were applied to the full text of selected papers by one reviewer and checked by a second reviewer, with differences resolved through discussion. The inclusion criteria were as follows:

- Patients: subfoveal CNV associated with wet AMD.
- Interventions: ranibizumab, pegaptanib, combinations of these with photodynamic therapy where the licensed indication allows.
- Comparators: best supportive care, photodynamic therapy with verteporfin for the subgroup with classic no occult lesions. If insufficient evidence was found using these comparators, sham injection was to be included for all subgroups, and photodynamic therapy with verteporfin was to be included for the subgroup with predominantly classic lesions.
- Outcomes: visual acuity, contrast sensitivity, adverse effects, adherence to treatment, health-related quality of life, costs, cost per quality-adjusted life-year (QALY).
- Types of studies: randomised controlled trials (RCTs), systematic reviews and meta-analyses of RCTs, economic evaluations. Abstracts were considered if sufficient information was presented. Non-English language studies were excluded.

Data extraction and quality assessment

Data extraction and quality assessment were undertaken by one reviewer and checked by a second, with differences resolved through discussion. The quality of included studies was assessed using criteria by the NHS Centre for Reviews and Dissemination (CRD).

Data synthesis

The clinical effectiveness data were synthesised through a narrative review with full tabulation of results. Meta-analysis was not undertaken due to differences in study populations and comparators.

Cost-effectiveness

A model was developed to estimate the cost-effectiveness of ranibizumab and of pegaptanib (separately), compared with current practice or best supportive care, from the perspective of the NHS and Personal Social Services. Two time horizons were adopted for each model. The first adopted time horizons determined by the available trial data. The second analysis extrapolated effects of treatment beyond the clinical trials, adopting a time horizon of 10 years.

The proportions of patients gaining and losing visual acuity reported in the clinical trials were converted to 3-month transition probabilities in the model and combined with published estimates of health state utilities to estimate the QALYs associated with each intervention.

Costs included in the model were drug costs, drug administration and patient monitoring while on treatment and management of treatment-related adverse events. Since the cost-effectiveness analysis adopted an NHS and Personal Social Services perspective, costs of services provided to people with visual impairment were included in the model.

Results

Number and quality of studies

The systematic review identified 266 citations, of which 28 were retrieved in full for further inspection. Subsequently, 23 were excluded from the review as they did not meet the inclusion criteria. The combined analysis of two RCTs of pegaptanib [0.3 mg (licensed dose), 1.0 mg and 3.0 mg] versus sham injection in patients with all lesion types was reported by three publications (the VISION study). Three published RCTs of ranibizumab were identified (MARINA, ANCHOR, FOCUS), and an additional unpublished RCT was provided by the manufacturer (PIER). The ranibizumab trials compared:

- 0.3 and 0.5 mg ranibizumab versus sham injection in patients with minimally classic or occult lesions (MARINA)
- 0.3 and 0.5 mg ranibizumab versus PDT with verteporfin in patients with predominantly classic lesions (ANCHOR)
- a reduced dose frequency regimen of 0.3 and 0.5 mg ranibizumab versus sham injection in patients with any lesion type (PIER, unpublished)
- 0.5 mg ranibizumab plus PDT versus PDT plus sham injection in patients with predominantly classic lesions (FOCUS).

The quality of reporting in the trials was generally good.

Summary of benefits and harms

Pegaptanib

- *Visual acuity*. Statistically significantly more pegaptanib patients (0.3 mg: 70% of patients; 1.0 mg: 71% of patients; 3.0 mg: 65% of patients) lost less than 15 letters of visual acuity at 12 months than sham injection patients (55% of patients). Doses of 0.3 or 1.0 mg also showed statistically significant improvements in all secondary measures of visual acuity, but the 3.0-mg dose was not consistent in producing a statistically significant difference. The proportion of patients gaining 15 letters or more was statistically significantly greater in the 0.3-mg (6%, $p = 0.04$) and the 1.0-mg group (7%, $p = 0.02$), but not the 3.0-mg group (4%, $p = 0.16$) compared with the sham injection group (2%). A gain of 15 letters in visual acuity is a clinically important outcome and would have a significant impact on quality of life. Pegaptanib patients lost statistically significantly fewer letters after 12 months of treatment than the sham group [mean letters lost: 7.5 (0.3 mg), 6.5 (1.0 mg) or 10 (3.0 mg) vs 14.5 (sham)].
- *Legal blindness*. Significantly fewer pegaptanib patients deteriorated to legal blindness [38% (0.3 mg), 43% (1.0 mg), 44% (3.0 mg) versus 56% (sham), $p < 0.001$].
- *Adverse events*. Most adverse events were mild to moderate transient events. Endophthalmitis was experienced by 1.3% of patients receiving pegaptanib in the first year.

Ranibizumab

- *Visual acuity*. Significantly more patients receiving ranibizumab (0.3 mg: 94.3–94.5%; 0.5 mg: 94.6–96.4%) lost less than 15 letters of

visual acuity after 12 months compared with sham injection (62.2%, $p < 0.0001$) or PDT (64.3%, $p < 0.0001$). A 0.5-mg dose of ranibizumab plus PDT significantly increased the proportion losing less than 15 letters compared with PDT plus sham injection (90.5 versus 67.9%, $p < 0.001$) in patients with predominantly or minimally classic lesions. The proportion of patients gaining 15 letters or more of visual acuity was statistically significantly higher in the ranibizumab groups (MARINA and ANCHOR, 0.3 mg: 24.8 and 35.7%; 0.5 mg: 33.8 and 40.3%, respectively) compared with sham injection (4.6%, $p < 0.0001$) or PDT (5.6%, $p < 0.0001$). This was also statistically significant for patients receiving 0.5 mg ranibizumab plus PDT compared with PDT plus sham injection (23.8 versus 5.4%, $p = 0.003$). In the MARINA and ANCHOR trials, ranibizumab patients gained letters of visual acuity at 12 months whereas patients with sham injection or PDT lost about 10 letters ($p < 0.001$). In the PIER study, patients lost on average 0.2 letters (0.5 mg) compared with a loss of 16.3 letters in the sham injection group ($p < 0.0001$).

- *Legal blindness*. Significantly fewer patients receiving ranibizumab deteriorated to legal blindness (MARINA and ANCHOR, 0.3 mg: 12.2 and 22.1%; 5 mg: 11.7 and 16.4%, respectively) versus sham injection (42.9%) or PDT (60.1%), $p < 0.0001$. Similarly, fewer patients receiving 0.5 mg ranibizumab plus PDT deteriorated to legal blindness compared with PDT plus sham injection (29.5 versus 46.4%, $p = 0.006$).
- *Adverse events*. Adverse events were common but most were mild to moderate. Endophthalmitis was reported by very few patients in the active treatment arms of the ranibizumab trials and none in the control arms.

Summary of costs

Drug acquisition costs for 1 year of treatment were estimated as £4626 for pegaptanib and £9134 for ranibizumab. Non-drug treatment costs (for administering injections and also patient monitoring while on treatment) accounted for an additional £2614 for pegaptanib (36% of total treatment costs) and £3120 for ranibizumab (25% of total treatment costs).

Further costs are associated with the management of injection-related adverse events – although the proportion of injections associated with adverse events is low, costs of managing each event range from £1200 to £2100. Injection-related adverse events are also associated with significant risks of severe loss of visual acuity.

Summary of cost-effectiveness

The incremental cost-effectiveness ratio (ICER) for pegaptanib compared with usual care in the short-term model is £163,603. This high ICER arises due to a relatively small QALY gain at 2 years and because treatment costs are realised in the first 2 years. The QALY gain is greater in the long-term model. By this stage, costs of services for visual impairment comprise the largest proportion of total costs, and although the difference in these costs between the pegaptanib-treated and usual care cohorts is not large enough to offset treatment costs fully, the ICER is reduced to £30,986.

For ranibizumab we undertook separate analyses for patients with predominantly classic lesions and for patients with minimally classic and occult no classic lesions. Total costs and the QALYs associated with each intervention were estimated. The incremental cost per QALY gained for ranibizumab against best supportive care, for all lesion types, and against PDT for patients with predominantly classic lesions was estimated.

The ICERs in the trial-based analyses are between £150,000 and approximately £200,000. Again, the high ICER arises due to relatively small QALY gains and treatment costs being concentrated in the first 2 years (with little opportunity to offset these costs by reducing costs of services for visual impairment). The QALY gain at 10 years is larger and incremental costs have reduced (since reduced costs of services for visual impairment in the ranibizumab-treated cohorts have offset some of the costs of treatment). The ICERs reduced to £15,638 for the comparison with PDT and £11,412 for the comparison with best supportive care. The ICER for patients with minimally classic and occult no classic lesions is £25,098 at 10 years.

Sensitivity analyses

Deterministic sensitivity analysis showed that the cost-effectiveness estimates in the base case were sensitive to the model time horizon and visual acuity of the cohort at baseline. Cost-effectiveness estimates were also sensitive to assumptions over post-treatment effects (with the ICER for pegaptanib reducing to £26,896 if the post-treatment effect was included in the model only for the year after treatment ceased and to £20,467 if the effect was assumed to persist for the patient's lifetime).

The cost-effectiveness estimates were particularly sensitive to assumptions over the cost of services for visual impairment and the uptake of these services. Using extreme values produced a situation where treatment with pegaptanib or ranibizumab was cost saving over a 10-year time horizon (assuming high cost and high uptake) or alternatively could be associated with a 30–70% increase over the base case estimate for incremental cost (assuming low cost and low uptake). Further analysis suggested that the cost-effectiveness estimates were most sensitive to assumptions over uptake, estimated as the proportion of eligible cases receiving services.

In a probabilistic sensitivity analysis for pegaptanib, the majority of simulations produced incremental cost-effectiveness estimates that were in the north-east quadrant of the cost-effectiveness map. That is, the majority of simulations were associated with increased QALYs but also increased costs. In this analysis, pegaptanib had a probability of being cost-effective (compared with usual care) of 17% at a willingness to pay threshold of £20,000 per QALY and 58% at a willingness to pay threshold of £30,000 per QALY.

In a probabilistic sensitivity analysis for ranibizumab (conducted separately for lesion types and alternative comparators), the majority of simulations were associated with increased QALYs but also increased costs. Ranibizumab for patients with predominantly classic lesions had a probability of being cost-effective (compared with PDT) of 72% at a willingness to pay threshold of £20,000 per QALY and 97% at a willingness to pay threshold of £30,000 per QALY. The equivalent values for the comparison with best supportive care were 95% at a threshold of £20,000 per QALY and 97% at a threshold of £30,000 per QALY. For patients with minimally classic and occult no classic lesions, the probabilistic sensitivity analysis shows a 15% probability of ranibizumab being cost-effective at a willingness to pay threshold of £20,000 per QALY and 81% at a willingness to pay threshold of £30,000 per QALY.

Conclusions

Patients with AMD of any lesion type benefit from treatment with pegaptanib or ranibizumab on measures of visual acuity when compared with sham injection and/or PDT. Patients who continued treatment with either drug appeared to maintain benefits after 2 years of follow-up. When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison through head-to-head trials and the lack of opportunity for indirect statistical comparison due to heterogeneity.

The cost-effectiveness analysis showed that the two drugs offered additional benefit over the comparators of usual care and PDT but at increased cost. For pegaptanib compared with usual care, the ICER ranged from £163,603 for the 2-year model to £30,986 for the 10-year model. Similarly, the ICERs for ranibizumab for patients with minimally classic and occult no classic lesions, compared with usual care, ranged from £152,464 for the 2-year model to £25,098 for the 10-year model. The ICER was influenced by the model's time horizon, the patient's baseline visual acuity, the disease-modifying effect of the treatment, whether injections were costed as an outpatient or day case procedure and assumptions over the cost and uptake of services for visual impairment.

Recommendations for further research

Suggested further research priorities are as follows:

- A trial to compare pegaptanib with ranibizumab and bevacizumab as well as the role of verteporfin PDT in combination with these drugs.
- A study to assess adverse events outside the proposed RCTs.
- Studies to determine the optimal dosing regimes of these drugs and the benefits of re-treatment after initial treatment.
- More detailed costing work, for example an independent survey of the costs associated with vision loss.
- Health state utilities and their relationship with visual acuity and contrast sensitivity. Further research is also required to reduce uncertainty over the relationship between duration of vision loss and the quality of life and functional impact of vision loss.
- Studies to assess whether the identification of being genetically at risk will alter behaviour, for example, inspire people to stop smoking.

Chapter 1
Background

Description of health problem

Age-related macular degeneration (AMD) is one of the leading causes of irreversible sight loss among adults registered blind.[1] The disease causes loss of central vision, resulting in sufferers being unable to read, recognise faces or drive a vehicle, and is associated with a decrease in quality of life and an increased risk of falls.

AMD is the late stage of age-related maculopathy (ARM), which is a disorder of the macular area of the retina and is most often clinically apparent after 50 years of age.[2] There are different types of late ARM (or AMD), which have different manifestations, prognoses and treatment strategies. AMD can itself be classified into early and late stages; the early stage is associated with minimal visual impairment[3] and is not discussed further here.

Late-stage AMD can be either of the geographic, atrophic form or of the neovascular exudative form, also known as wet AMD. Geographic atrophy is a form of extensive atrophy (wasting of cells) which results in patterns of damage that look similar to a map, and is associated with gradual, progressive loss of visual function. Neovascular AMD is due to choroidal neovascularisation (CNV), which involves the formation of immature blood vessels. These newly developed blood vessels grow between the retinal pigment epithelial cells and the photoreceptor cells in the subretinal space and/or underneath the retinal pigment epithelium. Wet AMD has a more variable course than geographic atrophy, and can progress much more quickly, sometimes within days or weeks.[3]

An international classification system for ARM has been proposed as follows:[2]

1. ARM
   (a) Soft drusen ⩾63 μm (drusen are discrete lesions consisting of lipids, proteins and other molecules deposited under the retina[4]).
   (b) Areas of increased pigment or hyperpigmentation (in the outer retina or choroid) associated with drusen.
   (c) Areas of depigmentation or hypopigmentation of the retinal pigment epithelium (RPE), most often more sharply demarcated than drusen, without any visibility of choroidal vessels associated with drusen.
2. Late ARM (AMD): geographic atrophy or dry AMD
   (a) Any sharply delineated roughly round or oval area of hypopigmentation, or apparent absence of RPE in which surrounding vessels are more visible than in surrounding areas that must be at least 175 μm.
3. Late ARM (AMD): neovascular AMD, wet AMD, disciform AMD or exudative AMD
   (a) RPE detachment(s), which may be associated with neurosensory retinal detachment, associated with other forms of ARM.
   (b) Subretinal or sub-RPE neovascular membrane(s).
   (c) Epiretinal (with exclusion of idiopathic macular puckers), intraretinal, subretinal or subpigment epithelial scar/glial tissue or fibrin-like deposits.
   (d) Subretinal haemorrhages that may be nearly black, bright red or whitish yellow and that are not related to other retinal vascular disease (haemorrhages in the retina or breaking through into the vitreous may also be present).
   (e) Hard exudates (lipids) within the macular area related to any of the above, and not related to other retinal vascular disease.

Approximately two-thirds of late-stage AMD cases[5–7] and the majority of patients with legal blindness due to AMD[8] have the neovascular form of the disease. This report is concerned with neovascular AMD.

CNV associated with neovascular AMD can be subdivided into different disease types according to its appearance on fluorescein angiography (FA), a technique used for examining blood vessels in the retina. Leakage patterns examined using this technique can be described as classic or occult, or

both classic and occult. In classic CNV, discrete areas hyperfluoresce early in the fluorescein photographic study, and continue to leak progressively. Occult CNV is characterised by stippled hyperfluorescence and late leakage, or leakage of undetermined origin.[9] A further subdivision has been created since the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) trial,[10] so that lesions can be classified as either 100% classic, predominantly classic (classic CNV at least 50% of lesion), minimally classic (classic CNV <50% but >0% of lesion) or occult (no classic).

Subdivisions can also be made according to where the lesions occur in relation to the fovea, which is the central part of the macula and the area of highest visual acuity: subfoveal (located behind the middle of the fovea); juxtafoveal (located within 200 μm of the fovea, but not the middle of it); and extrafoveal (located >200 μm outside the fovea). Assessment of the location of lesions in people with neovascular AMD showed that 78.5% were subfoveal, 16.5% juxtafoveal and 5% extrafoveal.[11] The type of lesion appeared to vary by location. For those people with subfoveal lesions, 73% were occult with no classic, 20% were predominantly classic and 7% were minimally classic. In contrast, for those with juxtafoveal or extrafoveal lesions, 51% were occult with no classic, 47% were predominantly classic and only 2% were minimally classic.[11]

Aetiology

The cause of AMD is not well defined, and conflicting evidence exists for many of the potential risk factors. It is evident from the studies examining the incidence and prevalence of AMD that age is a key risk factor.[12] The Age-Related Eye Disease Study (AREDS) Research Group[12] examined the risk factors for AMD through a prospective clinic-based cohort study of 3294 people aged 55–80 years. Multivariate logistic regression analysis confirmed the importance of age on the incidence of neovascular AMD, with older people having a significantly higher incidence than younger people (*Table 1*). However, other demographic, behavioural and medical risk factors have been shown to determine the occurrence of AMD and its neovascular form.

Oxidative processes and factors affecting these are thought to play a role in the development of AMD.[4] The most frequently cited modifiable risk factor for AMD is cigarette smoking. Smoking reduces plasma antioxidant levels, which leaves the body more susceptible to oxidative stress.[13] The AREDS Research Group[12] found that the incidence of neovascular AMD was significantly higher for people who smoke more than 10 pack-years (average of one pack of cigarettes smoked per day for 1 year; *Table 1*). Another study[14] found that current and former smokers had a 3.6 and 3.2 greater risk, respectively, of AMD compared with people who had never smoked. Schmidt and colleagues[15] reported statistical evidence for a gene–environment interaction, which suggests that people who are genetically susceptible to AMD and smoke cigarettes are at significantly higher risk of AMD than people with only one of these two risk factors.

A Cochrane review[16] found no overall link between dietary antioxidants and reduction in risk

TABLE 1 *Odds ratios for selected significant risk factors for neovascular AMD[12]*

Risk factor	Exposure		Odds ratios (95% CI)	
			Bilateral drusen (*n* = 2506)	**Unilateral advanced AMD (*n* = 788)**
Age (years)	65–69	<65	1.67 (1.05 to 2.67)	1.65 (1.00 to 2.72)
	>70	<65	2.37 (1.52 to 3.71)	1.94 (1.24 to 3.04)
Gender	Male	Female	0.83 (0.61 to 1.14)	0.70 (0.51 to 0.96)
AREDS treatment	Antioxidants	Placebo	0.72 (0.47 to 1.09)	0.73 (0.48 to 1.11)
	Zinc	Placebo	0.85 (0.57 to 1.28)	0.53 (0.35 to 0.81)
	Antioxidants + zinc	Placebo	0.83 (0.55 to 1.25)	0.39 (0.25 to 0.59)
Race	White	Other	6.77 (1.24 to 36.90)	
Smoking	>10 pack-years	⩽10 pack-years	1.55 (1.15 to 2.09)	
Diabetes	Present	Absent		1.88 (1.07 to 3.31)
Antacid use	Present	Absent	1.70 (0.99 to 2.95)	
Refractive error	Hyperopic	Myopic		1.70 (0.89 to 3.25)

CI, confidence interval.

of AMD. However, there is some evidence that progression in people who already have AMD could be reduced by dietary intervention. The AREDS group[17] found that people with intermediate AMD or advanced AMD in one eye and non-AMD in the other eye reduced the risk of developing advanced stage AMD by about 25% when treated with a high-dose combination of vitamins C and E, β-carotene and zinc. Another Cochrane review,[18] which included further results from AREDS, indicated that supplementation with antioxidants and zinc may be of modest benefit in delaying progression in people with AMD.

Higher body mass index and waist circumference have been linked with a statistically significant increased risk for progression to advanced AMD.[19] Analysis of AREDS data[20] found modifiable factors such as high body mass index altered the genetic susceptibility of people at high risk of AMD. There is some evidence that the incidence of neovascular AMD is significantly higher among people with diabetes.[12]

Other risk factors which have been suggested for AMD include family history of the condition, vascular disease,[21] hypertension,[21] gender (some studies indicate a slightly higher risk for women) and having light-coloured irides[9] (the coloured part of the eye). Some studies[12] indicate that being of white race is a risk factor for wet AMD, but there is conflicting evidence for this.[9]

Natural history

Subfoveal CNV due to AMD has a poor prognosis for vision loss, particularly among people with predominantly classic CNV or occult with no classic CNV.[22] A review[22] found that between 60 and 80% of eyes in patients with untreated subfoveal classic CNV (which could also have an occult CNV component) lost three or more lines of visual acuity during 2 years' follow-up. For untreated eyes with subfoveal occult with no classic CNV, approximately 60% lost three or more lines of visual acuity through the 2-year follow-up period. Losing three lines of visual acuity would have a significant impact on the patient's quality of life and, depending on the starting point, could mean the difference in being able to drive, to read or watch television or to live independently.

Bilateral AMD (i.e. the development of AMD in the patient's other eye) developed within 5 years in 43% of patients in the AREDS study[17] who had advanced AMD in one eye. The Royal College of Ophthalmologists[23] estimates that for people with AMD-related visual loss affecting one eye, the risk of losing vision in the other eye increases by 7–10% annually. Factors such as lesion composition, number or size of drusen, hyperpigmentation, pigment epithelial tear and definite systemic hypertension might affect the risk of developing AMD in the second eye.[22,23]

Klaver and colleagues[5] identified a strong association between incident AMD and the stage of ARM at baseline, with the more advanced stages of ARM having a greater incidence of ARM at follow-up. Whereas no people with ARM stage 0 or 1 at baseline progressed to AMD within 2 years, people in stage 2 and stage 3 had overall incidences of 14.0 per 1000 person-years (2-year cumulative incidence 3%) and 48.2 per 1000 person-years (2-year incidence 9%), respectively. They also found that for those with AMD in only one eye at baseline, involvement of the second eye was likely with an incidence rate of 170.6 per 1000 person-years (2-year cumulative incidence 28.9%). Van Leeuwen and colleagues[6] assessed the risk of developing AMD as a function of early fundus signs. The risk of developing AMD in the second eye appeared high, with an incidence rate of 97.8 per 1000 person-years (5-year cumulative incidence 38.7% [95% confidence interval (CI) 22.5 to 60.9%) and 89% chance it would be the same type of AMD as in the first eye.

Epidemiology of macular degeneration

Despite the importance of macular degeneration as a public health concern, difficulties persist in assessing the likely current and future burden of the condition. Available routine data tend to use the International Classification of Diseases definition (ICD10) and focus on disease registers. The wide variety of conditions encompassed within the ICD10 definition that includes macular degeneration and the inherent problems of under-reporting of registrations have rendered their use problematic. As a consequence, assessment of the incidence and prevalence of macular degeneration and its different forms has tended to rely on the use of representative population based clinical surveys. These too are affected by differences in methods used for diagnosing and assessing macular degeneration, variations in the definitions of AMD and its sub-classifications, methods used within the studies and different geographical and socio-demographic factors. Notwithstanding these difficulties, several studies have been undertaken within Europe, the USA, Australia and other countries. The following sections discuss key meta-analyses and population surveys assessing the incidence and prevalence of AMD and its

neovascular form. Also it uses these to provide some provisional estimates of the burden of disease.

Incidence

The incidence of AMD appears to vary, with rates differing depending on the type of AMD, the demographic composition of the population studied, the stage of the disease at outset and on the methods used to diagnose the condition and to assess its incidence (*Table 2*). In a population-based incidence study in Rotterdam in The Netherlands, Klaver and colleagues[5] examined the incidence and progression of AMD in a cohort of 4953 people aged 55 years and older. They found an overall incidence rate for AMD of 1.2 per 1000 person-years (2-year cumulative incidence 0.24%). The incidence increased with age from under 1.0 per 1000 person-years for those aged less than 75 years to 8.80 per 1000 person-years for those aged 85 years and over. Women (1.37 per 1000 person-years) tended to have a higher incidence of AMD than men (1.00 per 1000 person-years), although the differences were not statistically significant ($p = 0.99$). Van Leeuwen and colleagues[6] extended the analysis of Klaver and colleagues,[5] assessing the incidence of AMD after 5 years of follow-up. The overall incidence for AMD was higher at 1.8 per 1000 person-years. Although Van Leeuwen and colleagues[6] found a similar increase in incidence of AMD with age (*Table 2*), the rates by sex did vary. Men (2.0 per 1000 person-years) had a higher incidence than women (1.6 per 1000 person-years), although differences were not statistically significant. Also, the risk of suffering from neovascular AMD was shown to be higher than that for atrophic AMD with a ratio of 1.4:1.

TABLE 2 *Age-specific incidence of AMD (95% CI)*

Study	Age group (years)	Persons	Male	Female
Klaver et *al*., 2001[5]	55–64	0.0 (0 to1.0)		
(Rotterdam, The Netherlands)	65–74	0.75 (0.15 to 2.2)		
Design: population-based prospective cohort study	75–84	3.07 (1.1 to 6.7)		
(*n* = 4953)	85+	8.80 (1.8 to 25.8)		
Follow-up: 2 years	Total	1.22 (0.6 to 2.1)	1.00	1.37
Outcome: age-specific incidence (95% CI) per 1000 person-years				
Van Leeuwen et *al*., 2003[6]	55–59	0.0		
(Rotterdam, The Netherlands)	60–64	0.2 (0.0 to 1.1)		
Design: population-based prospective cohort study	65–69	0.8 (0.3 to 1.8)		
(*n* = 6418)	70–74	1.8 (1.0 to 3.4)		
Follow-up: 5 years	75–79	3.9 (2.3 to 6.6)		
Outcome: age-specific incidence (95% CI) per	⩾80	6.8 (4.2 to 11.0)		
1000 person-years	Total	1.8 (1.3 to 2.4)	2.0	1.6
Klein et *al*., 2002[24]	43–54	0.1	0.0	0.1
(Beaver Dam, USA)	55–64	1.0	1.5	0.6
Design: population-based prospective cohort study	65–74	4.4	4.6	4.3
(*n* = 2946)	75+	9.5	5.8	11.3
Follow-up: 10 years	Total	2.1	1.7	2.4
Outcome: age-specific incidence per 100 persons				
Mitchell et *al*., 2002[25]	49–60	0	0	0
(Blue Mountains, Sydney Australia)	60–69	0.6	0.5	0.8
Design: population-based prospective cohort study	70–79	2.4	2.4	2.4
(*n* = 2335)	80+	5.4	0	8.8
Follow-up: 5-years	Total	1.1	0.7	1.4
Outcome: age-specific incidence per 100 persons				
Bunce and Wormald, 2006[26]	0–15	0.01	0.00	0.02
(England and Wales)	16–64	1.01	0.91	1.10
Design: register study (*n* = 32,895)	65–74	39.69	31.10	46.47
Follow-up: 1 year	75–84	251.53	208.76	275.70
Outcome: registrations per 100,000	⩾85	699.02	682.94	697.37
	All	31.78	19.96	42.44

Similar associations between age and gender and the incidence of AMD were identified by Klein and colleagues[24] and Mitchell and colleagues.[25] In a 10-year study of 4926 people aged 43–86 years in Beaver Dam, WI, USA (*Table 2*), Klein and colleagues[24] found a 10-year incidence of 2.1%. Incidence rates were higher among women (2.4%) than men (1.7%) and increased with age for all persons from 1.0% or less for those aged 64 years or under to 9.5% for those aged 75 years and over. Mitchell and colleagues[25] examined the incidence of AMD in a 5-year study among 2335 people aged 49 years or older in the Blue Mountains area of Sydney, Australia. They found a 5-year incidence of 1.1%, with rates higher among women than men at all age groups, and an increasing incidence with age (*Table 2*).

In the UK, incidence studies have been limited to register-based studies of blindness, its causes and temporal patterns.[1,26] During the period between 1950 and 1990, Evans and Wormald[1] noted a 1.2-fold increase in registrations for blindness from 11,144 people to 13,566 people and a 5-fold increase in registrations of AMD from 1329 people to 6580 people. Whereas the increase in registrations for blindness were shown to reflect an ageing population in Britain and differences in overall registrations, 30% of the increase for AMD was not explained by these factors. Bunce and Wormald[26] examined the incidence in England and Wales between March 1999 and April 2000, noting an increase in those people registered as blind to 13,788 people, with 57.2% (7887 people) suffering from degeneration of the macula and posterior pole thought largely to be due to AMD. Although reasons for these changes were unclear, Bunce and Wormald[26] thought an ageing population, post-War smoking patterns and differences in data recording may have had an effect. As with previous studies, Bunce and Wormald[26] identified age and gender differences in the registrations of AMD per 100,000, with higher rates with increasing age and among women (*Table 2*).

The incidence of neovascular AMD was examined by Van Leeuwen and colleagues[6] and Mitchell and colleagues[25] (*Table 3*). As with AMD, incidence rates for neovascular AMD increased with age and were higher among women than men. Van Leeuwen and colleagues[6] found that people aged under 70 years had incidence rates below 1.0 per 1000 person-years compared with those aged 80 years and over having rates 3.6 per 1000 person-years. The overall incidence of wet AMD was 1.1 per 1000 person-years. Mitchell and colleagues[25] found an overall incidence of wet AMD of 1.0%. Again, incidence increased with age and women had higher incidence rates of AMD than men.

Prevalence

A systematic review of the prevalence of AMD was undertaken by Owen and colleagues[27] in 2003. The systematic review pooled data from six studies encompassing 22,206 people aged 65–79 years, including the Beaver Dam Eye Study,[28] Blue Mountains Eye Study,[29] Copenhagen City Eye Study,[30,31] North London Eye study,[32] Rotterdam Study[33] and Melbourne Visual Impairment Study.[34–36] The prevalence of AMD was shown to increase exponentially with age, whether considering the visual impairment caused by AMD

TABLE 3 *Age-specific incidence of neovascular AMD (95% CI)*

Study	Age group (years)	Persons	Male	Female
Van Leeuwen *et al.*, 2003[6]	55–59	0.0		
(Rotterdam, The Netherlands)	60–64	0.2 (0.0 to 1.1)		
Design: population-based prospective cohort study	65–69	0.3 (0.1 to 1.2)		
(n = 6418)	70–74	1.3 (0.6 to 2.7)		
Follow-up: 5 years	75–79	2.5 (1.3 to 4.8)		
Outcome: age-specific incidence (95% CI) per	⩾80	3.6 (1.9 to 6.9)		
1000 person-years	Total	1.1 (0.7 to 1.5)		
Mitchell *et al.*, 2002[25]	49–60	0.0	0.0	0.0
(Blue Mountains, Sydney Australia)	60–69	0.5	0.2	0.8
Design: population-based prospective cohort study	70–79	2.4	2.4	2.4
(n = 2335)	80+	3.6	0.0	5.9
Follow-up: 5 years	Total	1.0	0.6	1.2
Outcome: age-specific incidence per 100 persons				

or the type of AMD. Also, it showed that the prevalence of AMD varied by sex, although the specific relationship depended on the type of AMD. The meta-analysis showed a pooled prevalence of 0.35% (95% CI 0.14 to 0.57) for people aged 65–79 years with AMD-related partial sight.

The variation in the prevalence of AMD by age and sex shown by Owen and colleagues was also evident in other prevalence studies (*Table 4*). All showed a positive relationship between age and prevalence.[7,8,28,29,33,37,38] Ferris and colleagues,[8] Mitchell and colleagues[29] and Augood and colleagues[7] found that women consistently had

TABLE 4 *Age-specific prevalence of AMD*

Study	Age group (years)	Persons	Male	Female
Vingerling et *al*., 1995[33] (Rotterdam, The Netherlands) Design: population-based prospective cohort study (*n* = 6251) Outcome: age-specific prevalence per 100 person-years	55–64 65–74 75–84 85+	0.2 0.8 3.7 11.0		
Klein et *al*., 1992[28] (Beaver Dam, USA) Design: population-based prospective cohort study (*n* = 4771) Outcome: age-specific prevalence per 100 persons	43–54 55–64 65–74 75+	0.1 0.6 1.4 7.1		
Bressler et *al*., 1989[38] (Chesapeake Bay, USA) Design: population-based prospective cohort study (*n* = 755 men only) Outcome: age-specific prevalence per 100 persons	70–79 80+		4.3 13.6	
Mitchell et *al*., 1995[29] (Blue Mountains, Australia) Design: population-based prospective cohort study (*n* = 3654) Outcome: age-specific prevalence per 100 persons	49–54 55–64 65–74 75–84 85+ Total	0.0 0.2 0.7 5.4 18.5 1.9	0.0 0.0 0.6 4.3 12.5 1.3	0.0 0.3 0.9 6.1 21.8 2.4
Ferris et *al*., 1984[8] (Framingham, USA) Design: population-based prospective cohort study (*n* = 2361) Outcome: age-specific prevalence per 100 persons	52–64 65–74 ⩾75 Total	1.2 6.4 19.7 5.7	0.8 4.3 16.9 4.2	1.4 7.9 21.6 6.7
Augood et *al*., 2006[7] (European Eye Study) Design: population-based cross-sectional study (*n* = 5040) Outcome: age-specific prevalence per 100 persons (95% CI)	65–69 70–74 75–79 ⩾80 All	 3.32 (2.52 to 4.13)	0.90 (0 to 2.08) 1.97 (0.77 to 3.17) 4.07 (1.86 to 6.27) 6.94 (1.06 to 12.83) 2.49 (2.07 to 2.91)	1.03 (0.11 to 1.96) 2.36 (1.00 to 3.73) 3.15 (2.02 to 4.28) 15.00 (9.63 to 20.37) 4.00 (2.86 to 5.14)
Buch et *al*., 2001[37] (Copenhagen, Denmark) Design: population-based cross-sectional study (*n* = 944) Outcome: age-specific prevalence per 100 persons (95% CI)	60–64 65–69 70–74 75–80 All	0 (0.0 to 1.6) 0 (0.0 to 1.5) 0.8 (0.1 to 3.1) 2.4 (0.9 to 5.1) 0.85 (0.3 to 1.7)		
Reidy et *al*., 1998[32] (North London, UK) Design: cross-sectional survey (*n* = 13,371) Outcome: prevalence per 100 persons (95% CI)	⩾65	8 (5.8 to 10.8)		

higher prevalence rates in all age groups than males, although specific rates varied between the different studies. The overall prevalence for all persons ranged from 0.85% for those aged 60–80 years[37] to 8% for those aged over 65 years,[32] reflecting differences in the characteristics of populations included and methodology of the studies and the definition of AMD. Augood and colleagues[7] also noted a difference in prevalence between the different countries involved in their study, with prevalence rates ranging from 1.34% (95% CI 0.42 to 2.23%) in Spain to 4.71% (95% CI 2.44 to 6.97%) in Greece.

Two studies examined the prevalence of neovascular AMD (*Table 5*).[7,27] Owen and colleagues[27] pooled prevalence rates for neovascular AMD for people aged 65–79 years,[28–31,33–36] estimating a prevalence of 1.05% (95% CI 0.57 to 1.52%). The meta-analysis showed that women had a higher prevalence (1.03%; 95% CI 0.49 to 1.58%) than males (0.81%; 95% CI 0.52 to 1.11%). Owen and colleagues[27] noted differences in the prevalence rates between the included studies. Prevalence rates for males aged 65–79 years ranged from 1.45% (95% CI 0.56 to 2.34%) from the Beaver Dam Eye Study[28] to 0.53% (95% CI 0.14 to 0.92%) in the Rotterdam Eye Study,[33] although the differences were not statistically significant. In contrast, the differences in the prevalence of neovascular AMD for females aged 65–79 years were statistically significant, with prevalence ranging from 2.14% (95% CI 1.23 to 3.04%) in the Beaver Dam Eye Study[28] to 0.50% (95% CI 0.18 to 0.83%) in the Rotterdam Eye study.[33] Owen and colleagues[27] also found that prevalence increased with age group, ranging from under 1% for those aged less than 75 years to 11.27% for those aged 90 years and older. Augood and colleagues[7] found similar relationships between age, sex and the prevalence of neovascular AMD. The overall prevalence of neovascular AMD was 2.29% (95% CI 1.73 to 2.86%).

Burden of disease

Despite the lack of information on the epidemiology of AMD and its neovascular form, the data on the incidence and prevalence found provide some indication of the likely need and demand for treatment. The review of the epidemiology showed differing incidence and prevalence rates depending on the nature of the study and the characteristics of the population examined. Using the studies of the incidence and prevalence that had similar designs and population estimates for England and Wales,[39] it is possible to provide some provisional estimates of the number of people who might require treatment and care (*Table 6*). Given the differences in the studies, it will be important to interpret the figures with caution. Estimates of the incidence of AMD suggested that there could be between 18,000 and 46,000 new cases annually in England and Wales, with between 13,000 and 37,000 cases of neovascular AMD. Estimates of the prevalence of AMD ranged from around 70,000 to 300,000 cases, with the actual prevalence thought to be closer to the higher estimate. For neovascular AMD, the estimated prevalence was thought to be

TABLE 5 *Age-specific prevalence of neovascular AMD*

Study	Age group (years)	Persons	Male	Female
Owen *et al.*, 2003[27]	<50	0.0 (0.0 to 0.18)		
Age-specific prevalence (%) (95% CI)	50–54	0.06 (0.0 to 0.32)		
Design: systematic review of	55–59	0.03 (0.0 to 0.19)		
population-based studies (6 studies,	60–64	0.26 (0.12 to 0.49)		
n = 22,206)	65–69	0.33 (0.16 to 0.59)		
Outcome: age-specific prevalence per	70–74	0.85 (0.55 to 1.27)		
100 persons (95% CI)	75–79	2.29 (1.70 to 3.02)		
	80–84	4.65 (3.49 to 6.05)		
	85–89	6.99 (4.73 to 9.88)		
	90+	11.27 (6.58 to 17.65)		
Augood *et al.*, 2006[7]	65–69		0.38 (0 to 1.01)	0.92 (0.04 to 1.80)
(European Eye Study)	70–74		1.40 (0.51 to 2.29)	1.42 (0.34 to 2.50)
Design: population-based cross sectional	75–79		2.63 (0.78 to 4.49)	2.17 (0.96 to 3.37)
study (*n* = 5040)	⩾80		5.56 (0 to 11.48)	10.50 (6.65 to 14.35)
Outcome: age-specific prevalence per	All	2.29 (1.73 to 2.86)	1.69 (1.11 to 2.27)	2.78 (2.09 to 3.47)
100 persons (95% CI)				

TABLE 6 *Estimates of the number of patients with AMD in England and Wales*

Study	Age group (years)	Absolute annual incidence or prevalence of AMD (per 100 people)	Population in England and Wales (mid-2004)[39]	No. of AMD patients
Incidence				
AMD				
Klaver *et al*., 2001[5]	55 and over	0.12	14,811.6	17,774
Van Leeuwen *et al*., 2003[6]	55 and over	0.148	14,811.6	21,921
Klein *et al*., 2002[24]	43–84	0.21	22,122.6	46,457
Mitchell *et al*., 2002[25]	49 and over	0.22	18,719.5	41,183
Neovascular AMD				
Van Leeuwen *et al*., 2003[6]	55 and over	0.088	14,811.6	13,034
Mitchell *et al*., 2002[25]	49 and over	0.2	18,719.5	37,439
Prevalence				
AMD				
Mitchell *et al*., 1995[29]	49 and over	1.94	18,719.5	72,632
Augood *et al*., 2006[7]	65 and over	3.32	8,579.3	284,833
Buch *et al*., 2001[37]	60–80	0.85	9,246.5	78,595
Neovascular AMD				
Augood *et al*., 2006[7]	65 and over	2.29	8,579.3	196,466

TABLE 7 *Predicted prevalence of neovascular AMD (in thousands) (95% CI) for 2001 and 2011 in the UK*[27]

Age range (years)	2001	2011
50–54	2 (0 to 13)	2 (0 to 13)
55–59	1 (0 to 6)	1 (0 to 7)
60–64	7 (3 to 14)	10 (5 to 19)
65–69	8 (4 to 15)	10 (5 to 18)
70–74	20 (13 to 30)	21 (13 to 31)
75–79	45 (33 to 59)	45 (33 to 59)
80–84	61 (46 to 79)	67 (50 to 87)
85–89	53 (36 to 74)	60 (41 to 85)
90+	47 (27 to 74)	55 (32 to 86)
Total	245 (163 to 364)	271 (179 to 405)

Adapted from Owen and colleagues.[27]

around 200,000 cases. Owen and colleagues[27] have applied prevalence data from their meta-analysis to the UK population trend data to assess the burden of neovascular AMD (*Table 7*). They estimated that there were 245,000 (95% CI 163,000 to 364,000) people with neovascular AMD in the UK in 2001. It was estimated that the prevalence of neovascular AMD would increase by 2011 with 271,000 (95% CI 179,000 to 405,000) cases.

Meads and colleagues[40] provided estimates for the incidence and prevalence of AMD and neovascular AMD for a standard health authority with a population of 500,000. They estimated a 1-year incidence for AMD ranging from 186 to 537 cases and for neovascular AMD from 103 to 158 cases. Meads and colleagues thought that the prevalence of neovascular AMD would be approximately 1946 cases in a standard health authority.

Impact of health problem

Previous studies have suggested three main impacts of AMD for patients:

- increased risks of mortality and reduced life expectancy
- increased morbidity, particularly in relation to accidents and psychological ill-health
- reduced quality of life.

Studies have also demonstrated that patients with visual impairment tend to have longer hospitalisations,[41] make greater use of health and community care services[42] and are more likely to be admitted to nursing homes.[43]

In a population cohort aged 49 years or older at baseline, the Blue Mountains Eye study reported age- and sex-standardised 7-year cumulative mortality rates of 26% for people with visual impairment compared with 16% for those without visual impairment.[44] The relative risk of mortality associated with visual impairment was 1.7 (95% CI 1.2 to 2.3) after adjusting for factors such as age,

male sex, low self-rated health and low socio-economic status found to be significantly associated with mortality. Studies that have investigated associations between visual impairment and mortality for people with AMD or other causes of vision loss[45,46] suggest that AMD is not an independent risk factor for mortality. In a retrospective analysis of the standard analytical sample of Medicare beneficiaries,[47] Zhou and colleagues[45] estimated a 50% excess mortality for people with wet AMD and blindness compared with those in the dataset without an AMD diagnosis, but no excess mortality for people with AMD and less severe vision loss. In contrast, Thiagarajan and colleagues[46] found that adjusting for confounding factors reduced the mortality rate ratio for people with any cause of visual impairment from 1.6 (95% CI 1.47 to 1.74) to 1.17 (95% CI 1.07 to 1.27). For people whose impairment was due to AMD or cataract, there was no excess all-cause or cardiovascular mortality following adjustment.

A number of studies have reported on the association between falls or fall-related fracture and visual impairment.[48–54] Legood and colleagues[50] summarised the evidence from 20 studies assessing falls (of which eight related to hip fractures). The majority of the studies were in elderly populations and found that those with reduced visual acuity were 1.7 times more likely to have a fall and 1.9 times more likely to have multiple falls. The odds of a hip fracture were found to be between 1.3 and 1.9 times greater for those with reduced visual acuity. Ivers and colleagues[51] found that visual impairment was strongly associated with risk of hip fracture in the 2 years following eye examination, but not over a longer period. None of these studies was specific to visual impairment due to AMD.

Several studies have identified a strong association between low vision and depression,[55–60] with prevalences of between 7%[59] and 39%[60] for major depression. Prevalence estimates for all depression are typically around 30%.[55,57–59] These are substantially higher (two to four times) than among control groups within studies[57] or in similar community-dwelling populations without visual impairment[55] and are comparable with those reported by people with other chronic illnesses.[56] Depression in elderly patients with reduced vision has been shown to be independently associated with functional impairment,[57,58,60] suggesting that treatment of depression may reduce disability irrespective of the level of vision loss.

Studies have reported that quality of life scores, using either generic or condition-specific instruments, are lower for people with AMD than those without disease.[56,61–64] The results of studies using generic instruments have generally been less consistent than those using instruments based on visual function. For example, Hassell and colleagues[65] reported that mean Short Form with 12 Items (SF-12) scores for physical and mental health were similar to those reported for Americans of a similar age group from the general public. A complication of any simple view of declining quality of life with vision loss secondary to AMD is the recognition of patients' ability to adapt to vision loss and cope with disability.[66,67] A full review of the literature on quality of life and AMD is included in the section 'Review of research on quality of life in AMD' (p. 46).

Measurement of disease

Initial signs and symptoms of AMD include recent change in visual function affecting reading and face recognition, difficulties with change of lighting and distortion. Some people experience a dark patch on waking that fades rapidly. Assessment of visual function includes measurement of visual acuity, contrast sensitivity and visual field measurement. Other tests may include reading performance, colour contrast sensitivity, flicker sensitivity, macular sensitivity and adaptation.[68]

Visual acuity

Visual acuity can be defined as the capacity of the visual system to resolve fine detail and, specifically, to read small high-contrast letters.[69] It is a measure of the minimum angle of resolution (MAR),[70] which in normal vision is accepted as 1 minute of arc (1 minute of arc is 1/60th of a degree, 360° in a circle).[40] A number of charts are used to measure visual acuity. The most widely used is the Snellen chart, which consists of seven rows of letters which become smaller down the chart, and the smallest line of letters correctly read is recorded. In each row of letters the width of the lines forming the letter subtends an angle of 1 minute of arc at a certain specific distance.[40] For the largest letter the distance is 60 m, the next line is 36 m, then 18, 12, 9 and 6 m, and for the smallest letter 4 m. The outcome is expressed as a pseudofraction, where the numerator describes the chart viewing distance (usually 6 m in Europe and 20 ft in the USA). The denominator refers to the 'size' of the letter as measured in distances. Normal vision is assumed to be 6/6 (or 20/20 if measured in feet). If a person could only read the top line of the chart when at a distance of 6 m,

their visual acuity would be recorded as 6/60. This can be interpreted as the person being able to see at 6 m what someone with normal vision could see from 60 m away. If they are unable to read the largest letter on the chart they are moved closer, so, for example, 3/60 would mean they could read the largest letter at 3 m.

The Snellen chart has a number of limitations:

- The number of letters per row varies from one letter (6/60) to 8+ (6/4). It is easier to read a letter on its own than one surrounded by other letters (known as 'crowding' or 'contour interaction').[69]
- The spacing of the letters on each row bears no systematic relationship to the letter width, and the vertical spaces between the rows of letters are not logically related to the height of the letters. This means the contour interaction varies between rows, which affects the difficulty of the task.[69]
- There is an irregular progression of letter sizes. For example, 6/5 to 6/6 represents an increase in size of 120%, whereas the jump from 6/36 to 6/60 is 167%. Statements such as 'a two-line change in acuity' are meaningless, because it will depend on where those two lines are.[69]
- The chart is scored by recording the lowest line of letters which the patient can recognise. Sometimes the patient can read some letters but not others on a given line, and if this spreads over more than one line there is no satisfactory way of recording the result.[69]

The Bailey–Lovie chart has emerged as the preferred alternative to the Snellen chart, and employs the letter set specified in the British Standard.[70] It has five letters on each row, which ensures that the task is equivalent for each row, helps to ensure equal contour interaction and provides more letters for patients with poorer visual acuity. The letter spacing on each row is equal to one letter width and the row spacing is equal to the height of the letters below, so contour interaction is scaled in relation to letter size. Regular progression of letter sizes allows inter-line interpolation, improving the precision of the measurement. The letter size follows a logarithmic progression, increasing in 0.1 logMAR ($\log_{10}$ of the MAR) steps. Normal vision (6/6) equates to a logMAR of 0, with negative scores for smaller letter sizes (see *Table 8* for Snellen equivalents). Other logMAR charts are available; most cover the range –0.30 (6/3) to +1.00 (6/60). The drawbacks of the Bailey–Lovie and logMAR charts are that some mental arithmetic is required for the inter-line interpolation scoring, and also that good visual acuity is represented by negative logMAR scores which may seem counterintuitive.[70] Visual acuity rating (VAR) has been proposed as an alternative method of scoring to avoid these drawbacks, and is calculated as VAR = 100 – (50 × logMAR). With this system, normal vision (6/6 or logMAR 0) would score 100, 6/60 (logMAR 1.0) would score 50 and 6/3 (logMAR –0.3) would score 115.[70]

A chart developed for the Early Treatment Diabetic Retinopathy Study (ETDRS) is a variant of the Bailey–Lovie chart and is used in the ranibizumab and pegaptanib trials. The letters in the ETDRS chart area are all square, whereas the letters of the Bailey–Lovie chart are rectangular.

TABLE 8 *Snellen and logMAR equivalents*[69,71]

Snellen (m)	Snellen (ft)	LogMAR	VAR	Notes
6/3	20/10	–0.3	115	
6/6	20/20	0.0	100	Normal vision
6/7.5	20/25	0.1	95	
6/9	20/30	0.2		Legal limit for driving
6/12	20/40	0.3	85	
6/15	20/50	0.4	80	
6/18	20/60	0.5		
6/24	20/80	0.6	70	
6/30	20/100	0.7	65	
6/36	20/120	0.8		
6/60	20/200	1.0	50	Legal blindness in USA (used in trials)
6/96	20/320	1.2	40	
6/120 (3/60)	20/400	1.3	35	UK definition of severely sight impaired (blind)
6/240	20/800	1.6	20	

Contrast sensitivity

Contrast sensitivity refers to the ability of the visual system to distinguish between an object and its background. A person with low contrast sensitivity may have vision difficulties such as trouble seeing traffic lights or cars at night, not being able to see spots on clothes, counters or dishes, missing facial gestures, not seeing whether a flame is burning on a stove or needing a great deal of light to read. Whereas acuity measures only size, contrast sensitivity measures two variables, size and contrast. Contrast sensitivity readings are presented as a curve, which plots the lowest contrast level at which a person can detect a target of a given size. The higher the contrast sensitivity, the lower is the contrast level at which an object can be seen.[72] The Pelli–Robson chart was developed to measure contrast sensitivity in a clinical setting. It can be used in a similar way to visual acuity letter charts and has been shown to be reliable and sensitive.[68]

Visual field

The visual field is the total area in which objects can be seen in the peripheral vision while the eye is focused on a central point. Perimetry is the systematic measurement of differential light sensitivity in the visual field by the detection of the presence of test targets on a defined background.[73] In a confrontation visual field examination, a basic evaluation of the visual field is undertaken by the patient looking at the examiner's eye and stating when the examiner's hand can be seen. Perimetry more carefully maps and quantifies the visual field. With Goldmann or kinetic perimetry, the patient stares at a central target and an object is brought into the peripheral vision until it can be seen. Static automated perimetry involves a computer-driven programme, which flashes small lights of different brightness at different locations within a dome. A button is pressed when the patient can see the small lights. The patient's responses are compared with age-matched controls to determine the presence of defects within the visual field. Scanning laser ophthalmoloscopy provides an accurate means of determining visual field extent and assessing foveal and eccentric fixation (where the image falls outside the macula).[68] The ophthalmoscope takes a picture of the patient's retina and is able to map exactly where scotomas (holes in vision) exist. However, this is usually used as a research tool, and is not used routinely in clinical practice due to resource constraints.

Amsler grid

An Amsler grid is a detection method for patients. It consists of a grid of thick back lines and can be used to detect subtle abnormalities in central vision caused by fluid in the subretinal space. Macular abnormalities may be manifested as distortions in the lines of the grid.[3]

Definition of blindness

In the UK, patients are registered as severely sight impaired (blind) or sight impaired (partially sighted) using the Certificate of Vision Impairment (CVI). The National Assistance Act 1984 states that a person can be certified as severely sight impaired if they are 'so blind as to be unable to perform any work for which eye sight is essential'. This is assessed by testing visual acuity with appropriate spectacle correction if necessary. People can be certified as severely sight impaired if their visual acuity falls into one of three groups:[74]

- below 3/60 Snellen
- 3/60 but below 6/60 Snellen, and have a very contracted field of vision
- 6/60 Snellen or above, and have a contracted field of vision especially if the contraction is in the lower part of the field.

There is no legal definition of sight impairment. The guidelines are that a person can be sight impaired if they are 'substantially and permanently handicapped by defective vision caused by congenital defect or illness or injury'. To be certified as sight impaired (partially sighted), visual acuity should be:[74]

- 3/60 to 6/60 Snellen with a full visual field
- up to 6/24 Snellen with moderate contraction of the field, opacities in media or aphakia (absence of eye's lens)
- 6/18 Snellen or above but with a gross defect, for example hemianopia, or if there is a marked contraction of the visual field.

Current service provision

Management of disease

Treatment options for people with AMD are limited. For most patients with AMD, management consists of social support, visual rehabilitation and provision of low-vision aids. For those with extrafoveal CNV, laser photocoagulation therapy may be used to halt the rapid vision loss caused by the proliferation of blood vessels; however, only a small proportion of patients with wet AMD present with extrafoveal lesions.[11] Laser photocoagulation uses high-intensity thermal energy to coagulate CNV; however, it does not restore lost vision.[75]

The main limitations of photocoagulation are first that only 10–15% of all neovascular lesions are small enough and sufficiently delineated to be eligible. Second, there is at least a 50% chance that leakage will recur during the following 2 years. Third, at least half of patients have some CNV beneath the centre of the fovea, and laser treatment leads to an immediate reduction in central vision.[3] It is rarely used as the first treatment choice for subfoveal CNV due to associated loss of vision.[76]

Photodynamic therapy (PDT) involves intravenous injection of verteporfin, a photosensitive drug that remains in the new blood vessels, before treatment with a low-powered laser that activates the drug causing cell death.[40] The aim is to destroy CNV lesions without damaging the overlying retina, thereby slowing or halting the progression of vision loss. PDT with verteporfin has been recommended by the National Institute for Health and Clinical Excellence (NICE)[77] for the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal CNV, and for the subgroup with predominantly classic subfoveal lesions in the context of clinical trials. The main disadvantages include: the photosensitive drug remains in the body for up to 48 hours, therefore patients are required to avoid direct sunlight; adverse events from injection of the drug; long-term effects are unknown; recurrence is common; and overdose of the drug or laser can result in permanent irreversible vision loss.[40] Moreover, although PDT may be effective in treating established pathological vessels, it does not prevent new vessel formation.[78]

Bevacizumab (Avastin®, Roche) may be used off-label for AMD,[79] although its use is controversial.[80] Off-label use means that the licensed drug is used for an indication other than the one for which is it labelled. Bevacizumab is a humanised monoclonal antibody against vascular endothelial growth factor (VEGF) and is biologically similar to ranibizumab, being derived from the same mouse monoclonal antibody precurser.[81] It is licensed for first-line treatment of metastatic colorectal cancer and is given by intravenous infusion.[82] Intravitreal bevacizumab for AMD is currently widely used in private practice (Lotery A, Southampton University Hospitals Trust: personal communication, August 2006) and is beginning to become available on the NHS.[83] There is no long-term information on safety and efficacy, and the minimum effective dose, optimum dose and dose frequency are not known. However, preliminary data are described by the Royal College of Ophthalmologists as 'encouraging'.[83]

Current service cost

Diagnosis of AMD requires a specialist consultation during which a detailed history identifying changes in visual function and a clinical examination (including assessment of visual acuity, Amsler grid and slit lamp fundus examination) should be conducted. FA may be required to confirm diagnosis and should always be undertaken prior to initiating active treatment. Costs of diagnosing neovascular AMD are estimated based on the NHS Reference Cost[84] for an initial outpatient attendance for ophthalmology and for FA (outpatient HRG B01op). Annual costs of diagnosing and confirming neovascular AMD, assuming the range of new cases per year in England and Wales, estimated in the section 'Burden of disease' on pp. 7–8 of between 13,000 and 37,000, would be between £2.9 million and £8.2 million.

A number of estimates of the cost of PDT in UK practice have been reported as part of cost-of-illness studies[85] or within economic evaluations of PDT.[40,86,87] Although the categories of cost included have been the same in all cases, there are slight differences in unit costs and assumed treatment intensity that have given rise to differences in the estimated cost of PDT, from £4015 for 1 year of treatment[86] to between £6545[85] and £6666[40] for 2 years.

Bonastre and colleagues[85] estimated that there would be 4655 new cases per year eligible for PDT in the UK, based on the assumption that 15% of all new cases of AMD were of the neovascular form and that 30% of these would be eligible for PDT. Combining this with the estimated cost for 2 years of PDT treatment they derived a budget impact of PDT treatment of €51.0 million (£30.5 million) for a cost year of 2001, or €35.4 million (£21.2 million) for 1 year of treatment. Meads and colleagues[40] derived an estimate of £20.1 million, for the first year of treatment for a cohort of 5000 new cases of classic AMD in England and Wales, assuming the same frequency of treatment as in the TAP study.[10,88] Assuming that patients continue to receive PDT in the second and third years, and that treatment is initiated for a further 5000 new cases each year, costs would rise to £33.1 million in the second year and £41.3 million in the third year.

As discussed in the previous section, PDT is only recommended for a proportion of patients with

TABLE 9 *Unit costs and uptake of low vision aids and low vision rehabilitation in UK*

	Meads and colleagues[40]		Bonastre and colleagues[85]	
	Unit cost (£)	Uptake (%)	Unit cost (£)	Uptake (%)
Low-vision aids	136.33	33	30	90
Low-vision rehabilitation	205.30	11	251	20

the wet form of AMD – those with classic with no occult or predominantly classic subfoveal lesions. For patients experiencing vision loss secondary to other forms of wet AMD, current service provision consists of low-vision rehabilitation and the provision of low-vision aids. Estimates of the cost of low-vision rehabilitation and of low-vision aids for the UK are variable (*Table 9*).

On the basis of these assumptions and a prediction of 103,437 new cases of AMD per year, Bonastre and colleagues[85] estimated the annual cost of low-vision rehabilitation for the UK at €5.2 million (£3.1 million) and low-vision aids at €2.8 million (£1.7 million). Meads and colleagues[40] estimated that it would cost £5.4 million to provide low-vision aids and low-vision rehabilitation to all new wet AMD patients in England and Wales.

Relevant national guidelines

The most recent guidelines from the Royal College of Ophthalmologists were published in 2000.[23] They are now considered to be out of date and are in the process of being updated. Definitive guidelines will be published following the appraisal of ranibizumab and pegaptanib for AMD by NICE, but in the meantime interim guidelines are being produced. The current draft AMD interim guidelines make the following recommendations for the treatment of subfoveal CNV, but these may be updated before the definitive guidelines are produced (Wong D, Royal College of Ophthalmologists: personal communication, November 2006):

- Predominantly classic subfoveal CNV: patients may be offered PDT in the first instance. Where there is poor response to treatment in the treated eye, or in the other eye previously, trial of licensed anti-VEGFs may be used where available. In the absence of such availability, then the use of unlicensed products including Avastin may be justified.
- Occult subfoveal CNV: PDT may be considered for occult no classic CNV if costs are covered by local commissioning arrangements. In the absence of such arrangements, then the use of anti-VEGFs is recommended as above.
- Minimally classic subfoveal CNV: PDT is not recommended. Intraocular injections of anti-VEGFs should be considered as first-line treatment.
- When recommending intraocular bevacizumab, it is extremely important to inform patients that it is unlicensed for this indication and that it has not undergone the usual rigorous clinical trials and independent evaluation by regulatory authorities. Adequate follow-up information must also be maintained on these patients, and recorded appropriately.

Description of technology under assessment

Summary of interventions

Ranibizumab

Ranibizumab (Lucentis, Genentech, Inc. (USA)/Novartis Pharmaceutical Ltd) was approved by the US Food and Drug Administration (FDA) for the treatment of patients with neovascular (wet) AMD in June 2006. A UK licence for the improvement and maintenance of visual acuity and function and for the reduction of vascular leakage and retinal oedema in patients with wet AMD is expected at the end of 2006. Ranibizumab is a humanised therapeutic antibody fragment designed to bind and inhibit vascular endothelial growth factor-A (VEGF-A). Ranibizumab is designed to block new blood vessel growth and leakiness, which lead to wet AMD disease progression and vision loss.[89] It is administered at a dose of 0.5 mg (0.05 ml) by intravitreal injection once per month according to the product prescribing information.[90] [**Commercial-in-confidence (CIC) data removed**].[91] Contraindications are ocular or periocular infections and hypersensitivity. Endophthalmitis (severe infection inside the eye) and retinal detachments may occur following intravitreal injections, therefore patients should be monitored during the week following the injection. Increases in intraocular pressure have been noted within

60 minutes of injection with ranibizumab, therefore both intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately. There is a theoretical risk of arterial thromboembolic events as a low rate (<4%) was observed in the clinical trials. The most common adverse reactions (reported ⩾6% higher in ranibizumab-treated subjects than control subjects) are conjunctival haemorrhage, eye pain, vitreous floaters, increased ocular pressure and intraocular inflammation.[90]

Pegaptanib

Pegaptanib sodium (Macugen, Pfizer Ltd) was granted marketing authorisation by the European Medicines Agency on 31 January 2006 for the treatment of neovascular (wet) AMD. Pegaptanib is a pegylated modified oligonucleotide that binds with high specificity and affinity to extracellular vascular endothelial growth factor (VEGF165), inhibiting its activity. VEGF165 is the VEGF isoform preferentially involved in pathological ocular neovascularisation. Pegaptanib blocks VEGF165 so there is less growth of blood vessels and less bleeding and leakage. It is administered at a dose of 0.3 mg once every 6 weeks (nine injections per year) by intravitreal injection into the affected eye.[92] Contraindications are active or suspected ocular or periocular infection and hypersensitivity. Transient increases in intraocular pressure may be seen with intravitreal injections, therefore the perfusion of the optic nerve should be verified and elevation of intraocular pressure should be managed appropriately post-injection. Immediate and delayed intravitreous haemorrhages may occur following pegaptanib injections. The incidence of endophthalmitis, which is associated with intravitreal injection procedures, was found to be 0.1% per injection in clinical trials. Cases of anaphylaxis/anaphylactoid reactions, including angioedema, have been observed within several hours after administration in post-marketing experience. Serious ocular adverse events reported in clinical trials included retinal haemorrhage (<1%), vitreous haemorrhage (<1%) and retinal detachment (<1%). Very common (⩾1/10) ocular adverse reactions were anterior chamber inflammation, eye pain, increased intraocular pressure, punctate keratitis, vitreous floaters and vitreous opacities.[92]

Place in the treatment pathway

Ranibizumab and pegaptanib would be administered as soon as possible after diagnosis to minimise damage. Guidelines from the American Academy of Ophthalmology report the criteria for treatment with pegaptanib as described in the trial publications.[76] Both drugs can be given in combination with PDT with verteporfin, and a change in treatment regimen, for example from PDT with verteporfin to pegaptanib or vice versa, may be appropriate depending on the clinical response of a given patient.[76] Ranibizumab and pegaptanib are administered for as long as the patient benefits, but how this is determined in practice has not yet been agreed.

Current usage in the NHS

A UK licence for ranibizumab is expected towards the end of 2006 and it is therefore not currently available on the NHS, although it may be obtained on a named patient basis (Lotery A, Southampton University Hospitals Trust: personal communication, August 2006). Pegabtanib was licensed in the UK in January 2006, but it has not been made widely available on the NHS. The availability of pegaptanib on the NHS has been highlighted by the media, with headlines such as 'thousands denied eye drug over NHS costs' and claims that Primary Care Trusts are waiting for NICE to make a ruling on its effectiveness before they approve the treatment.[93,94]

Anticipated costs associated with intervention

The net price for a 300-μg vial of pegaptanib quoted in the current BNF[82] is £514. The recommended frequency of administration at this dosage is every 6 weeks. This corresponds to nine injections per year giving an annual acquisition cost of £4626. The net price for a 0.3-ml vial of ranibizumab is £761.20. If injections were provided monthly, as in the registration trials, this would correspond to 12 injections per year, at an annual cost of £9134. However, lower frequency of injection regimes have been proposed by the manufacturer.

In addition to the drug acquisition are costs of administration of the drugs, since intraocular injection requires aseptic procedures beyond those required for a standard outpatient appointment, and patient monitoring. Patients require FA prior to initiation of treatment to type and localise the lesion, and would be expected to have further FA at least once every 6 months while on treatment. Patients would also have optical coherence tomography and a vision assessment at each follow-up visit. It is anticipated that patient follow-up and drug administration would typically be carried out in outpatients. Assuming the frequency of dosage for each drug described above, and that the initial outpatient appointment to assess patients and initiate

TABLE 10 *Cost of first year of treatment with pegaptanib and ranibizumab*

	Outpatient		FA	OCT	Drug	Injection procedure	Total
	Initial visit and vision assessment	Follow-up and vision assessment					
Unit cost (£)	154.20	117.52	124.88	50.86		90.20	
Pegaptanib (£)	154.20	940.16	249.75	457.74	4,626	811.80	7,240
Ranibizumab (£)	154.20	1,292.72	249.75	610.32	9,134	1,082.40	12,254

OCT, optical coherence tomography.

treatment would be longer than follow-up appointments, the cost of 12 months of treatment with pegaptanib would be £7240 whereas 12 months of treatment with ranibizumab would cost £12,254 (*Table 10*).

Intraocular injections are associated with adverse events, some of which will require treatment. Clinical trials reports on each drug[95–97] show similar proportions of patients experiencing adverse effects associated with intraocular injection. Adverse events include endophthalmitis (1.4% patients), retinal detachment (0.4–0.7%) and lens damage (0.4–0.67%). Each of these is associated with treatment costs (from £1400 for lens damage to £2500 for endophthalmitis) and risk of severe vision loss for an individual patient, particularly for endophthalmitis. However, given the low event rates (0.07–0.16% per injection for pegaptanib[95]), on average these costs are minor compared with the costs of treatment described above.

Both pegaptanib and ranibizumab have annual costs greater than would be predicted for PDT with verteporfin (using the treatment intensity of 3.4 PDT treatments in the first year of the TAP study[10] and costing assumptions outlined in the section 'Current service cost', p. 12, the cost of the first year of PDT would be £4551). Since both drugs are likely to be indicated for all patients with neovascular AMD, rather than the selected subgroups identified in the TAP study[88] (and as recommended by NICE[77]), the budget impact is likely to be substantially higher than suggested by this comparison of annual costs of treatment. Ophthalmology services may anticipate an approximate tripling in the number of patients eligible for active treatment of neovascular AMD, using the assumption adopted by Bonastre and colleagues[85] that only 30% of incident cases are eligible for PDT. Taking this increase in patient numbers along with the increased frequency of treatment with pegaptanib (6-weekly) and ranibizumab (monthly), compared with PDT (3-monthly), ophthalmology departments estimate that the total workload may increase by 6–7 times its current level. This degree of increase in workload has significant implications on demand for specialist imaging services [FA and optical coherence tomography (OCT)] and capacity for providing vision assessments.

Chapter 2

Definition of the decision problem

Decision problem

The aim of therapy for people with wet AMD is to alter the progression of vision loss and improve vision if possible, but treatment options are limited. The clinical effectiveness and cost-effectiveness of ranibizumab and pegaptanib for AMD remain uncertain.

Interventions

The drugs included in this assessment are ranibizumab and pegaptanib.

Population including subgroups

The study population is adults with subfoveal CNV associated with wet AMD. Subfoveal lesions are the most common type, accounting for almost 80% of lesions.[11]

Potential subgroups can be described according to the appearance of the lesion (classic no occult, predominantly classic, minimally classic or occult no classic); however, the interpretation of FA may differ between readers,[98] therefore there may be some uncertainty regarding these diagnoses. Comment will only be made on the effectiveness of pegaptanib and ranibizumab for these patients if appropriate subgroup analyses are presented in the included studies.

Relevant comparators

Comparators for the interventions under assessment are those suitable for patients with subfoveal CNV associated with wet AMD used in the NHS. These would be:

1. Best supportive care, which includes provision of and training with low-vision aids, information about support charities (e.g. the Macular Disease Society and local societies for the blind or visually impaired), registration as visually impaired or blind depending on the level of acuity and advice about not smoking and vitamin supplementation.
2. Photodynamic therapy with verteporfin for the subgroup of patients with classic no occult subfoveal wet AMD, in accordance with NICE guidance.[77] PDT has also been recommended for people with predominantly classic subfoveal CNV (≥50% classic CNV with some occult CNV present), but only as part of clinical studies, whereas no recommendation has been made regarding the use of PDT in occult CNV, as the photosensitising agent (verteporfin) was not licensed for this indication when the appraisal began.[77] If insufficient evidence is found using PDT limited to patients with classic no occult CNV, then PDT for patients with predominantly classic subfoveal lesions will be considered.

Sham injection will also be considered as a comparator for the review of clinical effectiveness if insufficient evidence is found using the above comparators. Photocoagulation therapy will not be included as a comparator, because although it may be considered for new or recurrent subfoveal CNV with poor visual acuity, it is rarely used as the first treatment of choice due to associated loss of vision.[76]

Outcomes

Clinical outcomes will include visual acuity, contrast sensitivity, adverse effects of treatment, adherence to treatment, health-related quality of life and costs. Fifteen letters (three lines) on the ETDRS chart is generally accepted as a clinically significant change in visual acuity. This could lead to a significant change in quality of life, and could represent the difference in being able to drive, to live independently and to read or watch television, depending on the starting level of visual acuity. Direct costs will include estimates of all healthcare resources consumed in the provision of the interventions – drug acquisition, administration and monitoring costs – in addition to consequences of those interventions, such as treatment of adverse effects.

Overall aims and objectives of assessment

The aim of this report is to assess the clinical effectiveness and cost-effectiveness of ranibizumab and pegaptanib for subfoveal CNV associated with wet AMD.

Chapter 3

Assessment of clinical effectiveness

Methods for reviewing effectiveness

The *a priori* methods for systematically reviewing the evidence of clinical effectiveness are described in the research protocol (Appendix 1), which was sent to experts for comment. Although helpful comments were received relating to the general content of the research protocol, there were none that identified specific problems with the methods of the review. The methods outlined in the protocol are briefly summarised below.

Search strategy

A sensitive search strategy was developed, tested and refined by an experienced information scientist. Separate searches were conducted to identify studies of clinical effectiveness, cost-effectiveness, quality of life, resource use/costs and epidemiology/natural history. Sources of information and search terms are provided in Appendix 2. The most recent search was carried out in September 2006.

Searches for clinical and cost effectiveness were from database inception to the current date. Electronic databases searched included The Cochrane Database of Systematic Reviews (CDSR), The Cochrane Central Register of Controlled Trials, NHS Centre for Reviews and Dissemination (CRD) (University of York) Database of Abstracts of Reviews of Effectiveness (DARE), Health Technology Assessment (HTA) database and the NHS Economic Evaluation Database (NHS EED), MEDLINE (Ovid), MEDLINE In-Process (Ovid), EMBASE (Ovid), National Research Register, Current Controlled Trials, ISI Proceedings, Web of Science ISI Science Citation Index and BIOSIS. Ophthalmology conferences were searched for recent abstracts (from 2004). The searches were restricted to the English language. Bibliographies of related papers were screened for relevant studies, and the manufacturers' submissions to NICE were assessed for any additional studies. Experts were also contacted for advice and peer review, and to identify additional published and unpublished references.

Inclusion and data extraction process

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two reviewers. The full text of relevant papers was then obtained and inclusion criteria were applied by one reviewer and checked by a second reviewer. Data were extracted by one reviewer using a standard data extraction form and checked by a second reviewer.

Quality assessment

The quality of included RCTs and systematic reviews was assessed using criteria recommended by NHS CRD[99] (Appendix 3). Quality criteria were applied by one reviewer and checked by a second reviewer. At each stage, any differences in opinion were resolved through discussion or consultation with a third reviewer.

Inclusion criteria

Patients

The patients were people with subfoveal CNV associated with wet AMD.

Interventions

Studies reporting the following interventions were eligible for inclusion:

- ranibizumab (Lucentis, Genentech/Novartis Pharmaceuticals UK Ltd)
- pegaptanib sodium (Macugen, Pfizer Ltd)
- combination of the drugs with photodynamic therapy where the licensed indication and evidence allow.

Comparators

Comparators were the following:

1. Best supportive care.
2. For the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal wet AMD, PDT with verteporfin was also a comparator.
3. If insufficient evidence was found using the above comparators, the following comparators were also to be considered:

(a) sham injection (systematic review of clinical effectiveness only)
(b) photodynamic therapy with verteporfin for patients with subfoveal wet AMD with predominantly classic lesions.

Outcomes

Studies were included if they reported one or more of the following outcome measures:

- visual acuity
- contrast sensitivity
- adverse effects of treatment
- adherence to treatment
- health-related quality of life.

Types of studies

Systematic reviews and meta-analyses of randomised controlled trials (RCTs) and RCTs were included. Studies published only as abstracts or conference presentations were considered if sufficient information was presented to allow an appraisal of the methodology and assessment of results. Non-English language studies were excluded.

Full economic evaluations of the specified interventions were also included. A range of designs for studies on quality of life, epidemiology and natural history were considered.

Data synthesis

Data were synthesised through a narrative review with tabulation of results of all included studies. Full data extraction forms are presented in Appendix 4. It was not considered appropriate to combine the included RCTs in a meta-analysis due to heterogeneity in the patient groups and comparator treatments.

Results

Quantity and quality of research available

The number of published papers identified at each stage of the systematic review is shown in *Figure 1*. Selected references which were retrieved but later excluded are listed in Appendix 5. Abstracts of RCTs eligible for inclusion but which reported insufficient details to allow an appraisal

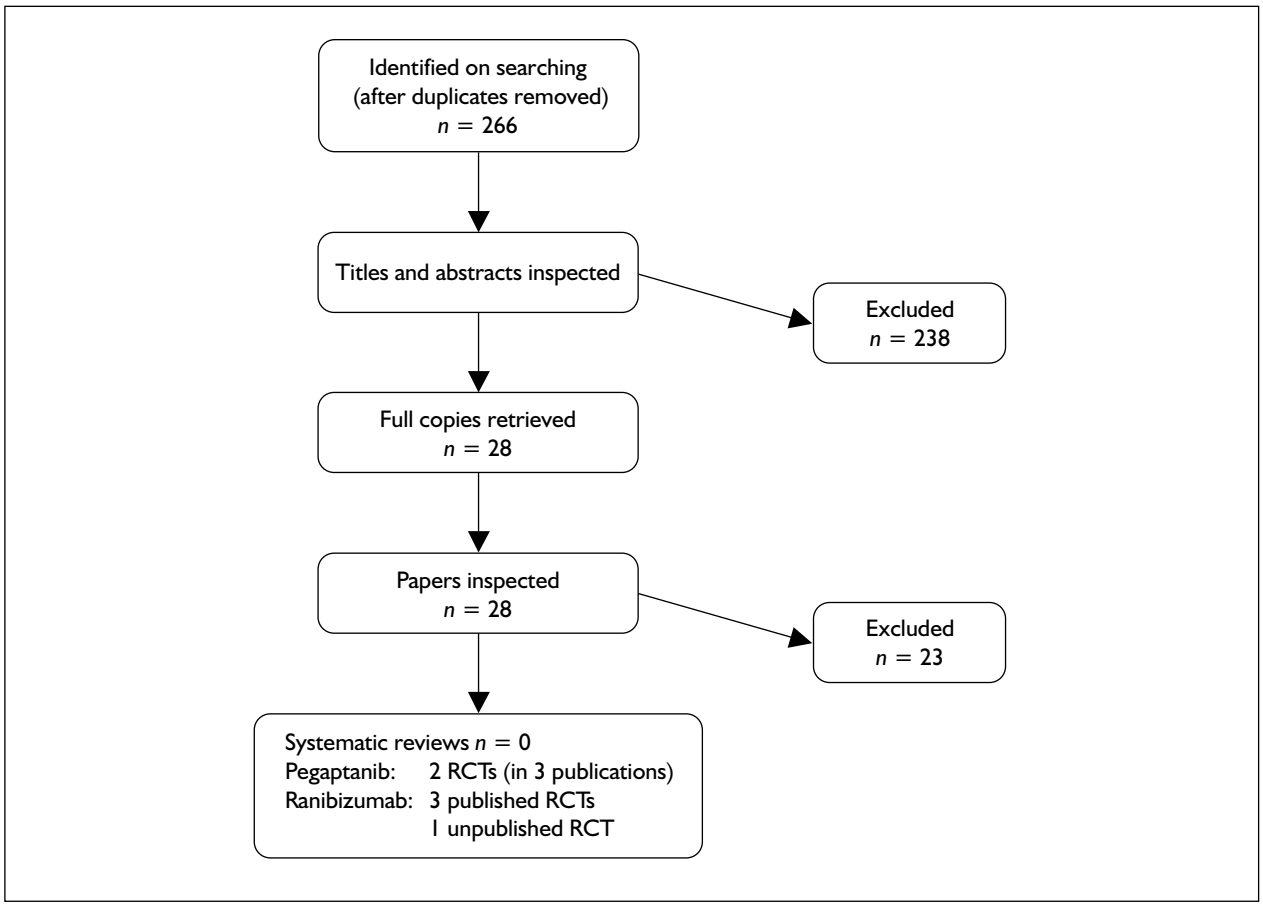

FIGURE 1 *Flowchart of identification of published studies for inclusion in the systematic review of clinical effectiveness*

of the methodology and assessment of the results are listed in Appendix 6. A list of ongoing studies is given in Appendix 7.

The searches identified three full publications[95,100,101] which reported the combined results of two RCTs of pegaptanib (the VISION study). Three fully published RCTs[96,97,102] of ranibizumab were identified. In addition, the ranibizumab manufacturers supplied full reports of one unpublished RCT of ranibizumab, and also full details and further results for the published RCTs. The key characteristics of the included studies are shown in *Table 11*. Further details are provided in the data extraction tables in Appendix 4. Industry submissions were received from Pfizer Ltd (pegaptanib) and Novartis Pharmaceuticals UK Ltd (ranibizumab); a critique of these is presented in Appendix 8.

The pegaptanib VISION study publications[95,100,101] reported the combined results of two concurrent RCTs [one in the USA and Canada (study 1004) and the other at centres worldwide (study 1003)]. The studies compared 0.3-mg (the licensed dose), 1.0-mg and 3.0-mg doses of pegaptanib with sham injection. Patients were also permitted to receive PDT where appropriate. At year one, both trials showed a significant difference between 0.3 mg of pegaptanib and the sham injection for the primary efficacy end-point (visual acuity loss of <15 letters), so the patients from the two trials were combined for analysis, as stated in the protocol, giving a total of 1208 patients. However, it has been noted that although study 1004 demonstrated efficacy at 2 years, study 1003 did not show efficacy for any of the active doses at 2 years.[103,104] Inclusion criteria for this study allowed patients with all angiographic subtypes of lesions to be eligible for the trial. Approximately 24–27% of the patients had predominantly classic (≥50% classic) lesions, between 34% and 38% had minimally classic (<50% classic) lesions and 38–40% had lesions classified as occult with no classic. The lesion subtypes were well balanced between treatment arms.

After 54 weeks, pegaptanib patients in the VISION study[100,101] were re-randomised to receive continued therapy or to discontinue treatment. Patients who had received sham injection in the first year were re-randomised to discontinue, continue with sham injection or receive one of the three study doses of pegaptanib. Updated safety analyses following the second year of treatment (after re-randomisation)[101] and efficacy data for the second year[100] were reported. The distribution of lesion subtypes in the re-randomised groups was not presented, which is a shortcoming that limits further analysis of these groups.[100]

TABLE 11 *Characteristics of included studies*

Study	Intervention	Participants
Pegaptanib VISION study year 1[95] VISION year 2[100,101] 2 concurrent RCTs 117 centres *Primary outcome*: Proportion losing <15 letters at week 54 *Length of follow-up*: 54 weeks, plus further 48 weeks treatment after re-randomisation	1. 0.3 mg pegaptanib (n = 297) 2. 1.0 mg pegaptanib (n = 305) 3. 3.0 mg pegaptanib (n = 302) 4. sham injection (n = 304) Injections every 6 weeks, total of 9 treatments Patients re-randomised after 54 weeks 0.3 mg: 0.3 mg n = 133 Discontinue n = 132 1.0 mg: 1.0 mg n = 133 Discontinue n = 131 3.0 mg: 3.0 mg n = 125 Discontinue n = 127 Sham: 0.3 mg n = 53 1.0 mg n = 55 3.0 mg n = 57 Sham n = 53 Discontinue n = 54	*Target population*: All angiographic subtypes of lesions *Angiographic subtype of lesion at baseline*: Predominantly classic (≥50% classic): (1) 24%, (2) 26%, (3) 27%, (4) 26% Minimally classic (<50% classic): (1) 38%, (2) 35%, (3) 35%, (4) 34% Occult with no classic: (1) 38%, (2) 38%, (3) 38%, (4) 40%

continued

TABLE 11 *Characteristics of included studies (cont'd)*

Study	Intervention	Participants
Ranibizumab MARINA[97] RCT 96 centres *Primary outcomes*: Proportion losing <15 letters at 12 months; safety and tolerability *Length of follow-up*: 24 months	1. 0.3 mg ranibizumab monthly (n = 238) 2. 0.5 mg ranibizumab monthly (n = 240) 3. Sham injection monthly (n = 238)	*Target population*: Occult CNV or minimally classic CNV *Angiographic subtype of lesion at baseline*: Predominantly classic (≥50% classic): (1) 0.4%, (2) 0%, (3) 0%[a] Minimally classic (<50% classic): (1) 36.1%, (2) 37.9%, (3) 36.6%[a] Occult with no classic: (1) 63.4%, (2) 62.1%, (3) 63.4%[a] Missing: (1) 0, (2) 0, (3) 0.4%[a]
ANCHOR[96] RCT 83 centres *Primary outcomes*: Proportion losing <15 letters; [**CIC data removed**] *Length of follow-up*: 24 months (ongoing)	1. 0.3 mg ranibizumab monthly + sham PDT every 3 months if needed (n = 140) 2. 0.5 mg ranibizumab monthly + sham PDT every 3 months if needed (n = 140) 3. Sham injection monthly + verteporfin PDT every 3 months if needed (n = 143)	*Target population*: Predominantly classic lesions *Angiographic subtype of lesion at baseline*: Predominantly classic (≥50% classic): (1) 95.7%, (2) 96.4%, (3) 98.6% Minimally classic (<50% classic): (1) 3.6%, (2) 3.6%, (3) 1.4% Occult no classic: (1) 0.7%, (2) 0, (3) 0
PIER RCT [**CIC data removed**] *Primary outcomes*: Mean change in best corrected visual acuity; [**CIC data removed**] *Length of follow-up*: 12 months (ongoing)	1. 0.3 mg ranibizumab monthly for 3 doses, then doses every 3 months [**CIC data removed**] 2. 0.5 mg ranibizumab monthly for 3 doses, then doses every 3 months [**CIC data removed**] 3. Sham injection monthly for 3 doses, then doses every 3 months [**CIC data removed**] [**CIC data removed**]	*Target population*: Any lesion type [**CIC data removed**]
FOCUS[102] RCT, single-masked, multi-centre *Primary outcomes*: Proportion losing <15 letters; safety and tolerability *Length of follow-up*: 12 months (ongoing)	1. 0.5 mg ranibizumab[b] monthly + verteporfin PDT (n = 106) 2. Sham injection + verteporfin PDT (n = 56)	*Target population*: Predominantly classic lesions *Angiographic subtype of lesion at baseline*: Predominantly classic (≥50% classic): (1) 65.7%, (2) 66.1% Minimally classic (<50% classic): (1) 30.5%, (2) 26.8% Occult with no classic: (1) 1.9%, (2) 7.1% Unclassified: (1) 1.9%, (2) 0%

[a] The numbers for the lesion subtype of the sham injection group appear to be incorrect in the MARINA publication[97] as they add up to n = 239 not n = 238. [**CIC data removed**].
[b] A lyophilised formulation of ranibizumab was used for the first 12 months.

Patients who were re-randomised to discontinue therapy in the second year were allowed to resume treatment at any point in year two if they had demonstrated benefit from treatment in the first year but then lost 10 or more letters of visual acuity during the second year. Of the 132 patients in the 0.3-mg dose group randomised to discontinue in the second year, 28 (21%) resumed therapy, at a mean of 73.7 [standard deviation (SD) 12.4] weeks into the study. Of the 54 patients who received sham injection in the first year and were randomised to discontinue in the second year, eight (15%) chose to resume therapy (with sham injection). The mean week during which therapy was reinstated was week 72.8 (SD 10.8). Patients who resumed treatment following randomised discontinuation appear to have been included in efficacy analyses in the appropriate 'discontinued' (i.e. as randomised) group.

Two of the ranibizumab RCTs (MARINA and PIER) compared 0.3 and 0.5 mg ranibizumab with sham injection. The MARINA trial used monthly injections of ranibizumab, whereas people in the PIER trial received monthly injections for the first 3 months, followed by a reduced schedule of injections every 3 months. The ANCHOR trial compared 0.3 and 0.5 mg ranibizumab plus sham PDT with sham injection and active verteporfin PDT. The FOCUS trial compared 0.5 mg ranibizumab plus verteporfin PDT with sham injection plus verteporfin PDT. A lyophilised formulation of ranibizumab was used for the first year of the FOCUS trial.

Inclusion criteria for the MARINA trial stated that patients should have occult or minimally classic lesions. Almost two-thirds of the patients had occult with no classic lesions, with the remainder having minimally classic lesions. A single patient had a predominantly classic lesion at baseline. The inclusion criteria for the ANCHOR trial stated that patients should have predominantly classic lesions, and almost all of the patients' lesions were classified as such. [**CIC data removed**]. Although the inclusion criteria of the FOCUS trial stated that patients should have predominantly classic lesions, about one-third of patients had minimally classic or occult with no classic lesions. There was a slight imbalance in the treatment arms for the number of patients whose lesions were classified as occult with no classic (1.9% in the ranibizumab + PDT arm and 7.1% in the sham injection + PDT arm) or minimally classic (30.5% versus 26.8%).

The included trials were quality assessed using standard criteria[99] (*Table 12*). Methodological quality and quality of reporting were generally good in the VISION study,[95] and adequate randomisation would have protected against selection bias.

Baseline characteristics were reported for the VISION study, and the treatment groups were similar at the start of the study.[95] However, when patients were re-randomised at the start of the second year, the resulting groups were unbalanced in terms of visual acuity levels. This was reported to have occurred purely by chance,[100] but might have an underlying influence on outcomes measured at the end of year two. If patients in one treatment group appear to have better visual acuity than others in another group at week 102, their week 54 levels would also have to be

TABLE 12 *Quality assessment of included studies, based on published data*

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	ITT analysis	Withdrawals explained
Pegaptanib										
VISION[95]	Ad	Ad	Rep	Ad	Ad	Ad	Ad	Ad	In	Par
Ranibizumab										
MARINA[97]	Ad	Ad	Rep	Ad	Ad	Ad	Ad	Ad	Ad	Ad
ANCHOR[96]	Un	Un	Rep	Ad	Ad	Ad	Ad	Ad	In	Ad
PIER	[**CIC data removed**]									
FOCUS[102]	Ad	Un	Rep	Ad	Ad	In	Ad	Ad	In	Ad

Ad, adequate; In, inadequate; Par, partial; Rep, reported; Un, unknown.

compared to see if this reflects differences at the start of year two or represents a real treatment difference.

The double-blind VISION study[95] reported adequate masking of assessors, care providers and patients, which would have minimised any performance bias. Appropriate outcome measures were reported, although strict intention-to-treat (ITT) analysis was not performed. Small numbers of patients were missing from the analyses due to not receiving at least one dose of the study drug, or not having a sufficiently standardised assessment of visual acuity completed at baseline. Three patients in the 0.3-mg pegaptanib group, five in the 1.0-mg group, six in the 3.0-mg group and six in the sham injection group were missing for these reasons.

Withdrawals among patients within the assessed population were balanced between the treatment arms in the VISION trials.[95] Approximately 1% of patients receiving pegaptanib or sham injection discontinued owing to adverse events, and approximately 2% of patients receiving either the study drug or the sham injection died. Since both arms lost the same proportion of patients, the results should be free from attrition bias.

The ranibizumab trials were generally of good methodological quality. The MARINA and FOCUS [**CIC data removed**] trials described an adequate method of randomisation which would have protected the studies from selection bias. Baseline characteristics were reported by the published ranibizumab studies [**CIC data removed**], with similar ocular and demographic characteristics in the trial arms (within studies). In the FOCUS study, mean visual acuity was slightly better in the sham + PDT group than in the ranibizumab + PDT group (48.5 versus 45.1 letters). Also, the majority of sham + PDT subjects (53.6%) were male, whereas in the ranibizumab + PDT group the majority of subjects (56.6%) were female. Otherwise, the groups were well balanced in terms of baseline characteristics.

To protect against bias, outcome assessors, care providers and patients in MARINA and ANCHOR [**CIC data removed**] were masked to treatment, and all injections were performed by separate ophthalmologists who were unmasked to treatment assignment. FOCUS was a single masked Phase I/II trial. The ranibizumab studies reported appropriate outcome measures, and ITT analysis was used by MARINA [**CIC data removed**]. ANCHOR and FOCUS excluded one or more patients [**CIC data removed**] from efficacy analyses, so these were not strictly ITT.

Withdrawals from the published ranibizumab studies were unbalanced, suggesting that attrition bias could have affected the results of the trials. In the MARINA study, discontinuations from treatment were approximately twice as high in the sham injection group as in the ranibizumab groups (28.6% sham injection group versus 12.6% 0.3-mg ranibizumab group and 13.8% 0.5-mg ranibizumab group). The most common reasons for the higher figures in the sham injection group were patient decision or patient's condition mandated other treatment. In the ANCHOR trial, 9.8% of patients in the PDT group discontinued treatment early, compared with 9.3% of the 0.3-mg ranibizumab group and 6.4% of the 0.5-mg ranibizumab group. The most common reason for discontinuation of treatment was adverse event, followed by patient's decision. Some patients who discontinued treatment in these trials remained in the studies, although study withdrawals followed the same pattern as treatment withdrawals. In the FOCUS trial, 8.9% of the sham + PDT arm and 11.3% of the ranibizumab + PDT arm discontinued, primarily due to adverse events. [**CIC data removed**].

Assessment of effectiveness

Visual acuity

The primary outcome for the included studies was visual acuity, measured by the proportion of patients losing fewer than 15 letters on the ETDRS chart (VISION, MARINA, ANCHOR and FOCUS) (*Table 13*) or mean change in best corrected visual acuity (PIER) (*Table 14*). Other reported measures of vision change in terms of number of letters gained/lost are also shown in *Table 13*, and *Table 15* shows deterioration in the study eye to the level of legal blindness (≤6/60 Snellen equivalent). The proportion of patients with a Snellen equivalent of 6/12, which is about equivalent to the legal limit for driving, is also reported. The studies included in this systematic review reported Snellen measures in feet, but these have been converted to the UK standard of metres to maintain consistency throughout the report (see *Table 8*, p. 10).

After the second year of re-randomised pegaptanib treatment, the VISION study[100] reported mean visual acuity from weeks 54 to 102, change in standardised area under the curve of visual acuity, progression to legal blindness, lines of vision gained and proportion of people losing fewer than 15 letters of visual acuity. The second

TABLE 13 *Proportion of patients with changes in visual acuity*

No. of patients (%) gaining or losing letters				
Pegaptanib				
VISION study year 1[95] **Lesion type: all**	**0.3 mg pegaptanib (*n* = 294)**	**1.0 mg pegaptanib (*n* = 300)**	**3.0 mg pegaptanib (*n* = 296)**	**Sham injection (*n* = 296)**
Loss of <15 letters at week 54	206 (70%)	213 (71%)	193 (65%)	164 (55%)
p-Value vs sham	<0.001	<0.001	0.03	
Maintenance or gain ≥0 letters	98 (33%)	110 (37%)	93 (31%)	67 (23%)
p-Value vs sham	0.003	<0.001	0.02	
Gain ≥5 letters	64 (22%)	69 (23%)	49 (17%)	36 (12%)
p-Value vs sham	0.004	0.002	0.12	
Gain ≥10 letters	33 (11%)	43 (14%)	31 (10%)	17 (6%)
p-Value vs sham	0.02	0.001	0.03	
Gain ≥15 letters	18 (6%)	20 (7%)	13 (4%)	6 (2%)
p-Value vs sham	0.04	0.02	0.16	
Loss ≥30 letters	28 (10%)	24 (8%)	40 (14%)	65 (22%)
p-Value vs sham	<0.001	<0.001	0.01	
VISION study year 2[100] (patients re-randomised)	**0.3 mg – 0.3 mg (*n* = 133)**	**0.3 mg – discontinue (*n* = 132)**	**Sham – any dose (*n* = 165)**	**Sham – discontinue or usual care (*n* = 107)**
Loss of <15 letters				
Week 54	66%	76%	56%	59%
Week 102	59%	62%	48%	45%
p-Value vs usual care at 102 weeks[105]	0.0385			
VISION study year 2[105] (patients re-randomised)	**0.3 mg – 0.3 mg (*n* = 133)**		**Sham – discontinue or usual care (*n* = 107)**	
Loss of ≥30 letters at 102 weeks	17 (13%)		28 (26%)	
p-Value vs usual care	0.0058			
VISION study year 2[100] (patients re-randomised)	**0.3 mg – 0.3 mg (*n* = 133)**	**0.3 mg – discontinue (*n* = 132)**	**Sham – discontinue or usual care (*n* = 107)**	
Lines of vision gained (estimated from graph)				
≥0 lines	35%	27%	26%	
≥1 lines	22%	19%	14%	
≥2 lines	15%	8%	6%	
≥3 lines	10%	8%	4%	
Ranibizumab				
MARINA[97] **Lesion type: occult/MC**	**0.3 mg ranibizumab (*n* = 238)**	**0.5 mg ranibizumab (*n* = 240)**	**Sham (*n* = 238)**	
Loss of <15 letters				
12 months (primary outcome)	225 (94.5%)	227 (94.6%)	148 (62.2%)	
95% CI of the %		[**CIC data removed**]		
p-Value (vs sham)	<0.0001	<0.0001		
24 months	219 (92.0%)	216 (90.0%)	126 (52.9%)	
95% CI of the %	88.6 to 95.5%	86.2 to 93.8%	46.6 to 59.3%	
p-Value (vs sham)	<0.0001	<0.0001		
Gain of ≥15 letters				
12 months	59 (24.8%)	81 (33.8%)	11 (4.6%)	
95% CI of the %	19.0[b] to 30.3%	27.8 to 39.7%	2.0 to 7.3%	
p-Value (vs sham)	<0.0001	<0.0001		
24 months	62 (26.1%)	80 (33.3%)	9 (3.8%)	
95% CI of the %		[**CIC data removed**]		
p-Value (vs sham)	<0.0001	<0.0001		

continued

TABLE 13 *Proportion of patients with changes in visual acuity (cont'd)*

	No. of patients (%) gaining or losing letters		
ANCHOR[96] **Lesion type: PC**	**0.3 mg ranibizumab + sham PDT (*n* = 140)**	**0.5 mg ranibizumab+ sham PDT (*n* = 139[a])**	**Sham injection + PDT (*n* = 143)**
Loss of <15 letters	132 (94.3%)	134 (96.4%)	92 (64.3%)
95% CI of the %	90.4 to 98.1%	93.3 to 99.5%	56.5 to 72.2%
Non-inferiority test vs PDT		[**CIC data removed**]	
Test for treatment difference (vs PDT)	<0.0001	<0.001	
Gain of ⩾15 letters	50 (35.7%)	56 (40.3%)	8 (5.6%)
95% CI of the %	27.8 to 43.7%	32.1 to 48.4%	1.8 to 9.4%
p-Value (vs PDT)	<0.0001	<0.0001	
PIER		[**CIC data removed**]	
FOCUS **Lesion type: PC/MC**	**0.5 mg ranibizumab + PDT (*n* = 105)**	**Sham + PDT (*n* = 56)**	
Loss of <15 letters	95 (90.5%)	38 (67.9%)	
95% CI of the %		[**CIC data removed**]	
p-Value	<0.001		
Gain of ⩾15 letters	25 (23.8%)	3 (5.4%)	
95% CI of the %		[**CIC data removed**]	
p-Value	0.003		

MC, minimally classic; PC, predominantly classic.
[a] 1 patient excluded [**CIC data removed**].
[b] [**CIC data removed**].

year results are presented in *Table 13–15* for the group who continued on 0.3-mg pegaptanib compared with those who received sham injection in the first year and were randomised either to discontinue or to receive a second year of sham injections. Responder rates (proportion losing <15 letters) (*Table 13*) are also shown for those who were randomised to discontinue the 0.3-mg dose and for those patients in the sham injection group who were re-randomised to receive one of the three doses of pegaptanib. Further results for those pegaptanib patients re-randomised to other doses of pegaptanib in the second year of the study are also reported,[100] but are not included in this review. Discussion of the second-year results is limited to the licensed 0.3-mg dose of pegaptanib.

The primary outcome measure for the MARINA, ANCHOR and FOCUS studies was the proportion of patients losing fewer than 15 letters of visual acuity from baseline to 12 months, at a starting test distance of 2 m. [**CIC data removed**].

Proportion of patients losing fewer than 15 letters of visual acuity

All pegaptanib doses performed statistically significantly better than sham injection for the primary outcome measure of loss of fewer than 15 letters between baseline and week 54 in the VISION study[95] (*Table 13*). The difference between pegaptanib doses was not significant for this outcome measure, but a slightly higher percentage of people receiving the 0.3- or 1.0-mg dose of pegaptanib lost fewer than 15 letters compared with the 3.0-mg group.

The proportion of people responding to treatment decreased for all arms of the VISION study during the second year.[100] The groups for the second year did not have equal proportions of responders at re-randomisation. Those who received pegaptanib for the first year of the study but were re-randomised to discontinue for the second year happened by chance to have a higher proportion of responders than those randomised to continue treatment with 0.3 mg pegaptanib for year two (76 versus 66%). By the end of the second year, the proportion of responders had dropped by 7% in the group who continued with pegaptanib, compared with a decrease of 14% in the group who discontinued 0.3 mg pegaptanib. Hence although the group who discontinued pegaptanib had a higher proportion of responders at week 102 than the continued treatment group, the group actually saw a greater decline. The group of patients who received sham injection for the first

TABLE 14 *Mean changes in visual acuity*

	Mean (SD) no. of letters of visual acuity, unless otherwise stated			
Pegaptanib				
VISION study year 1[95] **Lesion type: all**	**0.3 mg pegaptanib (*n* = 294)**	**1.0 mg pegaptanib (*n* = 300)**	**3.0 mg pegaptanib (*n* = 296)**	**Sham injection (*n* = 296)**
Change in VA at 54 weeks[a]	–7.5	–6.5	–10	–14.5
p vs sham	<0.002	<0.002	0.05	
VISION study year 2[100] (patients re-randomised)	**0.3 mg – 0.3 mg (*n* = 133)**	**0.3 mg – discontinue (*n* = 132)**		**Sham – discontinue or usual care (*n* = 107)**
Mean change in standardised area under the curve of VA				
Week 0 to week 54				
LS mean (SE)	–4.54 (1.18)			–8.16 (1.32)
p vs usual care	0.0129			
Week 0 to week 102				
LS mean (SE)	–5.88 (1.33)			–11.24 (1.49)
p compared with usual care	0.0012			
Week 54 to week 102				
LS mean (SE)	–0.60 (0.61)	–3.04 (0.60)		
p vs discontinuing	0.0041			
Mean VA[a]				
Week 54	44	47		39
Week 102	44	42		35
Ranibizumab				
MARINA[97] **Lesion type: occult/MC**	**0.3 mg ranibizumab (*n* = 238)**	**0.5 mg ranibizumab (*n* = 240)**	**Sham (*n* = 238)**	
Change in VA				
12 months	6.5 [**CIC data removed**]	7.2 [**CIC data removed**]	–10.5 [**CIC data removed**]	
95% CI of mean	4.9 to 8.1	5.4 to 9.1	–12.6 to –8.3	
p-Value (vs sham)	<0.0001	<0.0001		
24 months	5.4 [**CIC data removed**]	6.6 [**CIC data removed**]	–14.9 [**CIC data removed**]	
95% CI of mean	3.5 to 7.4	4.5 to 8.7	–17.3 to –12.5	
p-Value (vs sham)	<0.0001	<0.0001		
ANCHOR[96] **Lesion type: PC**	**0.3 mg ranibizumab + sham PDT (*n* = 140)**	**0.5 mg ranibizumab+ sham PDT (*n* = 139[b])**	**Sham injection + PDT (*n* = 143)**	
Change in VA	8.5 [**CIC data removed**]	11.3 [**CIC data removed**]	–9.5 (16.4)	
95% CI of mean	6.1 to 11.0	8.9 to 13.8	–12.3 to –6.8	
p-Value (vs PDT)	<0.0001	<0.0001		
PIER **Lesion type: all**	**0.3 mg ranibizumab** [**CIC data removed**]	**0.5 mg ranibizumab** [**CIC data removed**]	**Sham injection** [**CIC data removed**]	
Change in VA (primary outcome)	[**CIC data removed**]	–0.2 [**CIC data removed**]	–16.3 [**CIC data removed**]	
95% CI for mean	[**CIC data removed**]	[**CIC data removed**]	[**CIC data removed**]	
p-Value vs sham	[**CIC data removed**]	<0.0001		
FOCUS **Lesion type: PC/MC**	**0.5 mg ranibizumab + PDT (*n* = 105)**		**Sham + PDT (*n* = 56)**	
Change in VA	4.9 (14.7)		–8.2 (16.3)	
95% CI of the mean	[**CIC data removed**]		[**CIC data removed**]	
p-Value	<0.001			

LS, least squares; MC, minimally classic; PC, predominantly classic; SE, standard error; VA, visual acuity.
[a] Data estimated from figure.
[b] 1 patient excluded [**CIC data removed**].

TABLE 15 *Deterioration to legal blindness [visual acuity 6/60 (20/200) or worse]*

	Number of patients (%)			
Pegaptanib				
VISION study year 1[95] **Lesion type: all**	**0.3 mg pegaptanib (*n* = 294)**	**1.0 mg pegaptanib (*n* = 300)**	**3.0 mg pegaptanib (*n* = 296)**	**Sham injection (*n* = 296)**
VA 6/60 or worse	111 (38%)	128 (43%)	129 (44%)	165 (56%)
p-Value vs sham	<0.001	<0.001	0.001	
VISION study year 2[100] **(patients re-randomised)**	**0.3 mg – 0.3 mg (*n* = 133)**	**0.3 mg – discontinue (*n* = 132)**	**Sham – discontinue or usual care (*n* = 107)**	
Baseline VA better than 6/60	(*n* = 111)	(*n* = 116)	(*n* = 93)	
VA 6/60 or worse				
Week 54	38 (34%)	28 (24%)	44 (47%)	
Week 102	39 (35%)	44 (38%)	51 (55%)	
Ranibizumab				
MARINA[97] **Lesion type: occult/MC**	**0.3 mg ranibizumab (*n* = 238)**	**0.5 mg ranibizumab (*n* = 240)**	**Sham (*n* = 238)**	
VA 6/60 or worse				
12 months:	29 (12.2%)	28 (11.7%)	102 (42.9%)	
95% CI of the %	8.0 to 16.3%	7.6 to 15.7%	36.6 to 49.1%	
p-Value (vs sham)	<0.0001	<0.0001		
24 months:	35 (14.7%)	36 (15.0%)	114 (47.9%)	
95% CI of the %	10.2 to 19.2%	10.5 to 19.5%	41.6 to 54.2%	
p-Value (vs sham)	<0.0001	<0.0001		
ANCHOR[96] **Lesion type: PC**	**0.3 mg ranibizumab + sham PDT (*n* = 140)**	**0.5 mg ranibizumab + sham PDT (*n* = 139[a])**	**Sham injection + PDT (*n* = 143)**	
VA 6/60 or worse	31 (22.1%)	23 (16.4%)	86 (60.1%)	
95% CI of the %	15.3 to 29.0%	10.3 to 22.6%	52.1 to 68.2%	
p-Value (vs PDT)	<0.0001	<0.0001		
PIER		**[CIC data removed]**		
FOCUS	**0.5 mg ranibizumab + PDT**	**Sham + PDT**		
Lesion type: PC/MC	**(*n* = 105)**	**(*n* = 56)**		
VA 6/60 or worse	31 (29.5%)	26 (46.4%)		
95% CI of the %	**[CIC data removed]**	**[CIC data removed]**		
p-Value	0.006			

MC, minimally classic; PC, predominantly classic; VA, visual acuity.
[a] 1 patient excluded [**CIC data removed**].

year and any dose of pegaptanib during the second year had a decrease in the number of responders of 8%. By contrast, the group of patients who either continued with sham injections or discontinued sham treatment had a decrease in response rate of 14%. In summary, treatment with 0.3 mg pegaptanib during the second year halved the underlying decline in response rate seen in the groups who discontinued treatment. The manufacturer's submission to NICE reported that the difference between the group of patients who had 2 years of pegaptanib treatment and those who received sham injection during year one and either discontinued sham or received a second year of sham injections was statistically significant ($p = 0.0385$).[105]

In the MARINA trial, approximately 95% of the two ranibizumab groups had lost fewer than 15 letters of visual acuity at 12 months, compared with about two-thirds of the sham injection group ($p < 0.0001$). The difference was still significant at 24 months, with approximately 90% of ranibizumab patients and just over half of the sham injection group having lost fewer than 15 letters ($p < 0.0001$). [**CIC data removed**].

ANCHOR and FOCUS reported statistically significant differences between the ranibizumab groups and verteporfin PDT groups in terms of the proportion of patients losing fewer than 15 letters of visual acuity. In the ANCHOR trial, approximately 95% of people receiving either 0.3 or 0.5 mg ranibizumab lost fewer than 15 letters, compared with approximately two-thirds of the verteporfin PDT group ($p < 0.0001$). Similarly, approximately 90% of those receiving 0.5 mg ranibizumab plus PDT in the FOCUS trial lost fewer than 15 letters compared with around two-thirds of the sham injection plus verteporfin PDT group ($p < 0.001$).

Proportion of patients gaining letters of visual acuity

A small number of patients in the pegaptanib VISION study experienced an improvement in visual acuity, as measured by a gain in letters (*Table 13*). Statistically significantly more patients in the 0.3- and 1.0-mg pegaptanib groups gained at least five letters (22 and 23%, respectively), compared with 12% of the sham injection group.[95] Gains of at least 10 letters were statistically significantly more common in people treated with all doses of pegaptanib, compared with the sham injection group. Improvements of this kind were reported for 11% ($p = 0.02$), 14% ($p = 0.001$) and 10% ($p = 0.03$) of the 0.3-, 1.0- and 3.0-mg pegaptanib groups, respectively, compared with 6% of sham injection group. Very few people experienced gains of at least 15 letters of visual acuity. For the 0.3- and 1.0-mg pegaptanib groups, gains of this magnitude were significantly higher than for the sham injection group (6 and 7% versus 2%, $p = 0.04$ and 0.02, respectively). There was no statistically significant difference between the 3.0-mg group (4%) and the sham injection group (2%).

The MARINA study found that approximately one-quarter of the 0.3-mg ranibizumab group and one-third of the 0.5-mg ranibizumab group gained at least 15 letters of visual acuity at 24 months, compared with just under 4% of the sham injection group. Differences between the ranibizumab groups and the sham injection group were statistically significant at both 12 and 24 months. [**CIC data removed**].

Both the ANCHOR and FOCUS studies showed a statistically significant difference between the numbers of people who gained at least 15 letters of visual acuity in the ranibizumab groups compared with the verteporfin PDT groups. Approximately 36% of the 0.3-mg ranibizumab group and 40% of the 0.5-mg ranibizumab group gained at least 15 letters, compared with about 6% of the PDT sham injection plus verteporfin PDT group ($p < 0.0001$ for both groups). In the FOCUS study, 24% of the ranibizumab + PDT group and 5% of the sham injection + PDT group gained at least 15 letters ($p = 0.003$).

Mean change in visual acuity

The mean change in visual acuity, reported as the mean number of letters lost or gained, for people receiving 0.3 or 1.0 mg pegaptanib was approximately half that of people receiving sham injection (*Table 14*). Losses of 7.5 and 6.5 letters were observed in the respective pegaptanib groups, compared with a mean loss of 14.5 letters in the sham injection group by the end of 54 weeks of follow-up.[95] People receiving 3.0 mg pegaptanib lost an average of 10 letters of visual acuity, which was still significantly fewer than those lost in the sham injection group. The VISION study[95] also reported mean loss of visual acuity from baseline to each 6-weekly study visit. This was significantly lower for all pegaptanib groups than for the sham injection group ($p < 0.002$ at each time point for 0.3 or 1.0 mg, $p < 0.05$ at each time point for 3.0 mg).

The mean change in standardised area under the curve of visual acuity for patients re-randomised to continue or discontinue treatment in the second year of the VISION study was reported[100] (*Table 14*).The average decline from baseline to week 102 in people randomised to continue with the 0.3-mg treatment was 5.88 letters, compared with a decline of 11.24 letters in those who received sham injection for 2 years or discontinued treatment after 1 year of sham injections ($p = 0.0012$). There was little change between weeks 54 and 102 in the group who continued with the 0.3-mg pegaptanib treatment, with a decline of only 0.6 letters. By contrast, those who discontinued treatment after 1 year of 0.3-mg pegaptanib injections experienced a mean decrease of 3.04 letters ($p = 0.0041$). The group who continued for a second year of 0.3-mg pegaptanib treatment maintained an average of approximately 44 letters of visual acuity. Those who received 0.3-mg pegaptanib in the first year but discontinued during the second year lost approximately five letters of visual acuity on average, and those who did not receive pegaptanib at all during the 2-year study lost an average of four letters during the second year.

The MARINA, ANCHOR and FOCUS trials reported a mean increase from baseline in the

number of letters of visual acuity in ranibizumab treated patients and a mean decrease in visual acuity for the comparator arms (*Table 14*). At 12 months, increases in visual acuity in the MARINA and ANCHOR studies ranged from a mean of 6.5 to 11.3 letters with ranibizumab, compared with a decrease of 10.5 letters with sham injection and 9.5 letters with PDT. At 24 months, the increase from baseline with ranibizumab was 5.4 letters (0.3 mg) and 6.6 letters (0.5 mg) versus a decline of almost 15 letters with sham injection ($p < 0.0001$). Patients in the FOCUS trial gained on average 4.9 letters with 0.5 mg ranibizumab plus PDT compared with an average loss of 8.2 letters with PDT and sham injection ($p < 0.001$).

In the PIER study, patients received monthly injections for the first 3 months of the study, but this was then reduced to an injection every 3 months. For the first 3 months, ranibizumab patients experienced an increase in visual acuity, with a mean increase from baseline to month three of 2.9 and 4.3 letters for 0.3- and 0.5-mg doses, respectively, compared with a decline in visual acuity in the sham injection group. However, this was not maintained once the frequency of injections was reduced. Whereas ranibizumab patients in the MARINA, ANCHOR and FOCUS studies experienced a mean increase in visual acuity, people in the PIER study who received ranibizumab reported declining visual acuity at 12 months. However, the average decline in visual acuity from baseline was still statistically significantly lower with [**CIC data removed**] 0.5 mg ranibizumab than with sham injection ([**CIC data removed**] $p < 0.0001$ [**CIC data removed**]). People in the sham injection group lost an average of 16.3 letters by 12 months, compared with [**CIC data removed**] 0.2 letters in the 0.5-mg ranibizumab group (*Table 14*).

Severe vision loss and deterioration to legal blindness

Legal blindness was defined by the studies as a Snellen equivalent of 20/200 (6/60) or worse. Significantly fewer patients in the VISION study[95] receiving pegaptanib lost 30 or more letters (*Table 13*) or reached a reduced level of visual acuity the equivalent of legal blindness (*Table 15*), compared with patients receiving sham injection. Over half (56%) of the patients in the sham injection group were legally blind in the study eye by the end of the study, compared with 38% of the 0.3-mg pegaptanib group, 43% of the 1.0-mg pegaptanib group and 44% of the 3.0-mg pegaptanib group.

The patient groups for the second year of the VISION study were not equal at re-randomisation (week 54) in terms of levels of legal blindness.[100] Approximately one-third (34%) of those randomised to continue with 0.3 mg pegaptanib had a Snellen equivalent of 6/60 or worse, compared with 24% of those randomised to discontinue 0.3 mg pegaptanib and 47% of those in the control arm. By the end of the second year, the study eye of only one extra patient in the continued 0.3-mg pegaptanib group had deteriorated to the level of legal blindness. By contrast, a further 14% of those who discontinued 0.3 mg pegaptanib and 8% more of the control group deteriorated to this level of visual acuity.

[**CIC data removed**]. Approximately 15% of people treated with ranibizumab compared with 48% of the sham injection group met the criteria for legal blindness at 24 months in the MARINA trial. The differences were statistically significant for both groups at both 12 and 24 months ($p < 0.0001$). [**CIC data removed**].

Almost all of the people in the ANCHOR trial and approximately two-thirds of those in the FOCUS trial had predominantly classic lesions (despite the inclusion criteria of the FOCUS trial specifying predominantly classic). In the ANCHOR trial, 60% of people receiving sham injection and verteporfin PDT deteriorated to the level of legal blindness in the study eye, compared with 22% of those receiving 0.3 mg ranibizumab and sham PDT and 16% of people receiving 0.5 mg ranibizumab and sham PDT. Differences between both ranibizumab groups and the PDT group were statistically significant ($p < 0.0001$). The FOCUS trial also found a significant difference in deterioration to legal blindness between people treated with 0.5 mg ranibizumab and PDT compared with those receiving sham injection plus PDT ($p = 0.006$).

Proportion of patients with Snellen equivalent of 6/12 or better

The MARINA and ANCHOR trials reported the proportion of patients whose study eye reached a Snellen equivalent of 6/12 or better, which is approximately equivalent to the legal limit for driving. At 24 months in the MARINA trial, 34.5% of the 0.3-mg group and 42.1% of the 0.5-mg group had visual acuity of 6/12 or better, compared with just 5.9% of the sham injection group ($p < 0.001$ for each comparison). Similar results were reported by the ANCHOR trial. At 12 months, only 2.8% of the sham injection +

PDT group had visual acuity of 6/12 or better, compared with 31.4% of the 0.3-mg group and 38.6% of the 0.5-mg group ($p < 0.001$ for each comparison).

Subgroup analysis of visual acuity by lesion type

Lesion type was one of three patient characteristics prespecified in the statistical analysis plan by Gragoudas and colleagues for subgroup analysis of mean decrease in visual acuity.[95] They found a statistically significant difference between all three pegaptanib treatment groups and the sham injection group for patients with minimally classic or occult with no classic lesion types. But for patients with predominantly classic lesions, only the 0.3-mg pegaptanib dose was significantly more effective than sham injection in reducing visual acuity loss (*Table 16*). The results of multiple logistic-regression analyses found that no factor other than assignment to pegaptanib treatment was significantly associated with response (0.3-mg dose, $p < 0.001$).[95]

[**CIC data removed**].

Approximately one-third of people in the MARINA trial had minimally classic lesions. There was very little difference in response between these patients and those whose lesions were occult with no classic, and both subgroups of patients receiving either dose of ranibizumab had a statistically significantly better response than those receiving sham injection at both 12 and 24 months.

The majority of people in the ANCHOR trial did not have occult CNV present. Subgroup analysis showed that ranibizumab groups both had a statistically significantly higher response rate than people receiving PDT, regardless of whether or not occult CNV was present at baseline. For patients in the control arm receiving PDT, the response rate was higher among people without occult CNV than for people with occult CNV [**CIC data removed**].

[**CIC data removed**].

Subgroup analysis in the FOCUS trial compared people with predominantly classic lesions with those whose lesions were minimally classic or occult. Response rates were similar for the two subgroups. [**CIC data removed**].

Change in contrast sensitivity

The pegaptanib VISION study did not report changes in contrast sensitivity. [**CIC data removed**].

TABLE 17 *Change in contrast sensitivity*
[**CIC data removed**]

Anatomical changes

In addition to the outcome measures required by the inclusion criteria of this systematic review, changes in lesion size, CNV size and leakage area were reported by the studies (*Table 18*).

The VISION study[95] reported that only the 1.0-mg dose of pegaptanib was statistically

TABLE 16 *Subgroup analyses of visual acuity by lesion subtype*

	Visual acuity outcome (number of letters or proportion of patients)			
Pegaptanib				
VISION study year 1[95]	**0.3 mg pegaptanib**	**1.0 mg pegaptanib**	**3.0 mg pegaptanib**	**Sham injection**
Change in VA, no. of letters:[a]				
Predominantly classic	(*n* = 72)	(*n* = 78)	(*n* = 80)	(*n* = 76)
Mean decrease in VA	7.1	10.2	10.5	14
p vs sham	<0.05	NS	NS	
Minimally classic	(*n* = 111)	(*n* = 108)	(*n* = 105)	(*n* = 102)
Mean decrease in VA	7.3	6.5	9.4	14.2
p vs sham	<0.001	<0.001	<0.05	
Occult with no classic	(*n* = 112)	(*n* = 115)	(*n* = 111)	(*n* = 120)
Mean decrease in VA	9	6	9.5	17
p vs sham	<0.01	<0.001	<0.05	
VISION study year 2[100]		**[CIC data removed]**		

continued

TABLE 16 *Subgroup analyses of visual acuity by lesion subtype (cont'd)*

	Visual acuity outcome (number of letters or proportion of patients)		
Ranibizumab			
MARINA[97]	**0.3 mg ranibizumab**	**0.5 mg ranibizumab**	**Sham**
Proportion losing <15 letters			
12 months:			
Minimally classic CNV	(*n* = 86)	(*n* = 91)	(*n* = 87)
Response rate *n* (%)	80 (93.0%[b])	83 (91%[b])	54 (62%[b])
95% CI of the %		[**CIC data removed**]	
p-Value vs sham	<0.0001	<0.0001	
Occult without classic CNV	(*n* = 151)	(*n* = 149)[c]	(*n* = 150)[c]
Response rate *n* (%)	144 (95%[b])	143 (97%[b])	94 (62%[b])
95% CI of the %		[**CIC data removed**]	
p-Value vs sham	<0.0001	<0.0001	
24 months:			
Minimally classic CNV	(*n* = 86)	(*n* = 91)	(*n* = 87)
Response rate *n* (%)	77 (90%[b])	81 (89%[b])	44 (51%[b])
95% CI of the %		[**CIC data removed**]	
p-Value vs sham	[**CIC data removed**]	[**CIC data removed**]	
Occult without classic CNV	(*n* = 151)	(*n* = 149)	(*n* = 150)
Response rate *n* (%)	141 (93%[b])	135 (91%[b])	81 (54%[b])
95% CI of the %		[**CIC data removed**]	
p-Value vs sham	[**CIC data removed**]	[**CIC data removed**]	
ANCHOR[96]	**0.3 mg ranibizumab**	**0.5 mg ranibizumab**	**Verteporfin PDT**
Proportion losing <15 letters			
Occult CNV present	(*n* = 21)	(*n* = 18)	(*n* = 16)
Response rate *n* (%)		[**CIC data removed**]	
95% CI of the %		[**CIC data removed**]	
p-Value vs sham	[**CIC data removed**]	[**CIC data removed**]	
Occult CNV absent	(*n* = 119)	(*n* = 121)	(*n* = 127)
Response rate *n* (%)		[**CIC data removed**]	
95% CI of the %		[**CIC data removed**]	
p-Value vs sham	<0.0001	<0.0001	
PIER		[**CIC data removed**]	
FOCUS[a,b]	**Ranibizumab + PDT**	**Sham + PDT**	
Proportion losing <15 letters			
Predominantly classic	(*n* = 68)	(*n* = 37)	
Response rate *n* (%)	61 (90%)	25 (67%)	
95% CI of the %	83 to 97%	53 to 83%	
[**CIC data removed**]	[**CIC data removed**]		
Minimally classic/occult	(*n* = 37)	(*n* = 19)	
Response rate *n* (%)	34 (92%)	13 (68%)	
95% CI of the %	83 to 100.0%	48 to 89%	
[**CIC data removed**]	[**CIC data removed**]		

NS, not significant; VA, visual acuity.
[a] Data estimated from figures, total *n* per group assumed to be that listed for baseline characteristics.
[b] These are rounded figures from the respective publications.[97,102] Exact figures were given in the clinical study reports provided with the manufacturer's submission.
[c] [**CIC data removed**].

significantly more effective than sham injection in terms of changes in size of CNV and size of leakage between baseline and week 54 of the study. Both the 0.3- and 1.0-mg groups showed a statistically significantly lower increase in size of lesion than was reported for the sham injection group [1.8 disc area (DA) versus 2.5 DA]. The highest dose of pegaptanib (3.0 mg) showed no statistically significant difference in anatomical changes from baseline compared with the sham

injection group. The VISION study[100] reported individual results at 2 years (following re-randomisation) from the two RCTs which comprised the VISION study (trials 1003 and 1004), but did not report combined analyses. The only statistically significant angiographic difference between the continuing 0.3-mg pegaptanib group and the usual care group in study 1004 was in lesion size. The continuing 0.3-mg group's mean total lesion size was 5.4 DA at week 78 and 5.6 DA at week 102, compared with 7.5 DA and 8.1 DA, respectively, in the group who discontinued ($p < 0.05$). However, the corresponding patient groups in study 1003 did not show a significant difference (Appendix 4).

People in the MARINA trial treated with ranibizumab showed either no change in area of CNV (0.5-mg dose group) or a decrease in area of CNV of 0.32 DA (0.3-mg dose group) between baseline and the end of 2 years of treatment. By contrast, people in this study who received sham injection experienced an average increase in CNV area of 2.58 DA over 2 years. The difference between the ranibizumab groups and the sham injection groups was statistically significant ($p < 0.0001$). The mean change from baseline remained almost constant throughout 24 months in each of the ranibizumab groups, but the mean in the sham injection group increased further from 12 to 24 months. As a result, the difference between each ranibizumab group and the sham group at 24 months (*Table 18*) was somewhat greater than at 12 months. However, differences between groups were statistically significant at both 12 and 24 months ($p < 0.0001$).

[**CIC data removed**]. People in the ANCHOR and FOCUS trials who were treated with ranibizumab showed a statistically significant reduction in area of classic CNV compared with increases in mean area for those in the sham injection with verteporfin PDT groups, $p < 0.001$ (ANCHOR) and $p < 0.001$ (FOCUS).

Treatment with ranibizumab significantly reduced the mean area of leakage from CNV and intensive progressive RPE staining, compared with a mean increase in people in the control group in the MARINA and ANCHOR [**CIC data removed**] trials ($p < 0.0001$ for all groups compared with sham injection or PDT). In the MARINA trial, the difference between each ranibizumab group and the sham group was similar at 12 and 24 months. Both arms of the FOCUS trial experienced a reduction in total area of leakage from CNV and intense progressive RPE staining. People who received ranibizumab and PDT experienced an average reduction of 2.30 DA compared with an average reduction of 0.6 DA in the sham injection plus PDT arm ($p < 0.001$).

Change in Visual Function Questionnaire scores

Health-related quality of life changes in the VISION study, as assessed by the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25), was reported for a subgroup of 569 patients. However, this was only reported in abstract form[106] with very limited data presented, and is therefore not discussed further here. [**CIC data removed**].

TABLE 19 *Change from baseline in NEI-VFQ-25 scores* [**CIC data removed**]

Compliance with treatment

The pegaptanib manufacturer reported treatment compliance for the full 102 weeks of the

TABLE 18 *Anatomical changes from baseline*

	Mean (SD) DA			
Pegaptanib VISION study year 1[95] Lesion type: all	**0.3 mg pegaptanib (*n* = 294)**	**1.0 mg pegaptanib (*n* = 300)**	**3.0 mg pegaptanib (*n* = 296)**	**Sham injection**
Mean change in size of lesion, DA	1.8	1.8	2.5	2.5
p vs sham	<0.01	<0.01	NS	
Mean change in size of CNV, DA	1.6	1.2	1.8	2.1
p vs sham	NS	<0.01	NS	
Mean change in size of leakage, DA	1.0	0.5	1.2	1.6
p vs sham	NS	<0.01	NS	

continued

TABLE 18 *Anatomical changes from baseline (cont'd)*

	Mean (SD) DA		
Ranibizumab			
MARINA[97]	**0.3 mg ranibizumab**	**0.5 mg ranibizumab**	**Sham**
Lesion type: occult/MC	**(*n* = 238)**	**(*n* = 240)**	**(*n* = 238)**
Month 12:			
Area of CNV, DA	–0.29 [**CIC data removed**]	–0.03 [**CIC data removed**]	1.93 [**CIC data removed**]
95% CI of mean	–0.55 to –0.02	–0.27 to 0.21	1.57 to 2.29
p-Value vs sham	<0.0001	<0.0001	
Area of leakage from CNV + intense progressive RPE staining, DA	–1.96 [**CIC data removed**]	–1.88 [**CIC data removed**]	1.14 [**CIC data removed**]
95% CI of difference	–2.28 to –1.64	–2.18 to –1.58	0.68 to 1.59
p-Value vs sham	<0.0001	<0.0001	
Month 24:			
Area of CNV, DA	–0.32 [**CIC data removed**]	0.00 [**CIC data removed**]	2.58 [**CIC data removed**]
95% CI of mean	–0.63 to –0.01	–0.26 to 0.26	2.15 to 3.02
p-Value vs sham	<0.0001	<0.0001	
Area of leakage from CNV + intense progressive RPE staining, DA	–2.18 [**CIC data removed**]	–2.18 [**CIC data removed**]	0.76 [**CIC data removed**]
95% CI of difference	–2.52 to –1.85	–2.54 to –1.83	0.23 to 1.29
p-Value vs sham	<0.0001	<0.0001	
ANCHOR[96]	**0.3 mg ranibizumab + sham PDT**	**0.5 mg ranibizumab + sham PDT**	**Sham injection + PDT**
Lesion type: PC	**(*n* = 140)**	**(*n* = 140)**	**(*n* = 143)**
Area of classic CNV, DA	–0.52 (0.89)	–0.67 (1.10)	0.54 (2.37)
95% CI of mean	–0.67 to –0.37	–0.86 to –0.49	0.15 to 0.93
p-Value vs PDT	<0.0001	<0.0001	
Area of leakage from CNV + intense progressive RPE staining, DA	–1.80 (1.72)	–2.05 (1.98)	0.32 (3.09)
95% CI of mean	–2.09 to –1.51	–2.38 to –1.72	–0.19 to 0.83
p-Value vs PDT	<0.0001	<0.0001	
PIER	**0.3 mg ranibizumab**	**0.5 mg ranibizumab**	**Sham**
Lesion type: all	**(*n* = 59)**	**(*n* = 61)**	**(*n* = 63)**
Area of CNV, DA		[**CIC data removed**]	
95% CI of mean		[**CIC data removed**]	
p-Value vs sham	[**CIC data removed**]	[**CIC data removed**]	
Area of leakage from CNV [**CIC data removed**]		[**CIC data removed**]	
95% CI of mean		[**CIC data removed**]	
p-Value vs sham	[**CIC data removed**]	[**CIC data removed**]	
FOCUS	**0.5 mg ranibizumab + PDT**	**Sham + PDT**	
Lesion type: PC/MC	**(*n* = 102)**	**(*n* = 56)**	
Mean change (SD) in area of lesion, DA	–0.02 (1.3)	1.8 (2.3)	
[**CIC data removed**]	[**CIC data removed**]		
p-Value	<0.001		
[**CIC data removed**]	[**CIC data removed**]		
[**CIC data removed**]	[**CIC data removed**]		
[**CIC data removed**]	[**CIC data removed**]		
Area of leakage from CNV + intense progressive RPE staining, DA	–2.3 (2.4)	–0.6 (2.8)	
[**CIC data removed**]	[**CIC data removed**]		
p-Value	<0.001		

DA, disc area; MC, minimally classic; NS, not significant; PC, predominantly classic; VA, visual acuity.
p-Values are change from baseline in treatment group vs change from baseline in comparator arm.

TABLE 20 *Adverse events: pegaptanib VISION study*

Adverse event (AE)	Number of patients (%)				
	VISION study year 1[95]			VISION study year 2[101] (re-randomised): patients continued with:	
	All doses (n = 890)	Sham (n = 296)	p-Value	0.3 mg (n = 128)	Sham (n = 51)
Individuals with AE				122 (95)	46 (90)
Individuals with ocular AE (study eye)				92 (72)	39 (76)
Individuals with serious AE				22 (17)	14 (27)
Rate of discontinuation due to AE	1%	1%	NS	5 (4)	2 (4)
Death rate	2%	2%	NS	1 (1)	0
Vascular hypertensive disorders	10%	10%	NS		
Haemorrhagic AE	2%	3%	NS		
Thromboembolic events	6%	6%	NS		
Endophthalmitis	1.3%	0%	NR	0	0
Eye pain	34%	28%	NS	27 (21%)	9 (18%)
Vitreous floaters	33%	8%	<0.001	28 (22%)	2 (4%)
Punctuate keratitis	32%	27%	NS	31 (24%)	14 (27%)
Cataract	20%	18%	NS	23 (18%)	12 (24%)
Vitreous opacities	18%	10%	<0.001	13 (10%)	6 (12%)
Anterior chamber inflammation	14%	6%	0.001		
Visual disturbance	13%	11%	NS	4 (3%)	5 (10%)
Eye discharge	9%	8%	NS		
Corneal edema	10%	7%	NS	12 (9%)	4 (8%)
Increased intraocular pressure				26 (20%)	4 (8%)
Lacrimation increased				6 (5%)	6 (12%)
Eye redness				9 (7%)	6 (12%)

NR, not reported; NS, not significant.

pegaptanib study. A mean of 15.6 of 17 possible treatments were administered to patients receiving pegaptanib 0.3 mg and 16.3 of 17 possible treatments were administered to patients receiving usual care[105] (Appendix 4).

[**CIC data removed**].

Adverse events

Pegaptanib

All patients in the VISION study[95] underwent the same preparation procedure, regardless of their randomised group allocation. This included an ocular antisepsis procedure and an injection of subconjunctival anaesthetic, and it is possible that these procedures may themselves be related to ocular adverse effects. *Table 20* shows adverse events reported for patients in the pegaptanib VISION study.

The number of deaths during the study and rate of discontinuation due to adverse events were equal in the combined dose pegaptanib group and the sham injection group. The study did not provide details of the adverse events leading to discontinuation, other than to state that they were diverse and not clustered in relation to a particular system or organ.

Reported adverse events were similar between treatment arms, with the exception of: vitreous floaters (33% in pegaptanib groups versus 8% in sham injection group, $p < 0.001$), vitreous opacities (18 versus 10%, respectively, $p < 0.001$) and anterior chamber inflammation (14 versus 6%, $p = 0.001$). Year one of the VISION study[95] reported that the majority of adverse effects in the study eyes were transient and mild to moderate in severity, and attributed these to the injection procedure rather than to the study drug. They also found that eye-related adverse events were more common in the study eyes than in the other eyes among patients in the sham injection group. This suggests that the preparation procedure itself could be associated with adverse effects, even if no study drug is administered.

The VISION study also reported safety analyses for patients who received further treatment with pegaptanib beyond the initial study year.[101] The

second-year patient groups are not directly comparable with those in the first year, since the patients were re-randomised. However, the incidence of common ocular adverse events appears to be similar to those reported in year one. Most adverse events reported in the study eyes were transient, mild to moderate in severity, and attributed to the injection procedure itself rather than to the study drug. The rate of discontinuation due to adverse events in the second year was higher for both those who continued 0.3 mg pegaptanib and those who were randomised to usual care (4% for both groups).

There were 7545 injections in 890 patients in the first year of the VISION trial and 2663 injections in 374 patients in the second year. Endophthalmitis is the presence of extensive severe infection inside the eye, typically caused by eye surgery or trauma. It is an ocular emergency requiring immediate medical care and often surgery. Symptoms include floaters, light sensitivity, eye pain or discomfort, a red or pink eye and vision loss. Twelve patients experienced endophthalmitis in the first year (1.3% of patients) and approximately 75% of these remained in the trial. Two-thirds of the patients with this condition had been affected by a protocol violation, generally the result of failure to use an eyelid speculum to prevent bacteria from the eyelashes from contaminating the injection site. Five of the 890 patients experienced traumatic injury to the lens and six had retinal detachment in the study eye.

There were no cases of endophthalmitis or traumatic cataract reported by patients who were randomised to receive pegaptanib for more than 1 year. However, four cases of endophthalmitis and one case of traumatic cataract were reported among patients who either received sham injection in the first year and pegaptanib in the second year or who were randomised to discontinue pegaptanib in the second year but were later re-treated. The rate of retinal detachment in the second year of treatment for those patients who received 2 years of pegaptanib was 0.15% per injection (four cases out of 2663 injections). There was no evidence of cataract progression or persistent intraocular pressure elevation following multiple pegaptanib injections.

Ranibizumab

Published data on adverse events for the ANCHOR and MARINA trials are shown in *Table 21*. Appendix 9 shows CIC information on ocular adverse events for PIER, FOCUS, MARINA and ANCHOR studies, restricted to events experienced by at least two people in an individual study arm and reported by at least two of the trials. The data extraction tables in Appendix 4 contain complete listings of reported adverse events for each trial.

Incidences of severe ocular inflammation varied between treatment arms (*Table 21*). In the 24-month MARINA trial, reported rates were highest in the 0.5-mg ranibizumab group (20.9%) followed by the 0.3-mg group (16.8%) and the sham injection group (12.7%). Rates were lower in the 12-month ANCHOR results: 17.1% in the 0.5-mg ranibizumab group, 12.4% in the 0.3-mg ranibizumab group and 3.5% in the PDT group. No statistical test results were reported for the differences between trial arms. Serious ocular events were rare in the MARINA and ANCHOR trials. Three patients in each of the ranibizumab arms of the MARINA trial, and one patient in the 0.5-mg ranibizumab arm of the ANCHOR trial reported uveitis.

Endophthalmitis was reported by very few ranibizumab patients in the ranibizumab trials and none in the control arms. Five people in the MARINA trial (two in the 0.3-mg group and three in the 0.5-mg group, approximately 1% overall) and two people in the ANCHOR trial (0.5-mg ranibizumab dose group, approximately 0.7% of all ranibizumab patients) and two people in the FOCUS trial reported the condition. One of the presumed endophthalmitis cases in the 0.5-mg group of the MARINA trial was reported as uveitis by an investigator. [**CIC data removed**]. The rate per injection was five events out of 10,443 injections (0.05%) in the MARINA trial. The rate per injection was not reported for the ANCHOR trial.

Almost all of the patients in the [**CIC data removed**] FOCUS trial experienced at least one ocular adverse event (Appendix 9). [**CIC data removed**]. Intraocular inflammation had a particularly high incidence in the ranibizumab + PDT arm of the FOCUS trial (38.1 versus 5.4% in the sham + PDT group).

[**CIC data removed**]. Almost all of the participants in both arms of the FOCUS trial were affected by conjunctival haemorrhage, although it is not clear whether the PDT procedure or sham/ranibizumab injections were the likely cause. [**CIC data removed**].

[**CIC data removed**]. A postoperative intraocular pressure of 30 mmHg or more was reported by

TABLE 21 *Adverse events: ranibizumab MARINA and ANCHOR studies*

Adverse event (AE)	Number of patients (%)					
	MARINA[97] 24 months Lesion type: occult/MC			ANCHOR[96] 12 months Lesion type: PC		
	0.3 mg (*n* = 238)	0.5 mg (*n* = 239)	Sham (*n* = 236)	0.3 mg + sham PDT (*n* = 137)	0.5 mg + sham PDT (*n* = 140)	Sham + PDT (*n* = 143)
Serious ocular event						
Presumed endophthalmitis[a]	2 (0.8)	3 (1.3)	0	0	2 (1.4)	0
Culture not obtained	1 (0.4)	0	0	0	1 (0.7)	0
Culture negative	1 (0.4)	3 (1.3)[b]	0	0	0	0
Culture positive	0	0	0	0	1 (0.7)[d]	0
Uveitis	3 (1.3)	3 (1.3)[c]	0	0	1 (0.7)[e]	0
Rhegmatogenous retinal detachment	0	0	1 (0.4)	1 (0.7)	0	1 (0.7)[c]
Retinal tear	1 (0.4)	1 (0.4)	0	0	0	0
Vitreous haemorrhage	1 (0.4)	1 (0.4)	2 (0.8)	1 (0.7)	0	0
Lens damage	0	1 (0.4)	0	0	0	0
Most severe ocular inflammation						
None	198 (83.2)	189 (79.1)	206 (87.3)	120 (87.6)	116 (82.9)	138 (96.5)
Trace	19 (8.0)	35 (14.6)	24 (10.2)	11 (8.0)	13 (9.3)	4 (2.8)
1+	14 (5.9)	8 (3.3)	6 (2.5)	3 (2.2)	8 (5.7)	1 (0.7)
2+	2 (0.8)	2 (0.8)	0	1 (0.7)	1 (0.7)	0
3+	2 (0.8)	2 (0.8)	0	2 (1.5)	1 (0.7)	0
4+	3 (1.3)	3 (1.3)	0	0	1 (0.7)	0
Ocular adverse event						
Post-injection IOP						
⩾30 mmHg	31 (13.0)	42 (17.6)	8 (3.4)	12 (8.8)	12 (8.6)	6 (4.2)
⩾40 mmHg	5 (2.3)	5 (2.3)	0	4 (2.9)	4 (2.9)	1 (0.7)
⩾50 mmHg	1 (0.6)	1 (0.6)	0	NR	NR	NR
% with cataract	37 (15.5)	37 (15.5)	37 (15.7)	15 (10.9)	18 (12.9)	10 (7.0)
Non-ocular adverse event						
Investigator-defined hypertension	41 (17.2)	39 (16.3)	38 (16.1)	3 (2.2)	9 (6.4)	12 (8.4)
Key arterial non-fatal thromboembolic events						
Myocardial infarction	6 (2.5)[c]	3 (1.3)	4 (1.7)	1 (0.7)	3 (2.1)	1 (0.7)
Stroke	3 (1.3)	6 (2.5)	2 (0.8)	0	1 (0.7)	0
Cerebral Infarction	NR	NR	NR	1 (0.7)	0	1 (0.7)
Death	5 (2.1)	6 (2.5)	6 (2.5)	3 (2.2)	2 (1.4)	2 (1.4)
Vascular cause (APTC criteria)	3 (1.3)	3 (1.3)	4 (1.7)	1 (0.7)	2 (1.4)	1 (0.7)
Non-vascular cause	2 (0.8)	3 (1.3)	2 (0.8)	2 (1.5)	0	1 (0.7)
Non-occular haemorrhage						
Total	22 (9.2)	21 (8.8)	13 (5.5)	2 (1.5)	3 (2.1)	0
Serious adverse event	3 (1.3)	5 (2.1)	2 (0.8)	7 (5.1)	9 (6.4)	3 (2.1)
Serious non-ocular AE	NR	NR	NR	20 (14.6)	28 (20.0)	28 (19.6)

APTC, Antiplatelet Trialists' Collaboration; IOP, intraocular pressure; MC, minimally classic; NR, not reported; PC, predominantly classic.

[a] Events were categorised as presumed endophthalmitis in cases in which intravitreal or systemic antibiotics were administered.

[b] One event was reported as uveitis by an investigator.

[c] One patient had two episodes.

[d] Vitreous culture was positive for *Staphylococcus epidermis*.

[e] One patient had 2 episodes of intraocular inflammation that were reported as uveitis, but one of the episodes was classified as presumed endophthalmitis because it was treated with systemic antibiotics. In neither of these 2 episodes was a vitreous culture obtained, and neither was treated with intravitreal antibiotics.

higher numbers of ranibizumab patients than those in the control arms (*Table 21*). [**CIC data removed**].

[**CIC data removed**], In the FOCUS trial, the rate of ocular serious adverse events was approximately twice as high in the ranibizumab plus PDT arm as in the sham injection plus PDT arm. Very few patients discontinued the study or treatment due to adverse events. [**CIC data removed**].

[**CIC data removed**]. The FOCUS trial reported a higher rate of serious adverse events in the ranibizumab plus PDT group. [**CIC data removed**].

Selected non-ocular adverse events (not classified as 'severe') are shown in *Table 21* for the MARINA and ANCHOR studies. Hypertension was reported by 16.1–17.2% of patients in the MARINA trial and by 2.2–8.4% of patients in the ANCHOR trial. Whereas the incidence of hypertension was balanced between treatment arms in the MARINA trial, it was more common in the PDT arm than in the ranibizumab groups in the ANCHOR trial. [**CIC data removed**].

Very few deaths were reported in the ranibizumab trials, with numbers of deaths being approximately equal between trial arms (*Table 21* [**CIC data removed**]). The highest number of deaths occurred in the longer MARINA trial, as would be expected given the demographic profile of the study population. There were 17 deaths in the MARINA trial, 10 due to vascular causes and seven due to non-vascular causes. Seven people died during the first year of the ANCHOR trial, four from vascular causes and three from non-vascular causes.

Discussion of clinical effectiveness

Pegaptanib

Methodological quality and quality of reporting were generally good in the VISION study.[95] The randomised nature of the trial would have prevented selection bias. The study reported adequate blinding of assessors, care providers and patients, which would have minimised any performance bias. However, results of the trial were not analysed on an ITT basis. A small number of patients in each arm did not receive study treatment or an adequate baseline assessment, so they were excluded from analyses. Although there are slight differences in the number of such patients between treatment arms, there are no obvious imbalances or biases which would have affected results. There do not appear to have been systematic withdrawals from the VISION study, so the results should be free from attrition bias.

The published data for the VISION study are based on the combined results of two RCTs (studies 1003 and 1004) and data for these are not presented separately.[95] However, it has been noted[103] that the US FDA Medical Officer Review of the 2-year results states that although study 1004 demonstrates efficacy for all active doses of pegaptanib sodium at week 102, "this effect is not replicated in study 1003 which does not show efficacy for any of the active doses". The FDA also state that "for the combined data set, the results are equivocal concerning the need for further injections beyond the first year of treatment".[104] The reasons for the discrepancy between the RCTs at year two are unclear; one possible explanation is that the use of PDT confounded the results, and PDT may be more likely to be used in the USA (study 1004) (Lotery A, Southampton University Hospitals Trust: personal communication, October 2006).

The time horizon of 54 weeks' follow-up for the first study report is appropriate for assessing the effect of treatment on this condition. Patients treated with any of the three doses of pegaptanib (0.3, 1.0 or 3.0 mg) were significantly more likely to lose fewer than 15 letters of visual acuity than people who received sham injection by the end of year one. Fifteen letters is generally accepted to be a clinically significant change in visual acuity. It could have a significant impact on quality of life, and could represent the difference (depending on the starting point) in being able to live independently, drive, read or watch TV. The eyesight of people receiving pegaptanib was also significantly less likely to deteriorate to the level of legal blindness by the end of year one than that of people who received sham injection.

Patients were re-randomised to continue or discontinue treatment for the second year of the VISION study.[100] Although all patients were less likely to have lost fewer than 15 letters of visual acuity by the end of the second year of the study, the decrease was lower among patients who received a second year of pegaptanib treatment. The decline in the proportion of responders (i.e. those losing fewer than 15 letters of visual acuity) from week 54 to week 102 reported by the VISION study[100] was the same for those who discontinued 0.3 mg pegaptanib as for those who never received the drug (14%).

Subgroup analyses by lesion subtype were reported for the mean number of letters change in visual acuity at 1 year, rather than for the primary outcome (proportion of patients losing fewer than 15 letters). A letter to the Editor of *Ophthalmology*[103] notes that the data for subgroup analysis of the primary outcome can be found on the FDA website.[107] These data show that for the licensed 0.3-mg dose of pegaptanib, the proportion of patients losing fewer than 15 letters was not statistically different from sham injection for either predominantly classic lesions ($p = 0.15$) or occult with no classic lesions ($p = 0.14$).[107] This is in contrast to the data in the VISION study publication,[95] which demonstrate a statistically significant difference between 0.3 mg pegaptanib and sham injection for each of the three lesion subgroups, when looking at the mean change in visual acuity. Subgroup analyses are also presented separately for the individual RCTs on the FDA website.[107] Differences in statistical significance among the subgroups were evident between the two trials, with no obvious pattern apparent.

Although injection-related adverse events were rare, treatment with pegaptanib was linked with a greater likelihood of experiencing vitreous floaters, vitreous opacities and anterior chamber inflammation. These are all mild events, and not considered to be clinically important.

On the basis of the only published study identified by this review (the VISION study), pegaptanib appears to be clinically effective for the treatment of AMD. The generally good methodological quality of the study indicates that the results are likely to represent an unbiased estimate of the effect of pegaptanib on people with AMD who met the study entry criteria.

Ranibizumab

The systematic review identified three published RCTs of ranibizumab, and the manufacturer supplied a trial report for another unpublished study. The published [**CIC data removed**] studies were of good methodological quality. [**CIC data removed**]. The published trials [**CIC data removed**] masked outcome assessors, care providers and patients to treatment, which should have prevented bias in the reporting of results. Whereas the MARINA trial analysed results on an ITT basis, the ANCHOR and FOCUS trials excluded one or more patients. Withdrawals from the MARINA study were unbalanced, with more people in the sham injection groups choosing to discontinue. People in either the sham injection group or the 0.3-mg ranibizumab group were more likely to withdraw than those in the 0.5-mg injection group in the ANCHOR trial.

The studies were designed to include patients with different types of lesions, and they demonstrated that ranibizumab is effective for all types of lesion. Loss of fewer than 15 letters was demonstrated to be statistically significantly more likely in patients who received ranibizumab compared with the control arms, and this will have a significant impact on daily life. People in the ANCHOR and MARINA trials who received ranibizumab were also more likely to have a level of visual acuity that is approximately equivalent to the legal limit for driving. [**CIC data removed**]. Adverse effects with ranibizumab were common but most were mild to moderate. More serious ocular adverse events such as endophthalmitis were rare.

The good methodological quality of these studies provides a strong evidence base for the effectiveness of ranibizumab. Ranibizumab appears to be clinically effective for the treatment of AMD, with a greater proportion of patients losing less than 15 letters of visual acuity and patients gaining on average an improvement in vision.

Summary of clinical effectiveness

Pegaptanib

- The systematic review identified three publications[95,100,101] which reported the combined results of two good-quality RCTs (the VISION study) comparing pegaptanib with sham injection in patients with all lesion types.
- The primary outcome measure of visual acuity, measured by loss of fewer than 15 letters, was statistically significantly better in all the pegaptanib dose groups than in the sham injection group. People who continued to receive 0.3 mg pegaptanib were significantly more likely to have lost fewer than 15 letters by the end of a second year of treatment than those who discontinued pegaptanib after 1 year.
- For all secondary measures of visual acuity, 0.3 or 1.0 mg pegaptanib was statistically significantly better than sham injection after 1 year of treatment. With the exception of gains in visual acuity of at least five letters or at least 15 letters, the 3.0-mg pegaptanib dose was also statistically significantly better than sham injection after 1 year of treatment. A gain of at least 15 letters of visual acuity is generally accepted as a clinically important outcome which could have a significant impact on quality of life. Few people gained at least 15 letters of

visual acuity, but for the 0.3- and 1.0-mg doses, this was statistically significantly more than for sham injection.
- Significantly fewer patients receiving pegaptanib lost 30 or more letters or reached a reduced level of visual acuity the equivalent of legal blindness, compared with patients receiving sham injection. Continued treatment with 0.3 mg pegaptanib for a second year of treatment reduced the likelihood of deterioration to the level of legal blindness.
- Analysis of subgroups defined *a priori* found a statistically significant difference in mean change in visual acuity between all doses of pegaptanib treatment and sham injection for patients with minimally classic or occult with no classic lesions. Only the licensed 0.3-mg pegaptanib dose was significantly more effective than sham injection in reducing visual acuity loss in people with predominantly classic lesions after 1 year of treatment. Subgroup analyses were not performed on the primary outcome measure (proportion of patients losing fewer than 15 letters).
- The 1.0-mg dose of pegaptanib was associated with a statistically significantly lower increase from baseline in the size of the lesion, size of CNV and the size of leakage compared with sham injection. The effect of the 0.3-mg dose was statistically significant for the change in the size of the lesion only, while the 3.0-mg dose showed no statistically significant effects on these anatomical changes.
- Reported adverse events were similar between treatment arms in the pegaptanib study, with the exception of vitreous floaters, vitreous opacities and anterior chamber inflammation, which were all statistically significantly more common in patients treated with pegaptanib after 1 year of treatment.
- Injection-related adverse events were rare in patients treated with pegaptanib in the first year of the study. Only 12 patients (1.3%) experienced endophthalmitis; five experienced traumatic injury to the lens and six had retinal detachment in the study eye.

Ranibizumab

- The systematic review identified three good-quality published RCTs of ranibizumab compared with sham injection[97] or PDT.[96,102] The manufacturer submitted an additional unpublished [**CIC data removed**] RCT which met the inclusion criteria for this systematic review.
- MARINA and ANCHOR assessed the use of ranibizumab in people with different lesion subtypes (occult/minimally classic lesions and predominantly classic lesions, respectively). Patients in the PIER trial received a reduced frequency of ranibizumab injections. One trial (FOCUS) was a randomised, controlled Phase I/II study comparing 0.5 mg of ranibizumab plus PDT with sham injection plus PDT in patients with predominantly classic lesions.
- People treated with ranibizumab in the three published [**CIC data removed**] RCTs were significantly more likely than those in the comparator arms to lose fewer than 15 letters of visual acuity.
- Between about 25 and 40% of patients receiving ranibizumab alone or in combination with PDT gained at least 15 letters of visual acuity, significantly more than in the control groups (about 5% at 12 months). This is a clinically important outcome which could have a substantial impact on quality of life. [**CIC data removed**].
- Results from MARINA, ANCHOR and FOCUS indicated that treatment with a monthly injection of ranibizumab led to an increase in mean number of letters visual acuity, compared with an average decrease in comparator arms. However, results from the PIER study suggest that a reduced frequency of one injection every 3 months is insufficient to maintain an average increase in visual acuity.
- The study eyes of people treated with either 0.3 or 0.5 mg ranibizumab in the MARINA, ANCHOR and FOCUS trials [**CIC data removed**] were statistically significantly less likely to deteriorate to the level of legal blindness than those in the control arms.
- Subgroup analysis in the MARINA and ANCHOR [**CIC data removed**] trials found that the difference between the ranibizumab groups and the comparators in proportion of patients losing fewer than 15 letters was statistically significant for every lesion subgroup. [**CIC data removed**].
- [**CIC data removed**].
- A mean reduction or no change in the area of CNV and/or classic CNV and in the area of leakage from CNV plus intense progressive RPE staining was found with both doses of ranibizumab, either alone or in combination with PDT. The changes were statistically different from the increases in area found in the comparator group. [**CIC data removed**].
- [**CIC data removed**].
- Conjunctival haemorrhage was the most widely reported ocular adverse effect [**CIC data removed**]. Higher proportions of ranibizumab

patients than those in the control arms experienced increased intraocular pressure and vitreous floaters. [**CIC data removed**]. The incidence of non-ocular serious adverse events was reasonably balanced between treatment arms [**CIC data removed**]. Serious ocular events were rare in the MARINA and ANCHOR trials, and endophthalmitis was reported by very few ranibizumab patients (approximately 1% of the ranibizumab patients in the MARINA trial and 0.7% of the ranibizumab patients in the ANCHOR trial).

Chapter 4

Assessment of cost-effectiveness

Introduction

The aim of this chapter is to assess the cost-effectiveness of pegaptanib and ranibizumab compared with existing treatments (PDT for patients with a confirmed diagnosis of classic with no occult subfoveal CNV and best-corrected visual acuity 6/60 or better) or best supportive care in patients with AMD in England and Wales. The economic analysis comprises:

- a systematic review of the literature on the cost-effectiveness of pegaptanib and ranibizumab, of approaches to modelling disease progression and effects of treatment for patients with AMD and of quality of life for patients with AMD
- a review of the manufacturers' submissions (cost-effectiveness section) to NICE
- presentation of our economic model and cost-effectiveness evaluation.

As discussed in the section 'Visual acuity' (p. 9), visual acuity may be expressed in metres or feet. In our economic model and cost-effectiveness evaluation, visual acuity will be expressed in metres. However, the majority of economic evaluations and quality of life studies reviewed below used measurements in feet, therefore these have been converted to metres for consistency (see *Table 8*, p. 10).

Systematic review of existing cost-effectiveness evidence

Methods for the systematic review

A systematic literature search was undertaken to identify economic evaluations comparing pegaptanib and ranibizumab with existing treatments (PDT as described above) or best supportive care in patients with AMD. The details of the search strategy are documented in Appendix 2. The manufacturers' submissions to NICE were reviewed for additional studies.

Titles and abstracts of studies identified by the search strategy were assessed for potential eligibility by two health economists independently. Economic evaluations were eligible for inclusion if they reported on the cost-effectiveness of pegaptanib and/or ranibizumab versus existing treatments (PDT) or no treatment (best supportive care) in patients with AMD. Studies reporting the economic evaluation of comparator treatments were also identified and reviewed to highlight key methodological issues in the economic evaluation of treatment for AMD.

Results of the systematic review: cost-effectiveness of pegaptanib and ranibizumab

A total of 421 publications relating to cost-effectiveness in AMD were identified through our searches. None of these was a fully published economic evaluation of either drug. No additional publications were identified from the manufacturers' submissions. Three related conference abstracts, by Earnshaw and colleagues,[108–110] that reported model-based evaluations of pegaptanib were identified and are reviewed in outline.

The analyses used a six-state Markov model, defined for a US population, to estimate the lifetime costs and outcomes for cohorts of patients receiving pegaptanib or comparator treatments. The three abstracts present:

1. an overview of the model, including input data and assumptions for modelling treatments for subfoveal CNV secondary to AMD from a population perspective[110]
2. cost-effectiveness estimates for pegaptanib and PDT using verteporfin for AMD[108]
3. a cost-effectiveness analysis to determine the optimal timing of treatment with pegaptanib, based on initial visual acuity.[109]

As the three abstracts report analyses conducted using the same model, we do not distinguish between the abstracts when reviewing the model or methods of analysis. Individual sources will be identified when reporting results extracted from the abstracts or accompanying posters.

Health states in the model were defined in terms of visual acuity in the treated eye, with an approximately three-line range: greater than 6/12, 6/12 to >6/24, 6/24 to >6/60, 6/60 to >3/60 and ≤3/60. Transitions between states were based on a

gain of three or more lines, three to six line loss or loss of six or more lines on the visual acuity scale. This means that patients' vision could improve by one health state, worsen by one or two health states or remain the same in each model cycle. Mortality probabilities were based on age- and sex-specific rates from US National Vital Statistics (2002), with a relative risk of mortality due to blindness (visual acuity ≤6/60) of 1.5.

The effectiveness of pegaptanib was based on published 1-year results[95] and unpublished data for a second year of treatment. Disease progression in subsequent years was based on the efficacy in the sham arm of the VISION trial.[95] Effectiveness of PDT using verteporfin was based on 2 years of efficacy results from the TAP trial[10,88,111] and the Verteporfin in Photodynamic Therapy (VIP) trial.[112] To extrapolate outcomes beyond the clinical trials, data from the placebo arms of both trials[10,88,111,112] were used. Utilities applied to life expectancy in each of the model's health states were taken from a published source.[113]

The model used a 3-month cycle and adopted a lifetime horizon. Three-month transition probabilities were calculated based on the proportions of patients gaining or losing vision reported from the VISION,[95] TAP[10,88,111] and VIP[112] trials. The method for converting annual proportions to 3-month transition probabilities is not reported in the abstracts or accompanying posters. It was assumed in the model that treatment was discontinued once visual acuity fell below 3/60.

Costs included in the model were drug costs, AMD-related procedures (although these were not specified), excess costs associated with vision loss (depression and fracture treatment and also specialist nursing care and residential care), costs of visual rehabilitation and low-vision aids and costs of treating adverse events. Insufficient information is presented to judge the comprehensiveness of cost estimates – the main components of overall costs reported in the comparison of pegaptanib and PDT with verterporfin are 'other medical costs' (77 and 88% of total average costs, respectively) and drug costs (18 and 8% of total average costs, respectively) as reported in the accompanying poster.

The model outputs are expressed as vision years, quality-adjusted life years (QALYs), drug costs, costs of treating adverse events and other costs.

The analysis suggested that early treatment (visual acuity between 6/12 and 6/24) with pegaptanib was more cost-effective, compared with usual care, than delaying until disease had progressed, with an estimated incremental cost-effectiveness ratio (ICER) of US$49,480.[109]

No incremental analysis was reported for the comparison of pegaptanib with PDT with verterporfin,[108] the abstract reports the average cost per vision year and average cost per QALY for each intervention. This may be due to the absence of any reports of head-to-head comparison between pegaptanib and PDT with verterporfin, acknowledged by the abstract's authors. A further drawback (not acknowledged by the abstract's authors) is that the post-trial extrapolation of pegaptanib effectiveness is based on the sham arm of the VISION trial, in which a proportion of patients were reported as receiving PDT after baseline, whereas for PDT the post-trial extrapolation is based on the placebo arms of the TAP and VIP trials. This may overstate the average benefit of pegaptanib reported in the abstract.

Other treatments for AMD: published economic evaluations

In the absence of fully published economic evaluations of pegaptanib or ranibizumab, this section presents a brief review of economic evaluations of other treatments for age-related macular degeneration. We present an overview of methods used to model disease progression, estimate benefits/outcome and to estimate costs.

Overview

Eight fully published evaluations of treatments for subfoveal CNV secondary to AMD were identified.[40,86,87,114–118] A further five evaluations were identified that were reported only in abstract form; three of these are discussed in the previous section as they relate to one of the drugs being appraised.[108–110] The remaining two abstracts are not covered in this review as insufficient detail is reported in the abstracts.[119,120]

All the included evaluations are concerned with estimating the cost-effectiveness of PDT with verteporfin. However, one is also concerned with evaluating newer treatments for AMD.[117] Seven of the included evaluations used outcome data from the TAP study[10,88] to estimate the effectiveness of PDT, but used data from different reporting periods (1 year,[86] 2 years,[40,116] or longer[114,115]) or from selected subgroups of patients within the trial cohort.[87,114–116]

The principal treatment effect included in the models is the rate of decline of visual acuity for patients in the PDT and placebo group, and in all cases disease progression in the placebo group is treated as typical of that for patients receiving best supportive care. Differences in outcome are estimated using QALYs, by associating visual acuity states with published estimates of relevant health state utilities, or vision years, by estimating patient life expectancy in health states with a visual acuity greater than 6/60. None of the evaluations modelled survival differences between PDT and best supportive care cohorts since PDT, in itself, is not expected to have any impact on life expectancy. Where patients' risk of death associated with sight loss was included in evaluations, the same life expectancy was assumed for PDT-treated as untreated patients.[115]

Approaches to modelling the treatment effect for PDT varied substantially between included studies. The majority of evaluations are based on analysis of aggregate data from trial reports.[40,86,114–116] Simple models seeking to extrapolate the effectiveness of PDT over patients' lifetimes have tended to assume that treatment effects observed at 2 or more years can be projected forward over the patient's remaining life expectancy,[115] although there may be an assumed reduction in effectiveness over time.[116] Two studies[87,118] used a survival function derived from analysis of patient-level trial data for a subgroup of patients with predominantly classic lesions in the TAP trial. Transition probabilities derived from the survival analysis were used in a Markov model to estimate outcomes for PDT and placebo (supportive care) cohorts. Smith and colleagues[87] report 'trial-based' (i.e. 2-year) analyses in addition to results using a longer time horizon (5 years) for a patient cohort with initial visual acuity of 6/12 and another with initial visual acuity of 6/30.

In contrast, Meads and colleagues[40,86] only conducted cost-effectiveness studies using trial data and made no attempt to extrapolate effects beyond the clinical trial reports. These gave the least favourable estimates of the effectiveness of PDT for all the evaluations, except for Smith and colleagues' trial-based analysis for a cohort of patients with initial visual acuity of 6/30.[87] In the earlier publication,[86] there is no discussion of possible approaches to extrapolation nor of the advantages, disadvantages or likely impact of estimating cost-effectiveness in a longer-term model. In the later publication,[40] there is limited discussion on the possibility of modelling costs or outcomes beyond the clinical trial data. However, an addendum to the monograph discusses the benefits and limitations of extrapolation in detail.

Quality-adjusted outcomes in each of the evaluations were derived by applying health state utilities to relevant health states (defined by visual acuity levels). In each model, the utility declined with declining visual acuity. None of the evaluations reported primary empirical studies to develop health state utilities for patients with AMD and the majority[40,86,87,116,118] used the same published health state utility estimates that were derived using the time trade-off method in 72 patents with AMD.[113]

None of the evaluations used prospectively collected data on resource use for clinical trial patients, nor were data from observational studies used to develop intervention or health state costs. As discussed in the section 'Current service cost' (p. 12), treatment costs for PDT were typically based on the reported frequency of treatment in the TAP study. There is some variation in estimated costs depending on assumed duration of treatment. Unit costs of PDT treatment used in the evaluations vary by year and by currency, although in all cases the cost of verteporfin is the major component of the unit cost (ranging from around 70%[86,114] to approximately 80%[40,115,116]).

The evaluations vary as to whether additional health state costs, associated with disease progression, are included. Three studies[114–116] included only direct costs of treatment. Meads and Moore[86] developed costs of blindness based on NHS and Personal Social Services (PSS) provided to people with visual acuity below 6/60. Incorporating these into their short-term model had minimal effect and did not offset the additional costs of PDT.[40,86] Smith and colleagues[87] found that including costs of blindness and adopting a longer term horizon (5 years) gave more favourable cost-effectiveness estimates (£8823 per QALY gained for a cohort with baseline best corrected visual acuity of 6/12, compared with £89,464 when including only the costs of PDT treatment and adopting a 2-year time horizon for the same cohort).

Summary and conclusions of systematic review of cost-effectiveness studies

- No fully published economic evaluations of the interventions included in this review were found. Three related abstracts reporting model-based evaluations of pegaptanib were identified and briefly reviewed. Eight fully published

economic evaluations of treatments for subfoveal CNV secondary to AMD were identified and briefly reviewed.
- The placebo arms of clinical trials have been taken as the source of data on disease progression under best supportive care and have typically been used as source data on disease progression in models extrapolating beyond clinical trial data.
- All but one of the models estimated final outcomes in QALYs by mapping utility values to visual acuity. The majority of evaluations of treatments for subfoveal CNV secondary to AMD have used previously published utility values to translate changes in visual acuity to QALYs.
- Evaluations have differed in the perspective adopted, including direct costs only or adopting a third-party payer perspective and including costs of blindness borne by health and social services. In the case of PDT, choice of perspective (on its own) did not have a substantial impact on cost-effectiveness estimates.
- Evaluations have also differed in time horizon adopted. Three studies reported on models that used trial data only.[40,86,117] Two studies reported both 'trial-based' and extrapolated analysis.[87,116] The remainder reported only extrapolated analyses based on trial data or observational studies. Generally, time horizon has the greatest impact on cost-effectiveness estimates. Short-term models suggest that PDT is not cost-effective whereas extrapolated models suggest that PDT may be cost-effective, especially for patients with higher initial visual acuity.

Review of research on quality of life in AMD

The search strategy outlined in Appendix 2 identified 245 articles that were potentially relevant to this review. Each study was then categorised on the basis of its title and abstract where available following the criteria outlined below:

A. The study reports primary research (i.e. original data collected specifically for the study) on quality of life or health-related quality of life.
B. The study reports primary research on health state utilities.
C. The study reviews study research on A or B or both.
D. The study does not have any relevance to the research on quality of life in AMD.

Twenty-one studies were classified as A, four as B, three as C and the remainder as D.

Studies in the review included both treated and untreated patients with AMD. A variety of quality of life instruments were used – including both condition-specific, related to visual function and generic measures – and these are briefly summarised in tables in Appendix 11.

Studies using condition-specific instruments have reported quality of life scores that are lower for people with AMD compared with those without disease.[61,62] The quality of life impact is associated with lower visual acuity,[61,121–126] poorer contrast sensitivity and colour recognition,[126] severity of disease[127] and severity of visual loss.[65,128] Differences in overall score on NEI-VFQ (and in subscales such as near activities, dependency, driving, role difficulties, distance activities, mental health and general vision) were shown to be significantly related to differences in visual acuity of better-seeing eyes.[61,121–124] Berdeaux and colleagues[125] also reported that these scores were also significantly related to visual acuity of the worse-seeing eye. However, NEI-VFQ has been shown to be sensitive to differences in general health,[121] therefore adjustment for general health should be considered when comparing scores between patient groups.

Findings have been inconsistent regarding other factors that may be associated with lower quality of life scores for AMD patients, using condition-specific measures which focus on visual function. Neither patient's age nor gender was reported as an important explanatory variable in studies using the NEI-VFQ[124] and the Impact of Vision Impairment (IVI) questionnaire.[127] However, Cahill and colleagues[63] showed that important quality of vision subscales (general vision, difficulty with distance tasks, difficulty with near tasks) and vision-specific subscales (dependency, role difficulties, mental health, social function limitations) tended to correlate negatively with patient's age and duration of vision loss. There has been some inconsistency in the association between severity of visual loss and quality of life scores. Armbrecht and colleagues[128] found some patients reporting significant improvement in some quality of life aspects despite experiencing progressive vision loss. This may reflect patients' adaptation to their visual disability at the 12-month follow-up.[66,128]

Several studies have identified a strong association between AMD and depression. Forty-nine out of 151 patients (32.5%) with AMD and visual acuity of 6/18 or worse in the better-seeing eye enrolled in a randomised trial met the criteria for

depression in the structured clinical interview for the *Diagnostic and statistical manual*, 4th edition.[55] This was approximately double the prevalence observed in age-matched community controls. Williams and colleagues[56] reported that the average score for emotional distress among people with AMD was significantly worse than for similarly aged community-dwelling adults, using the Profile of Mood States (POMS), and was comparable with scores reported by people with other chronic illnesses. This study also reported that those blind in one eye were more significantly distressed than those blind in both eyes. This may reflect anxiety surrounding future vision loss in patients with one eye affected in addition to a greater acceptance and ability to adapt in those with both eyes affected.[66]

Studies using generic instruments have been less consistent in their findings. Studies have reported lower quality of life scores for people with AMD compared with community-dwelling adults of similar age and people with chronic disabling diseases. Williams and colleagues[56] reported a mean Quality of Well-Being (QWB) score of 0.581 for AMD patients with average age of 79 years compared to a mean score of 0.77 for adults with similar average age and a mean score of 0.659 for older adults with severe chronic obstructive pulmonary disease.[56] They also reported significant associations between visual acuity and quality of life, as measured using Self-Rated General Health Status, and also activities of daily living, using the Instrumental Activities of Daily Living Index. Cahill and colleagues[63] reported that mean SF-12 scores were correlated with patient age, duration of vision loss and visual function. They also found that patients with bilateral severe AMD reported similar vision-related quality of life to patients with low vision, but significantly poorer quality of life compared with people with varying severity of AMD and those without eye disease. In contrast, Hassell and colleagues[65] reported that mean SF-12 scores for physical and mental health were similar to those reported for Americans of a similar age group from the general population. Similarly, inconsistent findings are reported using the Short Form with 36 Items (SF-36) where some authors have reported significant associations between SF-36 domain scores and visual impairment[64] and others have not.[61,127]

An alternative approach to estimate the impact of disease is the use of preference-based techniques, such as time trade-off (TTO) and standard gamble (SG), to derive health state values or utilities. *Table 22* reports the mean utility values derived using the two methods for ophthalmologists and for patients with visual loss from AMD.[129]

These results suggest that there is a highly significant difference between the utilities obtained from clinicians who are familiar with AMD and those from patients who live with visual loss from AMD. Brown and colleagues[129] also reported a statistically significant difference between utility values derived using TTO and SG

TABLE 22 *Mean utility with TTO and SG for ophthalmologists and for AMD patients*

Visual acuity in better eye	Patients		Ophthalmologists		*p*-Value
	Mean	95% CI	Mean	95% CI	
TTO method					
6/6–6/7.5	0.89	0.82 to 0.96	0.992	0.986 to 0.998	0.01
6/9–6/15	0.81	0.73 to 0.89	0.97	0.96 to 0.98	<0.001
6/18–6/30	0.57	0.47 to 0.67	0.89	0.86 to 0.92	<0.001
6/60–3/60	0.52	0.38 to 0.66	0.77	0.71 to 0.83	0.008
Counting fingers to hand motions	0.40	0.29 to 0.50	0.69	0.64 to 0.74	0.004
Overall mean	0.72	0.66 to 0.78	0.86	0.84 to 0.88	NA
SG method					
6/6–6/7.5	0.96	0.92 to 1.00	0.998	0.993 to 1.00	0.06
6/9–6/15	0.88	0.83 to 0.93	0.99	0.98 to 1.00	0.005
6/18–6/30	0.69	0.52 to 0.86	0.96	0.94 to 0.98	0.01
6/60–3/60	0.71	0.57 to 0.85	0.88	0.84 to 0.92	0.03
Counting fingers to hand motions	0.55	0.36 to 0.74	0.77	0.71 to 0.83	0.08
Overall mean	0.81	0.76 to 0.86	0.93	0.91 to 0.95	NA

NA, not applicable.

methods, for both physicians and patients with AMD. Most typically, utilities obtained with the SG method are higher than those obtained with the TTO method. This has been attributed to the greater risk aversion associated with the standard gamble method.[130]

Similar large differences between utility values derived using the TTO method from clinicians and patients were reported by Stein and colleagues,[131] in a study which also included a sample of community members. AMD patients were stratified into three groups on the basis of best corrected visual acuity in the better-seeing eye of 6/9, 6/12 to 6/30 and 6/60 or worse as mild, moderate and severe AMD, respectively.

Mean valuations by respondent group, reported in *Table 23*, suggest that members of the general public and clinicians both considerably underestimate the impact that mild, moderate and severe AMD has on the quality of life when compared with values reported by the AMD patients. The study's authors did not exclude potential bias due to differences in demographic characteristics such as age (mean age for AMD patients was 75 years in comparison to 44 years for the general public sample and 29 years for the clinicians), sex and ethnic make-up between the respondents from the various groups. The values obtained by Stein and colleagues[131] are generally higher than those derived, using the same method and similar respondents, by Brown and colleagues.[129]

Summary and conclusion of review of research on quality of life in AMD

Evidence from a variety of studies using a range of instruments and valuation techniques shows that quality of life is lower with progression of visual loss associated with AMD. Central field loss impairs the ability of patients to conduct a wide range of daily activities. Visual disability is associated with an increased risk of emotional distress and clinical depression. However, some patients may adapt and cope with visual disability so that the quality of life impact may vary according to duration of vision loss.

Different measures indicate different relationships between visual acuity and quality of life. General quality of life measures may be less sensitive to the impact of vision loss due to AMD than vision specific instruments. Although the majority of published studies have used visual acuity as the primary outcome, there are other measurable aspects of vision (e.g. contrast sensitivity or colour recognition) that have an impact on quality of life. In addition, ophthalmologic outcomes assessment is complicated by the need to consider visual function in each eye and the interaction between them. The impact on quality of life of AMD in one eye may be profoundly affected by the status of the other eye.

Review of manufacturers' submissions

We received two manufacturers' submissions, each consisting of a written report and an electronic model supporting cost-effectiveness analyses reported within the submissions. Appendix 8 gives more details on each submission and a discussion of the clinical data presented.

The economic assessments within the manufacturers' submissions are reviewed in turn. The reviews consist of a brief overview of the cost-effectiveness analyses, including the approach taken to modelling disease progression and effects of treatment, followed by a critical appraisal of the cost-effectiveness analysis.

Pfizer submission to NICE:[105] cost-effectiveness analysis

Overview

The submission contains a brief review of the socio-economic burden of AMD and a cost-effectiveness analysis of pegaptanib for patients with AMD. The stated objective of the economic analysis in the submission is to assess the cost-effectiveness of the licensed dosage of pegaptanib (0.3 mg at 6-week intervals) relative to usual care for patients, in England and Wales, with subfoveal neovascular AMD in their better-seeing eye. Usual care in this evaluation is identified as best supportive care (visual rehabilitation and provision of visual aids) for all patients with the addition of PDT with verteporfin in patients with

TABLE 23 *Utility scores (mean and 95% CI) by AMD severity*

	General public	Clinicians	Patients	*p*-Value
Mild	0.960 (0.950 to 0.970)	0.929 (0.904 to 0.954)	0.832 (0.762 to 0.901)	<0.0001
Moderate	0.918 (0.902 to 0.934)	0.877 (0.846 to 0.909)	0.732 (0.669 to 0.795)	<0.0001
Severe	0.857 (0.834 to 0.879)	0.821 (0.785 to 0.857)	0.566 (0.487 to 0.645)	<0.0001

predominantly classic lesions. This corresponds to the pattern of care for patients in the control arm of the VISION trials.[95] Patients in the active treatment arm of the trials were also eligible for PDT treatment alongside treatment with pegaptanib (reported as 17% of the pegaptanib-treated cohort in year 1 by Gragoudas and colleagues[95]).

The submission does not report whether a systematic search was undertaken for studies of the socio-economic burden of AMD, nor is any systematic search reported for economic evaluations of pegaptanib or other treatments for AMD. The submission makes no reference to the conference abstracts reporting CEAs for pegaptanib discussed in the section 'Results of the systematic review: cost-effectiveness of pegaptanib and ranibizumab' (p. 43).

The base case analysis is presented for a cohort of all lesion types, with a best-corrected visual acuity in their better seeing eye of 6/12 to 6/96. Subgroup analyses by lesion type and lesion size are also reported, later in the submission. In the base case patients are treated with pegaptanib for a maximum of 2 years, with treatment discontinuing before this point if patients' visual acuity falls below 6/96 or has dropped by six or more lines from baseline level at the end of year 1. This is labelled scenario A in the submission. Cost-effectiveness of treatment adopting an alternative stopping rule, labelled scenario B, with a higher threshold visual acuity (6/60) for discontinuing pegaptanib treatment is also reported in the submission.

The perspective of the analysis is clearly stated as being that of the NHS and PSS, capturing direct costs and benefits only. The submission reports lifetime costs and outcomes (reported as vision years and QALYs) for each treatment arm and the incremental costs and outcomes for pegaptanib (with or without PDT) compared with usual care.

Model on cost-effectiveness of pegaptanib

The submission does not report any literature search for modelling studies relevant to the economic evaluation of treatment for AMD, nor does it discuss existing economic models for pegaptanib in this patient group. A new model was developed for this submission, following a similar approach to that adopted by Smith and colleagues.[87] Their study is referenced in the body of the submission (p. 32), but not discussed there or in the methodological appendix (Appendix 2 of the manufacturer's submission).

Below we outline the approach taken for the model and provide an outline review based on a checklist suggested for the critical appraisal of cost-effectiveness analysis by Drummond and colleagues,[132] the requirements of NICE for submissions on cost-effectiveness (reference case)[133] and a suggested guideline for good practice in decision modelling by Philips and colleagues.[134]

Modelling approach

A Markov state transition model was developed to estimate the difference in decline in visual acuity (including excess morbidity and costs resulting from declining visual acuity associated with progression of AMD) and treatment costs (over a maximum treatment duration of 2 years) between pegaptanib and usual care. The model has 12 states defined by declining visual acuity, plus an absorbing state (death). The majority of the non-absorbing health states correspond to a single line of visual acuity (6/12 through to 6/96). The states representing the best and worst visual acuity cover a range of values ($\geq$6/10 and $\leq$3/60, respectively). The rationale for these groupings is not discussed in the submission. However, a visual acuity value of 6/12 is regarded clinically as a threshold at which the impact of disease progression is more likely to have impact as it is the point where the patient cannot drive.

The model has a cycle length of 6 weeks, corresponding to treatment intervals for patients receiving pegaptanib and the frequency of assessment of patients' visual acuity in the VISION trial, and a 10-year time horizon. The model time horizon is equivalent to a lifetime horizon for patients with a mean age at diagnosis of 77 years, which was the mean age at baseline in the registration trial. The effect of shorter time horizons, on cost-effectiveness estimates, was tested in a sensitivity analysis and reported in Figure 3.11 of the submission.

Two forms of adverse events are incorporated into the model: those associated with treatment, which affect the treated eye only, and adverse events associated with declining visual acuity.

Adverse events associated with pegaptanib treatment are included in the model using probabilities derived from the proportion of patients experiencing endophthalmitis, traumatic lens injury and retinal detachment in the first year of the registration trial (Table 5[95]). It does not appear that any adjustment was made to quality of life scores for patients experiencing adverse events. Only the cost impact of adverse effects is

assessed based on treatment protocols based on expert opinion. No adverse events were assumed in the usual care cohort, although some adverse events may be expected with PDT, and no adverse effects of PDT were included for the pegaptanib cohort.

Health state utility values used in the model are taken from a published source.[113] These values have been widely used in cost–utility models of treatments for AMD, and were adopted in many of the evaluations of PDT[40,86,87,116] reviewed in the section 'Other treatments for AMD: published economic evaluations' (p. 44) (and are discussed in our review of research on quality of life in AMD in the section 'Review of research on quality of life in AMD', p. 46).

The costs applied in the submission were made up of two components. Costs of active treatment (pegaptanib and PDT) and monitoring of patients on-treatment were estimated separately from health states costs. The latter relate principally to service use associated with blindness and are applied to visual acuity states below 6/60.

Drug usage for pegaptanib was based on a dosage of 0.3 mg every 6 weeks for a maximum of 2 years (the licensed dosage and treatment frequency in the VISION trials). Resource use associated with pegaptanib treatment was estimated based on management protocols developed using expert opinion and assumed that all assessments and drug administration took place in outpatients. These gave a cost per cycle of treatment of £880.84 for first treatment and £659.32 for each subsequent treatment cycle. Costs in the usual care cohort were £276.64 for the first cycle and zero for subsequent cycles.

PDT costs consist of verteporfin plus the cost of the PDT procedure and FA to localise the lesion. The cost per PDT session used in the submission is slightly lower than in the studies by Meads and colleagues[40] and Smith and colleagues,[87] which also included the cost of a follow-up outpatient consultation. It appears that such follow-up may have been assumed to occur during consultations for pegaptanib treatment. The same cost per PDT session has been used for the pegaptanib and usual care cohorts, and so has not biased the evaluation. Also, the cost of an outpatient follow-up appointment would be a comparatively small component of the cost of a PDT session. The PDT cost per cycle for the pegaptanib cohort is £39.26 in year 1 and £9.66 for year 2. Equivalent figures for the usual care cohort are £53.64 and £19.42.

The scope of services (low-vision aids, low-vision rehabilitation, community care and residential care) included in the cost of blindness is the same as in previous UK evaluations.[40,87] The proportion of patients with visual acuity below 6/60 receiving services is taken from Meads and colleagues.[40] Unit costs used to estimate costs of blindness are taken from Meads and colleagues[40] and unit costs of community care.[135] Unit costs from different base years (from 2003 to 2005) have been included in the model. The cost year for the model is 2005 and, where required, costs have been inflated to 2005 values using the Hospital and Community Health Services (HCHS) Pay and Prices Index.

Model/cost-effectiveness results

The submission reports total costs (broken down by drug and administration/monitoring, management of adverse events, PDT co-administration, services for the blind, excess depression and excess fracture costs) and outcomes (vision years and QALYs) for each arm of the model separately, and also an incremental analysis in *Tables 3.10* and *3.11* of the manufacturer's submission. These tables correspond to the alternative stopping rules for pegaptanib. Both analyses use a 10-year time horizon and identical assumptions regarding the cohort of patients entering the model.

The results for both scenarios are very similar with a 0.298 QALY gain for pegaptanib treatment over usual care in scenario A and 0.289 in scenario B. The ICERs for the two scenarios are also similar at £15,819 and £14,202 per QALY for scenario A and B, respectively.

The submission concludes that pegaptanib is likely to be a cost-effective treatment, relative to usual care, although this finding holds for treatment of patients' better-seeing eye only. ICERs for treatment of the worse-seeing eye, or both eyes, would be expected to be considerably higher.

The largest component of total cost in each scenario is NHS and PSS care for the blind, at 55–56% of total costs in the pegaptanib cohort and 93% for usual care. Drugs and administration costs in each scenario are 41% of total costs in the pegaptanib cohort. Management of adverse events and the excess costs of depression and fractures are minor components of total costs.

The mean numbers of pegaptanib treatments over 2 years estimated in the model in scenarios A (12.6) and B (11.7) are both lower than the mean number of treatments reported in the trial (15.3, 8.4 in year 1 and 6.9 in year 2).

Outline appraisal of the cost-effectiveness analysis undertaken

A summary of the manufacturer's submission compared with the NICE reference case requirements is given in *Table 24*.

See Appendix 12 for a tabulation of the critical appraisal of the submission against Drummond and colleagues' checklist.[132]

Outline review of modelling approach

Model structure/structural assumptions. The model is similar in structure to that developed by Smith and colleagues[87] to model the cost-effectiveness of PDT, although this latter model used 15 visual acuity states, all of which corresponded to a single line of visual acuity (except for that indicating the worst sight, which was for visual acuity ≤6/240).

The effect of active treatment for AMD is to reduce the probability of disease progression compared with no active treatment (i.e. visual rehabilitation and low vision aids); these latter interventions are intended to reduce the impact of disease progression on usual activities rather than affect disease progression itself.

There is no evidence in the submission that the manufacturer undertook a systematic review of epidemiological studies to populate the model with assumptions on the excess risk of fractures, depression or mortality associated with visual loss. There is no discussion or justification in the submission of the values used to model these risks.

The time horizon adopted for the model appears to be appropriate to allow for differential effects of disease progression in the pegaptanib-treated and usual care cohorts. The cycle length of 6 weeks appears to be driven primarily by the treatment interval for pegaptanib and frequency of assessment of visual acuity in the VISION trial, rather than any consideration of its appropriateness to the rate of disease progression in either cohort in the model. There is no discussion or justification of the model cycle length in the submission.

The five health state valuations that were used in the model were defined over ranges of visual acuity. This means that the 12 visual acuity states in the model were collapsed down to these five states for calculation of QALYs. It is not clear from the submission whether this has any effect on the results presented – there is no discussion of possible impacts of this mapping on the cost-effectiveness estimates. Similarly, odds ratios used to estimate excess costs of treating depression and fractures required the visual acuity states in the model to be collapsed. Categories of vision loss reported by Zhou[136] were mapped to visual acuity categories in order to be applied in the model. Again, there is no discussion in the submission on any impact this mapping may have on cost-effectiveness estimates.

Data inputs. Patient-level data from the VISION trials[95] were analysed in a collection of survival models to estimate the probability of gaining or

TABLE 24 *Assessment of Pfizer submission against NICE reference case requirements*

NICE reference case requirements[a]	Included in submission
Decision problem: as per the scope developed by NICE	?[b]
Comparator: alternative therapies routinely used in the UK NHS	✓
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: all health effects on individuals	✓
Type of economic evaluation: cost-effectiveness analysis	✓ (CUA)
Synthesis of evidence on outcomes: based on a systematic review	?
Measure of health benefits: QALYs	✓
Description of health states for QALY calculations: use of a standardised and validated generic instrument	?[c]
Method of preference elicitation for health state values: choice based method (e.g. TTO, SG, not rating scale)	✓
Source of preference data: representative sample of the public	×[d]
Discount rate: 3.5% p.a. for costs and health effects	✓

CUA, cost–utility analysis.
[a] See detail in the NICE report.[133]
[b] Pegaptanib versus "usual care" not best supportive care.
[c] Utilities taken from published study using SG and TTO valuations (TTO valuations used in base case).
[d] Utilities taken from ARMD patients, not general public.

losing lines of visual acuity during treatment, based on the method used by Smith and colleagues.[87]

Based on partitioned analyses that suggested "the data represent a mixed population, a proportion of which are at very low risk of losing visual acuity", the patient populations were split into those who gained one or more lines and those who lost one or more lines of visual acuity from baseline to their final assessment. Those who neither gained nor lost were included in both populations. Separate time-dependent survival models were estimated for the loss (1–10 lines) and gain (1–4 lines) of visual acuity. The model coefficients are presented in Appendix 2 of the submission as is the method for deriving transition probabilities from the survival estimates.

A separate set of survival models were estimated to model disease progression for pegaptanib-treated patients once treatment was discontinued. These used data for patients treated with all dosages (0.3, 1 and 3 mg) of pegaptanib. There were sufficient data to estimate models for 1–3 line gain and 1–5 line loss in visual acuity; values beyond these needed to be imputed. It was assumed that these models, derived for the year following treatment discontinuation could be applied for the patients' remaining life expectancy.

The estimates of the resources used in monitoring patients while on treatment are low compared with those suggested by clinical experts who assisted in the development of this review. In the Pfizer model, patients have a single FA prior to treatment and no further imaging. Patients also have no vision assessments during their treatment. In contrast, the clinical experts we consulted stated that patients would have optical coherence tomography and vision assessment performed at every attendance. Moreover, they suggested that patients would have repeat FA every 6 months, although it may be good practice to consider offering FA every 3 months. The effect of adding these additional items of resource use on the cost-effectiveness estimates in the manufacturer's model was tested and is reported at the end of this section.

Health state valuations used in the model were derived from a sample of AMD patients, rating their own current state of health, rather than the general population. This seems appropriate, in the absence of credible published valuations derived from a general population sample. Health state valuations, estimated using both the SG and the TTO techniques, decrease with declining visual acuity. The mean values, elicited using the TTO technique, for each of the visual acuity states reported by Brown and colleagues[113] were used in the base case. SDs were extracted from the study report and used in estimating the beta distributions used in the probabilistic sensitivity analysis.

Adverse effects associated with declining visual acuity appear to be incorporated in the model in different ways for their impact on cost and on outcomes. Odds ratios for fracture and treated depression associated with declining visual acuity were taken from an unpublished analysis[136] and were applied to age- and sex-specific prevalence of treated depression[137] and annual fracture rates.[138] It appears that the odds ratios have been treated as relative risks and multiplied by the age/sex specific rates to estimate rates for patients with declining visual acuity due to AMD. These rates appear only to have been used to derive estimates of the cost impact of the adverse events, not their impact on efficacy or quality-adjusted life expectancy. The effect of morbidity and mortality due to these adverse events seems to have been captured in the model by applying a 50% elevated risk of all-cause mortality to all visual acuity states below 6/60 in the model. This elevated risk of mortality is taken from an analysis which is currently available only as an abstract.[45]

Assessment of uncertainty. Uncertainty is addressed using deterministic and probabilistic sensitivity analysis. The deterministic sensitivity analysis addresses issues of methodological uncertainty (varying discount rates, using alternative parametric forms of the post-treatment survival function and varying the model time horizon) and parameter uncertainty (using alternative assumptions for utility weights, number of pegaptanib treatments, number of FAs, method of monitoring adverse events, costs and probabilities of receiving services for visual impairment and excluding patients receiving PDT). Only the ICER is reported for these sensitivity analyses, so no comment can be made on changes in total cost or outcomes. However, the ICERs were largely insensitive to changes assessed in the deterministic sensitivity analysis, and were consistently lower for scenario B (although the difference is small). Exceptions to this were variations in estimates of costs and probabilities of receiving services for visual impairment and model time horizon. The ICER was between £55,000 and £60,000 per QALY for a 3-year time horizon, reducing to around £30,000 per QALY when the time horizon was increased to 5 years. This reflects the fact that

treatment costs are incurred in the first 2 years whereas benefits are expected to extend over the patient's lifetime. Also, the difference in costs of services to the blind between the pegaptanib cohort and usual care cohort, which would be expected partially to offset costs of treatment, are around £1000 at 2 years and around £2500 at 5 years (approximately 30 and 70%, respectively, of the difference estimated at 10 years). If costs and probabilities of receiving services for visual impairment are set at their upper limits, then pegaptanib treatment dominates usual care, whereas if they are set to their lower limits, the ICER is £25,358 for scenario A and £24,188 for scenario B.

In the assessment of parameter uncertainty in the deterministic sensitivity analysis, it is only in the case of costs and probabilities of receiving services for visual impairment that upper and lower parameter values were tested (although the submission does not state what those upper and lower limits were). In other cases, the changes in assumption are relatively small and may explain the relative insensitivity of ICER to these changes.

Parameter uncertainty is also addressed in a probabilistic sensitivity analysis. However, only a limited number of variables are included. For example, costs and probabilities of receiving services for visual impairment, which were shown to be influential in the deterministic sensitivity analysis, were not included. Variables included in the probabilistic sensitivity analysis were the number of pegaptanib treatments (normal distribution using mean and standard deviation observed in year 1 and year 2 of the trial), utility weights (beta distribution using mean and SD of TTO valuations from a published study[113]) and transition probabilities for vision loss and vision gain. To sample the transition probabilities for vision loss and vision gain, correlation between parameters in the survival function was handled using Cholesky decomposition. The choice of distribution and handling of correlation in the PSA is generally appropriate. However, the submission recognises that the use of a normal distribution for the number of pegaptanib treatments is likely to produce overestimates, since the distribution observed in the trial was highly skewed with a median of nine treatments and range of 1–9 treatments. No patient would be expected to have more than nine treatments. The use of a normal distribution is justified in the submission as an acceptable simplification, which biases the evaluation against pegaptanib treatment.

Heterogeneity in the study population has been taken into account through subgroup analyses presented in Section 3.5 of the submission. Subgroups examined were defined by patient age, sex, lesion type and lesion size. Very little variation in ICER was reported by these subgroups, except that the ICER was reduced to £10,940 (£9454 for scenario B) for patients aged under 75 years compared with £18,863 (£17,128 for scenario B) for patients aged 75 years and over. The submission reports that this difference was largely due to different mortality rates between the two age groups.

Summary of general concerns

- The analysis assumes that the post-treatment effect estimated in the first year following discontinuation of treatment can be applied for all subsequent years of the model. This may overestimate the benefit associated with pegaptanib treatment.
- The model uses a 10-year time horizon, which is the approximate lifetime for 75-year-old in the UK, but the baseline population in the model is based on a mixed cohort with ages ranging from 45 to 75 years. The time horizon in the model is not varied when conducting sensitivity analyses by patient age. This may be appropriate, as extrapolating from treatment effects estimated in 2 years of trial data and 1 year of data on post-treatment effects to longer time horizons may be questionable.
- The method for deriving the parameter estimates used in the model, through survival analysis of patient-level data, is generally made clear in the submission. However, the number of cases contributing data for each survival model (of which there are 14 separate models for on-treatment effects and appear to be eight for post-treatment) are not reported. Since visual acuity was assessed at each attendance for treatment, not continuously, patients' visual acuity may have changed by more than one state between observations. The date of this transition was estimated by linear interpolation – the submission does not report how many of the observations included in the survival analyses were derived by this interpolation procedure and what effect this procedure may have on the validity of their model results.
- The resource use protocols used to populate the model with treatment costs were missing some components that clinical experts suggested would be required during active treatment. The protocols did not include vision assessments

and OCT at each attendance. The reference case assumed that the FA was only performed prior to initiation of treatment, whereas clinical advisers suggested that it may occur every 3–6 months while patients are receiving active treatment.
- The model is very complex and requires a great deal of navigating between sheets to understand how calculations are constructed.

Further analysis by the TAR team using the manufacturer's model

Table 25 reports the results of further analyses undertaken using the manufacturer's model. These were mainly concerned with testing the sensitivity of the cost-effectiveness estimates to changes in assumptions on resource use for patient monitoring. Adding in costs for OCT increases the incremental cost by around £650 and the ICER rises by around £2000. Adding in the cost of vision assessments at each attendance increases the incremental cost and ICER by the same order of magnitude as for OCT. Assuming that patients have FA every 6 months while on treatment increases incremental costs by slightly less than OCT and vision assessments. The cumulative effect of all these changes is to increase the ICER from £15,815 per QALY gained, in the reference case, to £22,266 per QALY gained.

If the injection procedure is costed as if it were a day-case procedure, incremental costs rise by almost £4000 and the ICER increases to £35,197.

The utility values used in the submission suggest a large reduction in utility when visual acuity drops from the range 6/12–6/24 (0.81) to 6/24–6/60 (0.57) and a second large reduction when moving from 6/60–3/60 (0.52) to less than 3/60 (0.40). [**CIC data removed**]. When [**CIC data removed**] alternative utility values, derived from a general population and that have a more gradual decline, are used in the model the QALY difference reduces slightly 0.279 but the ICER is little changed, at £16,863.

Novartis submission to NICE:[91] cost-effectiveness analysis

Overview

The economic assessment of ranibizumab submitted by Novartis includes a cost-effectiveness analysis using 'vision years gained' (defined as years spent with a visual acuity >6/60) and a cost–utility analysis using utility values for AMD-specific health states derived in a study sponsored by the manufacturer.

The different types of wet AMD (minimally classic, occult no classic and predominantly classic) were analysed separately. The comparators include best supportive care for patients with minimally classic or occult no classic and both PDT with verteporfin and best supportive care for patients with predominantly classic lesions. Transition probabilities used to model patients' movement between health states when receiving treatment with ranibizumab, PDT or under best supportive care were derived for each lesion type using outcomes of visual assessments performed every 3 months during the relevant trials (ANCHOR for predominantly classic, MARINA for minimally classic and occult no classic). Since the ANCHOR trial did not include a sham arm, comparison of treatment with ranibizumab against best supportive care for patients with predominantly classic lesions required an indirect comparison against data from the TAP study (discussed later in this review). [**CIC data removed**]. Two years of clinical trial data are available for the MARINA study and 1-year data is available for the ANCHOR and PIER studies. [**CIC data removed**]. The submission is not always clear on the source of unit costs. The majority appear to be derived from routine sources, such as NHS Reference Costs.

The maximum duration of treatment in the model was that observed in the relevant clinical trial – 1 year for patients with predominantly classic lesions (based on the ANCHOR trial) and 2 years for patients with minimally classic or occult no classic lesions (based on the MARINA trial). For all

TABLE 25 *Summary of sensitivity analyses using manufacturer's model (pegaptanib)*

	Incremental cost (£)	Incremental QALYs	ICER (£)
OCT cost at each attendance	5,356	0.298	17,974
Vision assessment cost at each attendance	6,099	0.298	20,467
FA every 6 months	6,635	0.298	22,266
Cost injection as day-case procedure	10,489	0.298	35,197
[**CIC data removed**]			

patients a stopping rule was applied so that patients whose visual acuity declined below 3/60 ceased active treatment with ranibizumab. [**CIC data removed**]. It was assumed that the treatment effective persisted for up to 6 months after the end of treatment.

Since (at the time of writing this report) ranibizumab does not have marketing authorisation for this indication, there is no unit cost available in the BNF[82] or MIMS.[139] The price of a vial of Lucentis 0.5 mg used in the model was based on the manufacturer's target price for the UK [**CIC data removed**]. In addition to treatment and administration costs, the model also includes costs of managing treatment-related ocular adverse events and cost associated with blindness.

The study was undertaken from the perspective of NHS and PSS in England and Wales. An annual discount rate of 3.5% was applied to both costs and outcomes.

Model on cost-effectiveness of ranibizumab
It appears in the submission that no systematic search for cost-effectiveness studies had been undertaken and a novel model was developed based on the clinical data reported in ANCHOR, MARINA and PIER studies.

Below we outline the approach taken for the model and provide an outline review based on a checklist suggested for the critical appraisal of cost-effectiveness analysis by Drummond and colleagues,[132] the requirements of NICE for submissions on cost-effectiveness (reference case)[133] and a suggested guideline for good practice in decision modelling by Philips and colleagues.[134]

Modelling approach
A Markov model was developed to simulate the change in visual acuity levels for cohorts of patients with subfoveal CNV receiving treatment with ranibizumab or, where appropriate, PDT and for a cohort of patients receiving best supportive care. Wet AMD subtypes (minimally classic, occult no classic and predominantly classic) were modelled separately. The model consists of five health states defined by visual acuity level and an absorbing death state. The visual acuity ranges for the health states are 6/15 or better (least severe), 6/18 to 6/30, 6/38 to 6/48, 6/60 to 3/60 and less than 3/60 (most severe) – although there is some inconsistency between the model and written submission on the definition of these ranges. The baseline cohort in the model has a mean age of 77 years [**CIC data removed**]. The initial distribution of the cohort across visual acuity states uses the proportions observed at baseline in the relevant clinical trials. Transitions probabilities for movement between visual acuity states, which allow for improvement or deterioration [**CIC data removed**], were derived from each of the clinical trials. As the ANCHOR trial compared ranibizumab treatment with PDT, there is no direct comparison of ranibizumab treatment with best supportive care for patients with predominantly classic lesions. As a result, the model includes an indirect comparison using data from the ANCHOR trial and TAP study. The mortality risk included is based on UK age- and sex-specific mortality rates (source not given) with an assumed relative risk of mortality of 1.5 for patients with visual acuity less than 6/60.

The model has a 3-month cycle length and a time horizon of 10 years.

[**CIC data removed**].

The model also assumes there is continued benefit, in terms of an increased probability of improvement and lower probability of deterioration in visual acuity, for 6 months following cessation of treatment with ranibizumab. It was assumed that for 3 months 89% of the full (i.e. on-treatment) efficacy of ranibizumab would continue, which would reduce to 66% of full benefit for a further 3 months. [**CIC data removed**]. The submission does not mention how these post-treatment benefits were derived. [**CIC data removed**].

The utility values applied in the submission were obtained from a study, sponsored by the manufacturer, to derive appropriate health state valuations from a general population. Participants completed a TTO exercise prior to insertion of contact lenses that would mimic visual impairment due to AMD. [**CIC data removed**]. After this, they underwent a vision assessment which was followed by completion of a health questionnaire and a TTO valuation of their changed visual state. [**CIC data removed**].

Model/cost-effectiveness results
The submission reports total costs and outcomes (vision years and QALYs) of ranibizumab treatment for three lesion types separately (predominantly classic, minimally classic and occult no classic) compared with best supportive care in its Tables 3.5, 3.7 and 3.8, for all lesion types together compared to best supportive care

(based on data from the PIER trial) in Table 3.6 and for predominantly classic lesions compared to PDT in Table 3.4. These tables also report incremental analyses with incremental cost per vision year gained and incremental cost per QALY gained.

The ICERs for ranibizumab are variable by lesion type and by comparator. The ICERs for patients with predominantly classic lesions are £4489 per QALY gained for the comparison with PDT (*Table 26*) and £14,781 per QALY gained when compared with best supportive care (*Table 27*). The ICERs are less favourable for occult no classic and minimally classic at around £26,000 per QALY gained (*Tables 28* and *29*). The ICER for patients with all types of lesions, derived from the PIER study where fewer injections were provided, is £12,050 per QALY gained (*Table 30*).

The submission concludes that ranibizumab is cost-effective when compared with either PDT (for patients with predominantly classic lesions) or best supportive care for all lesion types. Similar results to the base case analyses are reported for the probabilistic sensitivity analyses with a probability of 100% of ranibizumab being cost-effective at a willingness to pay threshold of £30,000 for patients with predominantly classic lesions when compared with PDT. Equivalent values for the comparison with best supportive care are 96% for predominantly classic, 59% for minimally classic and 57% for occult no classic for a willingness to pay threshold of £30,000.

The results reported here are based on the assumption that frequency of dosage of ranibizumab can be reduced [**CIC data removed**]. The submission reports less favourable ICERs if the frequency of dosage observed in the trials (monthly injections or 12 per year) is used in the model (see the later section 'Assessment of uncertainty', p. 58).

Outline appraisal of the cost-effectiveness analysis undertaken

A summary of the manufacturer's submission compared with the NICE reference case requirements is given in *Table 31*.

See Appendix 13 for a tabulation of the critical appraisal of the submission against Drummond and colleagues' checklist.[132]

Outline review of modelling approach

Model structure/structural assumptions. The use of a Markov cohort model seems appropriate given the need to track deterioration or improvement of visual acuity, in order to apply different utility values and expected costs to each of the health states within the model. Defining health states by visual acuity is consistent with clinical evidence

TABLE 26 *ANCHOR – predominantly classic lesions: ranibizumab 0.5 mg versus PDT*

	Cost (£)	QALY	Cost/QALY (£)
Ranibizumab	35,501	4.21	
PDT	34,584	4.01	
Incremental	917	0.20	4,489

TABLE 27 *ANCHOR – predominantly classic lesions: indirect comparison of ranibizumab 0.5 mg versus best supportive care*

	Cost (£)	QALY	Cost/QALY (£)
Ranibizumab	35,501	4.21	
Best supportive care	31,432	3.94	
Incremental	4,068	0.28	14,781

TABLE 28 *MARINA – occult no classic lesions: ranibizumab 0.5 mg versus best supportive care*

	Cost (£)	QALY	Cost/QALY (£)
Ranibizumab	31,326	4.71	
Best supportive care	22,201	4.36	
Incremental	9,125	0.34	26,454

TABLE 29 *MARINA – minimally classic lesions: ranibizumab 0.5 mg versus best supportive care*

	Cost (£)	QALY	Cost/QALY (£)
Lucentis	34,408	4.52	
Best supportive care	25,914	4.19	
Incremental	8,494	0.33	25,796

TABLE 30 *PIER – all types of AMD lesions: ranibizumab 0.5 mg versus best supportive care*

	Cost (£)	QALY	Cost/QALY (£)
Ranibizumab	31,323	3.89	
Best supportive care	28,202	3.63	
Incremental	3,120	0.26	12,050

TABLE 31 *Assessment of Novartis submission against NICE reference case requirements*

NICE reference case requirements[a]	Included in submission
Decision problem: as per the scope developed by NICE	✓
Comparator: alternative therapies routinely used in the NHS	✓
Perspective on costs: NHS and PSS	✓
Perspective on outcomes: all health effects on individuals	✓
Type of economic evaluation: cost-effectiveness analysis	✓ (CEA and CUA)
Synthesis of evidence on outcomes: based on a systematic review	×[b]
Measure of health benefits: QALYs	✓[c]
Description of health states for QALY calculations: use of a standardised and validated generic instrument	✓[d]
Method of preference elicitation for health state values: choice based method (e.g. TTO, SG, not rating scale)	✓[d]
Source of preference data: representative sample of the public	✓[d]
Discount rate: 3.5% p.a. for costs and health effects	✓

[a] See detail in the NICE report.[133]
[b] The efficacy data inputs were derived from patient-level data in clinical studies. However, there are no descriptions about the derivation. The inputs for best supportive care for patients with predominantly classic wet AMD were derived using simple indirect comparison method.
[c] Also included vision year gained as a health benefit measurement.
[d] From Brazier J; Appendix 1[140] of manufacturer's submission.

and reflects the underlying pathological process of wet AMD.

No rationale was given in the submission for the chosen cycle length. However, the cycle length of 3 months is believed to be the minimum interval over which visual acuity levels are likely to alter for patients receiving these interventions, and therefore for transitions to occur between the health states in the model. The model's time horizon of 10 years is reasonable and would be the approximate life expectancy for a patient entering the model at the mean age of 77 years. [**CIC data removed**] this time horizon is long enough to show important differences between interventions. Both the cost and benefits assigned to each health state over the modelled time horizon have been appropriately discounted at an annual rate of 3.5%.

One of the key inputs to the model is the time-to-event data derived from the clinical trials, which are used to model the rate of disease progression (or improvement) for patients receiving active treatment or best supportive care in the model. These data are used to derive the transition probabilities for patients' movement between health states. There is no description in the submission of the methods used to derive these transition probabilities other than a statement that [**CIC data removed**]. A clarification from the manufacturer indicates that the 3-monthly transition probabilities were assessed in a multinomial logistic regression model (MLRM). For each observation, the value of the previous month was included in the MLRM as a predictive variable. Hence the MLRM estimated the probability of being in the current state based on the previous state. The residuals of the MLRM were used to assess whether certain periods required specific modelling. Between the time points where the residuals showed increased deviance, subgroups of time were made, and this variable was added into the model as a predictive variable.

[**CIC data removed**].

Data inputs. The derivation of transition probabilities is unclear in the report and the subsequent explanation from the manufacturer has not clarified this issue.

[**CIC data removed**]

As no direct comparison with best supportive care is available for patients with predominantly classic lesions, an indirect comparison was carried out using data from the ANCHOR trial and TAP studies. Since the TAP study population included patients with all lesion types (predominantly, minimally classic and occult no classic), the comparability of patient populations in the data used for the indirect comparison would need to be established (specifically whether the efficacy of PDT was based on only the subgroup of patients

with predominantly classic lesions in the TAP study) before generating efficacy estimates for the comparison of ranibizumab and best supportive care. [**CIC data removed**]. To avoid this problem, the log(risk ratio) or log(odds ratio), rather than risk difference, could be considered when performing indirect comparisons.

The cost of concomitant therapy for the PDT cohort was included as part of the AMD treatment and yet a separate concomitant treatment component was added when estimating the average total cost for each treatment cycle. This double counting error caused the comparator to be more costly [**CIC data removed**] in each treatment cycle, which meant that the cost difference between PDT and ranibizumab was underestimated.

As discussed earlier, the utility values applied in the submission were obtained from a sample of the general population in a study sponsored by the manufacturer. Custom-made contact lenses were used to simulate the visual impairment resulting from AMD. Participants attempted common daily activities while wearing the lenses and also had a vision assessment. While experiencing visual impairment, participants valued their current level of visual acuity using the TTO method. The valuations were reported for ranges of visual acuity used in the manufacturer's economic model. [**CIC data removed**].[140]

Assessment of uncertainty. One-way sensitivity analyses and probabilistic sensitivity analyses were reported in the submission. One-way sensitivity analyses were conducted for number of ranibizumab injections per year and duration of post-treatment effect for ranibizumab.

Probabilistic sensitivity analysis was conducted to explore the impact of uncertainty around the input parameters on incremental cost effectiveness ratios for ranibizumab. [**CIC data removed**]. Uncertainty around the occurrence of adverse events is not included. The choice of distributions assigned to parameters in the probabilistic sensitivity analysis is appropriate. Formulae in the model appear generally to be correct. However, the variances for parameters [**CIC data removed**] have been underestimated, which may lead to overestimation of the probability that ranibizumab is cost-effective compared with PDT or best supportive care. The exclusion of uncertainty around the occurrence of adverse events and inappropriate estimation of parameter variances are unlikely to have a substantial impact [**CIC data removed**].

Summary of general concerns
There are some general concerns which are discussed above. Of these, the main concern is the number of ranibizumab injections considered in the model, which is lower than the number used in the clinical studies. Further analyses were conducted using the manufacturer's model.

Further analysis by TAR team using manufacturer's model
The manufacturer's model was checked and the reported results were able to be replicated except those using the data from PIER studies. The results from the manufacturer's model, as reported in the submission and after modification to take account of the concerns raised above are reported in *Table 32*.

The table presents the incremental costs, incremental QALYs and ICERs for patients with predominantly classic lesions (using PDT as comparator) after removing the double counting error and for all comparisons after removing the costs of administering sham injections. The final entry for each comparison shows the incremental costs, incremental QALYs and ICERs using the number of injections of ranibizumab [**CIC data removed**] given in both the MARINA and ANCHOR studies. This shows that the main driving factor for ICERs is the number of ranibizumab injections. [**CIC data removed**].

[**CIC data removed**]. Assuming 12 injections in year 1, the manufacturer's estimate of the ICER for the comparison of ranibizumab with PDT for patients with predominantly classic lesions was £24,544 per QALY gained and the ICER for the comparison of ranibizumab with best supportive care was £29,662 per QALY gained. The manufacturer's estimate of the ICERs for the comparison of ranibizumab with best supportive care for patients with minimally classic and occult no classic lesions (assuming 12 injections in year 1 and year 2 of treatment) were both approximately £55,000 per QALY gained.

[**CIC data removed**].

Independent economic assessment

Statement of the decision problem and perspective for the cost-effectiveness analysis

We developed a model to estimate the cost-effectiveness of ranibizumab and of pegaptanib

TABLE 32 *Summary of sensitivity analyses using manufacturer's model (ranibizumab)*

Model changes	Incremental cost (£)	Incremental QALY	ICER (£)
Predominantly classic lesions			
(a) PDT as comparator			
As reported in submission	917	0.20	4,489
(i) Removing double counting of concomitant treatment cost	1,462	0.20	7,159
(ii) Removing the use of triamcinolone	1,095	0.20	5,361
(iii) Removing costs associated with sham injection	1,024	0.20	5,014
(iv) All the above (i)–(iii)	1,659	0.20	8,121
Using (iv) as a base case scenario for sensitivity analyses on number of injections per year			
(v) [**CIC data removed**]			
(vi) 12 in 1st year[a]	5,754	0.20	28,176
Predominantly classic lesions			
(b) Best supportive care as comparator			
As reported in submission	4,068	0.28	14,781
(i) Removing costs associated with sham injection	4,217	0.28	15,322
Using (i) as a base case scenario for sensitivity analyses on number of injections per year			
(ii) [**CIC data removed**]			
(iii) 12 in 1st year[a]	8,313	0.28	30,203
Minimally classic lesions			
BSC as comparator			
As reported in submission	8,494	0.33	25,796
(i) Removing costs associated with sham injection	8,947	0.33	27,174
Using (i) as a base case scenario for sensitivity analyses on number of injections per year			
(ii–iv) [**CIC data removed**]			
(v) 12 in 1st year; 12 in 2nd year	18,408	0.33	55,906
Occult no classic			
BSC as comparator			
As reported in submission	9,125	0.34	26,454
(i) Removing costs associated with sham injection	9,578	0.34	27,767
Using (i) as a base case scenario for sensitivity analysis on number of injections per year			
(ii–iv) [**CIC data removed**]			
(v) 12 in 1st year; 12 in 2nd year	19,398	0.34	56,234

[a] Injections were assumed in the first year only as observed in ANCHOR trial.

compared with current practice or best supportive care in a UK cohort of adults with AMD. The perspective of the cost-effectiveness analysis is that of the NHS and PSS. Each of the interventions is analysed separately – no comparisons are made between the cost-effectiveness of ranibizumab and pegaptanib.

Strategies/comparators

The scope for the appraisal, as issued by NICE, states that the interventions to be considered are ranibizumab and pegaptanib within their licensed indications. The comparators for these interventions are best supportive care and, for the subgroup with a confirmed diagnosis of classic, no occult subfoveal AMD, PDT with verteporfin. Best supportive care in this group of patients will include blind registration, provision of low vision aids and visual rehabilitation and may also include provision of residential and nursing care as a result of patients' loss of vision.

Methods

Model type and rationale for the model structure

The primary outcome in the clinical trials reviewed in the section 'Results' (p. 20) was loss of fewer than 15 letters of visual acuity (for pegaptanib[95] and for ranibizumab in the MARINA[97] and ANCHOR[96] trials) or mean change in best corrected visual acuity (for ranibizumab in the PIER trial). Among the secondary outcomes reported for each trial were the proportions of patients gaining 15 letters, losing between 15 and 30 letters and losing more than 30 letters of visual acuity. These end-points are interpreted clinically as being categories of response (loss of less than 15 letters), intermediate vision loss (loss of 15–30 letters) and severe vision

loss (loss of more than 30 letters). To estimate the impact of these changes in visual acuity we required an appropriate model of disease progression with AMD and its effect on patients' quality of life. We conducted a systematic search of the literature to identify source material on the natural history, epidemiology and treatment of AMD (see Appendix 2 for details of the databases searched and the search strategy). References identified by these searches, along with previous economic evaluations reviewed in the section 'Systematic review of existing cost-effectiveness evidence' (p. 43), informed the development of a Markov state transition model.

The state transition diagram describing the six health states within the model and the allowable transitions between these states is shown in *Figure 2*. This description of the model was discussed with clinicians involved in the care and treatment of patients with AMD to ensure its comprehensiveness and clinical validity. In this diagram, ellipses indicate health states and arrows indicate allowable transitions between health states. Each of the health states in the diagram corresponds to approximately three lines (or 15 letters) of visual acuity, which (as stated in the section 'Outcomes', p. 17) is generally accepted as a clinically significant difference.

The state transition model indicates that an individual with AMD, in any of the health states defined by visual acuity, may remain in their current health state or may experience further vision loss. Individuals experiencing vision loss may progress by one or two states in any cycle. The primary aim of treatment for AMD is to reduce the rate of disease progression (as reflected in the primary end-points for clinical trials of treatment for AMD) and would be expressed in this model as a reduced probability of progressing to a lower visual acuity health state in each model cycle. Subjects in each health state are exposed to risks of mortality. For visual acuity greater than 6/60 these were assumed to be the general population mortality risks; we assumed that states indicating lowest visual acuity would be associated with excess mortality risks.

Although the primary aim of treatment to date has been to reduce the probability of disease progression, clinical trials have shown some patients experiencing improvements in visual acuity. Patients in both arms in the TAP study showed improvement of at least three lines of visual acuity at the 12-month follow-up (6.0 and 2.4% for the PDT and placebo arms, respectively). The dashed lines from each visual acuity state to the next higher state indicate the possibility of improvement.

The model adopts a 3-month cycle length and is used initially to estimate cost-effectiveness over the time horizon of the clinical trials providing input data (i.e. 1 or 2 years). The model is also used to extrapolate the effects from the clinical trials over the patient's lifetime.

Baseline cohort of patients with AMD

The baseline cohort comprises patients with AMD with an initial visual acuity between 6/12 and 6/24, who have a mean age of 75 years and 50% of whom are male.

Data sources

Effectiveness data

We have reported on the findings from our systematic review on the clinical effectiveness of

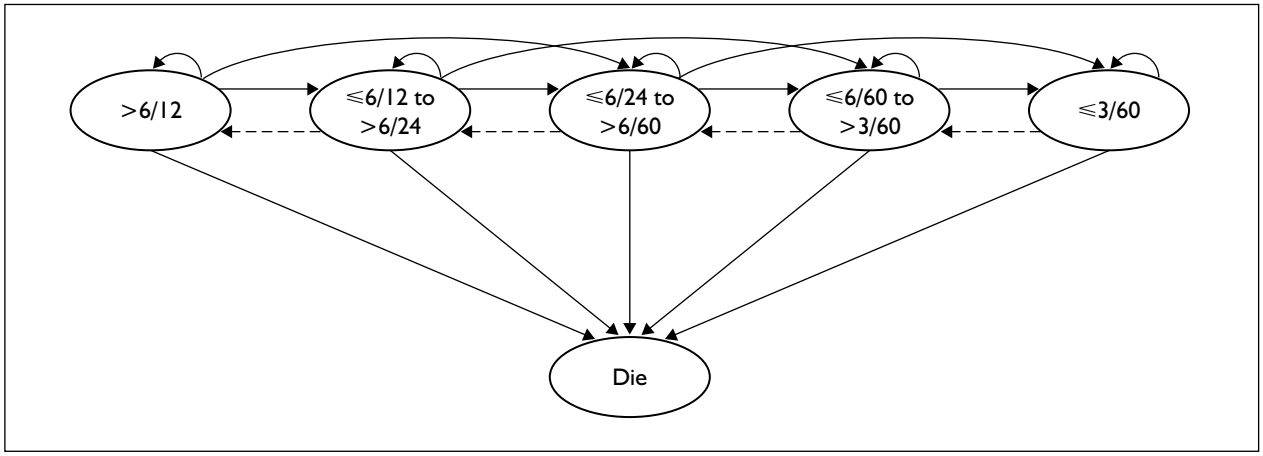

FIGURE 2 *State transition diagram*

ranibizumab and pegaptanib (see the section 'Assessment of effectiveness', p. 24) and also the findings of the review of natural history models and clinical effectiveness data used in economic evaluations of interventions included in this report (see the section 'Systematic review of existing cost-effectiveness evidence', p. 43).

Table 33 reports the transition probabilities applied in the model to estimate the effectiveness of pegaptanib. These were derived from the proportion of patients in the VISION study experiencing transitions indicated in the state transition diagram and are based on changes in visual acuity from baseline, reported for each year of the study (see *Table 13*, p. 25, for year 1 and year 2 results from the VISION study).

The annual proportions of patients in the VISION study reported as gaining or losing visual acuity were transformed to cycle probabilities using the density method proposed by Miller and Homan,[141] assuming that the transition rate remains constant during the period of observation. Transition probabilities applied in year 1 of the model were based on the proportions of patients gaining at least three lines, losing at least three and less than six lines and those losing at least six lines of visual acuity in the first year of the study. Year 2 transition probabilities were based on the proportions observed from baseline to year 2 of the study. These data are used directly in the short term (i.e. trial-based) analysis. To extrapolate effects beyond the trial period, the transition probabilities estimated for year 2 in the usual care cohort were applied to each arm of the model in years 3–10. Given that treatment with pegaptanib had stopped at this point, it meant that the benefits would decline at the same rate as those for usual care, although from a higher level of visual acuity. This assumption suggests that the benefits of pegaptanib are predominantly symptomatic. Mills and colleagues[142] reported that patients randomised to discontinuing treatment (following 54 weeks of treatment with pegaptanib in the VISION trials) continued to experience statistically significant benefit after another 48 weeks compared with those who received the sham treatment throughout the study period (*Table 34*). We included a disease-modifying effect for pegaptanib through sensitivity analysis in the model.

Adverse events associated with intraocular injection of pegaptanib were reported for the first year of the VISION trial and are discussed in the section 'Adverse events' (p. 35). Three serious adverse events (endophthalmitis, traumatic lens injury and retinal detachment), associated with significant risk of severe loss of visual acuity and also health care management costs, were identified[95] and their frequencies of occurrence are reported in *Table 35*. The proportion of adverse events, per injection, was treated as the

TABLE 33 *Transition probabilities used to model effectiveness of pegaptanib, derived from the VISION study*

	Year 1[95]		Year 2[105]	
	Pegaptanib	**Control**	**Pegaptanib**	**Control**
Gain at least 3 lines	0.0157	0.0051	0.0128	0.0048
Gain or lose less than 3 lines			Default	
Lose between 3 and 6 lines[a]	0.0555	0.0626	0.0412	0.0419
Lose at least 6 lines	0.0247	0.0601	0.0169	0.0372

[a] Not reported in Gragoudas and colleagues[95] or the manufacturer's submission. This was estimated as the difference between the total number of patients in the trial arm and those responding (i.e. losing less than 15 letters of visual acuity) or losing at least six lines, as reported in *Table 13*.

TABLE 34 *Disease-modifying effect of pegaptanib*

Dose (mg)	Relative risk of non-response (95% CI)	*p*-Value
All doses pooled	0.70 (0.57 to 0.88)	0.001
0.3	0.68 (0.51 to 0.90)	0.008
1	0.62 (0.46 to 0.83)	0.001
3	0.79 (0.61 to 1.03)	0.09

TABLE 35 *Injection-related adverse events in year 1 of the VISION trial*

Adverse event	Events per patient (n = 890) (%)	Events per injection (n = 7545) (%)
Endophthalmitis	1.35	0.16
Traumatic injury to lens	0.56	0.07
Retinal detachment	0.67	0.08

probability of each adverse event occurring, per injection received by patients in the pegaptanib cohort in the model.

This may overestimate the adverse event rate for pegaptanib, since the majority of endophthalmitis cases were associated with protocol violations. A reduced proportion of adverse events was reported following a change in aseptic procedures in the trial. However, we adopted the conservative assumption of using the proportion of adverse events observed during the trial.

Tables 36 and *37* report the transition probabilities applied in the model to estimate the effectiveness of ranibizumab in the treatment of patients with predominantly classic or minimally classic/occult no classic lesions, respectively. These were derived from the proportion of patients in the ANCHOR and MARINA trials experiencing the transitions indicated in the state transition diagram and are based on changes in visual acuity from baseline reported for each year of each study (see *Table 13*, p. 25).

The annual proportion of patients in each trial reported as gaining or losing visual acuity was transformed to cycle probabilities using the density method as described above.

For patients with predominantly classic lesions, two analyses were undertaken. The first analysis used data from the ANCHOR trial to estimate the cost-effectiveness of treatment with ranibizumab compared with PDT. Since PDT is not currently recommended by NICE for patients with predominantly classic lesions, other than in clinical trials,[77] a second analysis was undertaken comparing ranibizumab with best supportive care, based on an indirect comparison with the placebo arm of the TAP study, using data reported for the subgroup of patients with predominantly classic lesions.[111]

Transition probabilities derived from the MARINA trial were used to model the effectiveness of ranibizumab for patients with minimally classic and occult no classic lesions. Transition

TABLE 36 *Transition probabilities used in model, derived from the ANCHOR trial*

	Year 1	
	Ranibizumab	**Control**
Gain at least 3 lines	0.0624	0.0143
Gain or lose less than 3 lines	Default	
Lose between 3 and 6 lines[a]	0.0046	0.0614
Lose at least 6 lines	0.0000	0.0351

[a] Not reported in trial publication.[96] The proportion of patients losing between 3 and 6 lines was estimated by subtracting the proportion of patients responding (i.e. losing less than 15 letters of visual acuity) plus the proportion losing at least 6 lines from 1.

TABLE 37 *Transition probabilities used in model, derived from the MARINA trial*

	Year 1		Year 2	
	Ranibizumab	**Control**	**Ranibizumab**	**Control**
Gain at least 3 lines	0.0503	0.0127	0.0494	0.0096
Gain or lose less than 3 lines			Default	
Lose between 3 and 6 lines[a]	0.0053	0.0648	0.0097	0.0675
Lose at least 6 lines	0.0016	0.0378	0.0032	0.0623

[a] Not reported in trial publication.[97] The proportion of patients losing between 3 and 6 lines was estimated by subtracting the proportion of patients responding (i.e. losing less than 15 letters of visual acuity) plus the proportion losing at least 6 lines from 1.

probabilities applied in year 1 of the model were based on the proportions of patients gaining at least three lines, losing at least three and less than six lines and those losing at least six lines of visual acuity in the first year of the trial. Transition probabilities applied in the second year of the model were based on the proportions observed from baseline to year 2 in the trial. These data are used directly in the short-term (i.e. trial-based) analysis. To extrapolate effects beyond the trial period, the transition probabilities estimated for year 2 in the control arm of the trial were applied to each arm of the model in years 3–10.

Adverse events reported in the ANCHOR and MARINA trials are discussed in the section 'Adverse events' (p. 35). The proportions of patients experiencing serious adverse events during the ANCHOR trial are reported in *Table 38*. These annual proportions are converted to cycle probabilities using the density method.[141] The probabilities of experiencing an injection-related adverse event are applied in each model cycle during which treatment by intraocular injection occurs.

The proportions of patients experiencing serious adverse events during the MARINA trial are reported in *Table 39*. These are 2-year cumulative proportions and are converted to cycle probabilities using the density method.[141] The probabilities of experiencing an injection-related adverse event are applied in each model cycle during which treatment by intraocular injection occurs.

Health state values/utilities

The health state utilities adopted in the cost-effectiveness model are those reported by Brown and colleagues[113] and derived using the TTO method. These values were estimated in a population of consecutive patients seen at the Retina Vascular Unit at Wills Eye Hospital, Philadelphia, with vision loss due to AMD and whose visual acuity was 6/12 or worse in at least one eye. Utilities were elicited from 72 patients using both TTO and SG methods. For the TTO method, patients were asked how many years of their remaining life expectancy they would be prepared to trade to receive a technology that would guarantee permanent perfect vision in each eye. *Table 40* reports the mean TTO valuations relevant to health states in our model.

As noted in the review of research on quality of life in AMD, there is limited evidence on health state utilities, with one group of researchers providing the majority of published valuations (Brown and colleagues[113,129] and Sharma and colleagues[143]). The TTO valuations reported by Brown and colleagues[113] were adopted in our model as theirs are the most credible published utility values for visual loss associated with AMD, and the TTO valuations have been the most widely used in previous cost–utility studies of treatment for AMD[40,86,87,116] (see review in the section 'Systematic review of existing cost-effectiveness evidence', p. 43). To test the sensitivity of source of valuations, the SG values were used in the sensitivity analysis. The upper and lower CIs of the TTO valuations were used to test sensitivity of results to variation in parameter values.

Cost data. Costs in the model were developed in two stages. First the additional resource use, in terms of diagnostic tests, investigations and outpatient visits required for drug administration

TABLE 38 *Injection-related adverse events in the ANCHOR trial*

Adverse event	Events per patient (*n* = 140) (%)
Endophthalmitis	1.43
Traumatic injury to lens	0.00
Retinal detachment	0.36[a]
Uveitis	0.07

[a] One case of retinal detachment in the 0.3-mg ranibizumab arm – proportion for the model estimated as a proportion across both ranibizumab arms in the trial [i.e. 1/(137 + 140)].

TABLE 39 *Injection-related adverse events in the MARINA trial*

Adverse event	Events per patient (*n* = 239) (%)
Endophthalmitis	1.3
Uveitis	1.3
Retinal tear	0.4
Vitreous haemorrhage	0.4
Lens damage	0.4

TABLE 40 *Health state utilities used in economic model*

Visual acuity range	Mean utility	SD	95% CI
>6/12	0.89	0.16	(0.82 to 0.96)
6/12 to 6/24	0.81	0.20	(0.73 to 0.89)
6/24 to 6/60	0.57	0.17	(0.47 to 0.67)
6/60 to3/60	0.52	0.24	(0.38 to 0.66)
<3/60	0.40	0.12	(0.29 to 0.50)

and monitoring of patients while on treatment were identified, based on clinical guidelines and discussion with ophthalmic specialists at Southampton General Hospital Trust. These are described below as intervention costs. Second, literature describing the costs associated with vision loss was reviewed and appropriate estimates applicable to the UK setting were extracted and used in the analysis.

Intervention costs. The frequency and intensity of monitoring of patients being treated with ranibizumab and pegaptanib were identified based on clinical guidelines and discussion with ophthalmic specialists. The treatment pathways for patients with AMD receiving treatment with pegaptanib, ranibizumab, PDT or supportive care are illustrated in *Figure 3*.

All new patients are evaluated in the outpatient department, receiving an extended outpatient appointment for medical assessment, a vision assessment and imaging using FA and OCT. Those patients proceeding to active treatment are assumed to receive their first drug treatment immediately following their initial outpatient consultation. For subsequent treatments, patients are assumed to have a standard outpatient appointment, vision assessment and OCT followed by the drug administration procedure. While patients remain on treatment they receive monitoring of their condition using OCT at each attendance and additional FA every 3–6 months. On discontinuation of treatment (premature termination of treatment or at the scheduled end of treatment), patients are assessed using FA.

Patients treated with pegaptanib would be seen 17 times during 2 years of treatment (the maximum treatment duration in VISION trials). This corresponds to 6-weekly visits (or nine visits in year 1 and eight visits in year 2), as stated in the Summary of Product Characteristics (SPC).[92] Patients treated with ranibizumab would be seen 12 times during 1 year of treatment (the maximum treatment duration in the ANCHOR trial) and 24 times during 2 years of treatment (the maximum treatment duration in the MARINA trial). This corresponds to 4-weekly visits, which was the frequency of treatment in the trials as stated in the SPC. Administration of both drugs is assumed to occur during the patient's hospital attendance for outpatient follow-up, but incurs additional costs since the injection procedure is carried out under aseptic conditions requiring the use of surgical hand disinfection and sterile equipment.

In addition to the excess costs of health service contacts for patients undergoing treatment, the costs of the drugs also need to be estimated. Drug unit costs for pegaptanib were taken from the BNF.[82] Drug unit costs for ranibizumab were based on the the manufacturer's target price for the UK (since this report was written, ranibizumab has received marketing authorisation and the UK unit price has been confirmed at £761.20 for a 0.3-ml vial).

Drug costs for pegaptanib were calculated for a dosage of 0.3 mg administered as an outpatient procedure every 6 weeks for up to 2 years. A 0.3-mg vial of pegaptanib costs £514 and total drug cost for 1 year of pegaptanib treatment is therefore £4626 (or £9252 for a patient receiving the maximum of 2 years of treatment evaluated in the VISION study).

Drug costs for ranibizumab were calculated for a dosage of 0.5 mg administered as an outpatient procedure every month for up to 1 year in analysis using ANCHOR data and up to 2 years in analysis using MARINA data. A 0.3-ml vial of ranibizumab costs £761.20 and the total drug cost is £9134.40 for 1 year and £18,268.80 for 2 years.

The costs of managing the treatment related ocular adverse events were taken into account in our analyses. Management of endophthalmitis was assumed to require an intravitreal tap and injection, five extended outpatient visits and treatment with topical steroid. Traumatic lens injury requires cataract extraction, three extended outpatient visits and treatment with topical steroid, and retinal detachment requires cryotherapy with buckle/vitrectomy, three extended outpatient visits and treatment with topical antibiotic and topical steroid. Unit costs and sources are reported in *Table 41*.

Health state costs. Health state costs associated with vision loss are based on estimates developed in the systematic review and economic evaluation by Meads and colleagues.[40] These are applied to visual acuity states in the model ⩽6/60. Relevant categories of costs and the proportions of patients receiving services were taken from Meads and colleagues[40] to estimate resource use. Unit costs were taken from Unit Costs of Community Care (Curtis and Netten[135]) and NHS Reference Costs[84] as shown in *Table 42*. All costs are expressed as 2005 prices.

Blind registration, provision of low-vision aids and low-vision rehabilitation are one-off costs associated

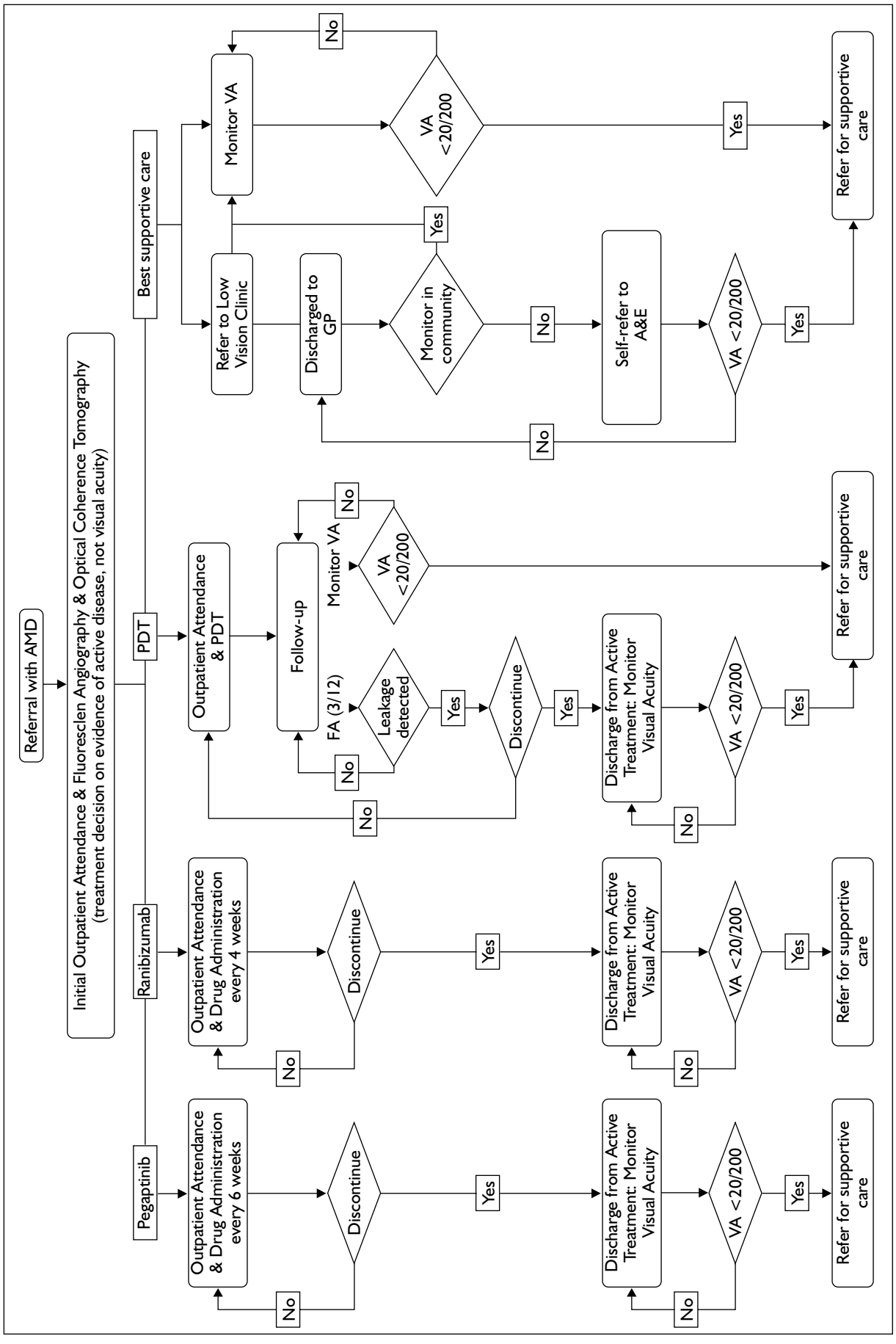

FIGURE 3 *Treatment pathways for patients with AMD referred for specialist care*

TABLE 41 *Management costs for injection-related adverse events*

Management of adverse event	Unit cost (£)	Source
Endophthalmitis		
Intravitreal tap and injection	2077	NHS Reference Costs[84]
Extended outpatient visit	96	NHS Reference Costs[84]
Topical steroid	3.21	BNF[82]
Traumatic injury to lens		
Cataract extraction	1119	NHS Reference Costs[84]
Extended outpatient visit	96	NHS Reference Costs[84]
Topical steroid	3.21	BNF[82]
Retinal detachment		
Cryotherapy with buckle/vitrectomy	1725	NHS Reference Costs[84]
Extended outpatient visit	96	NHS Reference Costs[84]
Topical steroid	3.21	BNF[82]
Topical antibiotic	1.32	BNF[82]

TABLE 42 *Additional costs associated with vision loss below best corrected visual acuity of 6/60 in better-seeing eye*

Service	% receiving services	Unit cost (£)	Source	Annual cost (£)[a]
Blind registration	95	115	Meads and colleagues,[40] Curtis and Netten[135]	109
Low-vision aids	33	150	Meads and colleagues[40]	50
Low-vision rehabilitation	11	259	Curtis and Netten[135]	28
Community care	6	6,552	Curtis and Netten[135]	393
Residential care	30	13,577	Curtis and Netten[135]	4,073
Depression	39	431	Knapp and colleagues[144]	168
Hip replacement	5	5,379	NHS Reference Costs, 2005[84]	269

[a] Annual cost is estimated by multiplying unit costs by the proportion of eligible patients estimated as receiving each service.

with loss of vision below 6/60. Unit costs were estimated using the doctor's sessional fee for completing the Certificate of Vision Impairment and an initial assessment by a community occupational therapist (1 hour) for blind registration. Unit costs reported by Meads and colleagues[40] (uplifted to 2005 values) were adopted for the provision of low-vision aids. The cost of an episode of care with a community occupational therapist was adopted as the unit cost for low-vision rehabilitation.

Community care costs were estimated as the annual cost for a local authority home care worker, and residential care costs were based on annual cost of private residential care (taking into account that approximately 30% of residents pay themselves).

Using the estimated annual costs in *Table 42* gives a cost of £5090 for the first year of blindness and £4903 for each subsequent year, since the first three items (blind registration, provision of low-vision aids and low-vision rehabilitation) are assumed only to be provided in the first year when visual acuity falls below 6/60.

Discounting of future costs and benefits

A discount rate of 3.5% was applied to future costs and benefits in line with current guidance from NICE.[133] Discount rates of 0 and 6% were applied in the sensitivity analyses.

Presentation of results

We report findings on the cost-effectiveness of interventions based on the analysis of a cohort of patients having age and sex characteristics, as discussed earlier. For the interventions being assessed in this report, comparisons for pegaptanib are made against usual care for a cohort of patients with AMD irrespective of lesion type. For ranibizumab, separate analyses are presented, based on MARINA and ANCHOR trial results, for predominantly classic, minimally classic and occult no classic lesions separately. For all comparisons a short-term analysis is presented,

without extrapolation beyond clinical trial data, and a longer term analysis extrapolating to a 10-year time horizon (the approximate life expectancy for patients aged 75 years, with AMD but with visual acuity levels greater than 6/60).

We report the results of these comparisons in terms of the incremental gain in QALYs and the incremental costs determined in the cohort analysis.

Assessment of uncertainty in the SHTAC analysis (sensitivity analysis)

Parameter uncertainty is addressed using probabilistic sensitivity analysis. Probability distributions are assigned to the point estimates used in the base case analysis. The point estimates for state transitions are reported in *Tables 33–37* and for health state costs in *Table 42*. Distributions are also assigned to the health state utilities reported in *Table 40* and these are sampled during the probabilistic analysis. Appendix 14 reports the variables included in the probabilistic sensitivity analysis, the form of distribution used for sampling and the parameters of the distribution.

Deterministic sensitivity analysis is used to address particular areas of uncertainty in the model related to:

- model structure
- methodological assumptions
- parameters around which there is considerable uncertainty or which may be expected, *a priori*, to have a disproportionate impact on study results.

The purpose of this analysis is to identify clearly the impact of this uncertainty and to test the robustness of the cost-effectiveness results to variation in structural assumptions and parameter inputs.

SHTAC cost-effectiveness model – summary of methods

- We devised a Markov state transition model to estimate the cost-effectiveness of treatment for AMD, from the perspective of the NHS and PSS. This was based on our systematic review of literature on natural history, epidemiology and health-related quality of life in AMD, together with a systematic review of the literature on the clinical effectiveness and cost-effectiveness of treatment.
- The model includes six health states (five defined by declining visual acuity and one for death from all causes). People with AMD and visual acuity less than 6/60 have a 50% higher risk of death than the general population.
- A cohort of patients pass through these states at different rates. The baseline cohort comprises patients with AMD with an initial visual acuity between 6/12 and 6/24, who have a mean age of 75 years and 50% of whom are male.
- The model has a 10-year horizon (the approximate life expectancy for patients aged 75 years, with AMD but with visual acuity levels greater than 6/60), with a cycle length of 3 months.
- Published quality of life weights estimated from valuations by patients with AMD were used to derive the QALYs associated with each treatment.
- To assess costs associated with treatment for AMD, resource use was estimated from clinical guidelines and advice from clinical practitioners. Where available, drug costs were taken from the current BNF.[82] Since no quoted UK price is available for ranibizumab, we used the manufacturer's target price for the UK. To estimate costs associated with blindness, values from a UK review and appropriate sources for UK unit costs were used.
- Costs and benefits were discounted at 3.5%.

Results

Cost-effectiveness of pegaptanib – base case analysis

Cost-effectiveness findings are presented for a cohort of patients with AMD having the age and sex characteristics reported in the literature and described in the section 'Methods' (p. 59). Discounted costs, identifying the contribution of drugs, drug administration and monitoring while on treatment, management of adverse events, co-administration of PDT and costs associated with vision loss, are presented along with life expectancy and quality-adjusted life expectancy for patients in the cohort. Findings are presented for the incremental cost per life-year gained, incremental cost per vision-year gained and incremental cost per QALY.

Costs and outcomes modelled for a cohort of AMD patients, with initial visual acuity between 6/12 and 6/24, receiving usual care or pegaptanib are presented in *Table 43*. Costs and health outcomes in the table have been discounted at 3.5%.

This comparison is based on patients receiving a maximum of 2 years of treatment with pegaptanib, with the frequency of drug administration as reported over the 2 years of the VISION study.[95,105]

TABLE 43 *Cost-effectiveness of pegaptanib against usual care – base case analysis*

Treatment	Cost (£)	Life-years	Vision-years	QALYs	Incremental cost per QALY gained (£)
2-Year time horizon (no extrapolation beyond trial data)					
Usual care	2,558	1.89	1.55	1.37	
Pegaptanib	12,817	1.90	1.73	1.43	163,603
10-Year time horizon					
Usual care	16,600	6.47	3.28	3.89	
Pegaptanib	24,662	6.55	3.99	4.15	30,986

TABLE 44 *Breakdown of total costs for each cohort by major categories – base case analysis*

Treatment	Cost (£)				
	Drug	Administration and monitoring	Managing adverse events	PDT	Blindness
2-Year time horizon (no extrapolation beyond trial data)					
Usual care	–	220	–	590	1,747
Pegaptanib	7,388	4,107	98	404	820
10-Year time horizon					
Usual care	–	220	–	590	15,789
Pegaptanib	7,388	4,107	98	404	12,666

As expected, for the trial-based analysis and for the 10-year time horizon, there is little difference in life expectancy between the pegaptanib and usual care cohorts, despite the assumed 50% increased mortality risk for patients with visual acuity below 6/60. Outcomes measured as vision-years emphasise the difference between the two cohorts in the proportion of life expectancy spent with visual acuity greater than 6/60 (difference in vision years of 0.19 for a 2-year time horizon and 0.71 for a 10-year time horizon), assuming an equal weighting for time spent in all health states with visual acuity greater than 6/60. The incremental gain is lower when measuring outcome in QALYs (0.06 QALYs at 2 years and 0.26 at 10 years).

There is a large cost difference between pegaptanib and usual care at 2 years. Pegaptanib costs are five times those for the usual care cohort, with an absolute difference of £10,259, which taken together with the small QALY gain leads to a large ICER of £163,603. The cost difference is reduced at 10 years (£8062, with costs for pegaptanib being 49% higher than for usual care). *Table 44* reports the breakdown of costs at 2 and 10 years, indicating that all excess costs of treatment are realised in the first 2 years whereas costs of blindness represent a small proportion of total costs. Although the difference in cost of blindness between the pegaptanib-treated and usual care cohorts at 10 years does not offset in full the costs of treatment with pegaptanib, the increased proportion of total costs accounted for by costs of disease progression, together with the increased QALY gain, yields a reduced ICER of £30,986.

Cost-effectiveness of pegaptanib – deterministic sensitivity analysis

We conducted a sensitivity analysis to consider the effect of uncertainty around the model structure and for variation in certain key parameters that were expected, *a priori*, to be influential on the cost-effectiveness results. The method we adopted was univariate sensitivity analysis, that is, varying one parameter at a time, leaving all other variables unchanged. This is to highlight the impact, if any, of each selected parameter alone on the cost-effectiveness results. The effects of uncertainty in multiple parameters were addressed using probabilistic sensitivity analysis, which is reported later in the section.

Table 45 reports the results of the sensitivity analysis. Except for the sensitivity analysis with respect to time horizon, all analyses were conducted using the 10-year model. The table is divided to distinguish between analyses undertaken due to uncertainties over structural

TABLE 45 *Deterministic sensitivity analysis – pegaptanib*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Reference case		8,062	0.26	30,986
Structural assumptions				
Time horizon	3 years	9,589	0.11	87,428
(10 years)	5 years	8,719	0.18	49,076
	8 years	8,170	0.24	34,409
Disease-modifying effect	Year 3 only	7,710	0.29	26,896
	Year 3 onwards	6,941	0.34	20,467
Stop treatment on entering 6/60 state		7,365	0.26	28,530
Methodological uncertainty				
Discount rates (3.5% for	0% for cost and outcome	7,893	0.29	26,782
costs and outcomes)	6% for cost and outcome	8,154	0.24	34,029
Baseline cohort characteristics				
Age of cohort at start of	–15 years	7,533	0.27	27,537
simulation (75 years)	–10 years	7,647	0.27	28,108
	+5 years	8,300	0.24	34,040
Proportion of cohort that is	40%	8,042	0.26	30,801
male (50%)	60%	8,062	0.26	30,986
Visual acuity at baseline	50% 6/12 to 6/24 and 50% 6/24 to 6/60	8,063	0.22	35,913
(6/12 to 6/24)	6/24 to 6/60	8,063	0.17	46,285
Parameter uncertainty				
Number of injections	9 in year 1 (8.4)	8,522	0.26	32,752
	8 in year 2 (6.9)	8,823	0.26	33,910
	9 in year 1 (8.4) and 8 in year 2 (6.9)	9,282	0.26	35,676
Cost of outpatient	25 percentile	7,766	0.26	29,846
attendance	75 percentile	8,362	0.26	32,140
Cost of injection procedure	Costed as day-case procedure	12,449	0.26	47,845
Health state utilities	SG values	8,062	0.21	38,226
	TTO values (lower CI)	8,062	0.28	28,749
	TTO values (upper CI)	8,062	0.24	33,142
Costs of blindness	High uptake/high costs	–236	0.26	Pegaptanib dominates
	Low uptake/low costs	10,559	0.26	40,582
	High costs/medium uptake	6,030	0.26	23,174
	Low costs/medium uptake	9,667	0.26	37,154
	High uptake/medium costs	3,703	0.26	14,230
	Low uptake/medium costs	9,774	0.26	37,563

assumptions in the model, uncertainties over the composition of the baseline cohort and uncertainty over parameter values.

As shown in *Table 43*, time horizon has a strong effect on the cost-effectiveness estimates for pegaptanib. As the time horizon increases, the incremental cost of pegaptanib reduces (greater disease progression in the usual care cohort leads to increased costs associated with services for visual impairment, which offset an increasing proportion of treatment costs for the pegaptanib cohort) and incremental QALY gain increases. This occurs where the same transition probabilities between states are assumed for the pegaptanib cohort post-treatment as for usual care. An analysis reported by Mills and colleagues[142] suggests that pegaptanib may have a disease-modifying effect, rather than simply treating AMD symptoms, which would have an impact on cost-effectiveness estimates for any extrapolated model. Based on an analysis of non-response (i.e. loss of at least 15 letters of visual acuity from baseline) in patients randomised to discontinue treatment at year 1 and those who were never treated, it is suggested that pegaptanib treatment is associated with a 30% reduction in non-response. This relative risk reduction was applied to the estimated transition probabilities for losing 3–6 lines and losing greater than six lines of visual acuity in the sensitivity analysis. Since this effect has only been demonstrated for patients in the year following discontinuation of treatment, it was first applied only in year 3 of the 10-year model.

This reduced the incremental cost by approximately £350 and increased the QALY gain by 0.03, yielding an ICER of £26,896. Subsequently the relative risk reduction was applied to the transition probabilities for losing visual acuity from year 3 through to year 10, reducing the ICER to £20,467.

In the base case, it was assumed that treatment with pegaptanib would be stopped when patients' visual acuity falls below 3/60. An alternative stopping rule was tested with treatment stopping when visual acuity falls below 6/60. For this analysis, the probability of losing visual acuity estimated for usual care was applied to patients in the pegaptanib cohort once their visual acuity fell below 6/60. This has very little impact on incremental QALYs, but reduces incremental cost by approximately £700, reducing the ICER to £28,530.

Varying the discount rates applied has comparatively little effect. Zero discount rates for costs and outcomes result in a slight reduction in incremental cost and a slight increase in incremental QALYs compared with baseline values. Conversely, applying a discount rate of 6% results in a slight increase in incremental cost and a reduction in incremental QALYs and hence a slightly higher ICER.

Varying the composition of the initial cohort of patients in the model by reducing the proportion of the cohort assumed to be male has little impact on cost-effectiveness. Varying the age of the cohort at the start of the model showed lower cost-effectiveness estimates for younger ages. Varying the distribution of initial visual acuity had a large impact on cost-effectiveness estimates. A cohort equally split between the 6/12 to 6/24 and 6/24 to 6/60 states produced an ICER of approximately £37,122, whereas a cohort with initial visual acuity of 6/24 to 6/60 produced an ICER of approximately £46,285.

The analyses presented in *Table 45* assumed that the intravitreal injection is provided in outpatients, and used an outpatient unit cost estimate. If the higher cost assumed for providing injections as day cases is used, the ICER increases substantially, to £47,845.

As suggested by the cost breakdown in *Table 44*, the estimated costs of blindness have a substantial impact on cost-effectiveness estimates. Adopting the high and low estimates for costs and uptake of services estimated by Meads and colleagues,[40] listed in *Table 46*, showed wide variations in incremental cost from a situation where pegaptanib was cost saving over a 10-year time horizon (assuming high cost and high uptake for each service) to a 31% increase over the base case estimate for incremental cost (assuming low cost and low uptake for each service).

To indicate which variable, costs or uptake, was more influential on cost-effectiveness estimates, additional analyses were undertaken using the extreme values for uptake combined with medium cost and extreme values for cost combined with medium uptake. *Table 45* shows that the cost-effectiveness estimates were most sensitive to assumptions over uptake, estimated as the proportion of eligible cases (i.e. with visual acuity less than 6/60) receiving services.

Other parameters included in the sensitivity analysis had comparatively little impact on the cost-effectiveness of pegaptanib.

Cost-effectiveness of pegaptanib – probabilistic sensitivity analysis

In a probabilistic sensitivity analysis for pegaptanib, where probabilities of losing or gaining visual acuity, the size of disease-modifying effect, health state utility values, cost of outpatient attendances, FA and OCT and costs of services for

TABLE 46 *Medium, high and low estimates of uptake of services and unit costs included in costs of blindness adopted in sensitivity analysis*

	Uptake of services (%)			Unit costs of services (£)		
	Medium	High	Low	Medium	High	Low
Blind registration	94.5	94.5	50.0	115	170	40
Low-vision aids	33.0	74.0	33.0	150	150	56
Low-vision rehabilitation	11.0	11.0	11.0	259	309	125
Community care	6.0	40.0	6.0	6,552	6,552	1,560
Residential care	30.0	56.0	13.0	13,577	23,988	6,500
Depression treatment	39.0	50.0	6.0	431	431	431
Hip replacement	5.0	24.7	0.5	5,753	6,886	3,481

visual impairment were sampled probabilistically, the majority of simulations produced incremental cost-effectiveness estimates that were in the north-east quadrant of the cost-effectiveness map (*Figure 4*). That is, the majority of simulations are associated with increased QALYs but also increased costs. However a small number of simulations have negative incremental costs. Simulations where costs for the pegaptanib cohort are lower than for the usual care cohort are most likely to be associated with extreme high values for costs of blindness.

In this analysis, pegaptanib had a probability of being cost-effective (compared with usual care) of 17% at a willingness to pay threshold of £20,000 per QALY and 58% at a willingness to pay threshold of £30,000 per QALY (*Figure 5*).

Cost-effectiveness of ranibizumab – base case analysis

Cost-effectiveness findings are presented for a cohort of patients with AMD having age and sex characteristics described in the section 'Methods' (p. 59). Discounted costs, identifying the contribution of drugs, drug administration and monitoring while on treatment, management of adverse events and costs associated with vision loss, are presented along with life expectancy and quality-adjusted life expectancy for patients in the cohort. Separate analyses are presented for patients with predominantly classic lesions (based on clinical data from the ANCHOR trial[96]) and for patients with minimally classic and occult no classic lesions (based on clinical data from the MARINA trial[97]). Findings are presented showing the life-years, vision-years and the QALYs associated with each intervention and the incremental cost per QALY for ranibizumab against best supportive care, for all lesion types, and against PDT for patients with predominantly classic lesions.

Costs and outcomes modelled over the clinical trial time horizons, for a cohort of AMD patients, with initial visual acuity between 6/12 and 6/24, receiving best supportive care (all lesion types), PDT (predominantly classic lesions) or ranibizumab are presented in *Table 47*. Where relevant, costs and health outcomes in the table have been discounted at 3.5%.

The analyses presented in *Table 47* have adopted the time horizons of the relevant clinical trial reports, hence the time horizon for the analyses of ranibizumab against PDT or against best supportive care for patients with predominantly classic lesions is 1 year, the reported duration of the ANCHOR trial. The time horizon for the comparison of ranibizumab against best supportive care for patients with minimally classic or occult no classic lesions is 2 years, the reported

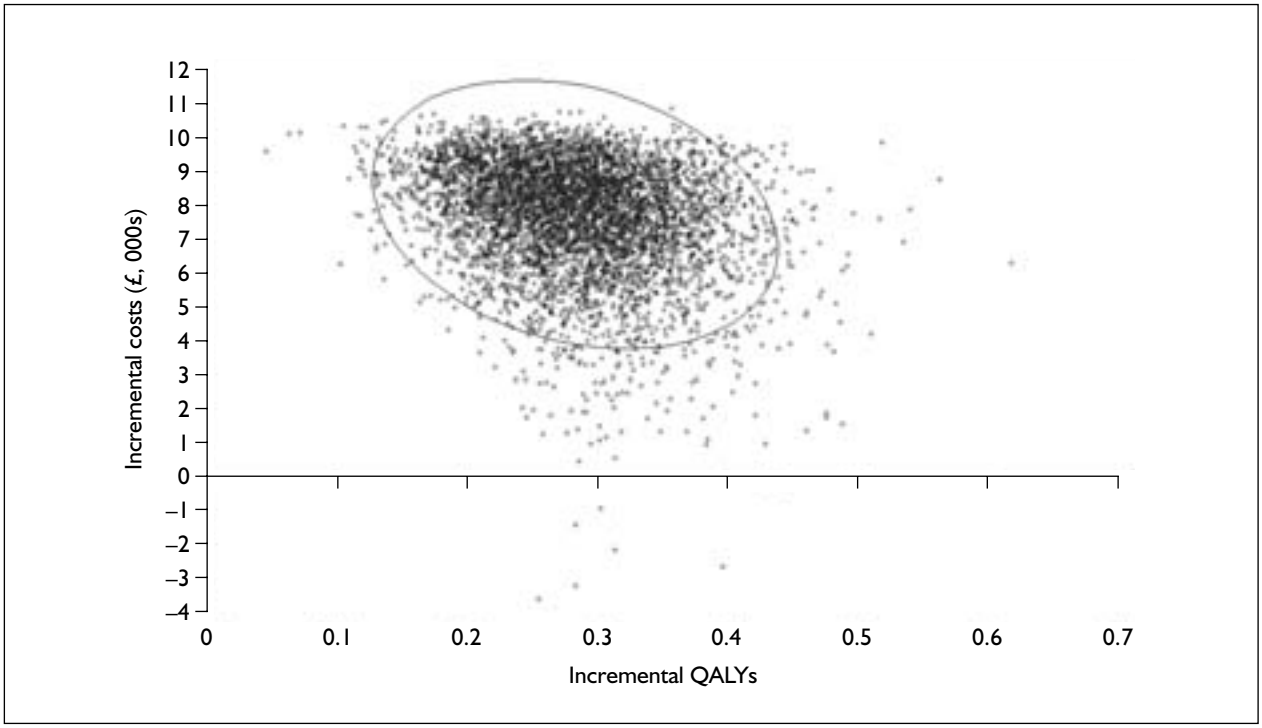

FIGURE 4 *Cost-effectiveness plane – incremental cost and incremental QALYs for pegaptanib compared with usual care*

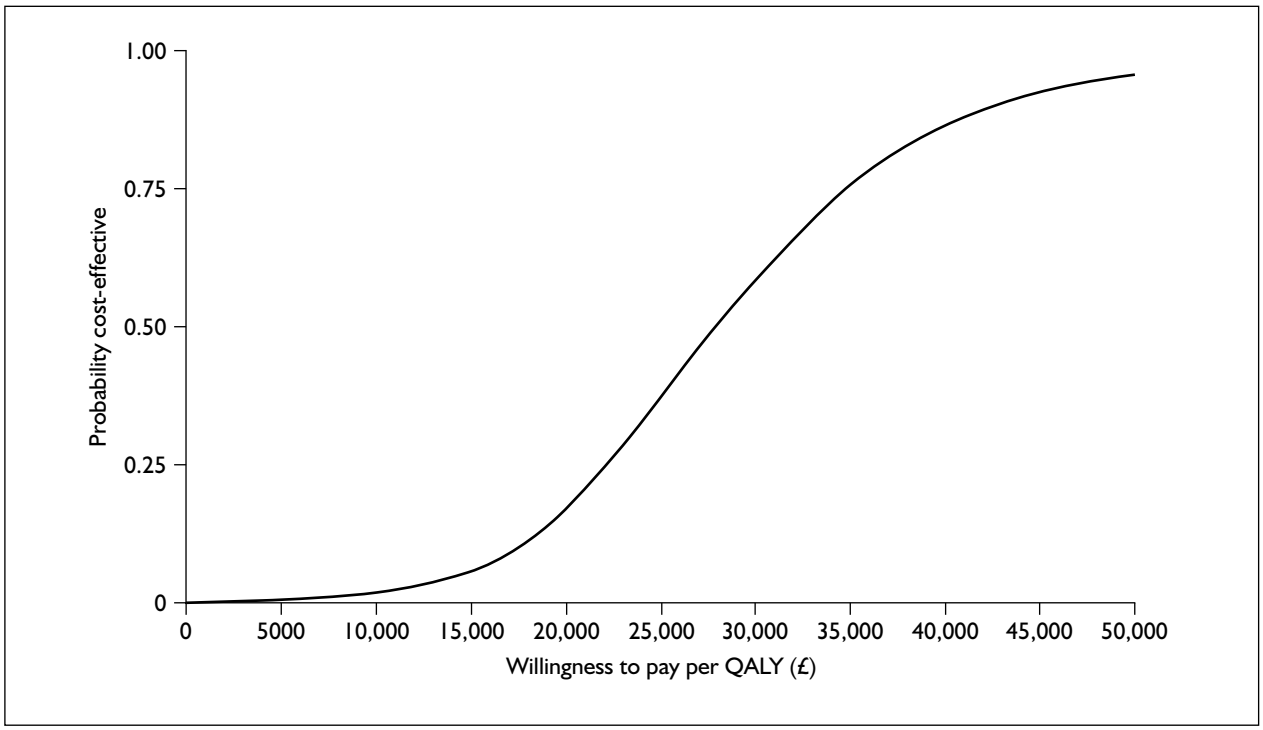

FIGURE 5 *Cost-effectiveness acceptability curve – pegaptanib probabilistic sensitivity analysis results*

TABLE 47 *Cost-effectiveness of ranibizumab against PDT or best supportive care – trial-based analysis*

	Cost (£)	Life-years	Vision-years	QALYs	Incremental cost per QALY gained (£)
Predominantly classic: ANCHOR trial. PDT as comparator					
PDT	4,182	0.98	0.94	0.77	
Ranibizumab	12,427	0.99	0.98	0.81	202,450
Predominantly classic: ANCHOR trial. Best supportive care as comparator					
Supportive care	933	0.98	0.85	0.74	
Ranibizumab	12,427	0.99	0.98	0.81	160,181
Minimally classic and occult no classic: MARINA trial. Best supportive care as comparator					
Supportive care	1,541	1.89	1.64	1.40	
Ranibizumab	23,902	1.90	1.87	1.54	152,464

duration of the MARINA trial. *Table 48* presents the same comparisons for a time horizon of 10 years. In each case it is assumed that treatment (ranibizumab or PDT) was only provided over the trial time horizon. That is, treatment for patients with predominantly classic lesions continued for a maximum of 1 year and consisted of either 12 injections of ranibizumab or the average number of PDT treatments observed in the control arm of the ANCHOR trial [**CIC data removed**]. For patients with minimally classic or occult no classic lesions, treatment continued for a maximum of 2 years and consisted of 12 injections of ranibizumab annually.

In each case there is little difference in life expectancy between the ranibizumab and comparator cohorts, despite the increased risk of mortality assumed for patients with visual acuity below 6/60. Outcomes measured as vision-years emphasise the difference between cohorts in the proportion of life expectancy spent with a visual acuity greater than 6/60. The difference in vision years is 0.71 at 10 years for patients with predominantly classic lesions when compared with PDT and 1.31 when compared with best supportive care. For patients with minimally classic or occult no classic lesions, treatment with ranibizumab is associated with a gain of 1.41 vision-years over a

TABLE 48 *Cost-effectiveness of ranibizumab against PDT or best supportive care – 10-year time horizon*

	Cost (£)	Life-years	Vision-years	QALYs	Incremental cost per QALY gained (£)
Predominantly classic: ANCHOR trial. PDT as comparator					
PDT	21,498	6.43	2.88	3.81	
Ranibizumab	26,888	6.51	3.59	4.15	15,638
Predominantly classic: ANCHOR trial. Best supportive care as comparator					
Supportive care	20,431	6.36	2.28	3.59	
Ranibizumab	26,888	6.51	3.59	4.15	11,412
Minimally classic and occult no classic: MARINA trial. Best supportive care as comparator					
Supportive care	13,787	6.52	3.78	4.10	
Ranibizumab	31,096	6.67	5.19	4.79	25,098

10-year time horizon, compared with best supportive care. The incremental gains are lower when measuring outcomes in QALYs (QALY gain of 0.34 for patients with predominantly classic lesions when compared with PDT and 0.57 when compared with best supportive care and a QALY gain of 0.69 for patients with minimally classic or occult no classic lesions when compared with best supportive care).

There is a large cost difference between ranibizumab-treated cohorts and comparator cohorts in all the 'trial-based' analyses. For patients with predominantly classic lesions, ranibizumab costs are approximately four times those for PDT and 12 times those for best supportive care, with an absolute difference of £8245 and £11,495, respectively. These high incremental costs, taken together with the small QALY gains at 1 year, lead to large ICERs of £202,450 for ranibizumab compared with PDT and £160,181 for ranibizumab compared with best supportive care. For patients with minimally classic and occult no classic lesions, the absolute cost difference between ranibizumab-treated patients and those receiving best supportive care is even greater (at £22,361), given that treatment is provided for up to 2 years and yields an ICER of £152,464. This analysis ignores any longer-run benefits that may arise from ranibizumab treatment. It is equivalent to assuming that patients only benefit while on treatment and that all patients experience a rapid worsening of their condition as soon as treatment stops, reverting to the state of visual deterioration they would have reached had they received no treatment.

In all cases, the cost difference between ranibizumab-treated patients and comparators observed in the trial-based analysis is reduced at 10 years. For patients with predominantly classic lesions the differences are £5392 and £6460 for comparison with PDT and best supportive care, respectively (reductions of 35 and 44%, respectively) and for patients with minimally classic or occult no classic lesions the difference is £17,309 (a reduction of 23%).

Table 49 reports the breakdown of costs in the 'trial-based' analyses and at the 10-year time horizon, indicating that all excess costs of treatment are realised during the first year (ANCHOR trial) or 2 years (MARINA trial), whereas costs associated with progression to blindness represent a small proportion of total costs in the ranibizumab-treated cohorts. At 10 years, costs of blindness constitute 24–54% of total costs for ranibizumab-treated patients, 82% of total costs for patients with predominantly classic lesions initially treated with PDT and 98–99% of total costs for patients in the best supportive care cohorts. The differences in costs of blindness between ranibizumab-treated and comparator cohorts at 10 years are £3113 for patients with predominantly classic lesions in the comparison with PDT and £5749 in the comparison with best supportive care. For patients with minimally classic and occult no classic lesions, the difference in costs of blindness between cohorts is £6254. Although the difference between cost of blindness in the ranibizumab-treated and comparator cohorts at 10 years does not fully offset the costs of treatment with ranibizumab, the increased proportion of total costs accounted for by progression to greater visual impairment and blindness, together with the increased QALY gain, yields the lower ICERs reported in *Table 48*.

Cost-effectiveness of ranibizumab – deterministic sensitivity analysis

We conducted a sensitivity analysis to consider the effect of uncertainty around the model structure

TABLE 49 *Breakdown of total costs for each cohort by major categories – ranibizumab base case analysis*

	Drug	Administration and monitoring	Managing adverse events	PDT	Blindness
Trial-based analyses (1- or 2-year time horizon)					
Predominantly classic: PDT as comparator					
PDT	–	–	78	3,845	259
Ranibizumab	8,997	3,316	114	–	0
Predominantly classic: best supportive care as comparator					
BSC	–	221	–	–	712
Ranibizumab	8,997	3,316	114	–	0
Minimally classic and occult no classic: best supportive care as comparator					
BSC	–	220	–	–	1,321
Ranibizumab	17,314	6,275	193	–	120
10-year time horizon					
Predominantly classic: PDT as comparator					
PDT	–	–	78	3,845	17,575
Ranibizumab	8,997	3,316	114	–	14,461
Predominantly classic: best supportive care as comparator					
BSC	–	221	–	–	20,210
Ranibizumab	8,997	3,316	114	–	14,461
Minimally classic and occult no classic: best supportive care as comparator					
BSC	–	220	–	–	13,567
Ranibizumab	17,314	6,275	193	–	7,313

and for variations in certain key parameters that were expected, *a priori*, to have a strong influence on the cost-effectiveness results. The method we adopted was univariate sensitivity analysis, that is, varying one parameter at a time, leaving all other variables unchanged. This is to highlight the impact, if any, of each selected parameter alone on the cost-effectiveness results. The effects of uncertainty in multiple parameters were addressed using probabilistic sensitivity analysis, which is reported in the next section.

Tables 50–52 report the results of the sensitivity analysis. Except for the sensitivity analysis with respect to time horizon, all analyses were conducted using the 10-year model. The tables are divided to distinguish between analyses undertaken due to uncertainties over structural assumptions in the model, uncertainties over the composition of the baseline cohort and uncertainty over parameter values.

Although the absolute values of the incremental costs, incremental QALYs and ICERs vary between the three sets of comparisons (ranibizumab versus best supportive care for patients with predominantly classic and minimally classic/occult no classic lesions and ranibizumab versus PDT for patients with predominantly classic lesions), the pattern of response to changes in underlying assumptions is similar in each analysis, and is discussed below.

As expected, time horizon has a strong effect on cost-effectiveness estimates. As the time horizon increases, the incremental cost of ranibizumab reduces (greater disease progression in the supportive care or PDT cohorts lead to increased costs associated with services for visual impairment, which offset an increasing proportion of treatment costs for the ranibizumab cohorts) and incremental QALY gain increases.

Varying the discount rates applied has comparatively little effect. Zero discount rates for costs and outcomes result in a slight reduction in incremental cost and a slight increase in incremental QALYs compared with baseline values. Conversely, applying a discount rate of 6% results in a slight increase in incremental cost and a reduction in incremental QALYs and hence a slightly higher ICER. The effects of applying different discount rates are most marked for the cohort of minimally classic and occult no classic patients.

Varying the age of the cohort at the start of the model shows higher QALY gains for younger patients and lower incremental costs – this is particularly apparent for patients with minimally

TABLE 50 *Deterministic sensitivity analysis – ranibizumab against PDT for patients with predominantly classic lesions*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Reference case		5,391	0.34	15,638
Structural assumptions				
Time horizon (10 years)	3 years	6,860	0.19	35,744
	5 years	5,922	0.27	21,801
	8 years	5,435	0.33	16,616
Methodological uncertainty				
Discount rates (3.5% for costs and outcomes)	0% for cost and outcome	5,078	0.38	13,345
	6% for cost and outcome	5,584	0.32	17,284
Baseline cohort characteristics				
Age of cohort at start of simulation (75 years)	–15 years	4,709	0.36	13,150
	–10 years	4,846	0.36	13,582
	+5 years	5,763	0.33	17,613
Proportion of cohort that is male (50%)	40%	5,362	0.35	15,510
	60%	5,419	0.34	15,766
Visual acuity at baseline (6/12 to 6/24)	50% 6/12 to 6/24 and 50% 6/24 to 6/60	5,222	0.33	15,637
	6/24 to 6/60	5,052	0.32	15,635
Parameter uncertainty				
Number of injections	9 in year 1 (12)	2,377	0.34	6,897
Cost of outpatient attendance	25 percentile	5,201	0.34	15,088
	75 percentile	5,582	0.34	16,194
Cost of injection procedure	Costed as day-case procedure	8,998	0.34	26,102
Health state utilities	SG values	5,391	0.29	18,912
	TTO values (lower CI)	5,391	0.37	14,423
	TTO values (upper CI)	5,391	0.32	16,905
Costs of blindness	High uptake/high costs	–2,350	0.34	Ranibizumab dominates
	Low uptake/low costs	7,869	0.34	22,827
	High costs/medium uptake	3,472	0.34	10,072
	Low costs/medium uptake	6,883	0.34	19,967
	High uptake/medium costs	1,044	0.34	3,029
	Low uptake/medium costs	7,097	0.34	20,587

classic and occult no classic lesions. Varying the proportion of the initial cohort of patients that is male has little impact on cost-effectiveness, as does varying the distribution of initial visual acuity.

Variations in assumptions regarding intravitreal injections, both their frequency and the cost of the injection procedure, have a large impact on the cost-effectiveness estimates. In the reference case, for each comparison the number of injections assumed during each year of treatment was that observed during the ANCHOR and MARINA clinical trials. In the sensitivity analysis, a range of different assumptions were tested – in all cases it was assumed that reduced frequency of injection had no impact on outcome. For patients with predominantly classic lesions, with an assumed maximum treatment duration of 1 year (as observed in the ANCHOR trial), reducing the number of injections from 12 to nine reduces incremental cost by around 56% for the comparison with PDT and around 47% for the comparison with best supportive care. For patients with minimally classic and occult no classic lesions, with an assumed maximum treatment duration of 2 years (as observed in the MARINA trial), reducing the number of injections in the second year of treatment from 12 to nine reduces incremental cost by around 16%. Reducing the number of injections in the first year of treatment from 12 to nine (with a further nine injections in year 2) reduces incremental cost by around 34% from the value in the reference case. If only six injections are given in year 2, following nine injections in year 1, the incremental cost of ranibizumab treatment, over best supportive care, is 50% of the value in the reference case.

TABLE 51 *Deterministic sensitivity analysis – ranibizumab against best supportive care for patients with predominantly classic lesions*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Reference case		6,457	0.57	11,412
Structural assumptions				
Time horizon (10 years)	3 years	8,697	0.32	26,774
	5 years	7,188	0.45	15,862
	8 years	6,496	0.54	12,035
Methodological uncertainty				
Discount rates (3.5% for costs and outcomes)	0% for cost and outcome	5,960	0.62	9,575
	6% for cost and outcome	6,767	0.53	12,732
Baseline cohort characteristics				
Age of cohort at start of simulation (75 years)	–15 years	5,244	0.58	9,107
	–10 years	5,485	0.58	9,521
	+5 years	7,134	0.54	13,126
Proportion of cohort that is male (50%)	40%	6,405	0.57	11,297
	60%	6,509	0.56	11,526
Visual acuity at baseline (6/12 to 6/24)	50% 6/12 to 6/24 and 50% 6/24 to 6/60	6,442	0.51	12,563
	6/24 to 6/60	6,426	0.46	13,979
Parameter uncertainty				
Number of injections	9 in year 1 (12)	3,444	0.57	6,087
Cost of outpatient attendance	25 percentile	6,216	0.57	10,985
	75 percentile	6,702	0.57	11,845
Cost of injection procedure	Costed as day-case procedure	10,065	0.57	17,787
Health state utilities	SG values	6,457	0.46	14,049
	TTO values (lower CI)	6,457	0.61	10,504
	TTO values (upper CI)	6,457	0.52	12,368
Costs of blindness	High uptake/high costs	–7,840	0.57	Ranibizumab dominates
	Low uptake/low costs	11,033	0.57	19,500
	High costs/medium uptake	2,913	0.57	5,149
	Low costs/medium uptake	9,212	0.57	16,281
	High uptake/medium costs	–1,571	0.57	Ranibizumab dominates
	Low uptake/medium costs	9,608	0.57	16,981

In the reference case we assumed that intravitreal injections were performed in outpatients. The unit cost assumed for these injections was based on the outpatient reference cost for operations on the eyelid, eyebrow and periorbital skin. This may be an underestimate of the cost of performing these injections. In the sensitivity analysis, a unit cost for performing the injection as a day-case procedure was adopted. This has a large impact on incremental costs – for patients with predominantly classic lesions, receiving a maximum of 1 year of treatment, the incremental cost increased by around 70% for the comparison with PDT and around 60% for the comparison with best supportive care. The ICER increased from £15,638 to £26,102 for the comparison with PDT and from £11,412 to £17,787 for the comparison with best supportive care. For patients with minimally classic and occult no classic lesions, receiving a maximum of 2 years of treatment, costing intravitreal injections as day-case procedures increased the incremental cost by around 40%, with the ICER increasing from £25,098 to £35,157.

Adopting health state utilities derived from AMD patients by Brown and colleagues[113] using the SG method yields lower estimated QALY gains and is therefore associated with an increased ICER.

Varying the costs of blindness, using the upper and lower limits of uptake of services for visual impairment and unit cost estimates produces wide variations in cost-effectiveness estimates. Using high uptake and high unit cost estimates produces a situation where ranibizumab is

TABLE 52 *Deterministic sensitivity analysis – ranibizumab against best supportive care for patients with minimally classic or occult no classic lesions*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Reference case		17,309	0.69	25,098
Structural assumptions				
Time horizon (10 years)	3 years	21,259	0.27	80,105
	5 years	19,422	0.45	43,441
	8 years	17,800	0.62	28,738
Methodological uncertainty				
Discount rates (3.5% for costs and outcomes)	0% for cost and outcome	16,833	0.79	21,383
	6% for cost and outcome	17,562	0.63	27,793
Baseline cohort characteristics				
Age of cohort at start of simulation (75 years)	–15 years	16,041	0.76	21,196
	–10 years	16,317	0.75	21,858
	+5 years	17,889	0.63	28,416
Proportion of cohort that is male (50%)	40%	17,261	0.69	24,893
	60%	17,355	0.69	25,303
Visual acuity at baseline (6/12 to 6/24)	50% 6/12 to 6/24 and 50% 6/24 to 6/60	16,647	0.66	25,179
	6/24 to 6/60	15,986	0.63	25,268
Parameter uncertainty				
Number of injections	12 in year 1 (12) and 9 in year 2 (12)	14,522	0.69	21,058
	9 in year 1 (12) and 9 in year 2 (12)	11,510	0.69	16,689
	9 in year 1 (12) and 6 in year 2 (12)	8,723	0.69	12,649
Cost of outpatient attendance	25 percentile	16,833	0.69	24,408
	75 percentile	17,789	0.69	25,795
Cost of injection procedure	Costed as day-case procedure	24,246	0.69	35,157
Health state utilities	SG values	17,309	0.56	30,712
	TTO values (lower CI)	17,309	0.75	23,044
	TTO values (upper CI)	17,309	0.63	27,295
Costs of blindness	High uptake/high costs	1,782	0.69	2,583
	Low uptake/low costs	22,285	0.69	32,313
	High costs/medium uptake	13,458	0.69	19,514
	Low costs/medium uptake	20,307	0.69	29,446
	High uptake/medium costs	8,591	0.69	12,456
	Low uptake/medium costs	20,732	0.69	30,062

dominant (lower cost with better outcome) compared with either PDT or best supportive care for patients with predominantly classic lesions. For patients with minimally classic or occult no classic lesions, costs are approximately equal in the ranibizumab and best supportive care cohorts. Using the low estimates for uptake and unit costs resulted in a 46% increase in incremental costs of ranibizumab treatment for patients with predominantly classic lesions compared with PDT and a 71% increase in incremental costs in the comparison with best supportive care. The increase in incremental cost for patients with minimally classic and occult no classic lesions when using the low estimates was 29%.

To indicate which variable, costs or uptake, was more influential on cost-effectiveness estimates, additional analyses were undertaken using the extreme values for uptake combined with medium cost and extreme values for cost combined with medium uptake. The results show that the cost-effectiveness estimates were most sensitive to assumptions over uptake, estimated as the proportion of eligible cases (i.e. with visual acuity less than 6/60) receiving services.

Cost-effectiveness of ranibizumab – probabilistic sensitivity analysis

In a probabilistic sensitivity analysis for ranibizumab, where probabilities of losing or

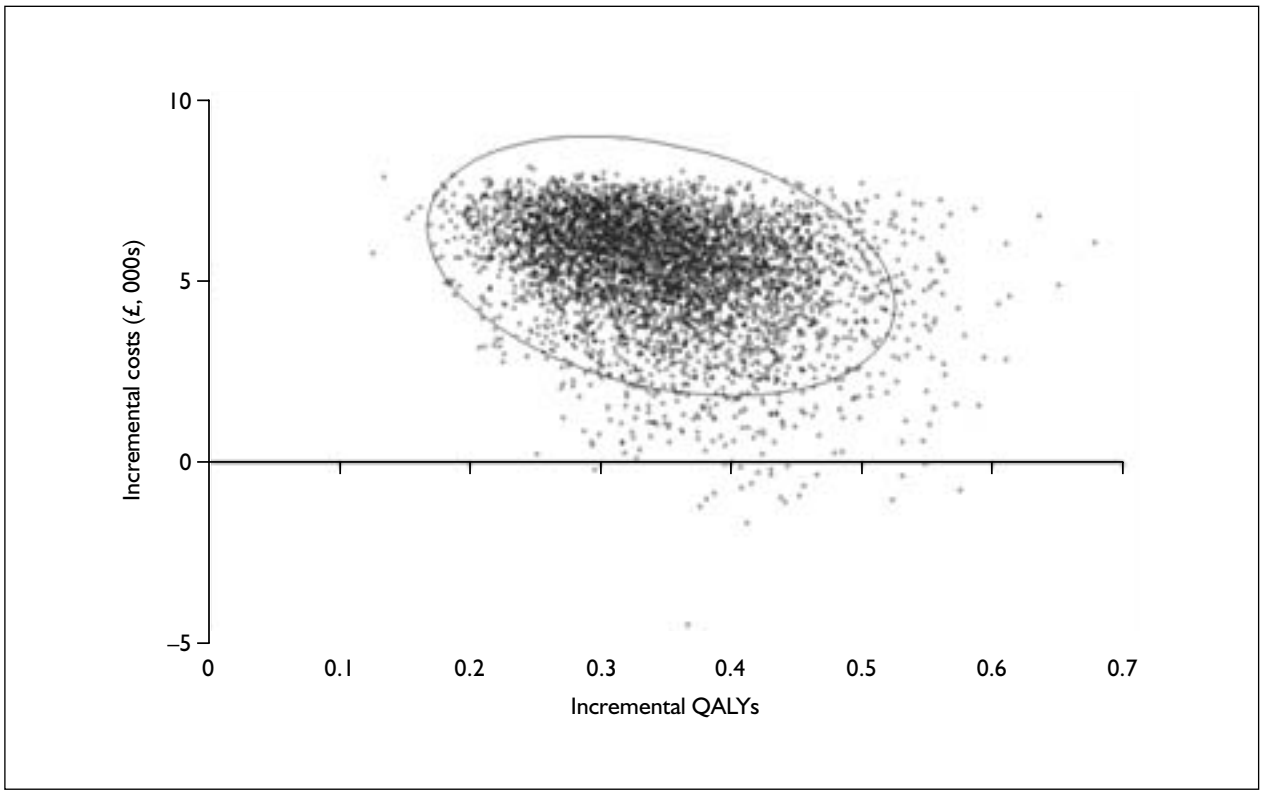

FIGURE 6 *Cost-effectiveness plane – incremental cost and incremental QALYs, ranibizumab for patients with predominantly classic lesions compared with PDT*

gaining visual acuity, health state utility values, cost of outpatient attendances, FA and OCT and costs of services for visual impairment were sampled probabilistically, the majority of simulations produced incremental cost effectiveness estimates that were in the north-east quadrant of the cost-effectiveness map (*Figures 6*, *8* and *10*). The majority of simulations, for each lesion type (and each comparison) are associated with increased QALYs but also increased costs. However, a small number of simulations have negative incremental costs. Simulations where costs for ranibizumab-treated patients are lower than for the PDT or best supportive care cohorts are most likely to be associated with extreme high values for costs of blindness.

The distributions assigned to each variable included in the probabilistic sensitivity analysis and the parameters of the distribution are reported in Appendix 14; 5000 simulations were run for each analysis. In addition to graphing the incremental cost and incremental QALYs for ranibizumab-treated patients on the cost-effectiveness plane, cost-effectiveness acceptability curves were derived for each analysis, representing the proportion of simulations where ranibizumab treatment is cost-effective for a range of willingness to pay thresholds, up to £50,000 (*Figures 7*, *9* and *11*).

Ranibizumab for patients with predominantly classic lesions had a probability of being cost-effective (compared with PDT) of 72% at a willingness to pay threshold of £20,000 per QALY and 97% at a willingness to pay threshold of £30,000 per QALY (*Figure 7*).

Ranibizumab for patients with predominantly classic lesions had a probability of being cost-effective (compared with best supportive care) of 95% at a willingness to pay threshold of £20,000 per QALY and 99% at a willingness to pay threshold of £30,000 per QALY (*Figure 9*).

Ranibizumab for patients with minimally classic and occult no classic lesions had a probability of being cost-effective (compared with best supportive care) of 15% at a willingness to pay threshold of £20,000 per QALY and 81% at a willingness to pay threshold of £30,000 per QALY (*Figure 11*).

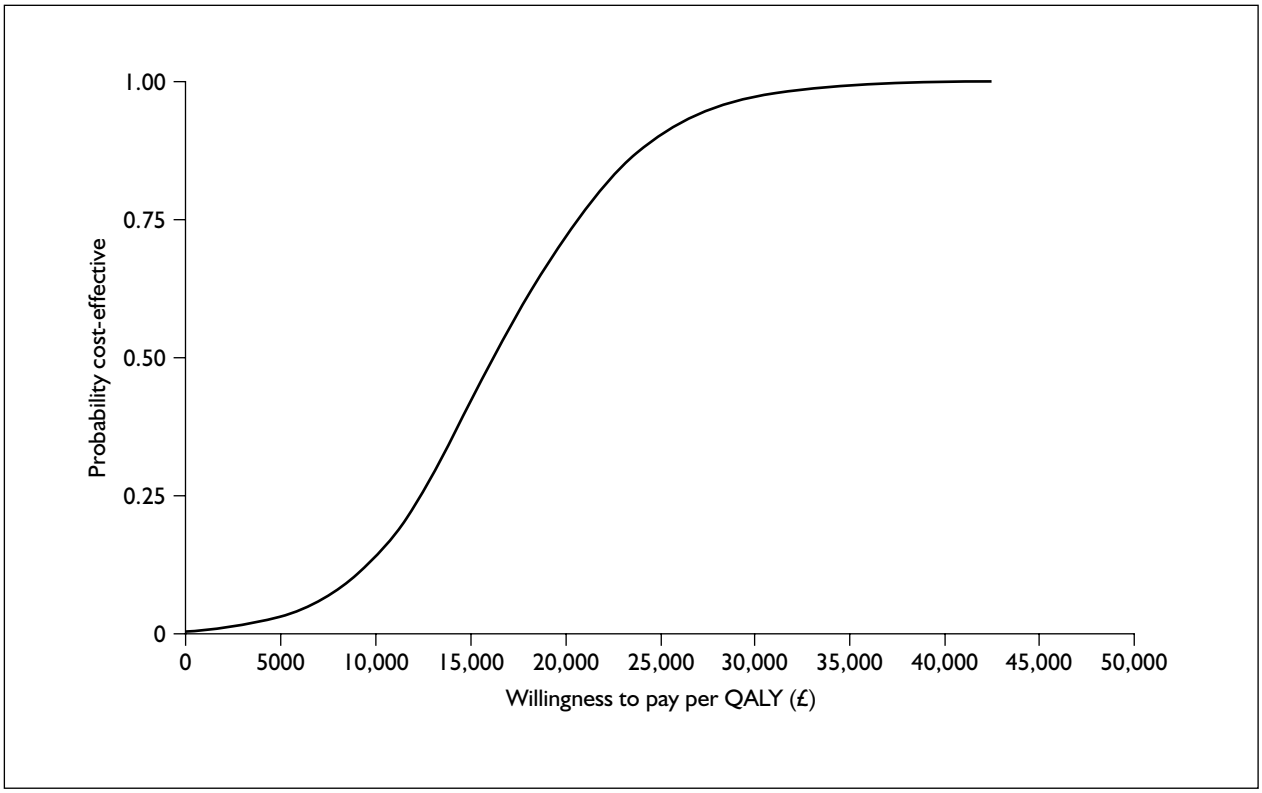

FIGURE 7 *Cost-effectiveness acceptability curve, ranibizumab for patients with predominantly classic lesions compared with PDT*

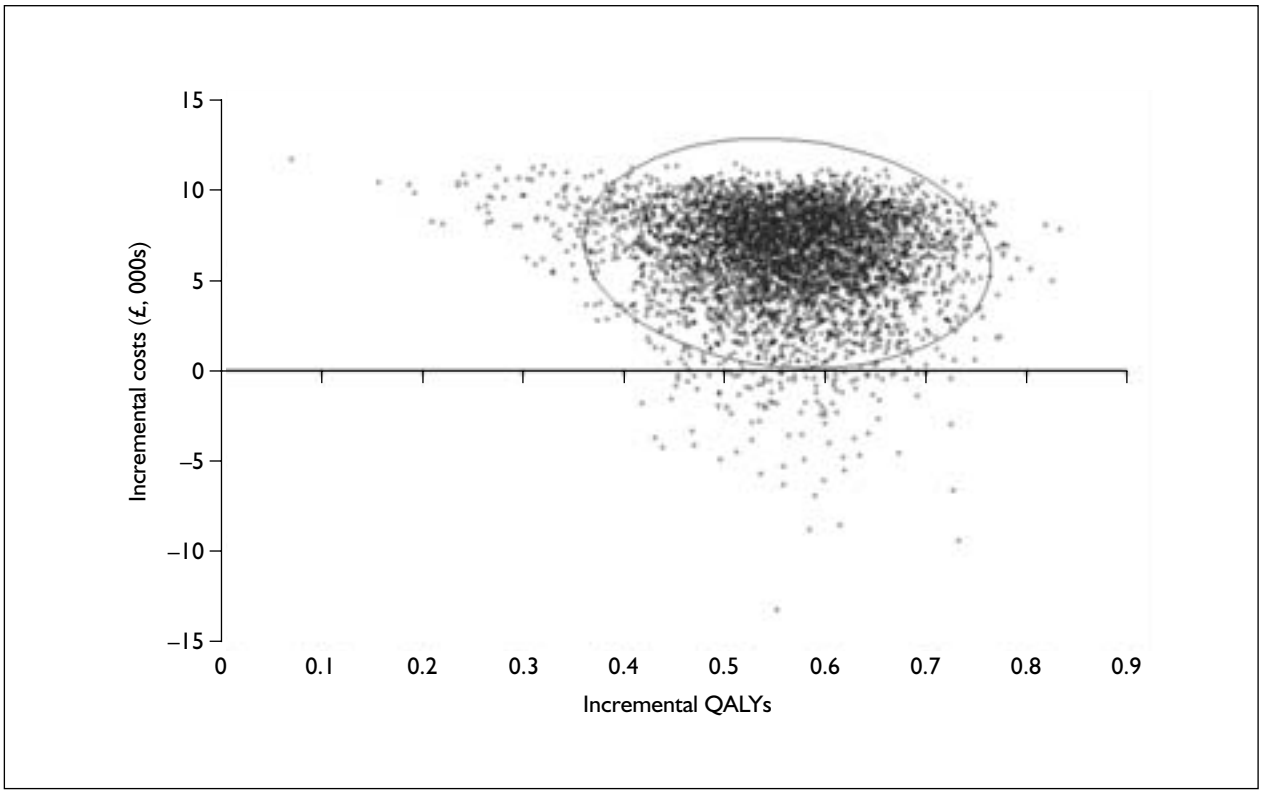

FIGURE 8 *Cost-effectiveness plane – incremental cost and incremental QALYs, ranibizumab for patients with predominantly classic lesions compared with best supportive care*

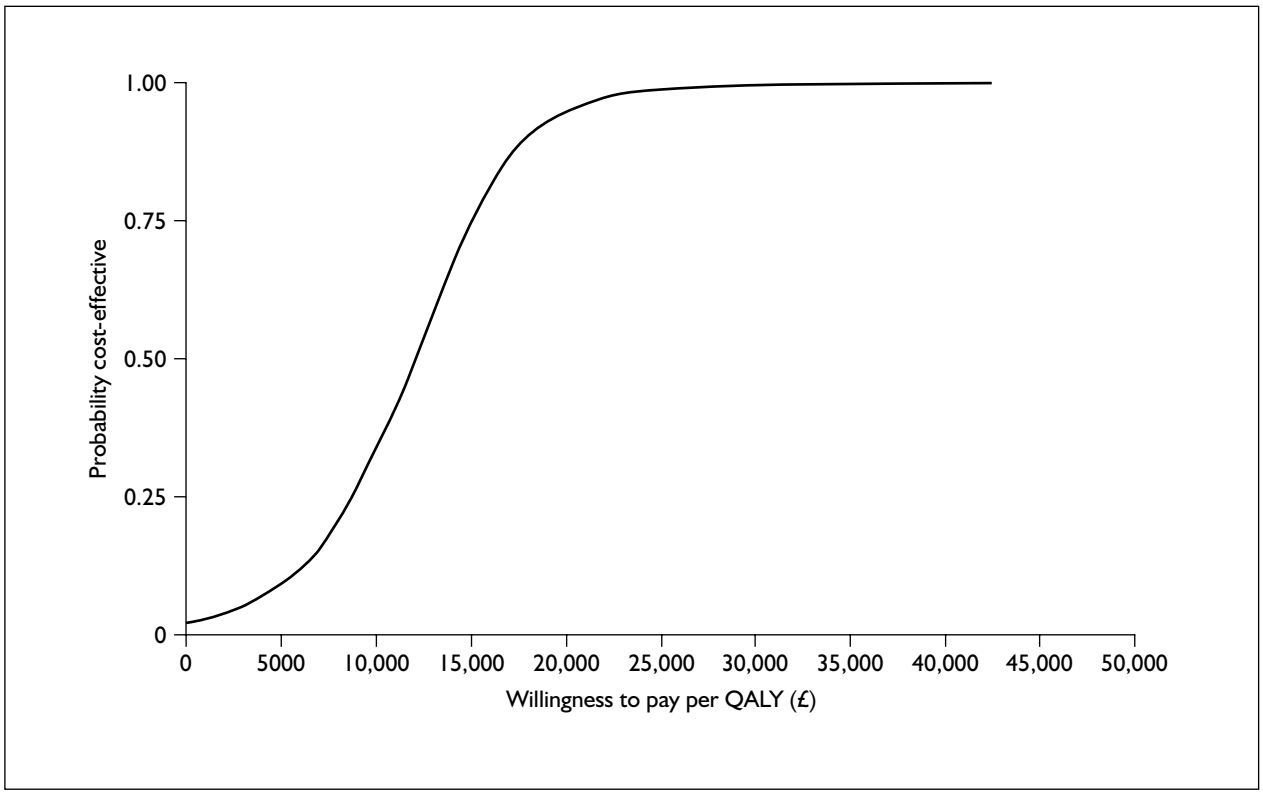

FIGURE 9 *Cost-effectiveness acceptability curve, ranibizumab for patients with predominantly classic lesions compared with best supportive care*

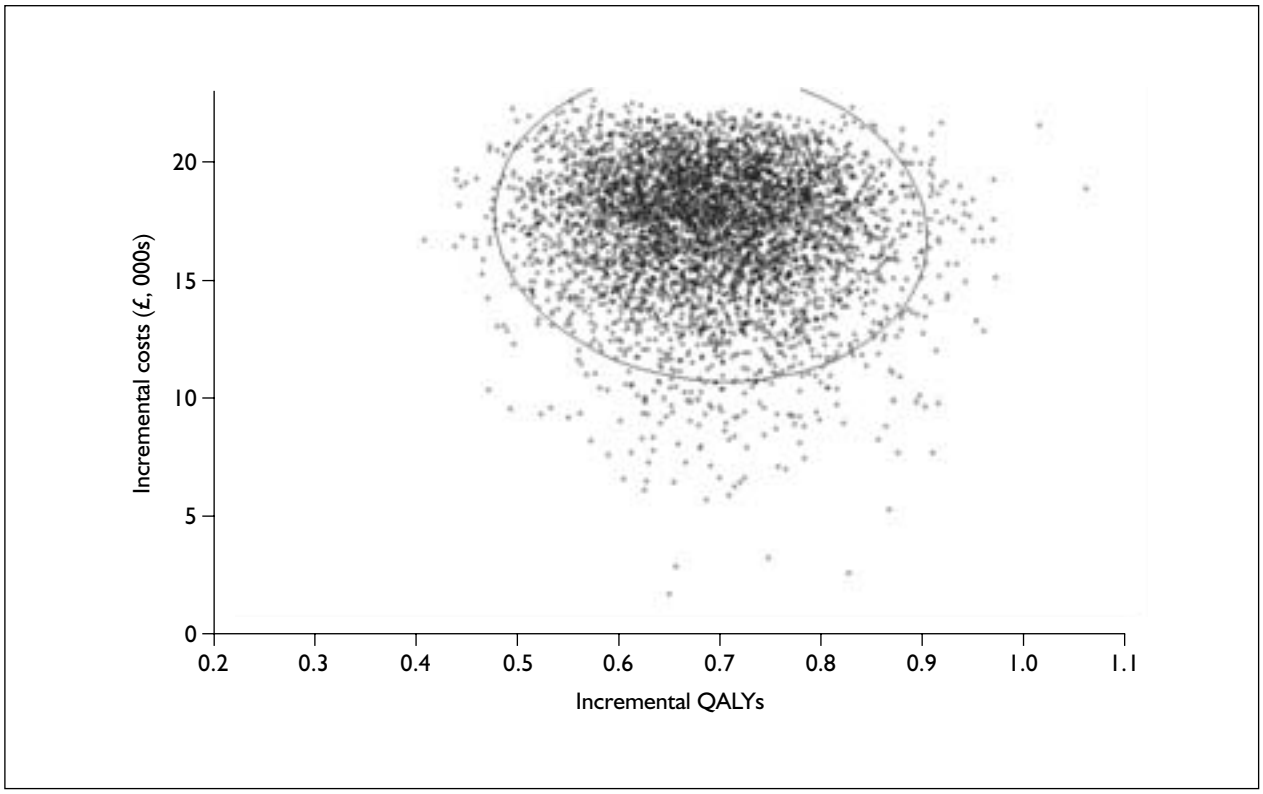

FIGURE 10 *Cost-effectiveness plane – incremental cost and incremental QALYs, ranibizumab for patients with minimally classic and occult no classic lesions compared with best supportive care*

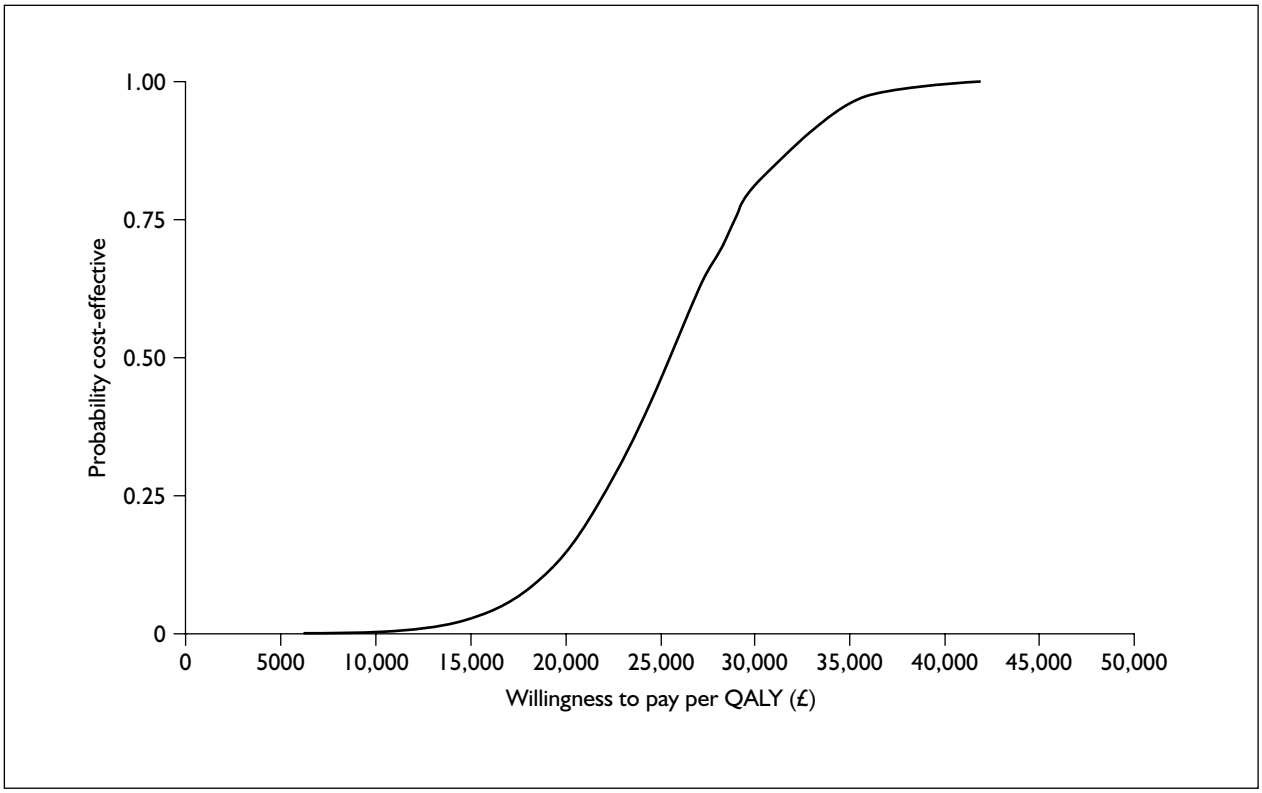

FIGURE 11 *Cost-effectiveness acceptability curve, ranibizumab for patients with minimally classic and occult no classic lesions compared with best supportive care*

Discussion

Summary of key results

- A systematic search of the literature found no fully published economic evaluations of pegaptanib or ranibizumab. A review of published economic evaluations of comparator treatments for wet AMD found that model time horizon appeared to have the greatest influence on cost-effectiveness estimates.
- A systematic search for published studies of quality of life for patient with AMD found that studies indicate that quality of life is lower for people with AMD compared with those without disease and that there is a strong association between vision loss and psychological illness, including depression. Published estimates of health state utilities for vision loss secondary to AMD have focused primarily on changes in visual acuity. Utility values decline with reduced visual acuity, although when groups other than patients with AMD are included in studies they tend to give lower values to the impact of vision loss compared with patients with AMD.
- Pfizer submitted a dossier in support of pegaptanib, including an economic evaluation based on clinical data from the VISION studies. This compares pegaptanib (with or without PDT) with usual care, which consists of best supportive care for all patients and also as PDT for patients with predominantly classic lesions. In the cost–utility model, health state valuations are based on a published study[113] that has been widely used in previous evaluations of treatment for AMD.
- The QALY gain for the pegaptanib-treated cohort estimated over 10 years was 0.298. The cost difference was £4705, giving an ICER of £15,815 per QALY gained. In the reference case, treatment with pegaptanib ceased when visual acuity fell below 6/96. Adopting an alternative stopping rule – treatment ceased when visual acuity fell below 6/60 – had little impact on incremental cost, QALY gain or ICER.
- Deterministic sensitivity analysis showed that the results were sensitive to time horizon and variation in the costs of blindness.
- Further analyses by the TAR team on the comprehensiveness of the costing of patient monitoring while on treatment produced an increase in costs for the pegaptanib cohort and increased the ICER to £22,476 per QALY gained. Further analysis on the choice of utility values adopted in the model had little impact.

- Novartis submitted a dossier in support of ranibizumab which includes an economic evaluation, based on clinical data from the ANCHOR, MARINA and PIER trials, comparing ranibizumab with best supportive care for patients with all lesion types and additionally with PDT for patients with predominantly classic. Separate analyses were undertaken for predominantly classic, minimally classic and occult no classic lesions.
- For patients with predominantly classic lesions, the QALY gain estimated over ten years was 0.20 for the comparison with PDT and 0.28 for the comparison with best supportive care. The cost differences were £917 (compared with PDT) and £4068 (compared with best supportive care), giving ICERs of £4489 and £14,781 per QALY gained, respectively.
- For patients with occult no classic lesions the QALY gain was 0.34 and for patients with minimally classic lesions the QALY gain was 0.33. The cost differences were £9125 and £8494, giving ICERs of £26,454 and £25,796 per QALY gained.
- Limited deterministic sensitivity analyses were undertaken, reporting the ICERs for increasing the number of injections given, up to the values observed in the clinical trials, which increased the ICER substantially (to £25,544 and £29,662 for patients with predominantly classic lesions compared with PDT and best supportive care, respectively). ICERs for patients with minimally classic and occult no classic lesions increased to around £55,000 per QALY gained. Further analyses were undertaken by the TAR team to remove double counting and inappropriate allocation of costs included – although these had an impact on incremental costs, they would not, by themselves, alter conclusions over the cost-effectiveness of ranibizumab according to conventionally accepted decision thresholds.
- We developed an independent model which includes five states of declining visual acuity and an absorbing death state. States in the model were defined to correspond to approximately three lines of visual acuity, which is generally accepted as a clinically significant difference. Individuals in the model could improve, in terms of visual acuity, by one state or deteriorate by one or two states in each model cycle.
- The proportion of trial participants gaining at least three lines, losing 3–6 lines and losing six lines or more of visual acuity for each year of the relevant clinical trials were extracted from clinical trial reports and used to estimate the transition probabilities for the model.
- The QALY gain after 2 years of treatment with pegaptanib, in the trial-based analysis, is small (0.06 QALYs) and the incremental cost is high (approximately £10,000). Given the small QALY gain and high incremental cost at 2 years, the ICER is high (£163,603).
- The QALY gain after 10 years is 0.26 QALYs and the incremental cost reduces to around £8000, giving a lower ICER of £30,986. If pegaptanib is assumed to have a disease-modifying effect, then the ICER may be lower – estimated as £26,896 in the model.
- Deterministic sensitivity analysis suggests that ICERs are less favourable for patients with older age on entry to the model and poorer initial visual acuity. Costing the injection procedure as a day case, rather than adopting a unit cost for an outpatient procedure, has a large impact on ICER, which increases to £47,845.
- Probabilistic sensitivity analysis shows a 17% probability of pegaptanib being cost-effective, compared with usual care, at a willingness to pay threshold of £20,000. The equivalent figure for a willingness to pay threshold of £30,000 is 58%.
- The QALY gain after 1 year of treatment with ranibizumab for patients with predominantly classic lesions, in the trial-based analysis, is small for the comparison with PDT (0.04 QALYs) and for the comparison with best supportive care (0.07 QALYs). The incremental costs are high: approximately £8000 for the comparison with PDT and £11,500 for the comparison with best supportive care. The QALY gain after 2 years of treatment for patients with minimally classic and occult no classic lesions is 0.14 QALYs and the incremental cost is £22,400. The ICERs for these comparisons in the trial-based analyses are between £150,000 and approximately £200,000.
- The QALY gain at 10 years for patients with predominantly classic lesions is 0.34 for the comparison with PDT and 0.57 for the comparison with best supportive care. The incremental costs reduced to £5391 and £6457, giving ICERs of £15,638 for the comparison with PDT and £11,412 for the comparison with best supportive care. The QALY gain at 10 years for patients with minimally classic and occult no classic lesions is 0.69 QALYs and the incremental cost reduced to £17,314, giving an ICER of £25,098.
- Deterministic sensitivity analysis suggests that ICERs are less favourable for patients with older age on entry to the model. However, poorer initial visual acuity has little effect on cost-

effectiveness estimates. Costing the injection procedure as a day case, rather than adopting a unit cost for an outpatient procedure, has a large impact on ICER (which for patients with predominantly classic lesions increases to £26,102 for the comparison with PDT and £17,787 for the comparison with best supportive care, and for patients with minimally classic and occult no classic lesions the ICER increases to £35,157). The ICER is also sensitive to choice of utility values and is particularly sensitive to variations in the costs of blindness.
- Probabilistic sensitivity analysis shows a 72% probability of ranibizumab being cost-effective for patients with predominantly classic lesions (compared with PDT) at a willingness to pay threshold of £20,000 per QALY and a 97% probability of being cost-effective at a threshold of £30,000 per QALY. For the comparison with best supportive care, the equivalent figures are 95 and 99%, respectively.
- For patients with minimally classic and occult no classic lesions, probabilistic sensitivity analysis shows a 15% probability of ranibizumab being cost-effective at a willingness to pay threshold of £20,000 per QALY and 81% at a willingness to pay threshold of £30,000 per QALY.

Generalisability

- The median age of patients in the clinical trials used as sources for the clinical effectiveness in the economic models is in the range 75–84 years [mean ages of 76.0 and 77.7 years for patients receiving ranibizumab (0.5 mg) and PDT, respectively in the ANCHOR trial[96] and 77 years for ranibizumab and sham injection in the MARINA trial;[97] mean ages were not reported for the VISION studies]. These reflect the age-specific incidence and prevalence discussed in the section 'Description of health problem' (p. 1), and would be expected to be broadly representative of patients presenting for treatment.
- The proportions of men and women in the trial populations are roughly equal in the VISION studies (45% male for patients receiving pegaptanib and 40% male for patients receiving usual care[95]) and the ANCHOR trial [54% male for patients receiving ranibizumab (0.5 mg) and 45% male for patients receiving PDT[96]]. However two-thirds of patients in the MARINA trial were women [63% for patients receiving ranibizumab (0.5 mg) and 67% male for patients receiving sham injection[97]]. Epidemiological evidence reviewed in the section 'Description of health problem' (p. 1) reported inconsistent results between published studies on sex differences in incidence and prevalence of AMD.
- The proportion of patients with predominantly classic lesions in the VISION studies is similar to that observed in an angiographic study of patients with subfoveal neovascular lesions[11] reviewed in the section 'Description of health problem' (p. 1) and also that assumed by Bonastre and colleagues,[85] discussed in the section 'Current service cost' (p. 12) (24% of patients receiving pegaptanib and 26% of patients receiving usual care[95]). The proportion of patients with minimally classic lesions in the VISION studies (38% of patients receiving pegaptanib and 34% of patients receiving usual care[95]) is higher than that observed in the angiographic study, which reported that 7% of subfoveal lesions were of this type.
- Baseline populations and relative risks of mortality, fractures or depression due to vision loss used in the economic models are based on epidemiological studies in different countries. It is difficult to establish the validity of these sources for UK populations where no UK evidence exists, although the pattern of significant increase in incidence and prevalence for ages over 75 years and higher proportions of women affected was also suggested in UK register-based studies reviewed in the section 'Description of health problem' (p. 1).
- The economic evaluations of pegaptanib and ranibizumab discussed and presented in this review have assumed that the majority of treatment is provided in outpatient departments of UK hospitals. Clinical experts who provided advice during this review confirmed that these treatments were most likely to be provided in outpatient settings. The facilities and staff required for monitoring and managing patients receiving treatment with pegaptanib and ranibizumab are available in outpatient departments, but there is uncertainty over appropriate provision. It is unclear whether injections can be provided as outpatient procedures or should be treated as day-case procedures since they require a nurse in attendance, a clean room, a tray of disposable specula, forceps, drapes and the use of surgical hand disinfection. An ideal treatment pathway may be to provide an integrated clinic for AMD patients having intravitreal injections, which would include medical assessments, visual assessments, imaging by OCT at each visit and FA every 3–6 months, followed by the injection procedure and post-injection care. The costings included in our economic model aim to reflect

this, but may have underestimated the overhead for establishing and maintaining such clinics.
- The frequency and duration of injections observed in the clinical trials may not be reflected in normal practice. [**CIC data removed**]. The Scottish Medicines Consortium refers to the possibility of restricting pegaptanib treatment to 1 year.[145]
- The economic analyses have used UK-derived resource use protocols to estimate treatment costs. Although there was general agreement on medical management and on the use of FA prior to treatment, OCT and repeat FA were not included in all protocols, nor were repeat visual assessments for patients undergoing treatment. As far as possible, the economic analyses used routinely available unit costs estimates – NHS Reference Costs[84] and Unit Costs of Community Care.[135] However, UK unit costs for all elements of resource use are not available. As discussed above, there is no reference cost for intravitreal injection and limited information on which to base unit cost estimates. There is, therefore, considerable uncertainty over the appropriate unit cost to use.
- The economic analyses have used published UK estimates of unit costs of services for visual impairment.[40,146]

Strengths and limitations

- We applied an identical model, using the same health state utilities and assumptions over resource use at each contact for each drug. The resource use assumptions were developed with advice from clinical experts who advised on the development of this review. Our resource use assumptions and unit cost estimates were compared with those included in the manufacturers' submissions to assess their comprehensiveness.
- Clinical evidence relevant to each drug was extracted from good-quality RCTs included in the systematic review. Response to treatment was assessed using an accepted measure of significant clinical difference (15 letters of visual acuity), to model cost and outcome differences over the time horizons of the clinical trials and over patients' lifetimes.
- The majority of the data included in the model are in the public domain. The model structure and data inputs are clearly presented in this report. This should facilitate replication and testing of our model assumptions.
- Review of previous economic evaluations of treatments for AMD allowed identification of factors that were particularly influential on cost and outcome estimates. The impact of these factors was tested in extensive sensitivity analyses.
- There is substantial uncertainty over treatment patterns with these drugs in normal clinical practice. Components of medical management of patients treated with ranibizumab and pegaptanib were identified by clinical experts as similar and there was agreement over the frequency of monitoring of patients (OCT and visual assessment at each attendance for injection, and FA every 3–6 months). In the absence of guidance on the frequency of dosage and on re-treatment, we assumed the frequency and duration of treatment adopted in the clinical trials. It is not clear whether the treatment regimens followed in the published clinical trials will be adopted in clinical practice. There are currently limited data on post-treatment effectiveness of these drugs and no published data on response for patients who have previously been treated with anti-VEGFs.
- There is limited use of intravitreal injection in current NHS practice and no reference cost estimate. In the model we used the reference cost for an ophthalmic outpatient procedure (as a low estimate) and the cost of an inpatient non-surgical ophthalmological day case (as a high estimate). These result in large variations in cost. However, it is not clear whether these are due to real resource differences that might arise from providing intravitreal injections in outpatients or in day-case settings.
- We used aggregate data to derive the transition probabilities used in the model. This requires an underlying assumption that the probability of gaining or losing visual acuity is independent of the patients' baseline visual acuity. This may not hold – the survival models developed in the Pfizer submission included three initial visual acuity levels. It is possible that the poorer the initial visual acuity (i.e. greater disease progression at baseline) the less likely the patient is to respond to treatment.
- There is substantial uncertainty over the costs of blindness. However, these are key to assessing the cost-effectiveness of interventions for AMD. As noted in the analysis in the sections 'Cost-effectiveness of pegaptanib – base case analysis' (p. 67) and 'Cost-effectiveness of ranibizumab – base case analysis' (p. 71) there is the potential to offset a proportion of treatment costs by averting some future demand for services for visual impairment. In the deterministic sensitivity analyses, variation in uptake and unit costs of services for visual impairment produced

extremes ranging from a situation where treatment was cost saving (using high uptake and high cost) to a situation where the incremental costs of treatment were between 29 and 71% higher than in the reference case (using low uptake and low cost).

- The validity of assumptions underlying our extrapolation from trial results to 10 years may be open to question. We assumed that progression in the best supportive care cohorts (observed at the end of the trials) can be used to model progression in the treated cohort. In the absence of evidence of post-treatment effects and with a lack of long-term follow-up of treated patients, we cannot rule out the possibility of a rebound effect (where all benefit, in terms of delayed progression and visual improvement, is lost shortly after treatment ends). In that case, the ICERs would be closer to the trial-based analysis than the extrapolated results and treatment would be very unlikely to be cost-effective. On the other hand, some evidence of a disease-modifying effect of pegaptanib has been provided – including this in the model reduces the ICER at 10 years from £30,986 to £26,896.
- Meads and colleagues[40] questioned the assumption – implicit in our analysis and common in economic models extrapolating from short-term outcomes observed in clinical trials – that utility associated with visual acuity in the better-seeing eye is constant over time. They argue that research suggests that utility improves over time, presumably due to patients' adaptation to their reduced visual function. This might be expected to reduce the QALY gain associated with treatment. However, it is unclear how this can be quantified.

Chapter 5

Assessment of factors relevant to the NHS and other parties

Interim guidelines on the management and treatment of AMD from the Royal College of Ophthalmologists (Wong D, Royal College of Ophthalmologists: personal communication, November 2006) state that "there are significant resource (including staffing), logistical and financial implications in commissioning anti-VEGF treatments for AMD". As a result of this, the College convened an AMD Provisions Sub-committee to determine AMD service configurations and distribution, staff and other resource requirements. It is generally anticipated that provision of anti-VEGF treatments will be based around the current PDT treatment centres. However, as suggested by the above statement (and others within the interim guidelines) and also patient advocacy organisations, such as the AMD Alliance,[147] there are concerns about the ability of current services to deal with the anticipated increase in workload and the potential impact on the delivery of ophthalmic services overall.

It is anticipated that the number of patients eligible for treatment each year will increase from 7000 to 26,000 (quoted by AMD Alliance,[147] attributed to the Royal College of Ophthalmologists). This approximate trebling in patient load will be compounded by the increased frequency of treatment, from 3-monthly attendances with PDT to 6-weekly attendances for pegaptanib or monthly attendances for ranibizumab. These combined factors have given rise to an estimate that workload will increase six- to seven-fold with the adoption of these treatments (Lotery A, Southampton University Hospitals Trust: personal communication, October 2006).

The increase in patient load and frequency of attendance will have implications for specialist imaging facilities. While the expected frequency of FA for patients receiving pegaptanib or ranibizumab (at 3–6-monthly intervals) is the same as or lower than for PDT, overall workload will increase due to the increase in number of eligible patients. There is likely to be a substantial increase in workload for OCT, which would be performed at each patient attendance, according to clinical experts advising on this review. There is also likely to be a substantial increase in workload for hospital-based optometrists and specialist nurses required to undertake vision assessments at each patient attendance.

The costing protocol developed for the economic evaluation of pegaptanib and ranibizumab identified each component of the management and treatment of patients. However, it is likely that providers will want to develop integrated clinics for AMD patients receiving intravitreal injections with dedicated optometry, photography and imaging staff and facilities. The costings used in the evaluations may underestimate the initial costs of establishing such services.

Although AMD predominantly affects people in the older age group, with approximately 90% of prevalent cases in the UK over the age of 70 years (see *Table* 7, p. 8), it also affects people in their 40s and 50s. In addition to the costs of services for visual impairment identified and incorporated into our economic model, these individuals may face disruption of their working lives and may be unable to continue in their careers, facing costs for retraining into alternative occupations, or may leave the workforce. This may affect their ability to support a family and lead to family disruption. There may also be substantial impacts on carers and family of people with AMD, in terms of lost productivity, changes in lifestyle and need to support relatives during treatment and rehabilitation following vision loss. These costs are outside the scope of the economic evaluation in this report, which adopted an NHS and PSS perspective as required by NICE.[133] However, these considerations are relevant to the wider evaluation of the impact of AMD, with associated vision loss, and the potential benefits of delaying disease progression.

There are potential equity concerns around the delays in diffusing the technology and possible delays in patients accessing treatment, if current services are unable to cope with the increase in workload. There has been much debate over

delays in commissioning of anti-VEGF treatments by PCTs[93,94,147] and concern that patients may feel that their only choice is to pursue private treatment. If these treatments are recommended for use in the NHS and should the concerns over the lack of capacity to deal with the expected workload prove true, this inequity of access to treatment may persist.

Chapter 6
Discussion

Statement of principal findings

Clinical effectiveness

The results from six RCTs were included in this systematic review. The combined results of two RCTs of pegaptanib (the VISION study) were reported in three publications. Three published RCTs (MARINA, ANCHOR and FOCUS) and an unpublished RCT (PIER) of ranibizumab were also included. The published [**CIC data removed**] included RCTs were of good methodological quality.

The primary outcome measure for most of the studies was the proportion of patients losing fewer than 15 letters of visual acuity after 12 months of treatment. The pegaptanib trials, which included patients with all lesion types, found significantly more patients receiving pegaptanib [0.3 mg (licensed dose), 70% of patients; 1.0 mg, 71% of patients; 3.0 mg, 65% of patients] lost less than 15 letters at 12 months than those receiving sham injection (55% of patients). Similarly, significantly more patients receiving ranibizumab (0.3 mg, 94.3–94.5%; 0.5 mg, 94.6–96.4%) lost less than 15 letters after 12 months compared with sham injection (62.2%) or PDT (64.3%). The patients included in these trials had occult or minimally classic lesions or predominantly classic lesions. A 0.5-mg dose of ranibizumab combined with PDT was found to increase significantly the proportion losing less than 15 letters compared with PDT alone (90.5 versus 67.9%) in patients with predominantly or minimally classic lesions. [**CIC data removed**].

For all secondary measures of visual acuity (maintenance or gain of at least one letter, gain of at least 5, 10 and 15 letters, loss of 30 or more letters), 0.3 mg (licensed dose) or 1.0 mg of pegaptanib showed statistically significant improvements compared with sham injection. However, for the outcome measures 'gains in visual acuity of at least 5 letters' or 'at least 15 letters', the difference between the 3.0-mg dose of pegaptanib and sham injection was not statistically significant. A gain of 15 letters or more of visual acuity is a clinically important outcome, and could have a substantial impact on quality of life. Depending on the starting point, an improvement of this magnitude could mean the difference in being able to drive, to live independently and to read or watch television. The proportion of pegaptanib patients gaining at least 15 letters, although statistically significant, was small (0.3 mg, 6% versus sham, 2%, $p = 0.04$). About 25–40% of patients receiving ranibizumab in the MARINA and ANCHOR trials gained at least 15 letters, compared with about 5% of the control groups ($p < 0.0001$), and similar results were obtained in the FOCUS trial. [**CIC data removed**].

Patients receiving pegaptanib lost on average 7.5 (0.3 mg), 6.5 (1.0 mg) or 10 (3.0 mg) letters after 12 months of treatment, which was significantly less than the 14.5 letters lost by the sham group. However, in the ranibizumab trials patients receiving ranibizumab gained on average 6.5–11.3 letters at 12 months compared with a loss of about 10 letters with sham injection or PDT. Ranibizumab combined with PDT resulted in a mean gain of 4.9 letters compared with a loss of 8.2 letters in the PDT group ($p > 0.001$). An average loss of visual acuity was found with the reduced dose schedule of ranibizumab, which resulted in a mean loss of [**CIC data removed**] 0.2 letters (0.5-mg dose). However, these losses were statistically significantly less than in the sham group, which lost on average 16.3 letters.

The VISION, MARINA, ANCHOR, FOCUS [**CIC data removed**] trials reported that significantly fewer patients deteriorated to legal blindness 12 months after receiving the study drugs.

The VISION study included patients with all angiographic subtypes of lesions. Subgroup analysis of lesion type defined *a priori* found a statistically significant difference in mean change in visual acuity (not reported for the primary outcome) between all doses of pegaptanib and sham injection for minimally classic or occult with no classic lesions. Only the licensed 0.3-mg dose was associated with a statistically significant difference for patients with predominantly classic lesions. Subgroup analyses for the primary outcome can be seen on the FDA website. These data show that the difference in the proportion of patients losing less than 15 letters between 0.3 mg pegaptanib and sham injection is statistically

significant for minimally classic lesions only, and not for predominantly classic lesions or occult with no classic lesions.[107]

The target population of the four ranibizumab studies was occult or minimally classic lesions; predominantly classic lesions; [**CIC data removed**] and any lesion type. In two of the trials [**CIC data removed**], the difference in visual acuity between ranibizumab and the comparator was statistically significant for every lesion subgroup. [**CIC data removed**].

Subgroup analysis should be viewed with caution as statistical tests may not have been powered to detect differences in small numbers of patients.

Contrast sensitivity was not reported by the pegaptanib trials. [**CIC data removed**].

The three doses of pegaptanib were not consistent in producing statistically significant differences from sham injection in anatomical changes, with only the 1.0-mg dose having a statistically significant effect on all three outcome measures: change in size of lesion, change in size of CNV and change in size of leakage. The MARINA and ANCHOR trials [**CIC data removed**] demonstrated statistically significant differences between 0.3 or 0.5 mg ranibizumab and the comparator for the area of CNV, area of leakage from CNV plus intense progressive RPE staining or area of classic CNV.

[**CIC data removed**].

Most of the adverse events reported by the pegaptanib study were mild to moderate transient events. The serious condition endophthalmitis was experienced by 1.3% of patients receiving pegaptanib in the first year. Adverse events were common for people in the ranibizumab trials, but most were mild to moderate. [**CIC data removed**]. The rate of serious ocular adverse events was approximately twice as high in the ranibizumab plus PDT group as in the sham injection plus PDT group.[102] The increased rate of intraocular inflammation (38%) with ranibizumab plus PDT may be attributable to the lyophilised formulation used in this trial. Endophthalmitis was reported by very few patients receiving ranibizumab. The condition occurred in up to 1.4% of 0.5-mg dose ranibizumab patients in the ANCHOR trial and the rate per injection was 0.05% in the MARINA trial. Endophthalmitis occurred in 2% of patients in the FOCUS trial [**CIC data removed**] (all doses).

Economic evaluation

A systematic search of the literature found no fully published economic evaluations of pegaptanib or ranibizumab. Three related abstracts of a model-based economic evaluation of pegaptanib, for a US population of AMD patients, were identified and reviewed.

Published economic evaluations of comparator treatments for wet AMD were identified and briefly reviewed to identify data and assumptions used to model disease progression, health-related quality of life and the influence of methodological assumptions on cost-effectiveness findings. Model time horizon appeared to have the greatest influence on cost-effectiveness estimates, particularly when adopting a third-party payer perspective (incorporating NHS and PSS costs of services for visual impairment).

A systematic search for published studies of quality of life for patients with AMD, identifying studies estimating health state utilities for declining visual function, was undertaken. Studies indicate that quality of life is lower for people with AMD compared to those without disease and may be lower than for people with other chronic disabling diseases. There is a strong association between vision loss and psychological illness, including depression.

Studies of the quality of life impact of AMD and associated vision loss are complicated by the observation that patients may adapt to vision loss (thereby reducing the perceived impact of visual impairment, over time) and that the impact of vision loss in one eye is perceived differently to vision loss in both eyes.

Published estimates of health state utilities for vision loss secondary to AMD have focused primarily on changes in visual acuity. Utility values decline with reduced visual acuity. Studies comparing valuations from different groups reported that clinicians and the general public gave lower estimates of the impact of vision loss compared with estimates from patients with AMD.

Pfizer submitted a dossier in support of pegaptanib which includes an economic evaluation, based on clinical data from the VISION studies, comparing pegaptanib (with or without PDT) with usual care (which consists of best supportive care for all patients as well as PDT for patients with predominantly classic lesions). The analysis was conducted using a Markov state transition model, consisting of 12 health states defined by declining

visual acuity and a death state. In the base case analysis, a cohort of patients of all lesion types, with best-corrected visual acuity in the better-seeing eye of between 6/12 and 6/96, received up to 2 years of treatment with pegaptanib and were followed up for 10 years. A proportion of patients in the usual care cohort received PDT (and visual rehabilitation) and patients received low-vision aids and visual rehabilitation once visual acuity had fallen below 6/60.

Clinical outcomes were modelled using patient-level data from the VISION studies and health state utilities from a published study of valuations by patients with AMD.[113] Costs were estimated based on the number of injections given to patients in the VISION studies, protocols for monitoring patients while on treatment and costs of services for visual impairment from a previous UK study.[40,146]

The QALY gain estimated over 10 years was 0.298 for the reference case, stopping treatment once visual acuity declined below 6/96, and 0.289 for the alternative stopping rule, where treatment ceased once visual acuity declined below 6/60. The cost difference for the reference case was £4705, and for the alternative stopping rule was £4109, giving ICERs of £15,815 and £14,202 per QALY gained, respectively. At 10 years, NHS and PSS costs are the majority of costs for each cohort in the model (55–56% of total costs for the pegaptanib cohort and 93% for the usual care cohort).

In a deterministic sensitivity analysis, results were sensitive to the model time horizon (the ICER was greater than £30,000 until the time horizon was over 5 years) and variation in the costs of blindness. Subgroup analyses were undertaken to examine heterogeneity in the study population. Subgroups were defined by patient age, sex, lesion type and lesion size. Very little variation in ICER was reported by these subgroups, except that the ICER was reduced to £10,940 (£9454 for alternative stopping rule of visual acuity less than 6/60) for patients aged under 75 years compared to £18,863 (£17,128 for alternative stopping rule of visual acuity less than 6/60) for patients aged 75 years and over. The submission reports that this difference was largely due to different mortality rates between the two age groups.

Further analyses were undertaken by the TAR team using the manufacturer's model, to address specific questions that arose during our critique of their submission; these related to the comprehensiveness of the costing of patient monitoring while on treatment and the choice of utility values adopted for the analysis.

Discussion with clinical experts suggested that resource use for monitoring patients during treatment would be greater than assumed in the submission. In particular, the submission did not include vision assessment or OCT, which experts suggested would occur each time patients attended for injection. Clinical experts also suggested that patients would have FA at least every 6 months while on treatment, although the frequency may be as high as every 3 months. When these assumptions are added into the model, whereas the QALY difference remains unchanged, incremental costs increase to £6473 and the ICER is £22,476.

The utility values used in the submission suggest a large reduction in utility when visual acuity drops from the range 6/12–6/24 (0.81) to 6/24–6/60 (0.57) and a second large reduction on moving from 6/60–3/60 (0.52) to less than 3/60 (0.40). [**CIC data removed**].

Novartis submitted a dossier in support of ranibizumab which includes an economic evaluation, based on clinical data from the ANCHOR, MARINA and PIER trials, comparing ranibizumab with best supportive care for patients with all lesion types and additionally with PDT for patients with predominantly classic lesions.

The analysis was conducted using a Markov state transition model, consisting of five health states defined by declining visual acuity and a death state. In the base case analysis for patients with predominantly classic lesions, a cohort of patients received up to 1 year of treatment with ranibizumab and were followed up for 10 years, irrespective of whether the incremental analysis was performed against PDT or best supportive care. In the base case analysis for patients with minimally classic and occult no classic lesions, a cohort of patients received up to 2 years of treatment with ranibizumab and were followed up for 10 years. [**CIC data removed**].

Clinical outcomes were modelled using patient-level data from the ANCHOR and MARINA trial and health state utilities from an unpublished study of valuations by a sample of members of the general public.[140] [**CIC data removed**].

The QALY gain estimated over 10 years for patients with predominantly classic lesions was 0.20 for the comparison with PDT and 0.28 for

the comparison with best supportive care. The cost difference was £917 for the comparison with PDT and £4068 for the comparison with best supportive care, giving ICERs of £4489 and £14,781 per QALY gained, respectively.

The QALY gain estimated over 10 years for patients with minimally classic lesions was 0.34 and for patients with occult no classic lesions it was 0.33. The cost difference was £9125 and £8494, giving ICERs of £26,454 and £25,796 per QALY gained, respectively.

Limited deterministic sensitivity analyses were undertaken, reporting the ICERs for increasing the number of injections given, up to the values observed in the clinical trials. This increased the ICERs substantially (to £25,544 and £29,662 for patients with predominantly classic lesions compared with PDT and best supportive care, respectively, and to around £55,000 per QALY gained for patients with minimally classic and occult no classic lesions). A further sensitivity analysis is reported, removing the assumption that ranibizumab has continued effectiveness after treatment ceases – this has little effect on ICERs.

Further analyses were undertaken by the TAR team using the manufacturer's model, to address specific questions that arose during our critique of their submission – these related to certain costs included for comparator treatments and the assumption that frequency of injection could be reduced below that observed in the clinical trials without affecting effectiveness.

[**CIC data removed**].

We developed an independent model which includes five states of declining visual acuity and an absorbing death state. States in the model were defined to correspond to approximately three lines of visual acuity, which is generally accepted as a clinically significant difference. Individuals in the model could improve, in terms of visual acuity, by one state or deteriorate by one or two states in each model cycle.

The model was used to estimate the cost-effectiveness of pegaptanib and ranibizumab, initially using the time horizon of the trials that provide input data on clinical effectiveness, and secondly for a time horizon of 10 years. This time horizon was chosen to allow for differences between interventions to become apparent and was the approximate life expectancy of patients entering the model.

The proportion of trial participants gaining at least three lines, losing 3–6 lines and losing six lines or more of visual acuity for each year of the relevant clinical trials were extracted from clinical trial reports and used to estimate the transition probabilities for the model. The occurrence of adverse events was also extracted from trial reports and converted to cycle probabilities for inclusion in the model.

Health state utilities used in the model were taken from a published source,[113] which has been widely adopted in previous economic evaluations of treatment for AMD. These valuations were derived from a sample of patients with AMD and not from the general public. However, no credible valuations from a general public sample, using sound methodology, were found in our review of the published literature.

Two main sets of resource use related to treatment and disease progression with AMD were identified and costed. Intervention costs were developed based on protocols for the management of patients on treatment developed with the assistance of clinical experts. Frequency of treatment was based on that observed in the clinical trials and dosage for pegaptanib was taken from the BNF.[82] Drug costs for pegaptanib were also taken from the BNF. The dosage of ranibizumab submitted for marketing authorisation by the manufacturer and the manufacturer's target price for the UK were used in this analysis (since this report was written, ranibizumab has received marketing authorisation and the UK unit price has been confirmed at £761.20, the value used in this analysis). Health state costs, calculated from estimates of the uptake and unit costs of services for visual impairment, are based on estimates published in a previous UK study,[40,146] inflated to 2005 prices.

The QALY gain after 2 years of treatment with pegaptanib, in the trial-based analysis, is small (0.06 QALYs) and the incremental cost is high (approximately £10,000). All treatment costs are realised within this time horizon, but few of the expected savings in costs of blindness, that may be expected by delaying disease progression in a proportion of patients, are apparent at this time. Given the small QALY gain and high incremental cost at 2 years, the ICER is high (£163,603).

The QALY gain after 10 years, assuming the same rates of disease progression for patients in the pegaptanib (post-treatment) as in the usual care cohort, is 0.26 QALYs. The incremental cost reduced to around £8000 as differences in the

proportion of patients progressing to severe visual impairment impact on the costs of blindness in each cohort. As a result, the ICER at 10 years reduced to £30,986.

Deterministic sensitivity analysis emphasises the influence of time horizon on cost-effectiveness, showing a sharp decline in ICER as time horizon increases beyond the clinical trial time horizon. The sensitivity analysis also suggests that ICERs are less favourable for patients with older age on entry to the model and with poorer initial visual acuity. Costing the injection procedure as a day case, rather than adopting a unit cost for an outpatient procedure, has a large impact on the ICER, which increases to £47,845. The ICERs are also sensitive to choice of utility values and are particularly sensitive to variations in the costs of blindness.

Probabilistic sensitivity analysis shows a 17% probability of pegaptanib being cost-effective, compared with usual care, at a willingness to pay threshold of £20,000. The equivalent figure for a willingness to pay threshold of £30,000 is 58%.

The QALY gain after 1 year of treatment with ranibizumab for patients with predominantly classic lesions, in the trial-based analysis, is small for the comparison with PDT (0.04 QALYs) and for the comparison with best supportive care (0.07 QALYs). The incremental costs are high: approximately £8000 for the comparison with PDT and £11,500 for the comparison with best supportive care. The QALY gain after 2 years of treatment for patients with minimally classic and occult no classic lesions is 0.14 QALYs and the incremental cost is £22,400. The ICER for these comparisons in the trial-based analyses are between £150,000 and approximately £200,000.

The QALY gain at 10 years for patients with predominantly classic lesions is 0.34 for the comparison with PDT and 0.57 for the comparison with best supportive care. The incremental costs reduced to £5391 and £6457, giving ICERs of £15,638 for the comparison with PDT and £11,412 for the comparison with best supportive care. The QALY gain at 10 years for patients with minimally classic and occult no classic lesions is 0.69 QALYs and the incremental cost reduced to £17,314, giving an ICER of £25,098.

In deterministic sensitivity analysis, the pattern of response to changes in underlying assumptions was similar for the different lesion types and for the different comparators. This analysis emphasises the influence of time horizon on cost-effectiveness, showing a sharp decline in ICER as the time horizon increases beyond the clinical trial time horizon. The sensitivity analysis also suggests that ICERs are less favourable for patients with older age on entry to the model. However, poorer initial visual acuity has little effect on cost-effectiveness estimates. Costing the injection procedure as a day case, rather than adopting a unit cost for an outpatient procedure, has a large impact on the ICER (which for patients with predominantly classic lesions increases to £26,102 for the comparison with PDT and £17,787 for the comparison with best supportive care and for patients with minimally classic and occult no classic lesions the ICER increases to £35,157). The ICER is also sensitive to choice of utility values and is particularly sensitive to variations in the costs of blindness.

In probabilistic sensitivity analyses for ranibizumab, where probabilities of losing or gaining visual acuity, health state utility values, cost of outpatient attendances, FA and OCT and costs of services for visual impairment were sampled probabilistically, the majority of simulations, for each lesion type (and each comparison) were associated with increased QALYs but also increased costs. In this analysis, ranibizumab for patients with predominantly classic lesions had a probability of being cost-effective (compared with PDT) of 72% at a willingness to pay threshold of £20,000 per QALY and 97% at a threshold of £30,000 per QALY. The equivalent figures for the comparison with best supportive care were 95 and 99%, respectively. For patients with minimally classic and occult no classic lesions, the probability of being cost-effective (compared with best supportive care) at a threshold of £20,000 per QALY was 15% and at a threshold of £30,000 per QALY it was 81%.

Strengths and limitations of the assessment

The systematic review has the following strengths:

- It is independent of vested interest.
- The systematic review brings together the evidence on the effectiveness of ranibizumab and pegaptanib for subfoveal CNV associated with AMD, applying consistent methods of critical appraisal and presentation.
- A broad and thorough systematic search of the literature identified all English-language RCTs

on ranibizumab and pegaptanib, and highlighted gaps in the literature and areas for further research.
- The systematic review was guided by the principles for undertaking a systematic review.
- Before undertaking the review, the methods were set out in a research protocol (Appendix 1), which was commented on by an advisory group. The protocol defined the research question, inclusion criteria, quality criteria, data extraction process and methods employed to undertake the different stages of the review.
- An advisory group has informed the review from its initiation, through the development of the research protocol and completion of the report.

In contrast, there were certain limitations:

- Owing to time constraints, there was a lack of follow-up with authors of the primary studies to clarify methodological details and results. However, it is unlikely that further details from the authors would have changed our conclusions.
- Inclusion was limited to English language due to time constraints. However, no non-English RCTs were identified by the manufacturers of the drugs.

Uncertainties

- The ANCHOR trial compared ranibizumab against PDT, with no sham control arm. In order to model the cost-effectiveness of ranibizumab against best supportive care, and in order to make extrapolations beyond the trial data, an indirect comparison against the sham arm of the TAP study was required. Outcomes for the subgroup of patients with predominantly classic lesions were used in the indirect comparison. However, the need to bring data from other trials into this analysis introduces further uncertainty.
- Treatment protocols, optimal dosing schedules and durations of treatment for pegaptanib and ranibizumab have not been established. As there is limited evidence on optimal treatment durations and on the effectiveness of retreatment, we adopted the frequency of treatment in the relevant clinical trials. It is not clear whether these frequencies of treatment will be adopted in normal clinical practice.
- There is a lack of published data on valuations of visual impairment secondary to AMD from general population samples. There is substantial divergence between valuations derived from people with AMD and valuations derived from clinicians and population samples. This raises concerns over what methods would be appropriate for deriving credible health state valuations for vision loss secondary to AMD. There are further concerns in the literature regarding the appropriateness of basing QALYs for visual function on visual acuity alone, rather than contrast sensitivity (or a combination of the two).
- There is uncertainty over the appropriate configuration of services, staffing and distribution of facilities to provide anti-VEGF treatments. Given the lack of certainty over appropriate service organisation, it is difficult to estimate the costs of providing appropriate care. The Royal College of Ophthalmologists has convened an AMD Provisions Sub-committee to address such issues.
- There is considerable uncertainty over the costs of services for visual impairment – sensitivity analyses in the economic evaluation showed that, using extreme values for uptake and unit costs of services, treatment with pegaptanib or ranibizumab could be cost-saving (high uptake and high unit cost) or could be associated with 30–70% increases in incremental cost (low uptake and low unit cost).

Other relevant factors

- The pegaptanib publications reported the combined results of two concurrent RCTs (VISION study). Both trials showed a significant difference between 0.3 mg of pegaptanib and sham injection for the primary efficacy end-point at year 1, so were combined for analysis as stated in the study protocol. However, an FDA review of the data for the individual trials noted that one of the trials did not show efficacy for any of the active doses at 2 years.[103,104] The reasons for this are not clear.
- We have attempted to discuss results according to lesion subtype where possible, but this is limited by the data presented by the studies.
- The pegaptanib trial included patients with all angiographic subtypes of lesions. The four ranibizumab trials included all subtypes (PIER), occult or minimally classic lesions (MARINA) or predominantly classic lesions (ANCHOR and FOCUS). This may limit generalisability.
- All trials identified in the systematic review were funded by the pharmaceutical industry.
- Although there were relatively few studies included in this review, they presented a wide

range of outcome measures. We have reported all those which were defined in the protocol as being relevant to this assessment. Consequently, the overall quantity and complexity of the information available complicates interpretation of the clinical evidence.

- The off-labelled use of bevacizumab (Avastin) for AMD (see the section 'Management of disease', p. 11) is beyond the remit of this report. According to the Royal College of Ophthalmologists, one of the main drives for the rapid adoption of bevacizumab is cost, with single treatments potentially costing as little as £3.[79] However, there are no RCT data on the efficacy of bevacizumab compared with standard treatment or any long-term safety data; therefore, further research is required.

Chapter 7
Conclusions

This report has shown that patients with AMD of any lesion type benefit from treatment with pegaptanib or ranibizumab on measures of visual acuity when compared with sham injection and/or PDT. These benefits were statistically significant and, depending on the starting point for each patient, likely to be clinically significant. Continued treatment with pegaptanib or ranibizumab appeared to maintain those benefits after 2 years of follow-up. Although adverse events were reported for both drugs, they appeared mild to moderate with few serious ocular events. When comparing pegaptanib and ranibizumab, the evidence was less clear due to the lack of direct comparison through head-to-head trials and the lack of opportunity for indirect statistical comparison due to heterogeneity.

The cost-effectiveness analysis showed that the two drugs offered additional benefit over the comparators of usual care and PDT, but at increased cost. For pegaptanib compared with usual care, the ICER ranged from £163,603 for the 2-year model to £30,986 for the 10-year model. Similarly, the ICERs for ranibizumab for patients with minimally classic and occult no classic lesions, compared with usual care, ranged from £152,464 for the 2-year model to £25,098 for the 10-year model. Sensitivity analysis suggested that the time horizon of the model, the patient's baseline visual acuity, the disease-modifying effect of the treatment and the provision of the service as a day-case rather than outpatient procedure influenced the ICER. Probabilistic sensitivity analysis showed that pegaptanib had a probability of being cost-effective compared with usual care of 58% at a willingness to pay threshold of £30,000 per QALY. In contrast, ranibizumab compared with PDT or usual care had a probability of being cost-effective for patients with predominantly classic lesions of 97% at a willingness to pay threshold of £30,000 per QALY. For patients with minimally classic and occult no classic lesions, the probability of being cost-effective at a willingness to pay threshold of £30,000 per QALY was 81%.

Implications for service provision

Interim guidelines on the management and treatment of AMD from the Royal College of Ophthalmologists (Wong D, Royal College of Ophthalmologists: personal communication, November 2006) recommend intraocular injection of anti-VEGFs for first-line treatment of minimally classic subfoveal CNV. They further recommend the use of anti-VEGF for treatment of occult no classic subfoveal CNV, where PDT is not covered by local commissioning, and for predominantly classic subfoveal CNV where there has been a poor response to PDT. The implication of these recommendations is that the number of patients eligible for active treatment is likely to increase substantially. Current estimates suggest that around 30% of patients with neovascular AMD are eligible for PDT. The AMD Alliance[147] state, citing the Royal College of Ophthalmologists, that patient numbers could increase from 7000 (currently eligible for treatment with PDT) to 26,000 per year and suggest that current services have insufficient capacity to deal with this volume of patients. Workload in ophthalmic services will increase beyond the approximate trebling in patient numbers, since the frequency of attendance and treatment is higher than for PDT. It has been suggested that ophthalmology services may face up to a six-fold increase in workload (Lotery A, Southampton University Hospitals Trust: personal communication, October 2006).

The Royal College of Ophthalmologists and patient advocacy groups have argued that current services will be unable to cope with this increased workload and there is a likelihood that this introduction of intravitreal therapy will have an effect on the ability of departments to deliver ophthalmic services overall. The Royal College guidelines indicate that, due to risks of serious adverse events, intravitreal injection should only be undertaken by or under supervision of ophthalmologists experienced in the procedure. They also emphasise the involvement of a multi-disciplinary team in delivering this treatment, including specialist nurses, optometrists and technicians. The increase in patient load and frequency of assessment associated with treatment with pegaptanib and ranibizumab is likely to require additional specialist imaging equipment (for FA and OCT) and also provision of clean rooms for performing the injection procedure.

Suggested research priorities

- This report has established that ranibizumab is clinically effective for delaying vision loss and improving vision in AMD. As discussed in the sections 'Management of disease' (p. 11) and 'Other relevant factors' (p. 94), bevacizumab (Avastin), which is biologically similar to ranibizumab, is being increasingly used off-label for the treatment of AMD. There are no long-term data on the safety and efficacy of bevacizumab and no RCTs have yet been conducted; however, one of the main drives for its adoption is its low cost. The US National Eye Institute of the National Institutes for Health announced in October 2006 that it will be funding a new multi-centre clinical trial to compare ranibizumab and bevacizumab for AMD. In the UK, an application to the HTA Clinical Trials Programme for a trial of bevacizumab versus ranibizumab with further randomisation to PDT has been short-listed and the applicants have been invited to submit a full proposal. These trials should establish whether bevacizumab is a clinically and cost-effective alternative to ranibizumab.
- Pegaptanib is clinically effective for delaying vision loss associated with AMD. Although the proportion of patients experiencing improvements in vision appears less with pegaptanib than ranibizumab, no head-to-head RCTs have been conducted. A trial comparing pegaptanib with ranibizumab and bevacizumab is recommended. The role of verteporfin PDT in combination with these drugs should also be investigated.
- A study to assess adverse events outside the proposed RCTs is also required.
- Further research is required on the optimal dosing regimes of these drugs and the benefits of re-treatment after initial treatment.
- More detailed costing work is required, for example an independent survey of the costs associated with vision loss.
- Further research is required into health state utilities and their relationship with visual acuity and contrast sensitivity. Further research is required to reduce uncertainty over the relationship between duration of vision loss and the quality of life and functional impact of vision loss.
- The genetic cause of AMD can be detected in 50% of patients. Research to determine whether being identified as genetically at risk will alter behaviour, for example, inspire people to stop smoking, would be useful.

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Contribution of authors

Jill Colquitt (Senior Research Fellow), Jeremy Jones (Principal Research Fellow), Andrea Takeda (Senior Research Fellow), Seng Chuen Tan (Research Fellow) and Andrew Clegg (Professor/Director of SHTAC) developed the protocol. Andrew Clegg drafted the epidemiology section. Alison Price (Information Scientist) conducted the literature searches. Andrea Takeda and Jill Colquitt were responsible for inclusion screening, data extraction and critical appraisal. Jeremy Jones and Seng Chuen Tan were responsible for the health economics section of the report. All authors contributed to drafting the report. Jill Colquitt was project coordinator.

References

1. Evans J, Wormald R. Is the incidence of registrable age related macular degeneration increasing? *Br J Ophthalmol* 1996;**80**:9–14.
2. Bird AC, Bressler NM, Bressler SB, Chisholm IH, Coscas G, Davis MD, *et al*. An international classification and grading system of age-related maculopathy and age-related macular degeneration. The International ARM Epidemiological Study Group. *Surv Ophthalmol* 1995;**39**:367–74.
3. Fine SL, Berger KW, Maguire MG, Ho AC. Age related macular degeneration. *New Engl J Med* 2000;**342**(7):483–92.
4. Evans J. Age-related macular degeneration. In Johnson GJ, Minassian DC, Weale R, editors. *The epidemiology of eye disease*. London: Chapman and Hall; 1998. pp. 356–72.
5. Klaver CCW, Assink JJM, van Leeuwen R, Wolfs RCW, Vingerling JR, Stijnen T, *et al*. Incidence and progression rates of age-related maculopathy: The Rotterdam Study. *Invest Ophthalmol Vis Sci* 2001;**42**:2237–41.
6. van Leeuwen R, Klaver CCW, Vingerling JR, Hofman A, de Jong PTVM. The risk and natural course of age-related maculopathy: follow-up at $6^1/_2$ years in the Rotterdam study. *Arch Ophthalmol* 2003;**121**:519–26.
7. Augood CA, Vingerling JR, de Jong PT, Chakravarthy U, Seland J, Soubrane G, *et al*. Prevalence of age-related maculopathy in older Europeans: the European Eye Study (EUREYE). *Arch Ophthalmol* 2006;**124**:529–35.
8. Ferris FL III, Fine SL, Hyman L. Age-related macular degeneration and blindness due to neovascular maculopathy. *Arch Ophthalmol* 1984; **102**:1640–2.
9. Ambati J, Ambati BK, Yoo SH, Ianchulev S, Adamis AP. Age-related macular degeneration: etiology, pathogenesis, and therapeutic strategies. *Surv Ophthalmol* 2003;**48**:257–93.
10. Arnold J, Blemenkranz M, Bressler NM, Bressler SB, Deslandes J, Donati G, *et al*. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials – TAP report 1. *Arch Ophthalmol* 1999;**117**:1329–45.
11. Olsen TW, Feng X, Kasper TJ, Rath PP, Steuer ER. Fluorescein angiographic lesion type frequency in neovascular age-related macular degeneration. *Ophthalmology* 2004;**111**:250–5.
12. Age-Related Eye Disease Study Research Group. Risk factors for the incidence of advanced age-related macular degeneration in the Age-Related Eye Disease Study (AREDS). AREDS Report No. 19. *Ophthalmology* 2005;**112**:533–9.
13. Brown MD, Bowling EL. Age-related macular degeneration – a therapeutic update. *Clin Refract Optom* 2005;**16**:240–8.
14. Delcourt C, Diaz J, Ponten-Sanchez A, Papoz L. Smoking and age-related macular degeneration: the POLA study. *Arch Ophthalmol* 1998;**116**:1031–5.
15. Schmidt S, Hauser MA, Scott WK, Postel EA, Agarwal A, Gallins P, *et al*. Cigarette smoking strongly modifies the association of LOC387715 and age-related macular degeneration. *Am J Hum Genet* 2006;**78**:852–64.
16. Evans JR, Henshaw K. Antioxidant vitamin and mineral supplements for preventing age-related macular degeneration. *Cochrane Database Syst Rev* 1999;(4):CD000253.
17. Age-Related Eye Disease Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss. AREDS Report No. 8. *Arch Ophthalmol* 2001;**119**:1417–36.
18. Evans J. Antioxidant vitamin and mineral supplements for slowing the progression of age-related macular degeneration. *Cochrane Database Syst Rev* 2006;(2):CD000254.
19. Seddon JM, Cote J, Davis N, Rosner B. Progression of age-related macular degeneration: association with body mass index, waist circumference, and waist–hip ratio. *Arch Ophthalmol* 2003;**121**:785–92.
20. Seddon JM, George S, Rosner B, Klein ML. CFH gene variant, Y402H, and smoking, body mass index, environmental associations with advanced age-related macular degeneration. *Hum Hered* 2006;**61**:157–65.
21. Hyman L, Schachat AP, He Q, Leske MC, for the Age-Related Macular Degeneration Risk Factors Study Group. Hypertension, cardiovascular disease, and age-related macular degeneration. *Arch Ophthalmol* 2000;**118**:351–8.
22. Pauleikhoff D. Neovascular age-related macular degeneration: natural history and treatment outcomes. *Retina* 2005;**25**:1065–84.

23. Royal College of Ophthalmologists. *Age related macular degeneration. Guidelines*. London: Royal College of Ophthalmologists; 2000.

24. Klein R, Klein BE, Tomany SC, Meuer SM, Huang GH. Ten-year incidence and progression of age-related maculopathy: the Beaver Dam eye study. *Ophthalmology* 2002;**109**:1767–79.

25. Mitchell P, Wang JJ, Foran S, Smith W. Five-year incidence of age-related maculopathy lesions: the Blue Mountains Eye Study. *Ophthalmology* 2002; **109**:1092–7.

26. Bunce C, Wormald R. Leading causes of certification for blindness and partial sight in England and Wales. *BMC Public Health* 2006;**6**:58.

27. Owen CG, Fletcher AE, Donoghue M, Rudnika AR. How big is the burden of visual loss caused by age related macular degeneration in the United Kingdom? *Br J Ophthalmol* 2003;**87**:312–17.

28. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy. The Beaver Dam Eye Study. *Ophthalmology* 1992;**99**:933–43.

29. Mitchell P, Smith W, Attebo K, Wang JJ. Prevalence of age-related maculopathy in Australia. The Blue Mountains Eye Study. *Ophthalmology* 1995; **102**:1450–60.

30. Vinding T. Visual impairment of age-related macular degeneration. An epidemiological study of 1000 aged individuals. *Acta Ophthalmol* 1990; **68**:162–7.

31. Vinding T. Age-related macular degeneration. An epidemiological study of 1000 elderly individuals. With reference to prevalence, funduscopic findings, visual impairment and risk factors. *Acta Ophthalmol Scand Suppl* 1995;(217):1–32.

32. Reidy A, Minassian DC, Vafidis G, Joseph J, Farrow S, Wu J, *et al*. Prevalence of serious eye disease and visual impairment in a north London population: population based, cross sectional study. *BMJ* 1998;**316**:1643–6.

33. Vingerling JR, Dielemans I, Hofman A, Grobbee DE, Hijmering M, Kramer CF, *et al*. The prevalence of age-related maculopathy in the Rotterdam Study. *Ophthalmology* 1995;**102**:205–10.

34. Vannewkirk MR, Nanjan MB, Wang JJ, Mitchell P, Taylor HR, McCarty CA. The prevalence of age-related maculopathy: the visual impairment project. *Ophthalmology* 2000;**107**:1593–600.

35. Vannewkirk MR, Weih L, McCarty CA, Taylor HR. Cause-specific prevalence of bilateral visual impairment in Victoria, Australia: the Visual Impairment Project. *Ophthalmology* 2001; **108**:960–7.

36. Weih LM, Vannewkirk MR, McCarty CA, Taylor HR. Age-specific causes of bilateral visual impairment. *Arch Ophthalmol* 2000;**118**:264–9.

37. Buch H, Vinding T, Nielsen NV. Prevalence and causes of visual impairment according to World Health Organization and United States criteria in an aged, urban Scandinavian population: the Copenhagen City Eye Study. *Ophthalmology* 2001; **108**:2347–57.

38. Bressler NM, Bressler SB, West SK, Fine SL, Taylor HR. The grading and prevalence of macular degeneration in Chesapeake Bay watermen. *Arch Ophthalmol* 1989;**107**:847–52.

39. Office for National Statistics. *Mid-2005 population estimates: England and Wales; estimated resident population by single year of age and sex*. URL: http://www.statistics.gov.uk/statbase/Expodata/Spreadsheets/D9389.xls. Accessed 16 October 2006.

40. Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C. Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2001;**7**(9).

41. Morse AR, Yatzkan E, Berberich B, Arons RR. Acute care hospital utilization by patients with visual impairment. *Arch Ophthalmol* 1999; **117**:943–9.

42. Wang JJ, Mitchell P, Cumming RG, Attebo K. Impact of visual impairment on use of community support services by elderly persons: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci* 1999;**40**:12–19.

43. Wang JJ, Mitchell P, Cumming RG, Smith W. Visual impairment and nursing home placement in older Australians: the Blue Mountains Eye Study. *Ophthalmic Epidemiol* 2003;**10**:3–13.

44. Wang JJ, Mitchell P, Simpson JM, Cumming RG, Smith W. Visual impairment, age-related cataract, and mortality. *Arch Ophthalmol* 2001;**119**:1186–90.

45. Zhou S, Javitt JC, Zlateva G, Shah SN. Evaluating the risk of mortality for exudative (wet) AMD patients compared to a control group. *Invest Ophthalmol Vis Sci* 2006;**47**:2213.

46. Thiagarajan M, Evans JR, Smeeth L, Wormald RPL, Fletcher AE. Cause-specific visual impairment and mortality: results from a population-based study of older people in the United Kingdom. *Arch Ophthalmol* 2005; **123**:1397–403.

47. Centers for Medicare and Medicaid Services. Standard analytical files – limited data set. URL: http://www.cms.hhs.gov/LimitedDataSets/10_StandardAnalyticalFiles.asp. Accessed 10 October 2006.

48. Jack CI, Smith T, Neoh C, Lye M, McGalliard JN. Prevalence of low vision in elderly patients admitted to an acute geriatric unit in Liverpool:

elderly people who fall are more likely to have low vision. *Gerontology* 1995;**41**:280–5.

49. Tromp AM, Pluijm SM, Smit JH, Deeg DJ, Bouter LM, Lips P. Fall-risk screening test: a prospective study on predictors for falls in community-dwelling elderly. *J Clin Epidemiol* 1995; **54**:837–44.
50. Legood R, Scuffham P, Cryer C. Are we blind to injuries in the visually impaired? A review of the literature. *Inj Prev* 2002;**8**:155–60.
51. Ivers RQ, Optom B, Cumming RG, Mitchell P, Simpson JM, Peduto AJ. Visual risk factors for hip fracture in older people. *J Am Geriatr Soc* 2003; **51**:356–63.
52. Felson DT, Anderson JJ, Hannan MT, Milton RC, Wilson PW, Kiel DP. Impaired vision and hip fracture. The Framingham Study. *J Am Geriatr Soc* 1989;**37**:495–500.
53. Cummings SR, Nevitt MC, Browner WS, Stone K, Fox KM, Ensrud KE, *et al*. Risk factors for hip fracture in white women. Study of Osteoporotic Fractures Research Group. *N Engl J Med* 1995; **332**:767–73.
54. Dargent-Molina P, Favier F, Grandjean H, Baudoin C, Schott AM, Hausherr E, *et al*. Fall-related factors and risk of hip fracture: the EPIDOS prospective study. *Lancet* 1996;**348**:145–9.
55. Brody BL, Gamst AC, Williams RA, Smith AR, Lau PW, Dolnak D, *et al*. Depression, visual acuity, comorbidity, and disability associated with age-related macular degeneration. *Ophthalmology* 2001; **108**:1893–900.
56. Williams RA, Brody BL, Thomas RG, Kaplan RM, Brown SI. The psychosocial impact of macular degeneration. *Arch Ophthalmol* 1998;**116**:514–20.
57. Rovner BW, Ganguli M. Depression and disability associated with impaired vision: the moVIES project. *J Am Geriatr Soc* 1998;**46**:617–19.
58. Casten RJ, Rovner BW, Tasman W. Age-related macular degeneration and depression: a review of recent research. *Curr Opin Ophthalmol* 2004; **15**:181–3.
59. Horowitz A, Reinhardt JP, Kennedy GJ. Major and subthreshold depression among older adults seeking vision rehabilitation services. *Am J Geriatr Psychiatry* 2005;**13**:180–7.
60. Shmuely-Dulitzki Y, Rovner BW, Zisselman P. The impact of depression on functioning in elderly patients with low vision. *Am J Geriatr Psychiatry* 1995;**3**:325–9.
61. Dong LM. Health- and vision-related quality of life among patients with choroidal neovascularization secondary to age-related macular degeneration at enrollment in randomized trials of submacular surgery: SST Report No. 4. *Am J Ophthalmol* 2004;**138**:91–108.
62. Shah VA, Gupta SK, Shah KV, Vinjamaram S, Chalam KV. TTO utility scores measure quality of life in patients with visual morbidity due to diabetic retinopathy or ARMD. *Ophthalmic Epidemiol* 2004;**11**:43–51.
63. Cahill MT, Banks AD, Stinnett SS, Toth CA. Vision-related quality of life in patients with bilateral severe age-related macular degeneration. *Ophthalmology* 2005;**112**:152–8.
64. Chia EM, Wang JJ, Rochtchina E, Smith W, Cumming RR, Mitchell P. Impact of bilateral visual impairment on health-related quality of life: the Blue Mountains Eye Study. *Invest Ophthalmol Vis Sci* 2004;**45**:71–6.
65. Hassell JB, Lamoureux EL, Keeffe JE. Impact of age related macular degeneration on quality of life. *Br J Ophthalmol* 2006;**90**:593–6.
66. Slakter JS, Stur M. Quality of life in patients with age-related macular degeneration: impact of the condition and benefits of treatment. *Surv Ophthalmol* 2005;**50**:263–73.
67. Moore LW, Constantino RE, Allen M. Severe visual impairment in older women. *West J Nurs Res* 2000; **22**:571–95.
68. Fletcher DC, Schuchard RA. Visual function in patients with choroidal neovascularization resulting from age-related macular degeneration: the importance of looking beyond visual acuity. *Optom Vis Sci* 2006;**83**:178–89.
69. Thompson D. VA testing in optometric practice. Part 1: the Snellen chart. *Optometry Today/Optics Today* 2005;55–7. http://www.optometry.co.uk
70. Thompson D. VA testing in optometric practice. Part 2: Newer chart designs. *Optometry Today/Optics Today* 2005;22–4. http://www.optometry.co.uk
71. Holladay JT. Visual acuity measurements. *J Cataract Refract Surg* 2004;**30**:287–90.
72. Encyclopedia – contrast sensitivity. URL: http://www.visionrx.com/library/enc/enc_contrast.asp. Accessed 14 August 2006.
73. *Perimetry*. URL: http://en.wikipedia.org/wiki/Perimetry. Accessed 16 August 2006.
74. Department of Health. *Certificate of Vision Impairment: explanatory notes for consultant ophthalmologists and hospital eye clinic staff*. August 2005. URL: http://www.dh.gov.uk/assetRoot/04/11/86/66/04118666.pdf
75. Kourlas H, Schiller DS. Pegaptanib sodium for the treatment of neovascular age-related macular degeneration: a review. *Clin Ther* 2006;**28**:36–44.
76. American Academy of Ophthalmology. *Age-related macular degeneration. Preferred practice pattern*. National Guidelines Clearinghouse; 2000. http://www.guidelines.gov

77. National Institute for Clinical Excellence. *Guidance on the use of photodynamic therapy for age-related macular degeneration*. Technology Appraisal Guidance. London: NICE; 2003. p. 68.

78. van Wijngaarden P, Coster DJ, Williams KA. Inhibitors of ocular neovascularization: promises and potential problems. *JAMA* 2005;**293**:1509–13.

79. Wong D. *Avastin is coming*? URL: http://www.rcophth.ac.uk/scientific/scientificnews. Accessed 10 May 2006.

80. Rosenfeld PJ. Intravitreal avastin: the low cost alternative to lucentis? *Am J Ophthalmol* 2006; **142**:141–3.

81. Steinbrook R. The price of sight – ranibizumab, bevacizumab, and the treatment of macular degeneration. *N Engl J Med* 2006;**355**:1409–12.

82. Joint Formulary Committee. *British National Formulary*. No. 52. London: British Medical Association and Royal Pharmaceutical Society of Great Britain; 2006.

83. The Royal College of Ophthalmologists. *The use of bevacizumab (avastin)*. URL: http://www.rcophth.ac.uk/scientific/avastin. Accessed 19 September 2006.

84. Department of Health (UK). *NHS Reference Costs. 2005*. URL: http://www.dh.gov.uk/PolicyAndGuidance/OrganisationPolicy/FinanceAndPlanning/NHSReferenceCosts/fs/en. Accessed 14 September 2006.

85. Bonastre J, Le Pen C, Anderson P, Ganz A, Berto P, Berdeaux G. The epidemiology, economics and quality of life burden of age-related macular degeneration in France, Germany, Italy and the United Kingdom. *Eur J Health Econ* 2002; **3**:94–102.

86. Meads C, Moore D. *The clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration*. Report No. 24. Birmingham: West Midlands Health Technology Assessment Collaboration, Department of Public Health and Epidemiology, University of Birmingham; 2001.

87. Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. *Br J Ophthalmol* 2004;**88**:1107–12.

88. Arnold J, Barbazetto I, Birngruber R, Blumenkranz MS, Bressler SB, Bressler NM, *et al*. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials – TAP report 2. *Arch Ophthalmol* 2001;**119**:198–207.

89. Genentech. *Preliminary Phase III data from head-to-head study of Lucentis shows Lucentis improved vision compared to Visudyne in patients with wet age-related macular degeneration*. Press release, 14 January 2006. URL: http://www.gene.com/gene/news/press-releases/display.do?method=detail&id=9307. Accessed 9 May 2006.

90. Genentech. *Full prescribing information. Lucentis™ (ranibizumab injection)*. URL: http://www.gene.com/gene/products/information/pdf/lucentis-prescribing.pdf. Accessed 3 July 2006.

91. Novartis Pharmaceuticals UK. *Lucentis (ranibizumab) therapy for the treatment of wet age-related macular degeneration*. Evidence submitted to the National Institute for Health and Clinical Excellence, August 2006.

92. Pfizer. *Summary of product characteristics. Macugen 0.3 mg solution for injection*. URL: http://www.emea.eu.int/humandocs/PDFs/EPAR/macugen/H-620-PI-en.pdf. Accessed 5 July 2006.

93. Hawkes N. *Thousands denied eye drug over NHS costs*. URL: http://www.timesonline.co.uk/article/0,,8122-2185672_2,00.html. Accessed 18 May 2006.

94. *Macugen to launch to NICE controversy*. URL: http://pharmatimes.com. June 2006.

95. Gragoudas ES, Adamis AP, Cunningham ET Jr, Feinsod M, Guyer DR, VEGF Inhibition Study in Ocular Neovascularization Clinical Trial Group. Pegaptanib for neovascular age-related macular degeneration. *N Engl J Med* 2004;**351**:2805–16.

96. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, *et al*. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1432–44.

97. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, *et al*. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1419–31.

98. Holz FG, Jorzik J, Schutt F, Flach U, Unnebrink K. Agreement among ophthalmologists in evaluating fluorescein angiograms in patients with neovascular age-related macular degeneration for photodynamic therapy eligibility (FLAP-study). *Ophthalmology* 2003;**110**:400–5.

99. NHS Centre for Reviews and Dissemination. *Undertaking systematic reviews of research on effectiveness*. CRD Report 4. 2nd ed. York: University of York; 2001.

100. VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group. Year two efficacy results of 2 randomized controlled trials of pegaptanib for neovascular age-related degeneration. *Ophthalmology* 2006; **113**:1508–21.

101. VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group. Pegaptanib sodium for neovascular age-related macular degeneration. Two-year safety results of the two prospective, multicenter, controlled clinical trials. *Ophthalmology* 2006;**113**:992–1001.

102. Heier J, Boyer J, Ciulla D, Ferrone T, Jumper P, Gentile J, *et al*. Ranibizumab combined with verteportin photodynamic therapy in neovascular age-related macular degeneration: year 1 results of the FOCUS study. *Arch Ophthalmol* 2006; **124**:1532–42.

103. Spaide R. New treatments for AMD. *Ophthalmology* 2006;**113**:160–1.

104. FDA Center for Drug Evaluation and Research. *Medical Officer's review of NDA 21-756 – Macugen final label*. December 2004. URL: http://www.fda.gov/cder/foi/nda/2004/21-756_macugen_medr.pdf

105. Pfizer. *Macugen (pegaptanib sodium)*. Submission to the National Institute for Health and Clinical Excellence, 31 July 2006.

106. Zlateva G, Patel M, Shah G, VEGF Inhibition Study in Ocular Neovascularization (VISION) Clinical Trial Group. Quality of life in patients with age-related macular degeneration: results from the VISION study. *Invest Ophthalmol Vis Sci* 2006;**47**:E-Abstract 2152.

107. EyeTech Pharmaceuticals. *Dermatologic and Ophthalmic Drugs Advisory Committee meeting. Pegaptanib sodium injection (Macugen)*. PowerPoint presentation, 2004. URL: http://www.fda.gov/ohrms/dockets/ac/04/slides/2004-4053S1_01_EyeTech-Main.ppt. Accessed 23 October 2006.

108. Earnshaw SR, Javitt JC, Zlateva GP, Pleil AM, Graham CN, Brogan AJ, *et al*. Cost-effectiveness model for age-related macular degeneration: Comparing Macugen to Visudyne. *Value Health* 2005;**8**:A176–7.

109. Earnshaw SR, Javitt JC, Zlateva GP, Pleil AM, Graham CN, Brogan AJ, *et al*. Cost-effectiveness model for age-related macular degeneration: comparing early and late macugen treatment. *Value Health* 2005;**8**:A177.

110. Earnshaw SR, Javitt JC, Graham CN, Brogan AJ, Zlateva GP, Pleil AM, *et al*. Modeling treatments for subfoveal choroidal neovascularization secondary to age related macular degeneration: cost-effectiveness methods. *Value Health* 2005; **8**:A179.

111. Bressler NM, Arnold J, Benchaboune M, Blumenkranz MS, Fish GE, Gragoudas ES, *et al*. Verteporfin therapy of subfoveal choroidal neovascularization in patients with age-related macular degeneration: additional information regarding baseline lesion composition's impact on vision outcomes – TAP report no. 3. *Arch Ophthalmol* 2002;**120**:1443–54.

112. Arnold J, Barbezetto I, Birngruber R, Bressler NM, Bressler SB, Donati G, *et al*. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: two-year results of a randomized clinical trial including lesions with occult with no classic choroidal neovascularization – Verteporfin in photodynamic therapy report 2. *Am J Ophthalmol* 2001;**131**:541–60.

113. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;**118**:47–51.

114. Brown GC, Brown MM, Campanella J, Beauchamp GR. The cost–utility of photodynamic therapy in eyes with neovascular macular degeneration – a value-based reappraisal with 5-year data. *Am J Ophthalmol* 2005;**140**:679–87.

115. Hopley C, Salkeld G, Mitchell P. Cost utility of photodynamic therapy for predominantly classic neovascular age related macular degeneration. *Br J Ophthalmol* 2004;**88**:982–7.

116. Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2001; **108**:2051–9.

117. Sharma S, Bakal J, Sharma SM, Covert D, Shah GK. Drug pricing for a novel treatment for wet macular degeneration: using incremental cost-effectiveness ratios to ensure societal value. *Can J Ophthalmol* 2005;**40**:369–77.

118. Greiner R-A. Cost of care for patients with age-related macular degeneration in Switzerland and cost-effectiveness of treatment with verteporfin therapy. *Semin Ophthalmol* 2001;**16**:218–22.

119. Barry SJ, Douglas PR, Becker DL, Hughes MS, Weinstein MC. Economic evaluation of photodynamic therapy (Visudyne®) compared to usual care in the treatment of age related macular degeneration (ARMD) in USA. *Value Health* 2006; **9**:A141–2.

120. Sharma S, Oliver-Fernandez A, Bakal P, Brown GC, Brown MM. Cost–utility of vitamins for the treatment of macular degeneration. *Value Health* 2002;**5**:553–4.

121. Scilley K, DeCarlo DK, Wells J, Owsley C. Vision-specific health-related quality of life in age-related maculopathy patients presenting for low vision services. *Ophthalmic Epidemiol* 2004;**11**:131–46.

122. Miskala PH, Hawkins BS, Mangione CM, Bass EB, Bressler NM, Dong LM, *et al*. Responsiveness of the National Eye Institute Visual Function Questionnaire to changes in visual acuity: findings in patients with subfoveal choroidal neovascularization – SST Report No. 1 [published erratum appears in *Arch Ophthalmol*. 2003; **121**:1513]. *Arch Ophthalmol* 2003;**121**:531–9.

123. DeCarlo DK, Scilley K, Wells J, Owsley C. Driving habits and health-related quality of life in patients with age-related maculopathy. *Optometry Vis Sci* 2003;**80**:207–13.

124. Hawkins BS. Health- and vision-related quality of life among patients with ocular histoplasmosis or

idiopathic choroidal neovascularization at enrollment in a randomized trial of submacular surgery: Submacular Surgery Trials Report No. 5. *Arch Ophthalmol* 2005;**123**:78–88.

125. Berdeaux GH, Nordmann JP, Colin E, Arnould B. Vision-related quality of life in patients suffering from age-related macular degeneration. *Am J Ophthalmol* 2005;**139**:271–9.
126. Mitchell J, Wolffsohn JS, Woodcock A, Anderson SJ, McMillan CV, Ffytche T, *et al*. Psychometric evaluation of the MacDQoL individualised measure of the impact of macular degeneration on quality of life. *Health Qual Life Outcomes* 2005;**3**:25–39.
127. Mangione CM, Gutierrez PR, Lowe G, Orav EJ, Seddon JM. Influence of age-related maculopathy on visual functioning and health-related quality of life. *Am J Ophthalmol* 1999;**128**:45–53.
128. Armbrecht AM, Aspinall PA, Dhillon B. A prospective study of visual function and quality of life following PDT in patients with wet age related macular degeneration. *Br J Ophthalmol* 2004;**88**:1270–3.
129. Brown GC, Brown MM, Sharma S. Difference between ophthalmologists' and patients' perceptions of quality of life associated with age-related macular degeneration. *Can J Ophthalmol* 2000;**35**:127–33.
130. Wakker P, Stiggelbout A. Explaining distortions in utility elicitation through the rank-dependent model for risky choices. *Med Decis Making* 1995; **15**:180–6.
131. Stein JD, Brown MM, Brown GC, Hollands H, Sharma S. Quality of life with macular degeneration: perceptions of patients, clinicians, and community members. *Br J Ophthalmol* 2003; **87**:8–12.
132. Drummond MF, O'Brien BJ, Torrance GW, Stoddart GL. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford University Press; 1997.
133. National Institute for Clinical Excellence. *Guide to the Methods of Technology Appraisal*. London: NICE; 2004.
134. Philips Z, Ginnelly L, Sculpher M, Claxton K, Golder S, Riemsma R, *et al*. Review of guidelines for good practice in decision-analytic modelling in health technology assessment. *Health Technol Assess* 2004;**8**(36).
135. Curtis L, Netten A. *Unit costs of health and social care*. Canterbury: Personal Social Services Research Unit, University of Kent; 2005.
136. Zhou SWD. *The economic burden of progression in vision loss in Medicare beneficiaries, 1999 to 2003*. Data on file. Surrey, UK: Pfizer; 2004.
137. Office for National Statistics. *Key health statistics from general practice 1998. Analyses of morbidity and treatment data, including time trends, England and Wales*. Series MB6 No. 2, 2000. URL: http://www.statistics.gov.uk/downloads/theme_health/Key_Health_Stats_1998.pdf
138. Brennan J, Johansen A, Butler J, Stone M, Richmond P, Jones S, *et al*. Place of residence and risk of fracture in older people: a population-based study of over 65-year-olds in Cardiff. *Osteoporos Int* 2003;**14**:515–19.
139. *Monthly index of medical specialties*. London: Haymarket Medical Publications; 2006.
140. Brazier JE, Kang K, Carlton J, Czoski-Murray CJ. *General population survey to obtain values for AMD visual impairment states using lenses – preliminary report*. 2006. Appendix 1. Lucentis (ranibizumab) therapy for the treatment of wet age-related macular degeneration. Evidence submitted to the National Institute for Clinical Excellence. Novartis Pharmaceuticals; August 2006.
141. Miller DK, Homan SM. Determining transition-probabilities – confusion and suggestions. *Med Decis Making* 1994;**14**:52–8.
142. Mills E, Heels-Ansdell D, Kelly S, Guyatt G. A randomized trial of pegaptanib sodium for age-related macular degeneration used an innovative design to explore disease-modifying effects. *J Clin Epidemiol* 2007;**60**:456–60.
143. Sharma S, Brown GC, Brown MM, Shah GK, Snow K, Brown H, *et al*. Converting visual acuity to utilities. *Can J Ophthalmol* 2000;**35**:267–72.
144. Knapp M, Beecham J, Fenyo A, Hallam A. Community mental health care for former hospital in-patients. Predicting costs from needs and diagnoses. *Br J Psychiatry* 1995;**166** (Suppl 27): 10–18.
145. Scottish Medicines Consortium. *Pegaptanib 0.3 mg, solution for intravitreal injection (Macugen). No. 290/06*. Accessed 6 November 2006. http://www.scottishmedicines.co.uk
146. Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003;**87**:1201–4.
147. McLaughlan B, Winyard S. *Left to pay for their own. How people facing sight loss from wet age-related macular degeneration are let down by the NHS. Report on the availability of anti-VEGF treatments for wet age-related macular degeneration*. Accessed 27 October 2006. http://www.rnib.org.uk/xpedio/groups/public/documents/publicwebsite/public_macugenreport.doc
148. Evers S, Goossens M, de Vet H, van Tulder M, Ament A. Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria. *Int J Technol Assess Health Care* 2005;**21**:240–5.
149. Brody BL, Roch-Levecq AC, Gamst AC, Maclean K, Kaplan RM, Brown SI. Self-management of age-

related macular degeneration and quality of life: a randomized controlled trial. *Arch Ophthalmol* 2002;**120**:1477–83.

150. Chakravarthy U, Stevenson M. Self-reported visual functioning and quality of life in age-related macular degeneration. *Curr Opin Ophthalmol* 2005;**16**:179–83.

151. Stevenson MR, Hart PM, Chakravarthy U, Mackenzie G, Bird AC, Owens SL, *et al*. Visual functioning and quality of life in the SubFoveal Radiotherapy Study (SFRADS): SFRADS Report 2. *Br J Ophthalmol* 2005;**89**:1045–51.

152. Lindblad AS, Clemons TE. Responsiveness of the National Eye Institute Visual Function Questionnaire to progression to advanced age-related macular degeneration, vision loss, and lens opacity: AREDS Report No. 14. *Arch Ophthalmol* 2005;**123**:1207–14.

153. Clemons TE, Chew EY, Bressler SB, McBee W, Age-Related Eye Disease Study Research Group. National Eye Institute Visual Function Questionnaire in the Age-Related Eye Disease Study (AREDS): AREDS Report No. 10. *Arch Ophthalmol* 2003;**121**:211–17.

Appendix 1

Protocol methods

Report methods for synthesis of evidence of clinical effectiveness

Search strategy

- A search strategy will be developed and tested by an experienced information scientist. The strategy will be designed to identify studies reporting clinical effectiveness, cost-effectiveness, health-related quality of life, resource use/costs and epidemiology/natural history.
- The draft search strategy for MEDLINE is given in Appendix 2.
- A number of electronic databases will be searched, including: The Cochrane Database of Systematic Reviews (CDSR); The Cochrane Central Register of Controlled Trials; NHS CRD (University of York) Database of Abstracts of Reviews of Effectiveness (DARE) and the NHS Economic Evaluation Database (NHS EED); MEDLINE (Ovid); EMBASE (Ovid); National Research Register; Current Controlled Trials; ISI Proceedings; Web of Science; and BIOSIS. Ophthalmology conferences will be searched for recent abstracts (from 2004). Bibliographies of related papers will be assessed for relevant studies where possible.
- The manufacturers' submissions to NICE will be assessed for any additional studies.
- Experts will be contacted to identify additional published and unpublished references.
- Searches will be carried out from the inception date of the database and will be limited to the English language. The searches will be updated around October 2006.

Inclusion and exclusion criteria

Patients

- People with the subfoveal CNV associated with wet age-related macular degeneration.
- If appropriate, potential subgroups will be considered according to the composition of the lesion in terms of classic and occult CNV.

Interventions

Studies reporting evaluations of the following interventions will be included:

- Ranibizumab (Lucentis, Genentech/Novartis Pharmaceuticals UK Ltd).
- Pegaptanib sodium (Macugen, Pfizer Ltd).
- Combination of the drugs with PDT will be considered where the licensed indication and the evidence allow.

Comparators

- Best supportive care.
- For the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal wet AMD, PDT with verteporfin is also a comparator.
- If insufficient evidence is found using the above comparators, the following comparators will be considered:
  (a) sham injection (systematic review of clinical effectiveness only)
  (b) PDT with verteporfin for patients with subfoveal wet AMD with predominantly classic lesions.

Outcomes

Studies reporting one or more of the following outcomes will be included:

- visual acuity
- contrast sensitivity
- adverse effects of treatment
- adherence to treatment
- health-related quality of life.

Types of studies

- Fully published RCTs or systematic reviews of RCTs will be included. Systematic reviews will be used as a source for RCTs and as a comparator. Indicators of a 'systematic' review include explicit search strategy, inclusion criteria, data extraction and assessment of quality.
- Studies published only as abstracts or conference presentations will be included in the primary analysis of clinical and cost-effectiveness if sufficient details are presented to allow an appraisal of the methodology and assessment of results.
- Non-English language studies will be excluded.

Inclusion and data extraction process

- Titles and abstracts of studies identified by the search strategy will be screened by one reviewer based on the above inclusion/exclusion criteria and checked by a second reviewer.

- The full text of relevant papers will be requested for further assessment. All full papers will be screened independently by one reviewer and checked by a second.
- Data will be extracted by one reviewer using a standard data extraction form and checked by a second reviewer.
- At each stage, any discrepancy will be resolved by discussion, with involvement of a third reviewer where necessary.

Quality assessment

- The quality of included RCTs and systematic reviews will be assessed using NHS CRD (University of York) criteria.
- Quality criteria will be applied by one reviewer and checked by a second reviewer, with differences in opinion resolved by discussion and involvement of a third reviewer where necessary.

Methods of analysis/synthesis

- Clinical effectiveness studies will be synthesised through a narrative review with tabulation of results of included studies.
- Where data are of sufficient quantity, quality and homogeneity, a meta-analysis of the clinical effectiveness studies will be performed, using appropriate software.

Methods for synthesising evidence of cost-effectiveness

Search strategy

Details of the draft search strategy for MEDLINE are given in Appendix 2. The sources to be searched are similar to those used in the clinical effectiveness review. All searches will be limited to the English language.

Inclusion and exclusion criteria

- Full economic evaluations and systematic reviews of economic evaluations, where relevant, will be included. Inclusion and exclusion criteria will be the same as those applied for the clinical effectiveness review.

Inclusion and data extraction process

- Titles and abstracts of studies identified by the search strategy will be screened by one reviewer based on the above inclusion/exclusion criteria and checked by a second reviewer.
- The full text of relevant papers will be requested for further assessment. All full papers will be screened independently by one reviewer and checked by a second.
- Data will be extracted by one reviewer using a standard data extraction form and checked by a second reviewer.
- Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

Study quality assessment

The methodological quality of the economic evaluations will be assessed using accepted frameworks such as the International consensus-developed list of criteria developed by Evers and colleagues[148] and Drummond and colleagues.[132] For any studies based on decision models, we will also make use of the checklist for assessing good practice in decision analytic modelling.[134] Published studies carried out from the UK NHS and PSS perspective will be examined in more detail.

Synthesis of evidence on costs and effectiveness

Published and submitted economic evaluations

Narrative synthesis, supported by the data extraction tables, will be used to summarise the evidence base from published economic evaluations and sponsor submissions to NICE.

Economic modelling

Where appropriate, an economic model will be constructed by adapting an existing model or developing a new one using best available evidence. If possible, the incremental cost-effectiveness of the interventions will be estimated in terms of cost per QALY gained, and also the cost per vision-year gained, that is, for an additional year of visual function, if data permit. The perspective will be that of the NHS and PSS. Both cost and outcomes (QALYs) will be discounted at 3.5%.

Model structure will be determined on the basis of research evidence and clinical expert opinion of:

- the biological disease process (i.e. knowledge of the natural history of the disease)
- the main diagnostic and care pathways for patients in the UK NHS context (both with and without the intervention(s) of interest)
- the disease states or events which are most important in determining patients' clinical outcomes, quality of life and consumption of NHS or PSS resources.

For example, we will need to consider developing a model of vision loss due to wet age-related macular degeneration which could reflect factors

such as patient age, visual acuity, baseline Snellen, time to vision loss, whether previous treatment is received and side-effects.

Parameter values will be obtained from relevant research literature, including our own systematic review of clinical effectiveness. Where required parameters are not available from good-quality published studies in the relevant patient group, we may use data from sponsor submissions to NICE or experts' clinical opinion. Sources for parameters will be stated clearly.

Resource use will be specified and valued from the perspective of the NHS and PSS. Cost data will be derived from local sources or extracted from published sources or from sponsor submissions to NICE, as appropriate.

To capture health-related quality of life effects, utility values will be sought from the relevant research literature.

Analysis of uncertainty will focus on cost–utility, assuming that the cost per QALY can be estimated. Uncertainty will be explored through one-way sensitivity analysis and, if the data and modelling approach permit, probabilistic sensitivity analysis. The outputs of the latter will be presented both using plots on the cost-effectiveness plane and cost-effectiveness acceptability curves.

The simulated population will be defined on the basis of both the published evidence about the characteristics of UK population with wet age-related macular degeneration and the populations for which good-quality clinical effectiveness data are available. The base case results will be presented for the population of the UK with wet age-related macular degeneration. The time horizon for our analysis will initially be governed by follow-up data available from included clinical trials – we will investigate the feasibility of extrapolating treatment effects beyond the clinical trials.

Handling the company submission(s)

All information submitted by the manufacturers/sponsors as part of the NICE appraisal process will be considered if received by the TAR team no later than 8 August 2006. Information arriving after this date will not be considered.

Industry submissions will be checked for additional studies that meet the inclusion criteria for data on clinical effectiveness, costs and on the current use of ranibizumab and pegaptanib.

Any economic evaluation included in a company submission, provided that it complies with NICE's advice on presentation, will be assessed for clinical validity, reasonableness of assumptions and appropriateness of the data used. Results of cost-effectiveness analyses from industry submissions will be compared with the SHTAC analysis.

Any 'academic-in-confidence' data or 'commercial-in-confidence' data taken from a company submission will be underlined and highlighted in the assessment report (followed by an indication of the relevant company name, e.g. in parentheses).

Appendix 2

Literature search strategies

The following databases were searched for published studies and recently completed and ongoing research. All searches were limited to English language only. Searches were updated in September 2006.

- Cochrane Library – Cochrane Database of Systematic Reviews
- Cochrane Library – Central Register of Controlled Trials (Clinical Trials)
- MEDLINE (Ovid) 1966–2006
- MEDLINE (Ovid) In process, Other non-indexed citations
- EMBASE (Ovid) 1980–2006
- Web of Science Science Citation Index 1970–2006
- Web of Science ISI Proceedings 2004–present
- BIOSIS meeting abstracts 2004–6
- DARE (NHS CRD)
- HTA (NHS CRD)
- NHS EED (NHS CRD)
- National Research Register
- Current Controlled Trials, including MRC Trials
- Clinical Trials.gov.

Clinical effectiveness searches

The following strategies were used to search MEDLINE (Ovid) 1966–2006 and EMBASE (Ovid) 1980–2006. These were translated to search the other databases listed above.

MEDLINE (Ovid) 1966 to May week 1 2006
Date searched: 17 May 2006

1 exp Macular Degeneration/ (7128)
2 (age related maculopath$ or maculopath$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1738)
3 age related macula$ degeneration.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3300)
4 macula$ degeneration.mp. (6975)
5 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (30)
6 (geographic$ adj5 atrophy).mp. (228)
7 (AMD or ARMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2498)
8 age related eye disease$.mp. (122)
9 senile macula$ degenerat$.mp. (309)
10 (neovascular$ adj5 macula$ degeneration).mp. (814)
11 (disciform adj5 macula$ degeneration).mp. (87)
12 (choroidal neovascularization or CNV).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2986)
13 Choroidal Neovascularization/ (1432)
14 (wet adj5 (macula$ degeneration or AMD or ARMD)).mp. (87)
15 (exudative adj5 (macula$ degeneration or AMD or ARMD)).mp. (442)
16 (dry adj5 (macula$ degeneration or AMD or ARMD)).mp. (71)
17 (non-neovascular$ adj5 macula$ degen$).mp. (3)
18 Neovascularization, Pathologic/ (16997)
19 or/1-18 (28360)
20 pegaptanib.mp. (47)
21 macugen.mp. (9)
22 ranibizumab.mp. (14)
23 lucentis.mp. (5)
24 (20 or 21) and 19 (42)
25 (22 or 23) and 19 (11)

EMBASE (Ovid) 1980 to 2006 week 19
Date searched: 18 May 2006

1 exp Retina Macula Degeneration/ (9011)
2 Retina Macula Age Related Degeneration/ (3651)
3 (age related maculopath$ or maculopath$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2427)
4 age related macula$ degeneration.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3189)
5 macula$ degeneration.mp. (5359)
6 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, abstract, subject headings, heading word, drug trade name,

original title, device manufacturer, drug manufacturer name] (54)
7 (geographic$ adj5 atrophy).mp. (230)
8 (AMD or ARMD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2830)
9 age related eye disease$.mp. (124)
10 senile macula$ degenerat$.mp. (160)
11 (neovascular$ adj5 macula$ degeneration).mp. (895)
12 (disciform adj5 macula$ degeneration).mp. (102)
13 (choroidal neovascularization or CNV).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2499)
14 Choroidal Neovascularization/ (2429)
15 Subretinal Neovascularization/ (2429)
16 (wet adj5 (macula$ degeneration or AMD or ARMD)).mp. (74)
17 (exudative adj5 (macula$ degeneration or AMD or ARMD)).mp. (423)
18 (dry adj5 (macula$ degeneration or AMD or ARMD)).mp. (73)
19 (non-neovascular$ adj5 macula$ degen$).mp. (3)
20 exp "Neovascularization (Pathology)"/ (14092)
21 or/1-20 (24135)
22 Pegaptanib/ (186)
23 pegaptanib.mp. (197)
24 macugen.mp. (124)
25 exp RANIBIZUMAB/ (85)
26 ranibizumab.mp. (86)
27 lucentis.mp. (54)
28 (22 or 23 or 24) and 21 (161)
29 (25 or 26 or 27) and 21 (74)

Cost-effectiveness searches

The clinical effectiveness strategies above were combined with the following cost-effectiveness filters and run in MEDLINE (Ovid) 1966–2006 and EMBASE (Ovid) (1980–2006). The strategies were translated and run in Ovid (MEDLINE) In Process; Web of Science ISI Science Citation Index 1970–2006; ISI Proceedings 2004–2006; Cochrane Database of Systematic Reviews; Central Register of Controlled Trials; and the NHS CRD databases NHS EED, DARE and HTA.

MEDLINE (Ovid) 1966 to May week 2 2006
Date searched: 19 May 2006

1 exp Macular Degeneration/ (7145)
2 (age related maculopath$ or maculopath$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1740)
3 age related macula$ degeneration.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3306)
4 macula$ degeneration.mp. (6985)
5 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (30)
6 (geographic$ adj5 atrophy).mp. (228)
7 (AMD or ARMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2504)
8 age related eye disease$.mp. (124)
9 senile macula$ degenerat$.mp. (309)
10 (neovascular$ adj5 macula$ degeneration).mp. (814)
11 (disciform adj5 macula$ degeneration).mp. (87)
12 (choroidal neovascularization or CNV).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (2993)
13 Choroidal Neovascularization/ (1438)
14 (wet adj5 (macula$ degeneration or AMD or ARMD)).mp. (88)
15 (exudative adj5 (macula$ degeneration or AMD or ARMD)).mp. (443)
16 (dry adj5 (macula$ degeneration or AMD or ARMD)).mp. (71)
17 (non-neovascular$ adj5 macula$ degen$).mp. (3)
18 Neovascularization, Pathologic/ (17021)
19 or/1-18 (28414)
20 pegaptanib.mp. (47)
21 macugen.mp. (9)
22 ranibizumab.mp. (14)
23 lucentis.mp. (5)
24 (20 or 21) and 19 (42)
25 (22 or 23) and 19 (11)
26 exp ECONOMICS/ (351955)
27 exp ECONOMICS, HOSPITAL/ (13981)
28 exp ECONOMICS, PHARMACEUTICAL/ (1636)
29 exp ECONOMICS, NURSING/ (3671)
30 exp ECONOMICS, DENTAL/ (3308)
31 exp ECONOMICS, MEDICAL/ (9953)
32 exp "Costs and Cost Analysis"/ (123629)
33 VALUE OF LIFE/ (4707)
34 exp MODELS, ECONOMIC/ (4746)
35 exp FEES/ and CHARGES/ (6868)
36 exp BUDGETS/ (9138)
37 (economic$ or price$ or pricing or pharmacoeconomic$ or pharma economic$).tw. (81071)

38 (cost$ or costly or costing$ or costed).tw. (177271)
39 (cost$ adj2 (benefit$ or utilit$ or minim$)).tw. (10965)
40 (expenditure$ not energy).tw. (9679)
41 (value adj2 (money or monetary)).tw. (536)
42 budget$.tw. (9968)
43 (economic adj2 burden).tw. (1214)
44 "resource use".ti,ab. (1877)
45 or/38-56 (510863)
46 letter.pt. (563271)
47 editorial.pt. (190799)
48 comment.pt. (301718)
49 or/46-48 (795148)
50 45 not 49 (478420)
51 (19 or 24 or 25) and 50 (237)

EMBASE 1980 to 2006 week 20
Date searched: 19 May 2006

1 exp Retina Macula Degeneration/ (9028)
2 Retina Macula Age Related Degeneration/ (3665)
3 (age related maculopath$ or maculopath$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2431)
4 age related macula$ degeneration.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3199)
5 macula$ degeneration.mp. (5373)
6 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (54)
7 (geographic$ adj5 atrophy).mp. (230)
8 (AMD or ARMD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2838)
9 age related eye disease$.mp. (124)
10 senile macula$ degenerat$.mp. (160)
11 (neovascular$ adj5 macula$ degeneration).mp. (897)
12 (disciform adj5 macula$ degeneration).mp. (102)
13 (choroidal neovascularization or CNV).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2503)
14 Choroidal Neovascularization/ (2437)
15 Subretinal Neovascularization/ (2437)
16 (wet adj5 (macula$ degeneration or AMD or ARMD)).mp. (75)
17 (exudative adj5 (macula$ degeneration or AMD or ARMD)).mp. (425)
18 (dry adj5 (macula$ degeneration or AMD or ARMD)).mp. (74)
19 (non-neovascular$ adj5 macula$ degen$).mp. (3)
20 or/1-19 (13122)
21 Pegaptanib/ (190)
22 pegaptanib.mp. (201)
23 macugen.mp. (126)
24 exp RANIBIZUMAB/ (87)
25 ranibizumab.mp. (88)
26 lucentis.mp. (55)
27 (21 or 22 or 23) and 20 (146)
28 (24 or 25 or 26) and 20 (68)
29 (cost$ adj2 effective$).ti,ab. (34561)
30 (cost$ adj2 benefit$).ti,ab. (8379)
31 cost effectiveness analysis/ (43148)
32 cost benefit analysis/ (23324)
33 budget$.ti,ab. (7287)
34 cost$.ti. (32082)
35 (cost$ adj2 (effective$ or utilit$ or benefit$ or minimi$)).ab. (38646)
36 (economic$ or pharmacoeconomic$ or pharmaco economic$).ti. (12515)
37 (price$ or pricing$).ti,ab. (9253)
38 (financial or finance or finances or financed).ti,ab. (19015)
39 (fee or fees).ti,ab. (4441)
40 cost/ (18278)
41 cost minimization analysis/ (962)
42 cost of illness/ (3132)
43 cost utility analysis/ (1615)
44 drug cost/ (26499)
45 health care cost/ (46879)
46 health economics/ (8411)
47 economic evaluation/ (3066)
48 economics/ (4890)
49 pharmacoeconomics/ (867)
50 budget/ (6448)
51 economic burden.ti,ab. (1180)
52 "resource use".ti,ab. (19011)
53 or/29-52 (209548)
54 (editorial or letter).pt. (470416)
55 53 not 54 (188736)
56 20 or 27 or 28 (13122)
57 56 and 55 (215)

Quality of life searches

The following strategy was used to search MEDLINE (Ovid), EMBASE (Ovid), MEDLINE In Process and the Cochrane Library Central Register of Controlled Trials.

MEDLINE (Ovid) 1966 to May week 3 2006
Date searched: 25 May 2006

1 exp Macular Degeneration/ (7154)
2 (age related maculopath$ or maculopath$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1742)
3 age related macula$ degeneration.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3313)
4 macula$ degeneration.mp. (6994)
5 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (30)
6 (geographic$ adj5 atrophy).mp. (228)
7 (AMD or ARMD or CNV).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3784)
8 age related eye disease$.mp. (125)
9 senile macula$ degenerat$.mp. (309)
10 (neovascular adj5 macular degeneration).mp. (286)
11 (disciform adj5 macular degeneration).mp. (84)
12 ((choroid$ or ocular) adj5 neovasc$).mp. (2779)
13 Choroidal Neovascularization/ (1443)
14 (wet adj5 (macular degeneration or AMD or ARMD)).mp. (89)
15 (exudative adj5 (macular degeneration or AMD or ARMD)).mp. (444)
16 (dry adj5 (macular degeneration or AMD or ARMD)).mp. (70)
17 (non-neovascular adj5 macula$ degen$).mp. (3)
18 or/1-17 (12638)
19 value of life/ (4710)
20 quality adjusted life year/ (2585)
21 quality adjusted life.ti,ab. (1831)
22 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (1446)
23 disability adjusted life.ti,ab. (317)
24 daly$.ti,ab. (396)
25 health status indicators/ (10184)
26 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (5299)
27 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (644)
28 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (622)
29 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (14)
30 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (259)
31 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (794)
32 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (1845)
33 (hye or hyes).ti,ab. (45)
34 health$ year$ equivalent$.ti,ab. (31)
35 health utilit$.ab. (330)
36 (hui or hui1 or hui2 or hui3).ti,ab. (366)
37 disutil$.ti,ab. (65)
38 rosser.ti,ab. (58)
39 quality of well being.ti,ab. (192)
40 quality of wellbeing.ti,ab. (1)
41 qwb.ti,ab. (105)
42 willingness to pay.ti,ab. (692)
43 standard gamble$.ti,ab. (385)
44 time trade off.ti,ab. (333)
45 time tradeoff.ti,ab. (120)
46 tto.ti,ab. (221)
47 or/19-46 (26818)
48 letter.pt. (563849)
49 editorial.pt. (191055)
50 comment.pt. (302253)
51 or/48-50 (796061)
52 47 not 51 (25575)
53 (Visual Function Questionnaire$ or VFQ35 or VFQ25).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (85)
54 (LVQOL or Low Vision Quality of Life Question$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4)
55 (IVI or Impact of Vision Impairment).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (118)
56 ((QOLVFQ or Quality of Life) and Vision Function Question$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4)
57 (QOLVFQ or (Quality of Life and Vision Function Question$)).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (4)
58 Visual Function Index.mp. (19)
59 NEI-VFQ.mp. (75)
60 53 or 54 or 55 or 56 or 57 or 58 or 59 (256)
61 47 or 60 (27006)
62 61 not 51 (25763)
63 (vision or sight).mp. (72650)
64 63 or 18 (82861)
65 64 and 62 (404)

66 limit 65 to (humans and english language) (367)
67 62 and 18 (110)

EMBASE 1980 to 2006 week 20
Date searched 25 May 2006

1 (Visual Function Questionnaire$ or VFQ35 or VFQ25).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (84)
2 (LVQOL or Low Vision Quality of Life Question$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (5)
3 (IVI or Impact of Vision Impairment).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (99)
4 ((QOLVFQ or Quality of Life) and Vision Function Question$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4)
5 (QOLVFQ or (Quality of Life and Vision Function Question$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (4)
6 Visual Function Index.mp. (19)
7 NEI-VFQ.mp. (67)
8 1 or 2 or 3 or 4 or 5 or 6 or 7 (234)
9 exp "quality of life"/ (66274)
10 quality adjusted life year/ (2442)
11 quality adjusted life.ti,ab. (1732)
12 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (1339)
13 disability adjusted life.ti,ab. (293)
14 daly$.ti,ab. (334)
15 (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirstysix or shortform thirty six or short form thirty six or short form thirtysix or short form thirty six).ti,ab. (5188)
16 (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).ti,ab. (755)
17 (sf12 or sf 12 or short form 12 or shortform 12 or sf twelve of sftwelve or shortform twelve or short form twelve).ti,ab. (594)
18 (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).ti,ab. (22)
19 (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twenty or short form twenty).ti,ab. (188)
20 (euroqol or euro qol or eq5d or eq 5d).ti,ab. (779)
21 (hql or hqol or h qol or hrqol or hr qol).ti,ab. (1775)
22 (hye or hyes).ti,ab. (25)
23 health$ year$ equivalent$.ti,ab. (23)
24 ((health or cost) adj5 utilit$).ab,ti. (2366)
25 (hui or hui1 or hui2 or hui3).ti,ab. (276)
26 disutil$.ti,ab. (68)
27 rosser.ti,ab. (48)
28 quality of well being.ti,ab. (519)
29 quality of wellbeing.ti,ab. (6)
30 qwb.ti,ab. (93)
31 willingness to pay.ti,ab. (679)
32 standard gamble$.ti,ab. (353)
33 time trade off.ti,ab. (322)
34 time tradeoff.ti,ab. (113)
35 tto.ti,ab. (235)
36 (index adj2 well being).mp. (1315)
37 (quality adj2 well being).mp. (2708)
38 (health adj3 utilit$ ind$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (237)
39 ((multiattribute$ or multi attribute$) adj3 (health ind$ or theor$ or health state$ or utilit$ or analys$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (133)
40 quality adjusted life year$.mp. (3039)
41 (15D or 15 dimension$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (513)
42 (12D or 12 dimension$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (168)
43 rating scale$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (47441)
44 linear scal$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (242)
45 linear analog$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (628)
46 visual analog$.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (14840)
47 (categor$ adj2 scal$).mp. [mp=title, abstract, subject headings, heading word, drug trade

name, original title, device manufacturer, drug manufacturer name] (755)
48 (letter or editorial or comment).pt. (470416)
49 or/8-47 (131234)
50 49 not 48 (123710)
51 exp Retina Macula Degeneration/ (9028)
52 Retina Macula Age Related Degeneration/ (3665)
53 (age related maculopath$ or maculopath$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2431)
54 age related macula$ degeneration.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3199)
55 macula$ degeneration.mp. (5373)
56 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (54)
57 (geographic$ adj5 atrophy).mp. (230)
58 (AMD or ARMD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2838)
59 age related eye disease$.mp. (124)
60 senile macula$ degenerat$.mp. (160)
61 (neovascular$ adj5 macula$ degeneration).mp. (897)
62 (disciform adj5 macula$ degeneration).mp. (102)
63 (choroidal neovascularization or CNV).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2503)
64 Choroidal Neovascularization/ (2437)
65 Subretinal Neovascularization/ (2437)
66 (wet adj5 (macula$ degeneration or AMD or ARMD)).mp. (75)
67 (exudative adj5 (macula$ degeneration or AMD or ARMD)).mp. (425)
68 (dry adj5 (macula$ degeneration or AMD or ARMD)).mp. (74)
69 (non-neovascular$ adj5 macula$ degen$).mp. (3)
70 or/51-69 (13122)
71 50 and 70 (304)
72 limit 71 to (humans and english language) (242)

Epidemiology searches

The following strategies were used to search MEDLINE (Ovid) 1966–2006, EMBASE 1980–2006 and MEDLINE (Ovid) In Process.

MEDLINE (Ovid) 1966 to May week 3 2006

1 exp Macular Degeneration/ (7154)
2 (age related maculopath$ or maculopath$).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (1742)
3 age related macula$ degeneration.mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3313)
4 macula$ degeneration.mp. (6994)
5 ((geographic$ adj5 macular degeneration) or GAMD).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (30)
6 (geographic$ adj5 atrophy).mp. (228)
7 (AMD or ARMD or CNV).mp. [mp=title, original title, abstract, name of substance word, subject heading word] (3784)
8 age related eye disease$.mp. (125)
9 senile macula$ degenerat$.mp. (309)
10 (neovascular adj5 macular degeneration).mp. (286)
11 (disciform adj5 macular degeneration).mp. (84)
12 ((choroid$ or ocular) adj5 neovasc$).mp. (2779)
13 Choroidal Neovascularization/ (1443)
14 (wet adj5 (macular degeneration or AMD or ARMD)).mp. (89)
15 (exudative adj5 (macular degeneration or AMD or ARMD)).mp. (444)
16 (dry adj5 (macular degeneration or AMD or ARMD)).mp. (70)
17 (non-neovascular adj5 macula$ degen$).mp. (3)
18 or/1-17 (12638)
19 *Epidemiology/ (3789)
20 *Incidence/ (353)
21 *Prevalence/ (451)
22 incidence.ti. (44140)
23 prevalence.ti. (42099)
24 epidemiol$.ti. (61452)
25 etiolog$.ti. (23642)
26 aetiolog$.ti. (4622)
27 or/19-26 (172930)
28 18 and 27 (308)
29 limit 28 to english language (258)

EMBASE 1980 to 2006 Week 20

1 incidence.ti. (28090)
2 prevalence.ti. (31494)
3 epidemiol$.ti. (37278)
4 ((natural$ or disease$) adj3 (progress$ or course$ or histor$)).ti. (10815)
5 1 or 2 or 3 or 4 (105211)

6 exp Retina Macula Degeneration/ep, et [Epidemiology, Etiology] (1648)
7 exp Retina Macula Age Related Degeneration/ep, et [Epidemiology, Etiology] (788)
8 (age related maculopath$ or maculopath$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (2431)
9 age related macula$ degeneration.mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer name] (3199)
10 macula$ degeneration.mp. (5373)
11 (wet adj5 (macula$ degeneration or AMD or ARMD)).mp. (75)
12 (exudative adj5 (macula$ degeneration or AMD or ARMD)).mp. (425)
13 (dry adj5 (macula$ degeneration or AMD or ARMD)).mp. (74)
14 (non-neovascular$ adj5 macula$ degen$).mp. (3)
15 Subretinal Neovascularization/et, ep [Etiology, Epidemiology] (303)
16 OR/6-15 (7854)
17 5 and 16 (600)
18 limit 17 to (english language and yr="1996 - 2006") (187)

Additional searching

Bibliographies: all references of articles for which full papers were retrieved were checked to ensure that no eligible studies had been missed.

Appendix 3

Quality assessment

Quality criteria for assessment of experimental studies (NHS CRD)[99]

Item	Judgement[a]
1. Was the assignment to the treatment groups really random?	
2. Was the treatment allocation concealed?	
3. Were the groups similar at baseline in terms of prognostic factors?	
4. Were the eligibility criteria specified?	
5. Were outcome assessors blinded to the treatment allocation?	
6. Was the care provider blinded?	
7. Was the patient blinded?	
8. Were the point estimates and measure of variability presented for the primary outcome measure?	
9. Did the analyses include an intention-to-treat analysis?	
10. Were withdrawals and dropouts completely described?	

[a] Adequate, inadequate, not reported, unclear.

Appendix 4

Data extraction tables

Reference and design	Intervention	Participants	Outcome measures
VISION study Gragoudas *et al*., 2004[95] VISION Clinical Trial Group, 2006[101] VISION Clinical Trial Group, 2006[100] [**CIC data removed**] USA; Canada; Europe; Israel; Australia; South America Study design: 2 concurrent, prospective, double-blind RCTs – final analysis Number of centres: 117 *Setting*: Not reported *Funding*: Eyetech Pharmaceuticals and Pfizer	1. Intravitreous injection of 0.3 mg pegaptanib into one eye every 6 weeks, total of 9 treatments 2. Intravitreous injection of 1.0 mg pegaptanib into one eye every 6 weeks, total of 9 treatments 3. Intravitreous injection of 3.0 mg pegaptanib into one eye every 6 weeks, total of 9 treatments 4. Sham injection into one eye every 6 weeks, total of 9 treatments Pegaptanib patients were then re-randomised (1:1) to either continue or discontinue pegaptanib. Sham patients were re-randomised (1:1:1:1:1) to discontinue, continue sham or receive 1 of the 3 pegaptanib doses *Duration of treatment*: 48 weeks then additional 48 weeks of treatment *Other interventions used*: Patients in all groups underwent an ocular antisepsis procedure and received injected subconjunctival anaesthetic PDT with verteporfin was permitted in the treatment of patients with predominantly classic lesions, although 78% of patients did not receive PDT during the study	*Target population*: Patients with all angiographic subtypes of lesions were enrolled *Number of participants*: 586 patients were included in the USA/Canada trial and 622 in the worldwide trial. The publication combines both study populations for the analysis data extracted here Total randomly assigned ($N = 1208$): 1. 0.3 mg $n = 297$ 2. 1.0 mg $n = 305$ 3. 3.0 mg $n = 302$ 4. Sham injection $n = 304$ Total receiving at least one dose of study treatment ($N = 1190$): 1. 0.3 mg $n = 295$ 2. 1.0 mg $n = 301$ 3. 3.0 mg $n = 296$ 4. Sham injection $n = 298$ 4 patients were excluded from the efficacy analysis because a sufficiently standardised assessment of visual acuity was not completed at baseline Total for efficacy analyses ($n = 1186$): 1. 0.3 mg $n = 294$ 2. 1.0 mg $n = 300$ 3. 3.0 mg $n = 296$ 4. Sham injection $n = 296$ 88% (1053/1190) were re-randomised at week 54 and 89% (941/1053) were assessed at week 102 Second year randomisation: 0.3 mg – 0.3 mg $n = 133$ 0.3 mg – discontinue $n = 132$ 1.0 mg – 1.0 mg $n = 133$ 1.0 mg – discontinue $n = 131$ 3.0 mg – 3.0 mg $n = 125$ 3.0 mg – discontinue $n = 127$ Sham – 0.3 mg $n = 53$ Sham – 1.0 mg $n = 55$ Sham – 3.0 mg $n = 57$ Sham – sham $n = 53$ Sham – discontinue $n = 54$ n assessed at week 102: 0.3 mg – 0.3 mg $n = 114$ 0.3 mg – discontinue $n = 117$ 1.0 mg – 1.0 mg $n = 119$ 1.0 mg – discontinue $n = 122$	*Primary outcome*: Proportion of patients who lost <15 letters of visual acuity (3 lines on the study eye chart) between baseline and week 54 *Secondary outcomes*: Maintenance, gain and severe loss of visual acuity Adverse events Year 2 efficacy outcomes (not all data extracted): mean change in visual acuity from week 54 to week 102; Kaplan–Meier proportions of the loss of an additional 15 letters from week 54 to 102; loss of <15 letters from baseline to week 102; progression to legal blindness in study eye; proportion of patients gaining ≥ 0, ≥ 1, ≥ 2, ≥ 3 lines of visual acuity; visual acuity changes for patients who resumed therapy after discontinuation; changes in lesion size, total CNV, leak area and area of serous sensory retinal detachment *Method of assessing outcomes*: A separate, blinded visual acuity examiner assessed distance visual acuity *Length of follow-up*: 54 weeks followed by re-randomisation and additional 48 weeks of treatment

continued

Reference and design	Intervention	Participants	Outcome measures
		3.0 mg – 3.0 mg $n = 113$ 3.0 mg – discontinue $n = 109$ Sham – 0.3 mg $n = 50$ Sham – 1.0 mg $n = 46$ Sham – 3.0 mg $n = 52$ Sham – sham $n = 51$ Sham – discontinue $n = 48$ *Sample attrition/drop-out*: Approximately 90% completed the study. In all groups, an average of 8.5 injections were administered per patient out of a possible total of 9 *Inclusion/exclusion criteria for study entry*: Age ⩾50 years with subfoveal sites of CNV secondary to age-related macular degeneration and a range of best corrected visual acuity of 20/40 to 20/320 in the study eye and of 20/800 or better in the other eye. Lesions with a total size up to and including 12 DA (including blood, scar or atrophy and neovascularisation) were permitted. Additional criteria reported in supplementary paper, not extracted	

Characteristics of participants

	0.3 mg pegaptanib ($n = 295$)	1.0 mg pegaptanib ($n = 301$)	3.0 mg pegaptanib ($n = 296$)	Sham injection ($n = 298$)
Sex: *n* (%)				
Male	133 (45)	136 (45)	105 (35)	120 (40)
Female	162 (55)	165 (55)	191 (65)	178 (60)
Race: *n* (%)				
White	283 (96)	291 (97)	286 (97)	284 (95)
Other	12 (4)	10 (3)	10 (3)	14 (5)
Age (years): *n* (%)				
50–64	19 (6)	21 (7)	18 (6)	21 (7)
65–74	86 (29)	105 (35)	90 (30)	94 (32)
75–84	155 (53)	147 (49)	153 (52)	160 (54)
⩾85	35 (12)	28 (9)	35 (12)	23 (8)
Angiographic subtype of lesion: *n* (%)				
Predominantly classic (⩾50% classic CNV)	72 (24)	78 (26)	80 (27)	76 (26)
Minimally classic (<50% classic CNV)	111 (38)	108 (35)	105 (35)	102 (34)
Occult with no classic	112 (38)	115 (38)	111 (38)	120 (40)
Size of lesion: no. of DA (± SD)	3.7 ± 2.4	4.0 ± 2.4	3.7 ± 2.5	4.2 ± 2.8
History of ocular surgery or laser treatment: *n* (%)	123 (42)	117 (39)	124 (42)	124 (42)
Visual acuity				
Study eye				
Mean ± SD	52.8 ± 12.6	50.7 ± 12.8	51.1 ± 12.9	52.7 ± 13.0
Median (range)	55 (11–75)	52 (19–77)	53 (14–76)	53 (11–77)

continued

	0.3 mg pegaptanib (*n* = 295)	1.0 mg pegaptanib (*n* = 301)	3.0 mg pegaptanib (*n* = 296)	Sham injection (*n* = 298)
Other eye				
Mean ± SD	56.2 ± 27.2	54.8 ± 27.6	56 ± 26.4	55.9 ± 27.0
Median (range)	68 (3–85)	67 (3–85)	65 (4–85)	67 (2–85)
Health status (%)				
Hypertension	55			48
Hypercholesterolaemia	21			18
Diabetes mellitus	10			7
Cardiac disorders	35			34
Cerebrovascular disease	3			1
Peripheral arterial disease	3			3
ECG abnormalities	53			48
History of PDT: *n* (%)	24 (8)	29 (10)	27 (9)	18 (6)

p-Values were not reported for baseline characteristics, but authors state that demographic and ocular characteristics of the patients at baseline were similar among the treatment groups.

Results (year 1)

Outcomes	0.3 mg pegaptanib (*n* = 294)	1.0 mg pegaptanib (*n* = 300)	3.0 mg pegaptanib (*n* = 296)	Sham injection (*n* = 296)
Visual acuity: loss of <15 letters at week 54: *n* (%)	206 (70)	213 (71)	193 (65)	164 (55)
p-Value vs sham	<0.001	<0.001	0.03	
The differences between the doses of pegaptanib were not significant. Authors state that "similar results were obtained when analyses were restricted to the subgroup of patients who were evaluated both at baseline and at week 54, indicating that the missing data probably did not influence results" (data not extracted). The results of the two trials were similar, with both reaching statistical significance for the primary efficacy end-point (0.3 mg of pegaptanib, $p = 0.03$ and 0.01).				
Maintenance or gain ⩾1 letters: *n* (%)	98 (33)	110 (37)	93 (31)	67 (23)
p-Value vs sham	0.003	<0.001	0.02	
Gain ⩾5 letters: *n* (%)	64 (22)	69 (23)	49 (17)	36 (12)
p-Value vs sham	0.004	0.002	0.12	
Gain ⩾10 letters: *n* (%)	33 (11)	43 (14)	31 (10)	17 (6)
p-Value vs sham	0.02	0.001	0.03	
Gain ⩾15 letters: *n* (%)	18 (6)	20 (7)	13 (4)	6 (2)
p-Value vs sham	0.04	0.02	0.16	
Loss ⩾30 letters: *n* (%)	28 (10)	24 (8)	40 (14)	65 (22)
p-Value vs sham	<0.001	<0.001	0.01	
Snellen equivalent visual acuity in study eye ⩽20/200 (legal blindness): *n* (%)	111 (38)	128 (43)	129 (44)	165 (56)
p-Value vs sham	<0.001	<0.001	0.001	
Mean change in visual acuity (no. of letters) at 54 weeks[a]	–7.5	–6.5	–10	–14.5
p-Value	<0.002	<0.002	0.05	
[a] Data estimated from figure. Mean loss of visual acuity from baseline to each study visit (every 6 weeks) was significantly lower for pegaptanib than sham ($p < 0.002$ at each time point for 0.3 or 1.0 mg, $p < 0.05$ at each time point for 3.0 mg).				

Subgroup analyses (year 1) – mean decrease in visual acuity (no. of letters)[a] (*p* compared with sham)

Outcomes	0.3 mg pegaptanib (*n* = 294)	1.0 mg pegaptanib (*n* = 300)	3.0 mg pegaptanib (*n* = 296)	Sham injection (*n* = 296)
Lesion type				
Predominantly classic	7.1 $p < 0.05$	10.2 NS	10.5 NS	14
Minimally classic	7.3 $p < 0.001$	6.5 $p < 0.001$	9.4 $p < 0.05$	14.2
Occult with no classic	9 $p < 0.01$	6 $p < 0.001$	9.5 $p < 0.05$	17
Baseline visual acuity				
<54 letters	5 $p < 0.01$	4.8 $p < 0.01$	6 $p < 0.05$	10.5
⩾54 letters	10.5 $p < 0.001$	10.5 $p < 0.001$	13.5 $p < 0.01$	19.5
Lesion size at baseline				
<4 DA	7.5 $p < 0.001$	8 $p < 0.001$	9 $p < 0.001$	16.5
⩾4 DA	8.5 $p < 0.05$	6 $p < 0.001$	11 NS	13.5

NS, not significant.
[a] Data estimated from figures.
For those receiving pegaptanib at 0.3 mg, a treatment benefit was observed among all patients with all angiographic subtypes of lesions ($p < 0.3$ for each subtype), baseline levels of visual acuity ($p < 0.01$ for each group) and lesion size at baseline ($p < 0.02$ for each group). Multiple logistic regression analyses revealed that no factor other than assignment to pegaptanib treatment was significantly associated with response (0.3-mg dose, $p < 0.001$).

Use of PDT at baseline: *n* (%)	36 (12)	31 (10)	38 (13)	40 (13)
Use of PDT after baseline: *n* (%)	49 (17)	55 (18)	57 (19)	62 (21)
Size of lesion (no. of DA)				
Baseline	3.7	4.0	3.7	4.2
Week 54	5.5	5.8	6.2	6.7
Change from baseline vs change in sham	$p < 0.01$	$p < 0.01$	NS	
Size of CNV (no. of DA)				
Baseline	3.1	3.5	3.2	3.7
Week 54	4.7	4.7	5.0	5.8
Change from baseline vs change in sham	NS	$p < 0.01$	NS	
Size of leakage (no. of DA)				
Baseline	3.3	3.4	3.4	3.6
Week 54	4.3	3.9	4.6	5.2
Change from baseline vs change in sham	NS	$p < 0.01$	NS	

NS, not significant.

Adverse events (year 1)	Pegaptanib (all doses)	Sham injection	*p*-Value
Rate of discontinuation due to AEs (%)	1	1	
Death rate (%)	2	2	NS
Vascular hypertensive disorders (%)	10	10	NS
Hemorrhagic AEs (%)	2	3	NS
Thromboembolic events (%)	6	6	NS
Gastrointestinal perforations (%)	0	0	NS
Local or systemic hypersensitivity attributable to pegaptanib (%)	0		
Common ocular adverse events in study eye			
Eye pain (%)	34	28	NS
Vitreous floaters (%)	33	8	<0.001
Punctuate keratitis (%)	32	27	NS
Cataracts (%)	20	18	NS
Vitreous opacities (%)	18	10	<0.001
Anterior chamber inflammation (%)	14	6	0.001
Visual disturbance (%)	13	11	NS
Eye discharge (%)	9	8	NS
Corneal oedema (%)	10	7	NS

AE, adverse event; NS, not significant.
Reasons for discontinuation due to AEs were diverse and were not clustered in relation to a particular system or organ. No further details provided.
No systemic AEs were definitively attributed by the independent data management and safety monitoring committee to the study drug, nor were any observed for any organ system in all 3 treatment groups.
Most AEs reported in the study eyes were transient, with a severity that was mild to moderate, and were attributed by the investigators to the injection procedure rather than to the study drug.
Eye events were more common in the study eyes than in the other eyes among patients in the sham injection group, suggesting that the preparation procedure was partly the cause, rather than the study drug.
No evidence of sustained elevation in intraocular pressure or of an acceleration of cataract formation in the treatment group compared with sham.
No evidence of AEs on retinal or choroidal vascular beds.
In the second year of the study, the incidence of common ocular AEs was similar to those reported in year 1. Most AEs reported in the study eyes were transient, mild to moderate in severity, and attributed to the injection procedure itself.

Injection-related adverse events in 890 patients treated with pegaptanib in the first year of the trial (total of 7545 injections)

Adverse event	No. of patients with event (%)	Events per injection (%)	Severe loss of visual acuity (≥30 letters): *n* (%)
Endophthalmitis	12 (1.3)[a]	0.16	1 (0.1)
Traumatic injury to lens	5 (0.6)	0.07	1 (0.1)
Retinal detachment	6 (0.7)	0.08	0[b]

[a] Three-quarters of patients with endophthalmitis remained in the trial. The condition was associated with protocol violation in two-thirds of the patients with this condition (most common protocol violation was failure to use an eyelid speculum to prevent bacteria from eyelashes contaminating injection site).
[b] Measurements of visual acuity after the event were not available for one patient.
Because multiple injections are required, the risk of endophthalmitis was 1.3% per patient during the first year of the trials. In the 374 patients who received pegaptanib for >1 year, there were no cases of endophthalmitis or traumatic cataract reported. The rate of retinal detachment was 4/2663 injections (0.15% per injection). No evidence of cataract progression or persistent intraocular pressure elevation following multiple pegaptanib injections was seen. No serious AEs were attributed to the study drug, and the drug was well tolerated systemically.

Year 2 results

Pegaptanib patients were re-randomised 1:1 to continue or discontinue therapy for 48 more weeks (eight injections). Those initially assigned to sham injection were re-randomised 1:1:1:1:1 to continue sham, discontinue sham, or receive one of three pegaptanib doses. Any patients who were randomised to discontinue but lost ⩾10 letters at one of the assessment points were permitted to have their year one treatment reinstated if they had benefited from it in year 1 (defined as the loss of ⩽0 letters between baseline and week 54). Data for the other dose groups and for sham – any pegaptanib dose groups are shown in an appendix to the Chakravarthy paper but not data extracted. Usual care = all patients in sham group in year 1 re-randomised to continue sham or to discontinue. Studies 1003 and 1004 represent the two RCTs.

Visual acuity at baseline and re-randomisation (reported separately for the 2 studies)	0.3 mg pegaptanib – 0.3 mg pegaptanib		0.3 mg pegaptanib – discontinue		Usual care	
	Study 1003 (*n* = 67)	Study 1004 (*n* = 66)	Study 1003 (*n* = 66)	Study 1004 (*n* = 66)	Study 1003 (*n* = 54)	Study 1004 (*n* = 53)
Mean visual acuity (letters)						
Week 0	53.6	52.3	53.8	52.7	49.8	55.7
Week 54	44.0	44.3	49.5	45.1	38.1	40.1
Responder rate: *n* (%)						
Week 54	46 (69)	42 (64)	53 (80)	47 (71)	35 (65)	28 (53)
Legal blindness: *n* (%)						
Week 0	7 (10)	15 (23)	7 (11)	9 (14)	9 (17)	5 (9)
Week 54	26 (38)	30 (45)	15 (23)	24 (36)	29 (54)	27 (51)
Re-randomisation produced visual acuity imbalances between treatment groups, within and between studies, at both week 0 and week 54; these imbalances are reported to have occurred purely by chance.						

Discontinued patients who resumed therapy in the re-randomised population	0.3 mg – discontinue (*n* = 132)	Sham – discontinue (*n* = 54)
Resuming therapy: *n* (%)	28 (21)	8 (15)
Week at which rescue initiated: mean (SD)	73.7 (12.4)	72.8 (10.8)
VA change from week 54 to rescue: mean letters (SD)	–12.6 (10.6)	–13.4 (5.6)
VA change from rescue to week 102: mean letters (SD)	–1.8 (12.5)	–4.8 (15.3)

Outcomes – year 2	0.3 mg pegaptanib – 0.3 mg pegaptanib (*n* = 133)	0.3 mg pegaptanib – discontinue (*n* = 132)	Usual care (*n* = 107)
Change in standardised area under the curve of visual acuity in the re-randomised population			
Week 0 to week 6			
LS mean (SE)	–0.56 (0.49)		–1.45 (0.55)
p-Value compared with usual care	0.1402		
Week 0 to week 54			
LS mean (SE)	–4.54 (1.18)		–8.16 (1.32)
p-Value compared with usual care	0.0129		
Week 0 to week 102			
LS mean (SE)	–5.88 (1.33)		–11.24 (1.49)
p-Value compared with usual care	0.0012		
Week 54 to week 102			
LS mean (SE)	–0.60 (0.61)	–3.04 (0.60)	
p-Value compared with discontinuing	0.0041		
Progression to legal blindness			
Baseline visual acuity better than 20/200: *n*	111	116	93
Visual acuity 20/200 or worse			
Week 54: *n* (%)	38 (34)	28 (24)	44 (47)
Week 102: *n* (%)	39 (35)	44 (38)	51 (55)
Mean visual acuity (estimated from graph): letters			
Week 54	44	47	39
Week 78	43.5	43	37
Week 102	44	42	35
Lines of vision gained (estimated from graph): % of patients			
⩾0 lines	35	27	26
⩾1 lines	22	19	14
⩾2 lines	15	8	6
⩾3 lines	10	8	4

LS, least squares; SE, standard errors.

Responder rates – loss of <15 letters (total *n* for groups not stated)	0.3 mg – 0.3 mg	0.3 mg – discontinue	Sham – any pegaptanib dose	Sham – usual care
Week 54 (%)	66	76	56	59
Week 102 (%)	59	62	48	45

Angiographic changes over time are shown for the 2 studies individually, but not the combined analysis of the two trials. Not data extracted at this stage. The only statistically significant difference was the difference in lesion size between the continuing 0.3-mg pegaptanib group and the usual care group in study 1004. The continuing 0.3-mg group's mean total lesion size was 5.4 DA at week 78 and 5.6 DA at week 102, compared with 7.5 DA and 8.1 DA, respectively ($p < 0.05$). The corresponding patient groups in study 1003 did not show a significant difference.

Outcomes – year 2: *n* (%)	0.3 mg pegaptanib (*n* = 133)	Usual care (*n* = 107)
No. of responders at 102 weeks (<15 letters lost)	78 (59)	48 (45)
p-Value compared with usual care	0.0385	
No. with loss ⩾30 letters (severe vision loss) at 102 weeks	17 (13)	28 (26)
p-Value compared with usual care	0.0058	
No. of patients completing the trial (week 102)	106 (80)	95 (89)

Continuation of pegaptanib treatment throughout year 2 demonstrated higher efficacy and significant benefit versus treatment discontinuation. There was a significant ($p < 0.05$) 67% relative reduction in non-responders (⩾15 letters loss) for continued 0.3-mg pegaptanib treatment versus usual care (16 versus 27%, respectively). Mean visual acuity in continued 0.3-mg pegaptanib group remained stable during the second year, whereas the loss in visual acuity resumed in individuals re-randomised to discontinue.

Adverse events – year 2: *n* (%)	0.3 mg pegaptanib (*n* = 128)	Sham (*n* = 51)
Individuals with AE	122 (95)	46 (90)
Individuals with ocular AE (study eye)	92 (72)	39 (76)
Individuals with serious AE	22 (17)	14 (27)
Withdrawals due to AE	5 (4)	2 (4)
Deaths (any cause)	1 (1)	0 (0)
Adverse events in ⩾10% of subjects – year 2		
Eye pain	27 (21)	9 (18)
Intraocular pressure increased	26 (20)	4 (8)
Punctate keratitis	31 (24)	14 (27)
Vitreous floaters	28 (22)	2 (4)
Vitreous opacities	13 (10)	6 (12)
Corneal oedema	12 (9)	4 (8)
Lacrimation increased	6 (5)	6 (12)
Eye redness	9 (7)	6 (12)
Vision blurred	4 (3)	5 (10)
Cataract	23 (18)	12 (24)

Incidence of serious adverse events (rate/injection) – 2-year results	Rate (% per injection) (cohort 1)[a]	Rate (% per injection) (All cohorts)[b]
Endophthalmitis	0	0.10
Traumatic cataract (lens injury)	0	0.02
Retinal detachment	0.15	0.17

[a] Cohort 1: all individuals re-randomised to continue on same treatment in the second year, $n = 374$; a total of 2663 injections of pegaptanib were administered.

[b] $n = 374$ for pegaptanib-treated patients re-randomised to pegaptanib; $n = 160$ for usual care patients re-randomised to pegaptanib; $n = 72$ for patients re-randomised to discontinue, retreated with pegaptanib. A total of 4091 injections of pegaptanib were administered.

Over the full 102 weeks of the study, patient compliance was high. A mean of 15.6 of 17 possible treatments were administered to patients receiving 0.3 mg pegaptanib and 16.3 of 17 possible treatments were administered to patients receiving usual care. Over the 2-year period, 92% of injections occurred within 1 week of the scheduled dose of both 0.3 mg pegaptanib and usual care.

[**CIC data removed**]

One year after discontinuation of treatment, pegaptanib still has a highly significant benefit compared with no treatment and this indicates that pegaptanib does not simply treat ARMD symptoms, but targets angiogenesis, the underlying pathologic process. [**CIC data removed**].

[**CIC data removed**]

In the VISION study, the development to legal blindness was defined as VA better than 6/60 (20/200) at baseline that progressed to 6/60 (20/200) or worse in the study eye. The positive effect of 0.3 mg pegaptanib on delaying progression to legal blindness at year 1 was maintained after years 1 and 2 versus usual care [pegaptanib 35% (39/111), usual care 55% (51/93); relative benefit 36%; $p < 0.01$].

Methodological comments

- *Allocation to treatment groups*: Patients were allocated in each trial to one of four arms by a dynamic procedure using a stochastic treatment allocation algorithm based on the variance method to minimise imbalances for study centre, angiographic lesion subtype and previous treatment with PDT.
- *Blinding*: To maintain masking of the investigators, the ophthalmologist responsible for patient care and for the assessments did not administer the injection. In all cases, a separate, certified visual acuity examiner masked to the treatment assignment and to previous measurements of visual acuity assessed distance visual acuity. All patients were treated identically, with the exception of scleral penetration, to maintain masking of patients.
- *Comparability of treatment groups*: No *p*-values were reported for baseline characteristics, but patients appeared to be similar at baseline. Re-randomisation produced visual acuity imbalances between treatment groups, within and between studies, at both week 0 and week 54; these imbalances are reported to have occurred purely by chance.
- *Method of data analysis*: The two studies were identical in design and similar in baseline characteristics. The Appendix states that results for the primary end-point reached significance in both trials, so results were combined as per protocol. A prestratified Cochran–Mantel–Haenszel test using stratification factors (lesion angiographic subtype, prior PDT), baseline visual acuity and baseline lesion size was applied to comparisons of binary end-points. Mean changes in visual acuity were analysed using an analysis of covariance model and observed mean changes for each time point; models included main effects for treatment and stratification factors, with baseline visual acuity and baseline lesion size as covariates. All *p*-values reported are two-sided and unadjusted for multiplicity. Point estimates and CIs are given where appropriate. States that for all efficacy analyses, patients were evaluated in the treatment group to which they were randomly assigned, and that safety analyses included all patients with at least one study treatment regardless of whether a baseline visual acuity was obtained. However, efficacy results are not ITT, as they exclude four patients who did not receive a sufficiently standardised assessment of visual acuity at baseline. Individual and combined analyses of studies 1003 and 1004 reported by VISION Clinical Trial Group[100] are reported to be ITT, including all patients who were re-randomised at week 54. Last observation carried forward (LOCF) for any missing efficacy data. Mean change in visual acuity from week 54 was determined for each treatment visit as a summary measure of treatment trends. These results were confirmed further using a standardised area under the curve, using the trapezoidal rule. Kaplan–Meier estimates of proportions with loss of $\geqslant$15 letters after week 54 were calculated for patients continuing with pegaptanib therapy versus those discontinuing at week 54. The 2-year control group (usual care) included all sham patients who were re-randomised either to continue sham or to discontinue at week 54.
- *Sample size/power calculation*: Power calculations were reported, and required 122 patients per individual trial arm to provide an overall power of 95%. States that the two studies were identically designed in order to fulfil the worldwide regulatory requirements of reaching statistical significance in two independent trials.
- *Attrition/drop-out*: 90% of patients completed the study. Four patients were excluded from analyses due to inadequate baseline assessments. 1% of both the treatment and sham groups discontinued, but no details are provided, other than the statement that "reasons for discontinuation were diverse and were not clustered in relation to a particular system or organ". 2% of patients died. Drop-outs appear to be balanced between treatment arms and the control group, so attrition bias should not affect outcomes. Discontinuations in the second year were generally due to patient request. Death and adverse events were the second and third most common reasons for dropping out. Mean number of treatments was balanced between all treatment groups.

General comments

- *Generalisability*: The study included people with different types of lesion, i.e. predominantly classic, minimally classic and occult with no classic.
- *Outcome measures*: Outcome measures were relevant to the study area and were measured appropriately. Loss of fewer than 15 letters of visual acuity was defined as three lines on the study eye chart, and was measured as loss between baseline and week 54. In relation to the visualisation of choroidal new vessels (classic) in the fluorescein angiogram, a predominantly classic lesion includes 50% or more classic choroidal neovascularisation and an occult lesion includes no classic choroidal neovascularisation. Size of lesion was measured as the number of DA (including blood scar or atrophy and neovascularisation), each of which is 2.54 mm^2.
- *Inter-centre variability*: Not reported.
- *Conflict of interests*: Eyetech Pharmaceuticals and Pfizer supported the trials. The Gragoudas study[95] has served as a paid consultant for the sponsor, and other authors are employees and shareholders of the sponsor.

Quality criteria for assessment of experimental studies

1.	Was the assignment to the treatment groups really random?	Adequate
2.	Was the treatment allocation concealed?	Adequate
3.	Were the groups similar at baseline in terms of prognostic factors?	Reported
4.	Were the eligibility criteria specified?	Adequate
5.	Were outcome assessors blinded to the treatment allocation?	Adequate
6.	Was the care provider blinded?	Adequate
7.	Was the patient blinded?	Adequate
8.	Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9.	Did the analyses include an ITT analysis?	Inadequate
10.	Were withdrawals and drop-outs completely described?	Partial

For ranibizumab studies, data were extracted from the clinical trial reports supplied with the manufacturer's submission. Consequently, much of the data is commercial-in-confidence. Three of the trials were published at a late stage of the review, and although the main tables in the report have been updated with the published data, the data extraction tables were not updated in full. Where possible, data on key outcomes has been updated, but no new data (particularly on adverse events) have been extracted from the publications.

Reference and design	Intervention	Participants	Outcome measures
Rosenfeld *et al*., 2006[97] [**CIC data removed**] USA Multi-centre RCT 96 centres *Funding*: Genentech and Novartis	1. 0.3 mg ranibizumab monthly 2. 0.5 mg ranibizumab monthly 3. Sham injection monthly *Duration of treatment*: Ranibizumab or sham injection monthly, last injection at month 23 Approximately 3 months prior to completion, patients in sham group could cross over to 0.5-mg ranibizumab for remaining period *Other interventions used*: Verteporfin PDT allowed for subjects who met certain criteria	*Target population*: Primary or recurrent minimally classic or occult subfoveal CNV *Number of participants*: Total randomised: 716 1. 0.3 mg ranibizumab: 238 2. 0.5 mg ranibizumab: 240 3. Sham injection: 238 *Sample attrition/drop-out*: 2 in the sham group and 1 in the 0.5-mg group did not receive any study drug 12 from the sham group crossed over to 0.5 mg: 5 received 2 injections and 7 received 1 injection prior to study completion *Main inclusion criteria for study entry*: Age ≥50 years, primary or recurrent subfoveal CNV, occult CNV or some classic CNV (classic CNV component <50% of the total lesion size), total area of CNV encompassed within the lesion ≥50% of total lesion size, total lesion area ≤12 DA, best corrected visual acuity (using ETDRS charts) of 20/40 to 20/320 Snellen equivalent. [**CIC data removed**] *Exclusion criteria*: Prior PDT, external beam radiation therapy or transpupillary thermotherapy in study eye, PDT treatment in fellow eye less than 7 days prior, previous participation in trial of anti-angiogenic drugs, previous intravitreal delivery in study eye, previous subfoveal focal laser photocoagulation in study eye, laser photocoagulation within 1 month in study eye, history of vitrectomy surgery, submacular surgery or other surgical intervention for AMD in study eye, previous participation in any studies of investigational drugs within 1 month, subretinal haemorrhage involving centre of fovea if size is either ≥50% of total lesion area or ≥1 DA in size, subfoveal fibrosis or atrophy, CNV in either eye due to other causes, retinal pigment epithelium tear involving the macular in the study eye. Other criteria reported but not extracted	[**CIC data removed**] *Primary outcomes*: Proportion losing fewer than 15 letters (~3 lines) in best corrected visual acuity (BCVA) at a test distance of 2 m at 12 months Safety and tolerability *Secondary outcomes for first year*: Prevention of vision loss: • mean change in visual acuity • proportion gaining at least 15 letters • proportion with Snellen equivalent of 20/200 or worse [**CIC data removed**] Size of classic CNV and amount of leakage *Secondary outcomes for second treatment year, outcomes at 24 months*: Proportion losing <15 letters at starting test distance of 2 m Proportion losing <15 letters at starting test distance of 4 m Mean change in BCVA Proportion gaining at least 15 letters Proportion with Snellen equivalent of 20/200 or worse [**CIC data removed**] Change in total area of CNV Change in total area of leakage from CNV [**CIC data removed**] *Method of assessing outcomes*: BCVA assessed by ETDRS chart CNV assessed by FA [**CIC data removed**] *Length of follow-up*: 24 months

continued

Characteristics of participants

	0.3 mg ranibizumab (*n* = 238)	0.5 mg ranibizumab (*n* = 240)	Sham (*n* = 238)
Age (years): mean (SD), range	77 (8) 52–95	77 (8) 52–93	77.0 (7) 56–94
Sex: *n* (%)			
Male	85 (35.7)	88 (36.7)	79 (33.2)
Female	153 (64.3)	152 (63.3)	159 (66.8)
Race: *n* (%)			
White	229 (96.2)	232 (96.7)	231 (97.1)
Other	9 (3.8)	8 (3.3)	7 (2.9)
	[**CIC data removed**]		
Visual acuity at starting test distance 2 m			
No. of letters (0–100): mean (SD)	53.1 (12.9)	53.7 (12.8)	53.6 (14.1)
	[**CIC data removed**]		
<55: *n* (%)	115 (48.3)	117 (48.8)	109 (45.8)
⩾55: *n* (%)	123 (51.7)	123 (51.3)	129 (54.2)
Approximate Snellen equivalent: *n* (%)			
	[**CIC data removed**]		
20/200 or worse	35 (14.7)	31 (12.9)	32 (13.4)
Better than 20/200 but worse than 20/40	176 (73.9)	173 (72.1)	170 (71.4)
20/40 or better	27 (11.3)	36 (15.0)	36 (15.1)
	[**CIC data removed**]		
Predominantly classic: *n* (%)	1 (0.4)	0	0
Minimally classic: *n* (%)	86 (36.1)	91 (37.9)	87 (36.6)
Occult without classic: *n* (%)	151 (63.4)	149 (62.1)	150 (63.0)
Missing: *n* (%)	0	0	1 (0.4)
Total area of lesion (DA): mean (SD), range	4.3 (2.5) 0.0–11.8	4.5 (2.6) 0.3–12.00	4.4 (2.5) 0.00–11.8
	[**CIC data removed**]		
Total area of CNV (DA): mean (SD), range	4.1 (2.5) 0.0–11.80	4.3 (2.5) 0.1–12.00	4.3 (2.4) 0.00–11.8
	[**CIC data removed**]		
Total area of leakage from CNV plus intense progressive retinal pigment epithelium staining (DA): mean (SD), range	3.6 (2.5) 0.0–12.0	3.5 (2.6) 0.0–13.50	3.5 (2.5) 0.0–12.9
	[**CIC data removed**]		
Any prior therapy for AMD in study eye: *n* (%)	140 (58.8)	139 (57.9)	135 (56.7)
Laser photocoagulation: *n* (%)	13 (5.5)	14 (5.8)	22 (9.2)
Medication: *n* (%)	1 (0.4)	3 (1.2)	3 (1.3)
Supplements: *n* (%)	134 (56.3)	127 (52.9)	121 (50.8)
Other: *n* (%)	3 (1.3)	3 (1.2)	8 (3.4)

Results

Outcomes	0.3 mg ranibizumab (*n* = 238)	0.5 mg ranibizumab (*n* = 240)	Sham (*n* = 238)
Proportion losing <15 letters compared with baseline (starting test distance 2 m): *n* (%)			
Month 12	225 (94.5)	227 (94.6)	148 (62.2)
	[CIC data removed]		
Difference in % (vs sham)	31.9	32.0	
	[CIC data removed]		
p-Value (vs sham)	<0.0001	<0.0001	
Month 24	219 (92.0)	216 (90.0)	126 (52.9)
	[CIC data removed]		
Difference in % (vs sham)	38.7	36.6	
	[CIC data removed]		
p-Value (vs sham)	<0.0001	<0.0001	
Visual acuity at starting test distance of 2 m, at 24 months			
	[CIC data removed]		
No. of letters change from baseline: mean (SD)	5.4 (15.2)	6.6 (16.5)	–14.9 (18.7)
	[CIC data removed]		
p-Value (vs sham)	<0.001	<0.001	
Gain of ⩾15 letters from baseline, response rate: *n* (%)	62 (26.1)	80 (33.3)	9 (3.8)
	[CIC data removed]		
Difference in % (vs sham)	21.9	29.2	
	[CIC data removed]		
p-Value (vs sham)	<0.001	<0.001	
Snellen equivalent			
20/200 or worse, response rate: *n* (%)	35 (14.7)	36 (15.0)	114 (47.9)
	[CIC data removed]		
Difference in % (vs sham)	–33.6	–33.4	
	[CIC data removed]		
p-Value (vs sham)	<0.001	<0.001	
Approximate Snellen equivalent			
	[CIC data removed]		
20/40 or better: *n* (%)	82 (34.5)	101 (42.1)	14 (5.9)

12-month data reported but not extracted. [**CIC data removed**].
[**CIC data removed**].

Outcomes	0.3 mg ranibizumab (*n* = 238)	0.5 mg ranibizumab (*n* = 240)	Sham (*n* = 238)
Minimally classic CNV at baseline	(*n* = 86)	(*n* = 91)	(*n* = 87)
Response rate: *n* (%)	77 (90)	81 (89)	44 (51)
	[CIC data removed]		
Difference in % (vs sham)	39	38	
	[CIC data removed]		
p-Value vs sham	<0.001	<0.001	
Occult without classic CNV at baseline	(*n* = 151)	(*n* = 149)	(*n* = 150)
Response rate: *n* (%)	141 (93)	135 (91)	81 (54)
	[CIC data removed]		
Difference in % (vs sham)	39	37	
	[CIC data removed]		
p-Value vs sham	<0.001	<0.001	
	[CIC data removed]		

Change from baseline CNV area and leakage reported in full in manufacturer's submission, but published paper only gives charts which are difficult to interpret accurately. Therefore, only the CIC information has been data extracted below.

[**CIC data removed**]

Adverse effects (safety-evaluable subjects) during 2-year period	0.3 mg ranibizumab (*n* = 238)	0.5 mg ranibizumab (*n* = 239)	Sham (*n* = 236)
	[**CIC data removed**]		
Ocular events: study eye			
	[**CIC data removed**]		
Endophthlamitis: *n* (%)	2 (0.8)	[**CIC data removed**] 3 (1.3)	0
	[**CIC data removed**]		

Methodological comments

- *Allocation to treatment groups*: Randomisation conducted by an independent group. Subjects randomised through an interactive voice response system. Randomisation was stratified by visual acuity score at day 0 (⩽54 letters (approximately worse than 20/80) versus ⩾55 letters (approximately 20/80 or better) based on ETDRS chart at 2 m), by type of CNV and by study centre. A dynamic randomisation scheme used to obtain an approximately 1:1:1 ratio, [**CIC data removed**].
- *Blinding*: Described as double-masked. Each site had at least one evaluating physician, who was masked to treatment assignment and conducted all ocular assessments, and at least one injecting physician, who was unmasked to treatment assignment and performed ranibizumab or sham injection procedures but was masked to ranibizumab dose. [**CIC data removed**].
- *Comparability of treatment groups*: States that demographic and baseline characteristics were well balanced, in addition to ocular and anatomical characteristics of the study eye. [**CIC data removed**].
- *Method of data analysis*: States ITT analysis used for efficacy. The population used for safety analyses included randomised subjects who received at least one of the treatments. [**CIC data removed**]. Missing data were imputed using the last observation carried forward approach. Primary end-point compared using Cochran χ^2 test stratified by CNV classification at baseline and baseline visual acuity score. Test performed at an overall significance level of 0.0497 after adjusting for interim analysis. The Hochberg–Bonferroni multiple comparison procedure used to adjust for the two pairwise treatment comparisons.
- *Sample size/power calculation*: Reported. Based on the analysis of the primary efficacy end-point. 720 subjects required.
- *Attrition/drop-out*: 664 (92.7%) completed month 12 of study and 615 (85.9%) completed the 2-year study period. 131 (18.3%) discontinued from treatment prior to month 12, with most as a result of subject decision. The sham group had a higher drop-out rate and treatment discontinuation rate than the ranibizumab groups. Approximately 10% of the sham group discontinued from treatment because of disease progression that mandated another therapeutic intervention, whereas only one (0.4%) in the 0.3-mg group and none in the 0.5-mg group discontinued for such a reason. Reasons for discontinuation reported but not extracted.

General comments

- *Generalisability*: Almost two-thirds had occult no classic subfoveal CNV, about one-third had minimally classic subfoveal CNV. Subjects mainly white and two-thirds were female.
- *Outcome measures*: Outcome measures were appropriate.
- *Inter-centre variability*: Not reported.
- *Conflict of interests*: Study funded by ranibizumab manufacturers.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Adequate
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Adequate
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Adequate
10. Were withdrawals and drop-outs completely described?	Adequate

Reference and design	Intervention	Participants	Outcome measures
Brown *et al*., 2006[96] ANCHOR [**CIC data removed**] USA, Europe, Australia Multi-centre RCT 83 centres *Funding*: Genentech, Novartis	1. 0.3 mg ranibizumab monthly + sham PDT with saline infusion every 3 months if needed 2. 0.5 mg ranibizumab monthly + sham PDT with saline infusion and every 3 months if needed 3. Sham injection of ranibizumab monthly + active verteporfin PDT every 3 months if needed *Duration of treatment*: Ranibizumab or sham injection monthly for 23 months (24 injections). Active or sham PDT on day 0 and every 3 months if needed (determined by fluorescein angiograms) for 21 months *Other interventions used*: None	*Target population*: Predominantly classic subfoveal CNV *Number of participants*: Total randomised: 423 1. 0.3 mg ranibizumab: 140 2. 0.5 mg ranibizumab: 140 3. Verterporfin PDT: 143 *Sample attrition/drop-out*: 3 subjects in the 0.3-mg group did not receive any ranibizumab during study *Main inclusion criteria for study entry*: Age ⩾50 years, primary or recurrent predominantly classic subfoveal CNV eligibility for treatment with verteporfin PDT according to Visudyne product labelling, future treatment with verteporfin PDT anticipated or expected in study eye, classic CNV component ⩾50% of the total lesion size, total lesion size ⩽5400 μm in greatest linear dimension, best corrected visual acuity (BCVA) (using ETDRS charts) of 20/40 to 20/320 Snellen equivalent. [**CIC data removed**]. *Exclusion criteria*: Prior PDT in study eye, prior PDT treatment in fellow eye less than 7 days prior, previous participation in trial of anti-angiogenic drugs, previous intravitreal delivery in study eye, previous subfoveal focal laser photocoagulation in study eye within 1 month, history of vitrectomy surgery, submacular surgery or other surgical intervention for AMD in study eye, subretinal haemorrhage involving centre of fovea if size is either ⩾50% of total lesion area or ⩾1 DA in size, subfoveal fibrosis or atrophy, CNV in either eye due to other causes, retinal pigment epithelium tear involving the macular in the study eye. [**CIC data removed**]	[**CIC data removed**] *Primary outcomes*: Proportion losing fewer than 15 letters (~3 lines) in BCVA at a test distance of 2 m. [**CIC data removed**] *Secondary outcomes*: Prevention of vision loss: • mean change in visual acuity • proportion gaining at least 15 letters • proportion with Snellen equivalent of 20/200 or worse [**CIC data removed**] Size of classic CNV and amount of leakage [**CIC data removed**] *Method of assessing outcomes*: BCVA assessed by ETDRS chart. CNV assessed by FA [**CIC data removed**] *Length of follow-up*: 12 months (study ongoing)

Characteristics of participants

	0.3 mg ranibizumab (*n* = 140)	0.5 mg ranibizumab (*n* = 140)	Verteporfin PDT (*n* = 143)
Age (years): mean (SD), range	77.4 (7.5)	76.0 (8.6)	77.7 (7.8)
Sex: *n* (%)	54–97	54–93	53–95
Male	73 (52.1)	75 (53.6)	64 (44.8)
Female	67 (47.9)	65 (46.4)	79 (55.2)
Race: *n* (%)			
White	137 (97.9)	136 (97.1)	140 (97.9)
Other	3 (2.1)	4 (2.9)	3 (2.1)
	[CIC data removed]		
Visual acuity at starting test distance 2 m	(*n* = 140)	(*n* = 139)	(*n* = 143)
No. of letters (0–100), mean (SD)	47.0 (13.1)	47.1 (13.2)	45.5 (13.1)
	[CIC data removed]		
⩽44: *n* (%)	63 (45.0)	60 (43.2)	66 (46.2)
⩾45: *n* (%)	77 (55.0)	79 (56.8)	77 (53.8)
Approximate Snellen equivalent (2 m): *n* (%)			
Median	20/100	20/125	20/100
20/200 or worse	35 (25.0)	32 (23.0)	46 (32.2)
Better than 20/200 but worse than 20/40	103 (73.6)	101 (72.7)	97 (67.8)
20/40 or better	2 (1.4)	6 (4.3)	0
	[CIC data removed]		
Predominantly classic: *n* (%)	134 (95.7)	135 (96.4)	141 (98.6)
Minimally classic: *n* (%)	5 (3.6)	5 (3.6)	2 (1.4)
Occult without classic: *n* (%)	1 (0.7)	0	0
Total area of lesion (DA): mean (SD), range	1.89 (1.44) 0.12–7.20	1.79 (1.54) 0.05–10.00	1.88 (1.40) 0.07–5.75
	[CIC data removed]		
Total area of CNV (DA): mean (SD), range	1.48 (1.33) 0.11–6.80	1.31 (1.24) 0.05–7.50	1.48 (1.25) 0.07–5.55
Area of classic CNV (DA): mean (SD), range	1.28 (1.05) 0.00–6.40	1.21 (1.12) 0.05–5.30	1.36 (1.13) 0.07–5.55
Total area of leakage from CNV plus intense progressive retinal pigment epithelium staining (DA): mean (SD), range	3.00 (1.92) 0.20–11.00	2.92 (2.08) 0.25–9.00	3.06 (1.81) 0.20–8.20
	[CIC data removed]		
Any prior therapy for AMD in study eye: *n* (%)	63 (45.0)	58 (41.4)	64 (44.8)
Laser photocoagulation: *n* (%)	23 (16.4)	20 (14.3)	19 (13.3)
Medication: *n* (%)	1 (0.7)	1 (0.7)	1 (0.7)
Supplements: *n* (%)	48 (34.3)	45 (32.1)	51 (35.7)

Results

Outcomes (at 12 months)	0.3 mg ranibizumab (*n* = 140)	0.5 mg ranibizumab (*n* = 140)	Verteporfin PDT (*n* = 143)
Proportion losing <15 letters compared with baseline (starting test 2 m): *n* (%)	(*n* = 140) 132 (94.3) [**CIC data removed**]	(*n* = 139) [**CIC data removed**] 134 (96.4)	(*n* = 143) 92 (64.3)
Difference in % (vs PDT)	30.1 [**CIC data removed**]	32.6	
Test for treatment difference (vs PDT): *p*-value	<0.001 [**CIC data removed**]	<0.001	
No. of letters change from baseline: mean [CIC data removed]	(*n* = 140) 8.5 [**CIC data removed**] [**CIC data removed**]	(*n* = 139) 11.3 [**CIC data removed**]	(*n* = 143) –9.5 [**CIC data removed**]
p-Value (vs PDT)	<0.001	<0.001	
Gain of ⩾15 letters from baseline: *n* (%)	(*n* = 140) 50 (35.7) [**CIC data removed**]	(*n* = 139) 56 (40.3)	(*n* = 143) 8 (5.6)
p-Value (vs PDT)	<0.001	<0.001	
Snellen equivalent 20/200 or worse: *n* (%)	31 (22.1) [**CIC data removed**]	23 (16.4)	86 (60.1)
Change in area of classic CNV (DA): mean (SD)	–0.52 (0.89)	–0.67 (1.10)	0.54 (2.37)
95% CI of mean	–0.67 to –0.37 [**CIC data removed**]	–0.86 to –0.49	0.15 to 0.93
p-Value (vs PDT)	<0.001	<0.001	
Change in total area of leakage from CNV + intense progressive RPE staining (DA): mean (SD)	–1.80 (1.72)	–2.05 (1.98)	0.32 (3.09)
95% CI of mean	–2.09 to –1.51 [**CIC data removed**]	–2.38 to –1.72	–0.19 to 0.83
p-Value (vs PDT)	<0.001 [**CIC data removed**]	<0.001	
Endophthalmitis (published data)	[**CIC data removed**]	2 (1.4)	
Deaths Total	3 (2.2) [**CIC data removed**]	2 (1.4)	2 (1.4)

Methodological comments

- *Allocation to treatment groups*: [**CIC data removed**]. Randomisation was stratified by visual acuity score at day 0 [⩽44 letters (approximately worse than 20/125) vs ⩾45 letters (approximately 20/125 or better) based on ETDRS chart at 2 m]. [**CIC data removed**].
- *Blinding*: Described as double-masked. Each site had at least one evaluating physician, who was masked to treatment assignment and conducted all ocular assessments, and at least one injecting physician, who was unmasked to treatment assignment and performed ranibizumab or sham injection procedures and active or sham PDT, but was masked to ranibizumab dose. Administration of sham PDT with saline infusion mimicked that of active verteporfin PDT to preserve masking. FA, colour fundus photography and OCT data interpreted at a designated central reading centre. Subjects and other study site personnel masked.
- [**CIC data removed**].
- *Method of data analysis*: States ITT analysis used for efficacy. The population used for safety analyses included randomised subjects who received at least one of the treatments. Missing data were imputed using the last observation carried forward approach. Non-inferiority to control tested using a one-sided testing procedure and a non-inferiority limit. To adjust for multiple comparisons of two ranibizumab dose groups and one control group, a Hochberg–Bonferroni multiple comparison procedure was used. [**CIC data removed**].
- *Sample size/power calculation*: Reported. Based on the analysis of the primary efficacy endpoint for treatment differences between each ranibizumab dose group and the control group. 426 subjects required.
- *Attrition/drop-out*: 386 (91.3%) completed month 12 of study; 36 (8.5%) discontinued from treatment prior to month 12. The most common cause of treatment discontinuation was adverse event. Reasons for discontinuation reported but not extracted.

General comments

- *Generalisability*: Most patients had predominantly classic subfoveal CNV.
- *Outcome measures*: Outcome measures appropriate.
- *Inter-centre variability*: Not reported.
- *Conflict of interests*: Study funded by ranibizumab manufacturers.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Unclear, based on published data [**CIC data removed**]
2. Was the treatment allocation concealed?	Unclear, based on published data [**CIC data removed**]
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Adequate
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and drop-outs completely described?	Adequate

[**CIC data removed**]

Reference and design	Intervention	Participants	Outcome measures
Heier *et al*., 2006[102] FOCUS [**CIC data removed**] USA Phase I/II RCT, single-masked 25 sites [**CIC data removed**] *Funding*: Genentech and Novartis	1. Ranibizumab + PDT: 0.5 mg ranibizumab[a] injection administered monthly (every 30 ± 7 days); starting on day 7 ± 2, + verteporfin PDT 7 days prior to initial study drug administration 2. Sham + PDT: Sham injection administered monthly (every 30 ± 7 days); starting on day 7 ± 2, + verteporfin PDT 7 days prior to initial study drug administration *Duration of treatment*: 24 months (up to 24 injections) *Other interventions used*: Subjects were allowed to receive further verteporfin PDT if deemed necessary by the investigator [**CIC data removed**]	*Target population*: Subjects with predominantly classic lesions with primary or recurrent subfoveal CNV secondary to AMD *Number of participants*: Total randomised: 162 1. Ranibizumab + PDT $n = 106$ 2. Sham + PDT $n = 56$ *Sample attrition/drop-out*: 1 subject randomised to ranibizumab + PDT did not receive ranibizumab injection. 152 subjects remained on study at the end of the first 12 months (94.6 % of sham + PDT group and 93.4% of ranibizumab + PDT group) *Main inclusion criteria for study entry*: aged ⩾50 years; eligible for treatment with PDT using vertepofin in the study eye; primary or recurrent subfoveal CNV lesions secondary to AMD in the study eye; classic CNV ⩾50% of total lesion area; total lesion size ⩽5400 μm; best corrected visual acuity, using ETDRS charts, of 20/40 to 20/320 (Snellen equivalent) in the study eye. [**CIC data removed**] *Exclusion criteria*: Verteporfin treatment in the study eye <3 months prior to study or <7 days in the fellow eye; >3 prior treatments with verterporfin PDT in the study eye within 12 months preceding day 0; prior treatment with external bean radiation therapy or transpupillary thermotherapy in the study eye; previous participation in a clinical trial (for either eye) involving anti-angiogenic drugs; previous intravitreal drug delivery in the study eye; previous subfoveal focal laser photocoagulation in the study eye; laser photocoagulation (juxtafoveal or extrafoveal) in the study eye within 1 month preceding day 0; history of vitrecomy, submacular surgery or other surgical intervention for AMD in the study eye; previous participation in any studies of investigational drugs within 1 month preceding day 0; [**CIC data removed**]	*Primary outcomes*: proportion of subjects losing <15 letters of visual acuity; safety and tolerability [**CIC data removed**] *Length of follow-up*: 12 month data reported here, 24 month data will be reported at a later date

[a] A lyophilised formulation of ranibizumab was used until at least the month 12 visit. [**CIC data removed**].

Characteristics of participants

	Ranibizumab + PDT (*n* = 106)	Sham + PDT (*n* = 56)
Age (years): mean (SD), range	74.7 (7.2)	73.0 (8.7)
Sex: *n* (%)	50–91	51–93
Male	46 (43.4)	30 (53.6)
Female	60 (56.6)	26 (46.4)
Race: *n* (%)		
White	104 (98.1)	56 (100)
Other	2 (1.9)	0
	[**CIC data removed**]	
Visual acuity (2 m):		
No. of letters (0–100): mean (SD)	45.1 (13.8)	48.5 (14.1)
	[**CIC data removed**]	
Approximate Snellen equivalent		
	[**CIC data removed**]	
20/200 or worse: *n* (%)	40 (37.7)	15 (26.8)
	[**CIC data removed**]	
	(*N* = 105)	(*N* = 56)
Predominantly classic: *n* (%)	69 (65.7)	37 (66.1)
Minimally classic: *n* (%)	32 (30.5)	15 (26.8)
Occult without classic: *n* (%)	2 (1.9)	4 (7.1)
Cannot classify: *n* (%)	2 (1.9)	(0.0)
	[**CIC data removed**]	
Any prior therapies for AMD: *n* (%)	81 (76.4)	45 (80.4)
Laser photocoagulation: *n* (%)	20 (18.9)	13 (23.2)
Photodynamic therapy: *n* (%)	48 (45.3)	29 (51.8)
Medication: *n* (%)	1 (0.9)	(0.0)
Supplements: *n* (%)	48 (45.3)	22 (39.3)
Other: *n* (%)	(0.0)	1 (1.8)

Results

Outcomes (at 12 months), starting test distance = 2 m	**Ranibizumab + PDT (*n* = 105)**	**Sham + PDT (*n* = 56)**
Loss of <15 letters from baseline *n* (%)	95 (90.5)	38 (67.9)
	[**CIC data removed**]	
Difference in %	22.6	
	[**CIC data removed**]	
p-Value	<0.001 [**CIC data removed**]	
	[**CIC data removed**]	
Number of letters change from baseline Mean (SD)	4.9 (14.7)	–8.2 (16.3)
	[**CIC data removed**]	
p-Value	<0.001	
Gain of ⩾15 letters from baseline *n* (%)	25 (23.8)	3 (5.4)
	[**CIC data removed**]	
Difference in %	18.5	
	[**CIC data removed**]	
p-Value	0.003	

continued

Outcomes (at 12 months), starting test distance = 2 m	**Ranibizumab + PDT (*n* = 105)**	**Sham + PDT (*n* = 56)**
Snellen equivalent of 20/200 or worse		
***n* (%)**	31 (29.5)	26 (46.4)
	[**CIC data removed**]	
Difference in %	–16.9	
	[**CIC data removed**]	
p-Value	0.006	
Change in the total area of lesion (DA)	(*N* = 102)	(*N* = 56)
Mean (SD)	–0.02 (1.3)	1.8 (2.3)
	[**CIC data removed**]	
p-Value	<0.001	
	[**CIC data removed**]	
Change in the total area of leakage from CNV + intense progressive RPE staining (DA)	(*N* = 102)	(*N* = 56)
Mean (SD)	–2.3 (2.40)	–0.6 (2.80)
	[**CIC data removed**]	
p-Value	<0.001	
Change in the area of serous sensory retinal detachment/subretinal fluid	(*N* = 104)	(*N* = 52)
Mean (SD)	–2.9 (3.0)	–0.60 (4.0)
	[**CIC data removed**]	
p-Value	0.001	
Change in the area of CNV	(*N* = 102)	(*N* = 56)
Mean (SD)	–0.1 (1.5)	1.3 (2.2)
	[**CIC data removed**]	
p-Value	<0.001	
Verteporfin PDT treatment in the study eye during the first treatment year		
Subjects retreated with any verteporfin PDT		
n (%)	29 (27.6)	51 (91.1)
p-Value	<0.001	
	[**CIC data removed**]	

Loss of <15 letters from baseline at 12 months	**Ranibizumab + PDT**	**Sham + PDT**	**Ranibizumab + PDT**	**Sham + PDT**
N	68	37	37	19
		[**CIC data removed**]		
Subgroup analyses were presented in bar charts in the published paper. Not data extracted, as full results were available (and data extracted) from the CIC manufacturer's submission. [**CIC data removed**].				

Adverse effects (safety-evaluable subjects)	Ranibizumab + PDT (*n* = 105)	Sham + PDT (*n* = 56)
Ocular (study eye)		
All adverse events (a): *n* (%)	105 (100)	56 (100.0)
Serious adverse events (b): *n* (%)	16 (15.2)	4 (7.1)
	[**CIC data removed**]	
Endophthalmitis: *n* (%)	2 (1.9)	0 (0.0)
Intraocular inflammation: *n* (%)		
Total: *n* (%)	40 (38.1)	3 (5.4)
Serious: *n* (%)	12 (11.4)	0 (0.0)
	[**CIC data removed**]	
Serious adverse events: *n* (%)	17 (16.2)	11 (19.6)
	[**CIC data removed**]	
(a) Ocular adverse events in the study eye: *n* (%)		
Total with at least one adverse event	105 (100)	56 (100)
Conjunctival haemorrhage	102 (97.1)	54 (96.4)
Macular degeneration	29 (27.6)	28 (50.0)
Eye pain	34 (32.4)	11 (19.6)
Retinal haemorrhage	16 (15.2)	22 (39.3)
Vitreous floaters	30 (28.6)	3 (5.4)
Eye irritation	15 (14.3)	13 (23.2)
Vision blurred	21 (20.0)	5 (8.9)
Foreign body sensation in eyes	15 (14.3)	8 (14.3)
Iritis	20 (19.0)	3 (5.4)
Visual acuity reduced	14 (13.3)	9 (16.1)
Vitritis	20 (19.0)	2 (3.6)
Iridocyclitis	21 (20.0)	0 (0.0)
Retinal detachment	11 (10.5)	9 (16.1)
Visual disturbance	16 (15.2)	4 (7.1)
Intraocular pressure increased	17 (16.2)	1 (1.8)
Blepharitis	16 (15.2)	1 (1.8)
Vitreous detachment	14 (13.3)	3 (5.4)
Subretinal fibrosis	9 (8.6)	8 (14.3)
	[**CIC data removed**]	
Photopsia	2 (1.9)	7 (12.5)
	[**CIC data removed**]	
(b) Serious ocular adverse events in the study eye: *n* (%)		
Total with at least one serious adverse event	16 (15.2)	4 (7.1)
Iridocyclitis	7 (6.7)	0 (0.0)
Uveitis	4 (3.8)	0 (0.0)
Vitreous haemorrhage	2 (1.9)	2 (3.6)
Endophthalmitis	2 (1.9)	0 (0.0)
Choroidal haemorrhage	0 (0.0)	1 (1.8)
Choroidal neovascularisation	0 (0.0)	1 (1.8)
Iritis	1 (1.0)	0 (0.0)
Macular degeneration	0 (0.0)	1 (1.8)
Retinal tear	1 (1.0)	0 (0.0)
Visual acuity reduced	1 (1.0)	0 (0.0)
Vitritis	1 (1.0)	0 (0.0)
	[**CIC data removed**]	

Methodological comments

- *Allocation to treatment groups*: The randomisation schedule was generated by a designee of Genetech using a static randomisation method with an adequate block size to maintain the 2:1 ratio between ranibizumab and sham injection assignment.
- *Blinding*: An unmasked investigator, hospital pharmacist or registered nurse prepared the ranibizumab or sham injection. The visual acuity examiner, fundus photographer and study subject were masked to treatment assignment. Fluorescein angiograms and colour fundus photographs were interpreted at a designated masked central reading centre. Sham and ranibizumab injections were performed by ophthalmologists unmasked to treatment assignment.
- [**CIC data removed**].
- *Method of data analysis*: Safety and efficacy comparisons only included subjects who received at least one dose of study drug/sham, so were not carried out on an ITT basis. One ranibizumab patient was excluded from all analyses as he/she never received a study dose. Comparisons were based on subject randomisation assignment for efficacy endpoints and on treatment actually received for safety endpoints. All statistical tests were two-sided at the $\alpha = 0.05$ level. The last observation carried forward approach was used for missing data imputation on visual acuity endpoints. Pearson's χ^2 test was used to compare the two groups for the primary efficacy endpoint. [**CIC data removed**].
- *Sample size/power calculation*: [**CIC data removed**]. The sample size [**CIC data removed**] gave the study 80% power to detect a difference between the 2 treatment groups in the proportion of subjects who lost <15 letters at month 12 compared with baseline. This assumes a rate of 86% for the ranibizumab group and a rate of 67% for the control group (two-sided Pearson's χ^2 test and an α level of 0.05).
- *Attrition/drop-out*: 5 (8.9%) of sham + PDT subjects and 12 (11.3%) of ranibizumab + PDT subjects discontinued treatment prior to month 12. The primary reason for treatment discontinuation and study discontinuation was adverse event. Adverse event was reason for treatment discontinuation in 7 (6.6%) ranibizumab + PDT subjects and 2 (3.6%) sham + PDT subjects. Adverse event was reason for study discontinuation in 3 (2.8%) ranibizumab + PDT subjects and 1 (1.8%) sham + PDT subjects.

General comments

- *Generalisability*: Subjects with predominantly classic lesions with primary or recurrent subfoveal CNV secondary to AMD were enrolled in the study.
- *Outcome measures*: Outcome measures appropriate.
- *Inter-centre variability*: Not reported. Analysis of efficacy end-point results was not performed by study site.
- *Conflict of interests*: Study funded by ranibizumab manufacturers.

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	Adequate
2. Was the treatment allocation concealed?	Unknown
3. Were the groups similar at baseline in terms of prognostic factors?	Reported
4. Were the eligibility criteria specified?	Adequate
5. Were outcome assessors blinded to the treatment allocation?	Adequate
6. Was the care provider blinded?	Inadequate
7. Was the patient blinded?	Adequate
8. Were the point estimates and measure of variability presented for the primary outcome measure?	Adequate
9. Did the analyses include an ITT analysis?	Inadequate
10. Were withdrawals and drop-outs completely described?	Adequate

Appendix 5

List of selected excluded studies

Capone A. Intravitreous pegaptanib sodium (Macugen) in patients with age-related macular degeneration (AMD): safety and pharmacokinetics. *Invest Ophthalmol Vis Sci* 2005; 46.
Reason: not an RCT.

D'Amico DJ, Bird AC. VEGF inhibition study in ocular neovascularization-1 (VISION-1): safety evaluation from the pivotal Macugen (TM) (pegaptanib sodium) clinical trials. *Invest Ophthalmol Vis Sci* 2004;**45**:2363.
Reason: duplicates data from included study.

Heier JS, Antoszyk AN, Pavan PR, Leff SR, Rosenfeld PJ, Ciulla TA, *et al*. Ranibizumab for treatment of neovascular age-related macular degeneration: a phase I/II multicenter, controlled, multidose study. *Ophthalmology* 2006;**113**:633–42.
Reason: not an RCT.

Gonzales CR, VEGF inhibition study in ocular neovascularization. Enhanced efficacy associated with early treatment of neovascular age-related macular degeneration with pegaptanib sodium: an exploratory analysis. *Retina* 2005;**25**:815–27.
Reason: not an RCT.

Gragoudas ES, Adamis AP, Feinsod M. Pegaptanib and age-related macular degeneration – reply. *N Engl J Med* 2005;**352**:1721.
Reason: not an RCT (correspondence relating to included RCT).

Gragoudas ES. VEGF inhibition study in ocular neovascularization-1 (VISION-1): efficacy results from phase II/III Macugen (TM) (pegaptanib sodium) clinical trials. *Invest Ophthalmol Vis Sci* 2004;**45**:2364.
Reason: duplicates data from included study.

Heier JS, Rosenfeld PJ, Antoszyk AN, Hantsbarger G, Kim R, Shams N. Long-term experience with lucentis (ranibizumab) in patients with neovascular age-related macular degeneration (AMD). *Invest Ophthalmol Vis Sci* 2005;**46**:E-abstract 1393.
Reason: not an RCT.

Rakic JM, Blaise P, Foidart JM. Pegaptanib and age-related macular degeneration. *N Engl J Med* 2005; **352**:1720–1.
Reason: Letter to Editor.

Schuman S, Rogers AH, Duker JS, Reichel E, Baumal CR. Six-week outcomes after pegaptanib. *Ophthalmology* 2006;**113**:501.
Reason: Letter to Editor.

Appendix 6

List of eligible abstracts

The following abstracts were eligible for inclusion in the review but did not present sufficient details to allow an appraisal of the methodology and assessment of results.

Brown DM, Shapiro H, Schneider S, ANCHOR study group. Subgroup analysis of first-year results of ANCHOR: a phase III, double-masked, randomized comparison of ranibizumab and verteporfin photodynamic therapy for predominantly classic choroidal neovascularization related to age-related macular degeneration. *Invest Ophthalmol Vis Sci* 2006; **47**:2963.

Chang TS, Fine JT, Bressler N. Self-reported vision-specific quality of life at 1 year in patients with neovascular age-related macular degeneration in 2 phase III randomized clinical trials of ranibizumab (Lucentis). *Invest Ophthalmol Vis Sci* 2006;**47**:5252.

Heier JS, Shapiro H, Singh AA Sr. MARINA study group. Randomized, controlled phase III study of ranibizumab (Lucentis) for minimally classic or occult neovascular age-related macular degeneration: two-year efficacy results of the MARINA study. *Invest Ophthalmol Vis Sci* 2006;**47**:2959.

Heier JS, Sy JR, McCluskey ER, rhuFab V2 study group. RhuFab V2 in wet AMD – 6 month continued improvement following multiple intravitreal injections. *Invest Ophthalmol Vis Sci* 2003;**44**:972.

Miller JW, Shapiro H, Acharya N, MARINA study group. Randomized, controlled phase III study of ranibizumab (Lucentis) for minimally classic or occult neovascular age-related macular degeneration: two-year safety results of the MARINA study. *Invest Ophthalmol Vis Sci* 2006;**47**:3539.

Appendix 7

List of ongoing studies

Pegaptanib

- The VISION study is ongoing, with further results due to be reported in 2008.
- Protocol EOP1009 – a Phase II prospective, randomised, double-masked, sham-controlled, dose-ranging, multi-centre trial to assess the effect of pegaptanib sodium on foveal thickening in patients with exudative subfoveal ARMD. Expected completion date is June 2006.

The following records on the ClinicalTrials.gov website would not meet our inclusion criteria (due to lack of a usual care control arm) but may be of interest:

- "A Phase IIIb/IV randomized, double-masked, active-controlled, dose-ranging, multi-center comparative trial, in parallel groups, to compare the safety and efficacy of intravitreal injections of pegaptanib sodium (Macugen) given every 6 weeks for 102 weeks, to pegaptanib sodium plus photodynamic therapy (PDT) with Visudyne, in patients with exudative age-related macular degeneration (AMD)." Study start March 2005, expected completion in October 2008. ClinicalTrials.gov identifier: NCT00134667.
- "An exploratory randomized, double-masked, multi-center comparative trial, in parallel groups, to explore the safety and efficacy of three different doses of intravitreous injections of pegaptanib sodium (anti-VEGF pegylated aptamer) given every 6 weeks for 102 weeks, in patients with subfoveal neovascular age-related macular degeneration (AMD)." Study start April 2006, expected completion June 2009. ClinicalTrials.gov identifier: NCT00312351.

Ranibizumab

- Year 2 results for the ANCHOR trial are due in the third quarter of 2006.
- PROTECT: a Phase II open-label combination treatment trial, in patients with occult or predominantly classic neovascular AMD. No control group. Objectives: to evaluate the safety of the same-day administration of PDT with verteporfin and an injection of 0.5 mg of ranibizumab. Completion date not given.
- EXCITE: a Phase IIIb randomised, double-masked, active-controlled, multi-centre study, in patients with subfoveal CNV secondary to AMD. No control group. Objectives: efficacy and safety of ranibizumab administered as three consecutive monthly injections of 0.3 or 0.5 mg, followed by quarterly injections (alternative dosing) of the same doses, respectively, versus monthly 0.3-mg injections. Completion date not given.
- HORIZON: a Phase III open-label, multi-centre extension study, in patients with subfoveal CNV secondary to AMD. Sham injection control. Objectives: to investigate the long-term safety, tolerability and efficacy of multiple intravitreal ranibizumab. Completion date not given.
- SAILOR: a Phase IIIb single-masked, 1-year multi-centre study (ClinicalTrials.gov identifier: NCT00299078). Ranibizumab in naïve and previously treated subjects with subfoveal CNV secondary to AMD. About 5000 subjects will be enrolled and randomised 1:1 for 0.3 and 0.5 mg ranibizumab (no 'usual care' study arm). The primary outcome is the incidence of serious adverse events. Study start March 2006. Completion date not given.
- SUSTAIN: a Phase IIIb open-label, multi-centre study in patients with subfoveal CNV secondary to AMD. No control group. Objectives: efficacy and safety of ranibizumab administered as three consecutive monthly injections followed by PRN re-treatment, in subjects treated with 0.3 mg intravitreal ranibizumab. Completion date not given.
- SUMMIT Mont-Blanc: a 12-month randomised, double-masked, controlled, multi-centre, Phase II study assessing the safety and efficacy of verteporfin PDT administered in conjunction with ranibizumab versus ranibizumab monotherapy in patients with subfoveal choroidal neovascularisation secondary to AMD. Start date March 2007, target of 250 patients.

Appendix 8

Critique of industry submissions

Pfizer – pegaptanib sodium (Macugen)

Pegaptanib is a selective VEGF inhibitor that specifically targets VEGF16, to suppress pathological neovascularisation. Pegaptanib is indicated for the treatment of neovascular (wet) AMD. The licensed dose is 0.3 mg administered by intravitreal injection once every 6 weeks.

Submitted

One report (80 pp. including appendices); one spreadsheet containing a cost-effectiveness model; CIC checklist. An unpublished paper [**CIC data removed**] and papers by Chakravarthy and colleagues and D'Amico and colleagues were available by request.

Clinical effectiveness

The manufacturer states that a systematic review was conducted in 2005 which was updated for the submission to NICE in May 2006. The search strategy for MEDLINE and EMBASE is provided in an appendix of the submission, but no further details of the systematic review are given (e.g. inclusion/exclusion criteria or a QUOROM flow chart). Only one trial (the VISION study) was identified, so meta-analysis was not appropriate. The manufacturer assessed the quality of the included study using the JADAD criteria, tabulated data from the study and provided a narrative summary of the evidence. The manufacturer's submission cites a paper by Gonzales (2005) in a list of publications related to the VISION study. However, there is no further reference to this paper, and it is not included in the bibliography. The Gonzales paper was identified in the SHTAC systematic review, but the paper did not meet our inclusion criteria as it only reports exploratory analyses of data from the VISION study.

RCTs included in the review

The VISION study is the only RCT included in the manufacturer's submission. It consisted of two separate RCTs which were combined for analysis. Publications from VISION are:

- year 1 safety and effectiveness (Gragoudas and colleagues)
- year 2 safety (D'Amico and colleagues)
- year 2 effectiveness (Chakravarthy and colleagues)
- [**CIC data removed**].

Summary of key outcome measures

The VISION trial's primary efficacy outcome measure was the proportion of responders, defined as patients losing <15 letters of visual acuity. The submission reported year 1 results for the 0.3-mg dose group compared with sham injection, and year 2 results were reported for those who were re-randomised to continue 0.3 mg pegaptanib for 2 years compared with those who were re-randomised to receive usual care.

Patients losing <15 letters of visual acuity (responders)

Year 1 results showed a significantly higher proportion of responders in the 0.3-mg pegaptanib group than in the control group. Those who continued to receive 0.3 mg pegaptanib in the second year were significantly more likely to be classified as responders than those who discontinued 0.3 mg pegaptanib treatment after 1 year.

Maintenance or gain in visual acuity

Significantly more people in the 0.3-mg pegaptanib group had a maintenance or gain of ≥0 letters at the end of year 1.

Mean changes in visual acuity

Mean changes in visual acuity were significantly better for the 0.3-mg pegaptanib group than for the control group at the end of year 1.

Proportion of patients gaining ≥5, ≥10 or ≥15 letters of visual acuity

Significantly more people in the 0.3-mg pegaptanib group than those in the sham injection group gained ≥5, ≥10, or ≥15 letters of visual acuity.

Severe vision loss (loss of ≥30 letters)

Significantly fewer people who received 0.3 mg pegaptanib reported severe vision loss at the end of year 1 than those who received sham injection. Severe vision loss was also significantly less likely to be reported among those who continued 0.3 mg pegaptanib for a second year compared with those who received usual care.

Adverse events
All adverse events and serious adverse events were recorded as outcome measures. These are all discussed in detail in the TAR. The submission reports that adverse events were transient and of mild to moderate severity.

Health-related quality of life
Four of the NEI-VFQ 25 subscales were prospectively designated as primary outcomes: Near Vision, Distance Vision, Role Limitation and Dependency. The Distance Vision and Role Limitations domains were consistently better with pegaptanib treatment across all doses. The least-squares mean score difference between the 0.3-mg and usual care groups on Distance Vision does not appear to be statistically significant (4.3, $p = 0.059$). Analysis of responders and non-responders was reported to have showed a statistically significant benefit for the responders in the four primary domains, but data are not presented.

'Added value' of submission (i.e. data presented that are not currently in the public domain)
The manufacturer's submission is primarily based on three published papers. Data from an additional, unpublished paper [**CIC data removed**] is included in the manufacturer's submission. The manufacturer supplied the [**CIC data removed**] paper at SHTAC's request. [**CIC data removed**].

The conclusion presented in the submission, namely that pegaptanib is significantly more effective than usual care in preserving visual acuity, is supported by the conclusions of SHTAC's systematic review.

Cost-effectiveness
See the section 'Pfizer submission to NICE:[105] cost-effectiveness analysis' (p. 48) for discussion of the Pfizer cost-effectiveness model.

Novartis – ranibizumab (Lucentis)

Ranibizumab is not currently licensed for the treatment of AMD in the UK, although the manufacturer expects that it will receive its licence during the appraisal process.

Submitted
One report (50 pp.); 12 appendices; one spreadsheet containing a Markov cost-effectiveness model; CIC checklist. The 12 appendices included the Health Economics final report (91 pp.) and the following trial reports: MARINA year 1 report (194 pp.); MARINA year 2 report (177 pp.); ANCHOR (198 pp.); [**CIC data removed**]. Although the Novartis submission report itself was only 50 pages long, the extensive trial reports included as appendices increased it to an extremely lengthy size.

Clinical effectiveness
The manufacturer did not conduct a systematic review, and the submission is based on two recently published RCTs (MARINA and ANCHOR) and one unpublished RCT (PIER) of ranibizumab. A fourth Phase I/II RCT (FOCUS) was provided by the manufacturer but not discussed in the submission in any detail. This study has since been published, and is included in the TAR. [**CIC data removed**].

RCTs included in the review
- ANCHOR
- MARINA
- PIER (unpublished)
- FOCUS (unpublished at the time of submission) was also briefly discussed, but results were not tabulated.

Summary of key outcome measures
Patients losing <15 letters of visual acuity (responders)
The ANCHOR, MARINA and FOCUS [**CIC data removed**] data are discussed in the submission. They reported the proportion of patients who lost fewer than 15 letters of visual acuity. Results were significantly better for both 0.3- and 0.5-mg doses compared with sham injection or PDT at the 1-year follow-up in the [**CIC data removed**], ANCHOR and FOCUS trials, and at both years 1 and 2 in the MARINA trial.

Mean changes in visual acuity
Results were significantly better for both 0.3- and 0.5-mg doses compared with sham injection or PDT at the 1-year follow-up in the [**CIC data removed**], ANCHOR and FOCUS trials, and at both years 1 and 2 in the MARINA trial.

Proportion of patients gaining ⩾15 letters of visual acuity
[**CIC data removed**]. Results were significantly better for both 0.3- and 0.5-mg doses compared with sham injection or PDT at the 1-year follow-up in the ANCHOR and FOCUS trials, and at both years 1 and 2 in the MARINA trial.

Proportion losing >30 letters (severe vision loss)
The submission reports that for predominantly classic lesions (ANCHOR) there was no severe

vision loss in ranibizumab-treated patients and for minimally classic and occult lesions (MARINA) the incidence was approximately 1%. [**CIC data removed**]. The SHTAC team made an *a priori* decision to extract only primary and secondary outcomes (plus outcomes listed in the SHTAC protocol) from the extensive CIC study reports.

Proportion of patients deteriorating to legal blindness

Patients treated with either 0.3 or 0.5 mg were significantly less likely to deteriorate to legal blindness compared with those in the sham injection or PDT groups at the 1-year follow-up in the [**CIC data removed**], ANCHOR and FOCUS trials, and at both years 1 and 2 in the MARINA trial.

Angiographic changes

Significantly better angiographic changes were reported for both 0.3- and 0.5-mg doses compared with sham injection or PDT at the 1-year follow-up in the [**CIC data removed**], ANCHOR and FOCUS trials, and at both years 1 and 2 in the MARINA trial.

Health-related quality of life

[**CIC data removed**]. MARINA and ANCHOR reported significant differences between both the 0.3- and 0.5-mg dose groups and sham/PDT control groups for distant activities, near activities and vision-specific dependency subscales. FOCUS did not report this outcome.

Adverse events

Adverse events were reported by the trials, and these are discussed in the TAR.

'Added value' of submission

The RCTs provided by the manufacturer form the evidence base for ranibizumab AMD treatment. [**CIC data removed**].

The manufacturer's conclusion that ranibizumab improves visual acuity is supported by the conclusions from SHTAC's systematic review. The manufacturer states that the licensed dose of 0.5 mg results in a clinically meaningful improvement of 15 or more letters in over one-third of patients. Although this is true of the patients in the two pivotal trials (MARINA and ANCHOR), results were not as good in the FOCUS trial, which combined ranibizumab with PDT (23.8%) [**CIC data removed**].

Cost-effectiveness

See the section 'Novartis submission to NICE:[91] cost-effectiveness analysis' (p. 54) for discussion of the Novartis cost-effectiveness model.

Appendix 9

Ocular adverse events in study eye: CIC information from ranibizumab studies

Adverse event (AE)	Number of patients (%)								
	MARINA (24-month data) Lesion type: occult/MC			ANCHOR Lesion type: PC			[CIC data removed]	FOCUS Lesion type: PC/MC	
	0.3 mg (*n* = 238)	0.5 mg (*n* = 240)	Sham (*n* = 238)	0.3 mg + sham PDT (*n* = 140)	0.5 mg + sham PDT (*n* = 140)	Sham + PDT (*n* = 143)		0.5 mg + PDT (*n* = 105)	Sham + PDT (*n* = 56)
All AE (a)								105 (100)	56 (100)
Serious AE (b)				[CIC data removed]				16 (15.2)	4 (7.1)
[CIC data removed]									
Endophthlamitis	2 (0.8)	3 (1.3)	0	0	1 (0.7)	0	[CIC data removed]	2 (1.9)	0 (0.0)
Intraocular inflammation									
Total				[CIC data removed]				40 (38.1)	3 (5.4)
[CIC data removed]									
(a) Ocular AE[a]									
Conjunctival haemorrhage								102 (97.1)	54 (96.4)
Macular degeneration								29 (27.6)	28 (50.0)
Retinal haemorrhage								16 (15.2)	22 (39.3)
Visual acuity reduced								14 (13.3)	9 (16.1)
Eye pain								34 (32.4)	11 (19.6)
Intraocular pressure increased								17 (16.2)	1 (1.8)
Vitreous floaters				[CIC data removed]				30 (28.6)	3 (5.4)
Vitreous detachment								14 (13.3)	3 (5.4)
Subretinal fibrosis								9 (8.6)	8 (14.3)
Vitritis								20 (19.0)	2 (3.6)
[CIC data removed]									
Eye irritation								15 (14.3)	13 (23.2)
Foreign body sensation in eyes								15 (14.3)	8 (14.3)
(b) Most common ocular serious AE									
Reduced visual acuity				[CIC data removed]				1 (1.0)	0 (0.0)
Retinal haemorrhage				[CIC data removed]					

MC, minimally classic lesion; PC, predominantly classic lesion.
[CIC data removed]

Appendix 10

Non-ocular adverse events: CIC information from ranibizumab studies

Adverse event (AE)	**Number of patients (%)**								
	MARINA (24-month data) Lesion type: occult/MC			**ANCHOR Lesion type: PC**			[**CIC data removed**]	**FOCUS Lesion type: PC/MC**	
	0.3 mg (*n* = 238)	**0.5 mg (*n* = 240)**	**Sham (*n* = 238)**	**0.3 mg + sham PDT (*n* = 140)**	**0.5 mg + sham PDT (*n* = 140)**	**Sham + PDT (*n* = 143)**		**0.5 mg + PDT (*n* = 105)**	**Sham + PDT (*n* = 56)**
				[**CIC data removed**]					
Non-ocular events									
[**CIC data removed**]									
Serious AE				[**CIC data removed**]				17 (16.2)	11 (19.6)
[**CIC data removed**]									
Deaths	5 (2.1)	6 (2.5)	6 (2.5)	3 (2.2)	2 (1.4)	2 (1.4)	[**CIC data removed**]		

MC, minimally classic lesion; PC, predominantly classic lesion.

Appendix 11

Summary of measures reported in studies included in the review of quality of life in AMD

Measure of quality of life	Description
General	
Instrumental Activities of Daily Living Index	Assesses functional independence, examines competence in managing one's own affairs and independent living. Participants' ability to carry out daily activities is assessed with the domains of managing medications, shopping for necessities, managing finances, using the telephone, maintaining a household and preparing meals. Possible responses to each item are yes, yes with difficulty and no. A composite Instrumental Activities of Daily Living Index score is created by averaging the responses to 12 items. Possible scores range from 1 to 3, with 1 representing complete independence in these activities and 3 indicating inability to carry out any of the tasks[56]
Self-Rated General Health Status	This self-evaluation of overall health status has been widely used because it provides a succinct way of summarising diverse aspects of health status from the individual's perspective. Participants were asked to rate their overall health as excellent, very good, good fair or poor[56]
Profile of Mood States (POMS)	65-item, self-report symptom inventory designed to assess mood state in the past week, which has been validated in elderly people. Participants respond to each item on a five-point scale, ranging from 'not at all' to 'extremely'. There are 6 subscales (tension/anxiety, depression/dejection, vigour/activity, confusion/bewilderment, fatigues/inertia and anger/hostility) and a total score that ranges from 0 to 232[56,149,150]
Hospital Anxiety and Depression Scale (HADS)	Identifies symptoms of anxiety and depression among outpatients. It consists of 14 items to form two summary scales, the anxiety scale (7 items) and the depression scale (7 items). The anxiety scale consists of items on tension, fear of the future, worries, inability to relax, restlessness and panic. The depression scale consists of items on decreased enjoyment, sense of humour, cheerfulness and optimism. Each item is scored 0 to 3; the scores from all 7 items of such scale are summed to calculate a scale score. HADS scores range from 0 to 21, with a higher score representing more symptoms of anxiety or depression. It is also recommended using categories of 0 to 7, 8 to 10, and 11 or higher to define 'non-cases', 'doubtful cases' and 'definite cases' of anxiety or depression[61]
Structured Clinical Interview for the *Diagnostic and Statistical Manual*, 4th Edition	A semi-structured, clinician administered interview for making major *Diagnostic and Statistical Manual* (4th edition) Axis I diagnoses, it includes an introductory overview followed by 9 modules, 7 of which represent the major Axis I diagnostic classes. It can be adapted for use in studies in which particular diagnoses are of interest. Output is recorded as presence or absence of each disorder being considered, for current episode (past month) and lifetime occurrence[55]
SF-36 health survey	A 36-item generic measure of health-related QoL designed for chronically ill patients, which addresses 8 general health subscales: physical functioning, role limitations due to physical problems, bodily pain, general health, energy/vitality, social functioning, role limitations due to emotional problems and mental health. The answers to the questions are then summarised into the physical composite score (PCS) and mental composite score (MCS). The scores are then transformed to a norm-based scoring system by the addition of a population-based constant, resulting in a 100-point scale in which 100 represents the best possible score and 0, the worst[61,64,121,127,151]
SF-12 health survey	A short, validated version of the SF-36 to evaluate the participants' physical and mental health. It is composed of 12 questions that address the same 8 general health subscales as in SF-36[63,65]

continued

Measure of quality of life	Description
Quality of well-being (QWB)	A comprehensible measure of health-related QoL that includes functional scales for mobility, physical activity and social activity. In addition, the QWB scale includes a section on symptoms and problems. The scoring system for the QWB scale applies estimates of QoL to combinations of functioning and symptoms. The quality estimates were obtained from an independent panel of judges. The scoring system places each case on a continuum ranging from 0.0 for dead to 1.0 for optimum function with no symptoms[56]
Visual-related	
Activities of Daily Vision Scale	This consists of 21 multiple-response items representing common visual activities categorised into five subscales: night driving, daytime driving, distance vision activities that do not require driving, near-vision activities and activities subject to glare. Additionally, the subscales can be combined into an overall visual function score. All scale scores range from 0 to 100, where 100 represents no difficulty and 0 means the activities are no longer performed because of visual impairment. Items are structured such that if the subject indicates that an activity is difficult because of limitations not caused by vision, the item does not contribute to the scale score. Similarly, if a subject does not perform an activity, that item would not be rated for degree of difficulty[127]
MacDQoL	An individualised measure of the impact of MD on QoL, based on the design of the Audit of Diabetes Dependent Quality of Life (ADDQoL). It begins with two overview items, measuring (a) present QoL (In general, my present quality of life is:), scored from +3 (excellent), through 0 (neither good nor bad) to –3 (extremely bad), (b) MD-specific QoL (If I did not have MD, my quality of life would be:), scored from –3 (very much better) through 0 (the same) to +1 (worse). There are 26 domain-specific items and each has questions asking about both the impact of MD on that aspect of life and the importance of the aspect of life to QoL. For the domain specific items, impact scores (from –3 to +1) are multiplied by importance scores (from 0 to 3) to give a weighted impact score for each domain of between –9 and +3. The use of impact and importance scores permits an estimation of the impact of MD on an individual's QoL, not merely on function. A final item asks the respondent whether MD affects his/her life in any ways not already covered, with a space to write a response for people who reply 'yes'[126]
National Eye Institute Visual Function Questionnaire (NEI-VFQ)	Three versions of the NEI-VFQ have been published, containing 25, 39 and 51 items. A 51-item questionnaire was originally devised in the USA from focus groups of people with major causes of eye disease. The questionnaire was later shortened to 25 items, based predominantly on the responses from those with eye disease and visual impairment, and also from a minority group without eye disease. The 25-item version and the appendix of additional questions have been published (http://rand.org/health/survey/vfq25). The 25-item NEI-VFQ and the appendix could be combined to create a 29-item NEI-VFQ. These items could be divided to create 12 subscale scores and an overall score. They are general health, general vision, ocular pain, near-vision activities, distance-vision activities, vision-specific social functioning, vision-specific mental health, vision-specific role difficulties, dependency due to vision, driving, peripheral vision and colour vision. The overall score and each subscale score range from 0 to 100, with a higher score representing better visual function[61,63,121–125,149,152,153]
AMD Self-Efficacy Questionnaire	As conceptualised in Bandura's social cognitive model, self-efficacy is a person's assessment of his or her abilities and encompasses the degree of certainty and underlying expectations about his or her ability to succeed in a given circumstance. Based on this theory, a self-efficacy questionnaire had been developed to address issues salient to AMD and shown to be reliable. The scale ranges from 1 to 100, with high scores indicating that participants feel very confident they can accomplish the task related to AMD vision loss described in the question. Higher scores indicate greater self-efficacy[149]
Visual Function Questionnaire 14-item scale (VF-14)	Measures difficulty in performing 14 vision-dependent everyday activities: reading small print; reading a newspaper or book; reading a large-print book or numbers on a telephone; recognising people nearby; seeing steps, stairs or curbs; reading traffic, store or street signs; doing fine handiwork; writing cheques or completing forms; playing games; playing sports; cooking; watching television; driving during the day; and driving at night. Each item is assigned a score: 4 for 'no difficulty', 3 for 'a little difficulty', 2 for 'a moderate amount of difficulty', and 1 for 'a great deal of difficulty'[128]

continued

Measure of quality of life	Description
Daily Living Tasks Dependent on Vision (DLTV)	A 33-item questionnaire divided into 4 dimensions covering tasks relating to visual function, with and without the use of magnification aids, and general aspects of visual health. In the majority of the instances, each item is scored on a 4-point ordered categorical scale where the minimum possible score is 1 (inability to do the task) and the maximum is 4 (no difficulty with the task). The scores from each item within a dimension are averaged and converted into a scale between 0 and 100. Where a task is not applicable, this item is not scored and the percentage DLTV score is adjusted for the number of items answered[151]
Impact of Vision Impairment (IVI) questionnaire	A validated 32-item questionnaire aims to describe vision-specific restriction to participation (handicap) that is not captured in clinical measures (impairment) or self-reported or assessed performance (disability). It has 5 domains, namely leisure and work, consumer and social interaction, household and personal care, mobility and emotional reaction to vision loss. Responses to the IVI items are rated as 'not at all' (0), 'rarely' (1), 'a little' (2), 'a fair amount' (3), 'a lot' (4) and 'can't do because of eyesight' (5)[65]
Time trade-off	Respondents were asked how many additional years they had expected to live and how many of those years (if any) they would trade in return for perfect vision in each or both eyes. The utility value was then calculated by subtracting from 1.0 the number of years given up divided by the number of additional years they had expected to live[62,113,129,143]
Standard gamble	Respondents were presented with the scenario of a treatment that when it worked, always worked perfectly and restored permanent perfect vision in each or both eyes. However, when it did not work the alternative would be immediate death. They were asked the highest risk of dying (in percentage) they would be willing to take (if any) before refusing the treatment. The utility value was calculated by subtracting from 1.0 the percentage risk the respondent was willing to assume before refusing treatment[113,129]

MD, macular degeneration; QoL, quality of life.

Appendix 12

Critical appraisal checklist of economic evaluation in Pfizer submission

Item	Critical appraisal	Reviewer comment
Is there a well-defined question?	✓	Cost-effectiveness of 0.3 mg pegaptanib versus usual care for treatment of patients with subfoveal neovascularisation in better-seeing eye
Is there a clear description of alternatives?	✓	Pegaptanib at licensed dosage, with 'minimal' PDT (18.11% with mean treatments of 1.71 in year 1 and 6.77% with mean treatments of 1.00 in year 2) versus usual care consisting of supportive care (visual rehabilitation and provision of low-vision aids) with PDT (20.59% with mean treatments of 2.051 in year 1 and 8.82% with mean treatments of 1.54 in year 2) for patients with predominantly classic lesions
Has the correct patient group/ population of interest been clearly stated?	✓	Trial population had best-corrected visual acuity between 6/12 and 6/96 in treated eye and 6/240 or better in other eye and sub-retinal haemorrhage comprising ≤50% total lesion size and total lesion size up to 12 DA 26% predominantly classic lesions 36% minimally classic 39% occult lesions with no classic component Patients could have had prior PDT These are patients covered by the indication SPC for pegaptanib, but how does this compare with presenting cases in England and Wales?
Is the correct comparator used?	?	Appropriate if analysing presenting cohort of ARMD patients and treating irrespective of lesion type. Ideally distinguish subtypes of ARMD? Separate analysis of pegaptanib vs supportive care where PDT not appropriate, then supportive care plus PDT versus pegaptanib where PDT appropriate
Is the study type reasonable?	✓	Cost–utility study appropriate – required for NICE reference case, but also principal impact of disease progression is loss of vision (measured by visual acuity) and valued by utilities for respective health states. Some impact of disease progression on mortality once progression to blindness (visual acuity 6/60) Two base case scenarios presented base on maximum 2 years of treatment and alternative stopping rules: Scenario A: discontinue when visual acuity falls below 6/96 or for those with severe loss (greater than 6 Snellen lines) at end of year 1 Scenario B: discontinue when visual acuity falls below 6/60 or for those with severe loss (greater than 6 Snellen lines) at end of year 1
Is the perspective of the analysis clearly stated?	✓	NHS and PSS – required for NICE reference case
Is the perspective employed appropriate?	✓	Yes. Incorporates direct costs of treatment/monitoring, managing main adverse effects of treatment, PDT co-administration, health sector costs of disease progression (fractures and depression), costs of vision aids and rehabilitation, costs of residential and nursing care and also blind registration
Is effectiveness of the intervention established?	✓	Direct clinical trial evidence – bespoke patient-level data analysis eliciting survival functions for gain and loss of visual acuity

continued

Item	Critical appraisal	Reviewer comment
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	✓	10 years – approximate lifetime for patient age 75 years. Median age in EOP1003; EOP1004 trials reported in SPC was 77 years. Variable time horizons considered in sensitivity analysis
Are the costs and consequences consistent with the perspective employed? *Covered in detail in questions below*	✓	Costs consistent with NHS and PSS perspective. Principally valued through NHS reference costs or PSSRU Unit Costs. Consequences presented as vision years (cut-off at 6/60) and quality-adjusted life expectancy using utility weights from a published source
Is differential timing considered?	✓	Costs and outcomes discounted at 3.5%
Is incremental analysis performed?	✓	Average costs and consequences for usual care and pegaptanib reported and incremental cost-effectiveness for pegaptanib versus usual care
Is sensitivity analysis undertaken and presented clearly?	✓	One-way sensitivity analysis Reduce time horizon from 10 to 3 years Discount rates (0 and 6%) Alternative extrapolation models (Weibull or exponential, versus log-logistic) Use utilities elicited using standard gamble rather than TTO All patients not explicitly discontinuing treatment have drug in each cycle (rather than use mean observed treatments) Increase number of FAs (from one on initiation of treatment) for pegaptanib only Use upper and lower limits for NHS and PSS services to visually impaired reported by Meads and colleagues[40] Telephone consultation for monitoring adverse events 'accounting for prior PDT' PSA parameters Mean number of administrations of pegaptanib (mean and SD using normal distribution) Transition probabilities (mean, standard error and covariance of VISION survival model parameter estimates – use Cholesky decomposition) Utility weights (beta using mean and SD from published study) Limited sensitivity analysis on costs Maybe do analysis for costs and uptake of NHS and PSS services to visually impaired for each item separately in addition to all together Possible sensitivity analysis tests on model structure?

PSA, probabilistic sensitivity analysis; PSSRU, Personal Social Services Research Unit.

Appendix 13

Critical appraisal checklist of economic evaluation in Novartis submission

Item	Critical appraisal	Reviewer comment
Is there a well-defined question?	✓	
Is there a clear description of alternatives?	✓	Bevacizumab (Avastin) has been used as off-label medication in clinical practice. It has not been included in the evaluation as it is not licensed for the indication under this assessment The manufacturer of anecortave acetate (Retaane) had withdrawn from its regulatory application, so it was removed from the alternatives list
Has the correct patient group/population of interest been clearly stated?	✓	
Is the correct comparator used?	✓	PDT with verteporfin (Visudyne) and best supportive care were used as a comparator separately for patients with predominantly classic wet AMD in the evaluation. However, NICE recommended PDT only for patients with 'classic with no occult', not predominantly classic wet AMD in clinical practice (TA068). So the comparator of interest for patients with predominantly classic wet AMD is best supportive care in this evaluation The efficacy data inputs for all the treatment arms were derived from the patient-level data reported in the clinical studies. However, no descriptions of the derivation were included in the report The efficacy inputs for comparison against best supportive care were derived using an indirect comparison method Best supportive care was used as the comparator for patients with either minimally classic or occult no classic wet AMD
Is the study type reasonable?	✓	Both cost-effectiveness studies in incremental cost per vision-year gained and cost–utility studies in incremental cost per QALY gained
Is the perspective of the analysis clearly stated?	✓	Both the perspectives of NHS and PSS in England and Wales
Is the perspective employed appropriate?	✓	
Is effectiveness of the intervention established?	✓	As reported in clinical studies such as ANCHOR, MARINA and PIER, sponsored by manufacturer, in terms of improvements or delay in deteriorations of visual acuity over the period when studies were conducted
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	×	A time horizon of [**CIC data removed**] with the model entry age at 77 years old was used and it was justified as the intervention being assessed is indicated for only the first 2 years and thus the horizon used in the model is sufficient to reflect its treatment benefits against the comparator
Are the costs and consequences consistent with the perspective employed?	✓	
Is differential timing considered?	✓	Both costs and benefits were discounted annually at 3.5%

continued

Item	Critical appraisal	Reviewer comment
Is incremental analysis performed?	✓	Incremental cost and benefits and ICER for cost per vision-year gained and cost per QALY gained
Is sensitivity analysis undertaken and presented clearly?	✓	The number of injections per year in the base case scenario was derived from a dosage regimen model. Sensitivity analyses on number of injections per year, which included the actual number of injections used in the clinical studies, were presented Post-treatment efficacy was considered in the base case scenario so sensitivity analyses for different post-treatment efficacy rates were presented No sensitivity analysis was conducted on the impact of removing costs and adverse events associated with sham injection in the comparator arms as sham injection would not be given in clinical practice

Appendix 14

Variables included in probabilistic sensitivity analysis

Health state utilities	Distribution	Alpha	Beta	Mean
>6/12	Beta	68.30819	8.44259	0.89
⩽6/12 to >6/24	Beta	74.82381	17.55127	0.81
⩽6/24 to >6/60	Beta	53.66787	40.48629	0.57
⩽6/60 to >3/60	Beta	25.43830	23.48151	0.52
⩽3/60	Beta	33.44944	50.17416	0.40

Proportion uptake of services for visual impairment	Distribution	Alpha	Beta	Mean
Blind registration	Beta	3.0189	0.1757	0.945
Low-vision aids	Beta	6.6695	13.5410	0.330
Community care	Beta	0.4498	7.0470	0.060
Residential care	Beta	5.2355	12.2162	0.300
Depression	Beta	7.3639	11.5179	0.390
Fracture	Beta	0.6231	11.8398	0.050

Costs	Distribution	Alpha	Beta	Mean
First outpatient attendance	Gamma	92.6854	1.0297	95.44
Outpatient follow-up	Gamma	114.9876	0.5110	58.76
FA	Gamma	96.0365	0.7706	74.01
OCT	Gamma	96.0365	0.5296	50.86
Blind registration	Gamma	12.1775	9.4765	115.40
Low-vision aids	Gamma	39.4712	3.8002	150.00
Low-vision rehabilitation	Gamma	30.4453	8.5071	259.00
Community care	Gamma	26.4701	247.5250	6552.00
Residential care	Gamma	9.2622	1465.8652	13577.20
Fracture treatment	Gamma	38.3543	140.2449	5379.00

Transition probabilities: pegaptanib and usual care			Distribution	Parameter		Mean
Pegaptanib	Year 1	Gain at least 3 lines	Beta	$n = 294$	$r = 18$	0.0612
		Lose ⩾3 and <6 lines	Beta	$n = 294$	$r = 60$	0.2041
		Lose ⩾6 lines	Beta	$n = 294$	$r = 28$	0.0952
	Year 2	Gain at least 3 lines	Beta			
		Lose ⩾3 and <6 lines	Beta	**[CIC data removed]**		
		Lose ⩾6 lines	Beta			
Usual care	Year 1	Gain at least 3 lines	Beta	$n = 296$	$r = 6$	0.0203
		Lose ⩾3 and <6 lines	Beta	$n = 296$	$r = 67$	0.2264
		Lose ⩾6 lines	Beta	$n = 296$	$r = 65$	0.2196
	Year 2	Gain at least 3 lines	Beta			
		Lose ⩾3 and <6 lines	Beta	**[CIC data removed]**		
		Lose ⩾6 lines	Beta			

n, total number of patients in trial; *r*, number of events (patients gaining or losing vision).

Transition probabilities: predominantly classic lesion and best supportive care			Distribution	Parameter	Mean
Ranibizumab	Year 1	Gain at least 3 lines	Beta	[CIC data removed]	
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
Best supportive care	Year 1	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		

Transition probabilities: predominantly classic lesion and PDT			Distribution	Parameter	Mean
Ranibizumab	Year 1	Gain at least 3 lines	Beta	[CIC data removed]	
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
PDT	Year 1	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		

Transition probabilities: minimally classic lesion and OCT			Distribution	Parameter	Mean
Ranibizumab	Year 1	Gain at least 3 lines	Beta	[CIC data removed]	
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
Best supportive care	Year 1	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ⩾3 and <6 lines	Beta		
		Lose ⩾6 lines	Beta		

Appendix 15

Additional analysis commissioned by the NHS R&D HTA Programme on behalf of the National Institute for Health and Clinical Excellence

Models of second eye treatment in AMD

Question 1 *To give an indication of the range of ICERs to be expected if both eyes are treated (or if only one eye is affected, treatment of that eye without waiting for a second to be affected). What is the expected ICER of treating the whole group of patients (some of whom will first seek medical attention with one eye affected, some with both) with this approach? What are the limitations of the evidence base for the assumptions for utility values in this analysis?*

Deliverable(s)

To produce an analysis indicating the range of ICERs to be expected if both eyes are treated (or if only one eye is affected, treatment of that eye without waiting for a second to be affected). Given the complex nature of the underlying disease and effects of treatment, the related challenges and barriers to building and interpreting models of treating the worse-seeing eye, and the time constraints between Appraisal Committee meetings, this analysis would be expected to be an indicative/exploratory analysis. The Assessment Group will list any outstanding issues that it has not been able to reflect in the indicative analysis, but considers to be important in interpreting the results. Can sensitivity analyses be presented around the assumptions for utility gain from treating one or the worst-seeing, as opposed to the better-seeing, eye only?

Overview

The following section briefly reviews the evidence, with respect to the proportion of patients presenting with their first eye affected and the risk of second eye involvement. We identify major uncertainties in modelling the cost and outcomes of treating one or both eyes and present estimates of the cost implications of treating first and second eyes. We do not present any estimates of the expected outcomes for alternative scenarios of treating one or both eyes. Further work is required to determine the feasibility of modelling outcomes (in terms of visual acuity and quality-adjusted life expectancy) and the costs associated with vision loss in patients who receive treatment in one or both eyes.

Assumptions

Proportion presenting with first eye affected

Widely quoted figures are that 30% to one-third of patients currently present with disease in one eye only (the 'first eye'). A substantial (i.e. published or fully referenced) source has not been found for this, but responses to the Appraisal Consultation Document (ACD) included:

- "At present, approximately one-third of patients present with first eye" (Royal National Institute for the Blind (RNIB) response to ACD).
- "Current data show that 30% of patients present with wet AMD in the first eye" (Welsh Assembly Government, although they do not indicate where the data come from).
- "We expect … to develop CNV in Northern Ireland. Of these 70% will be second eyes …" (Professor Usha Chakravarthy on behalf of Department of Health, Social Services and Public Safety for Northern Ireland).

Risk of second eye involvement

A commonly quoted figure is that 40% of people with CNV in one eye will have second eye involvement within 5 years. We have sought for evidence and found the following:

- Page 1 of the PDT TAR[A1] states, "[A] key issue concerning natural history of wet AMD is that developing the disease in one eye is highly predictive of disease developing in the other eye (up to 42% within 5 years).[A2] The original reference for this estimate appears to be a publication from the Macular Photocoagulation Study Group.[A3] Pieramici and Bressler[A2] quote annual incidence for second eye involvement from 4 to 12%. The 5-year risk of CNV in the second eye ranges from 7% in a subgroup with no risk factors to 87% for those with four risk factors (presence of five or more drusen (relative risk = 2.1), focal hyperpigmentation (relative risk = 2.0), one or more large drusen (relative risk = 1.5) and definite systemic hypertension (relative risk = 1.7).

- The Royal College of Ophthalmologists guidelines[A4] state, "With AMD-related visual loss affecting one eye the risk of losing vision in the fellow eye increases to between 7 and 10% annually (referencing the following publications[A5–A7]). The 5-year risk is lowest in the absence of large drusen or pigment hyperplasia but increases with one of these risk factors to 30% or with both to over 50%.[A8] The highest risk is for those with a pigment epithelial tear in one eye for whom the annual risk of second eye involvement is closer to 40%."[A9]
- For people with advanced AMD in one eye, the 5-year risk for developing advanced AMD in the second eye was 14.8, 35.4 and 53.1% for patients with two, three or four risk factors, respectively.[A10] In this study, two risk factors were assigned for the presence of advanced AMD in the first eye and additional risk factors were added for presence of large drusen and/or pigment abnormalities in the eye at risk.

An annual incidence of 10%, which corresponds to 41% at 5 years (see *Figure A1*), will be used for the cost estimates.

Proportion of second eyes suitable for treatment

Need to consider issue raised by the Department of Health:

> *In making the draft recommendation that treatment be for the better seeing eye only, is NICE satisfied that it has considered and given appropriate weight to evidence on the likelihood of a patient developing AMD in their second eye and the probability of developing a treatable form? Has NICE assessed the risk of AMD in the second eye not being treatable, whilst AMD in the first eye could have been (but was not) treated?*

Major uncertainties

- How many patients will take up treatment in first eye?
- What happens to patients who develop (treatable) AMD in second eye, while being treated for AMD in first eye? The current assumption is that treatment continues up to 2 years on the first eye then treatment switches to the second eye.
- If the lesion type in the first eye is predominantly classic, what is the probability that the second eye will be minimally classic/occult no classic?
- What is the procedure for monitoring patients who present with first eye involvement, but receive no treatment? Current assumptions are twice-yearly outpatient assessment with optometry, OCT and FA.
- What is the probability that AMD developing in the second eye will be of a treatable form?

An exploration of the cost implications of first eye and second eye presentation

Treatment with pegaptanib

Table A1 reports estimated costs for alternative treatment strategies for patients presenting with

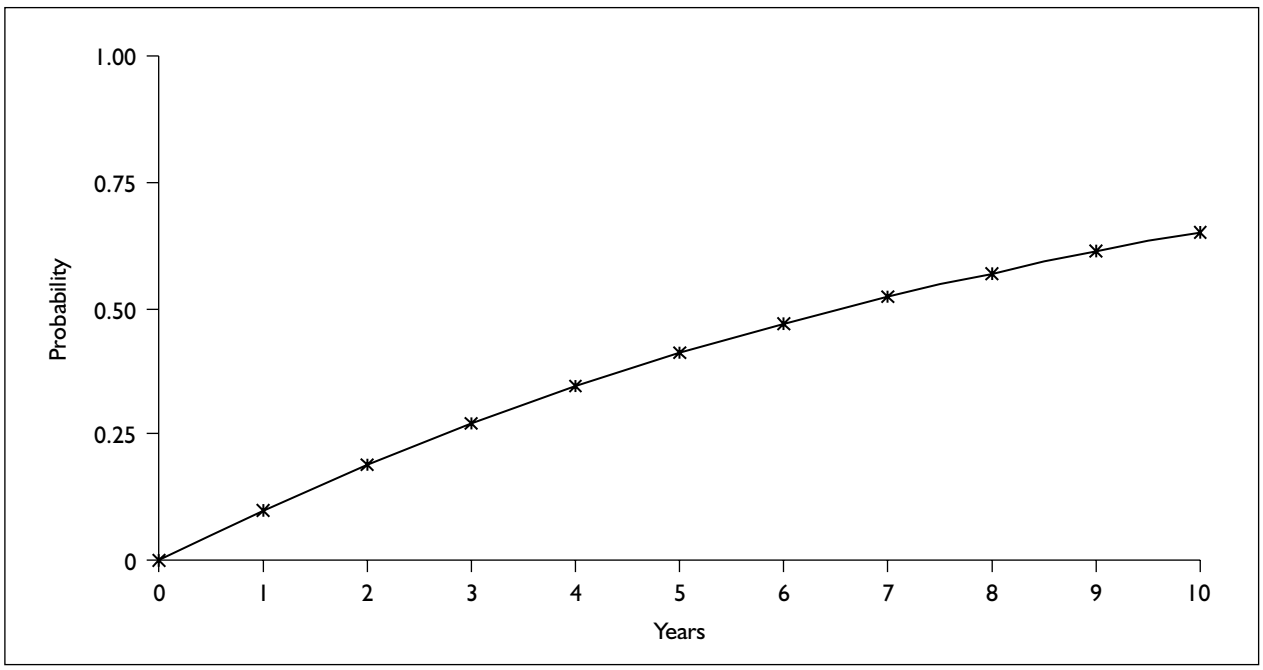

FIGURE A1 *Cumulative probability of developing CNV in the second eye (10% annual incidence) following CNV in the first eye*

TABLE A1 *Pegaptanib treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 8.4	Treat both eyes	11,134	5,301	1,366	17,802	9,974
Year 2 = 6.9	Treat second eye only	0	5,373	2,455	7,828	
Year 1 = 9	Treat both eyes	12,072	5,752	1,366	19,190	10,905
Year 2 = 8	Treat second eye only	0	5,830	2,455	8,285	

CNV in the first eye. The modelled treatment strategies are to treat both eyes (i.e. treat current CNV with up to 2 years of pegaptanib and then treat CNV in second eye if it develops). The alternative strategy is to leave the first eye and only treat once CNV develops in second eye – assuming a 10% risk of second eye involvement for those with CNV in the first eye. Under these assumptions, 38% of the original cohort develop CNV in their second eye within 5 years (41% of patients who survive 5 years have developed CNV in their second eye). These costs assume that all first and second eyes are eligible for treatment, and all eligible patients accept treatment.

Figure A2 shows the distribution of treatment costs over time for patients presenting with CNV in their first eye. The bars with the darker shading show costs for treating disease in patients' second eye. The lighter shaded bars show the additional costs associated with treating patients' first eyes.

Treatment costs in this model are those applied in the base case analysis in the assessment report, that is, the injection has been costed as an outpatient procedure. Sensitivity analyses will be presented for costing the injection as a day-case procedure and also using the costs presented in the Royal College of Ophthalmologists Commissioning Guidance.

In this model, we assume that patients who present for treatment with CNV in their first eye are monitored for development of disease in their second eye, given the high probability that those patients will develop CNV in their second eye (as discussed earlier). We assume that all patients will attend twice per year for a vision assessment, OCT and FA on their second eye, regardless of whether

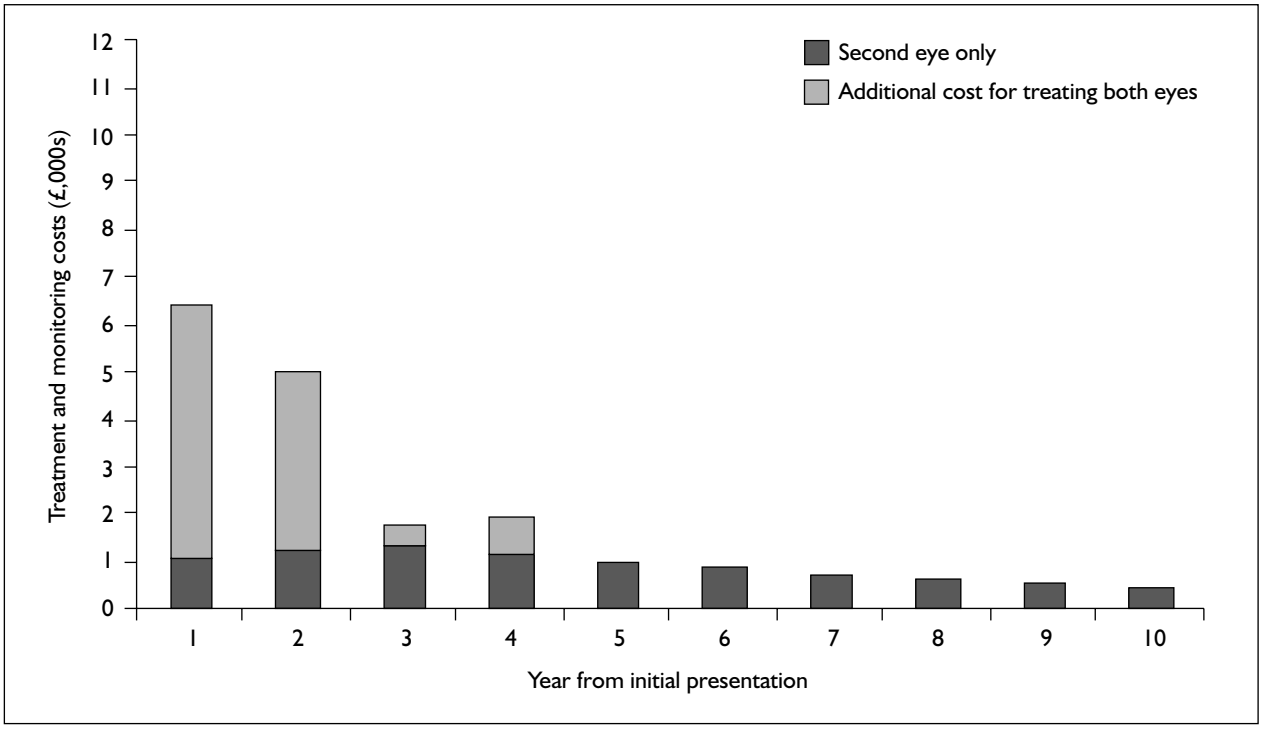

FIGURE A2 *Pegaptanib treatment cost distribution over time for different strategies (assuming 6-weekly assessment and injections over 2 years for the first eye and for those patients who develop CNV in their second eye); discounted at 3.5%*

their first eye was treated. The cost associated with this level of monitoring of disease progression in second eye is labelled 'monitoring costs' in *Table A1*. Treatment costs consist of drug acquisition costs, the injection procedure, plus OCT, vision and medical assessments with FA every 6 months on the treated eye.

Impact of alternative assumptions

Injection costed as a day-case procedure. *Table A2* shows that the cost difference between the two strategies increases by around 40% if the injection procedure is costed as a day-case rather than an outpatient procedure.

Royal College of Ophthalmologists Commissioning Guidance costings. *Table A3* shows a similar pattern as *Table A2*, with cost difference between the two strategies increasing by around 40–50%.

Intensity of monitoring. *Table A4* shows that increasing the intensity of monitoring reduces the cost difference between the two strategies, although the difference is marginal (around 8%).

Treatment with ranibizumab

Table A5 reports estimated costs for alternative treatment strategies of treating both eyes, or the second eye only, for patients presenting with CNV in the first eye treated with ranibizumab.

Treatment costs in this model are those applied in the base case analysis in the assessment report. The table presents five different scenarios, in which the number of intravitreal injections is varied. The first three scenarios (12 injections in year 1 and year 2, nine injections in year 1 and year 2 and nine injections in year 1 with six injections in year 2) were included in the deterministic sensitivity analyses included in the assessment report (see *Tables 50–52*). Monthly injections correspond to the treatment frequency in the pivotal trials, that provided evidence of efficacy for ranibizumab.[A11,A12]

TABLE A2 *Pegaptanib treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality; injection costed as a day-case procedure*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 8.4 Year 2 = 6.9	Treat both eyes Treat second eye only	15,458 0	7,360 7,461	1,366 2,455	24,185 9,915	14,270
Year 1 = 9 Year 2 = 8	Treat both eyes Treat second eye only	16,869 0	8,038 8,147	1,366 2,455	26,273 10,602	15,671

TABLE A3 *Pegaptanib treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality; treatment costed using Royal College of Ophthalmologists Commissioning Guidance values*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 8.4 Year 2 = 6.9	Treat both eyes Treat second eye only	15,866 0	7,555 7,658	1,366 2,455	24,788 10,113	14,675
Year 1 = 9 Year 2 = 8	Treat both eyes Treat second eye only	16,809 0	8,009 8,118	1,366 2,455	26,184 10,572	15,612

TABLE A4 *Pegaptanib treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality; quarterly monitoring of disease progression in second eye*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 8.4 Year 2 = 6.9	Treat both eyes Treat second eye only	11,134 0	5,301 5,373	2,732 4,649	19,168 10,023	9,145
Year 1 = 9 Year 2 = 8	Treat both eyes Treat second eye only	12,072 0	5,752 5,830	2,732 4,649	20,556 10,479	10,077

TABLE A5 *Ranibizumab treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 12	Treat both eyes	22,780	10,870	1,366	35,016	21,543
Year 2 = 12	Treat second eye only	0	11,018	2,455	13,473	
Year 1 = 9	Treat both eyes	18,061	8,618	1,366	28,046	16,855
Year 2 = 9	Treat second eye only	0	8,736	2,455	11,191	
Year 1 = 9	Treat both eyes	15,796	7,512	1,366	24,674	14,605
Year 2 = 6	Treat second eye only	0	7,614	2,455	10,069	
Year 1 = 5.6	Treat both eyes	12,714	6,067	1,366	20,147	11,543
Year 2 = 5.6	Treat second eye only	0	6,149	2,455	8,604	
Year 1 = 6.5	Treat both eyes	11,864	5,636	1,366	18,866	10,699
Year 2 = 3.3	Treat second eye only	0	5,712	2,455	8,167	

Evidence submitted by the manufacturer, in support of the ranibizumab submission to NICE, included a disease and dosage schedule model that suggested that a reduced frequency of injection could achieve outcomes equivalent to those observed in the pivotal trials. These supported a dose frequency of nine in year 1 and six in year 2.

The estimate of 5.6 injections in year 1 was derived from the published reports on the PRONTO study,[A13] which investigated the effectiveness of a reduced dosing schedule, using an 'as required' protocol rather than the fixed dosing schedule adopted in the PIER study. The PRONTO study has only published data up to 1 year – hence the same value (5.6 injections applied to year 2). PRONTO is a small (n = 40), uncontrolled observational study and it remains to be seen whether the early findings from that study will be confirmed by the larger (n = 600) SUSTAIN study that is currently recruiting and aims to provide additional data on effectiveness of a reduced dosing protocol and frequency of drug administration.

The final scenario in Table A5 is based on information supplied by the manufacturer during consultation on the ACD, which stated that results up to 2 years in the PRONTO study gave a mean number of injections of 9.9 over 2 years – these data do not seem to be published. This number of injections was distributed across each year of treatment based on responses to a survey of ophthalmologists with experience of treating patients with ranibizumab, reported by the manufacturer. This suggested that 58% of patients would receive between three and six injections over 12 months and 38% would receive between six and 12 injections. These are the least evidence-based estimates of frequency of treatment under the reduced frequency protocol and fall well below the values adopted in the Royal College of Ophthalmologists Commissioning Guidance (eight in year 1 and six in year 2).

Figure A3 shows the distribution of treatment costs over time for patients presenting with CNV in their first eye. The bars with the darker shading show costs for treating disease in patients' second eye (51% of the cohort over 10-year time horizon). The lighter shaded bars show the additional costs associated with treating patients' first eyes.

Impact of alternative assumptions

Injection costed as a day-case procedure. *Table A6* shows that costing injection as a day-case procedure increases cost by approximately 30% where 12 injections are administered per year. The increase is slightly lower for the reduced frequency dosing regimes.

Royal College of Ophthalmologists Commissioning Guidance costings. *Table A7* shows that, as was the case with pegaptanib, using the Royal College of Ophthalmologists' costs gives very similar results as using the day-case procedure cost.

Intensity of monitoring. *Table A8* shows that an increased intensity of monitoring for patients, to detect disease in their second eye, marginally reduces the difference in cost between strategies.

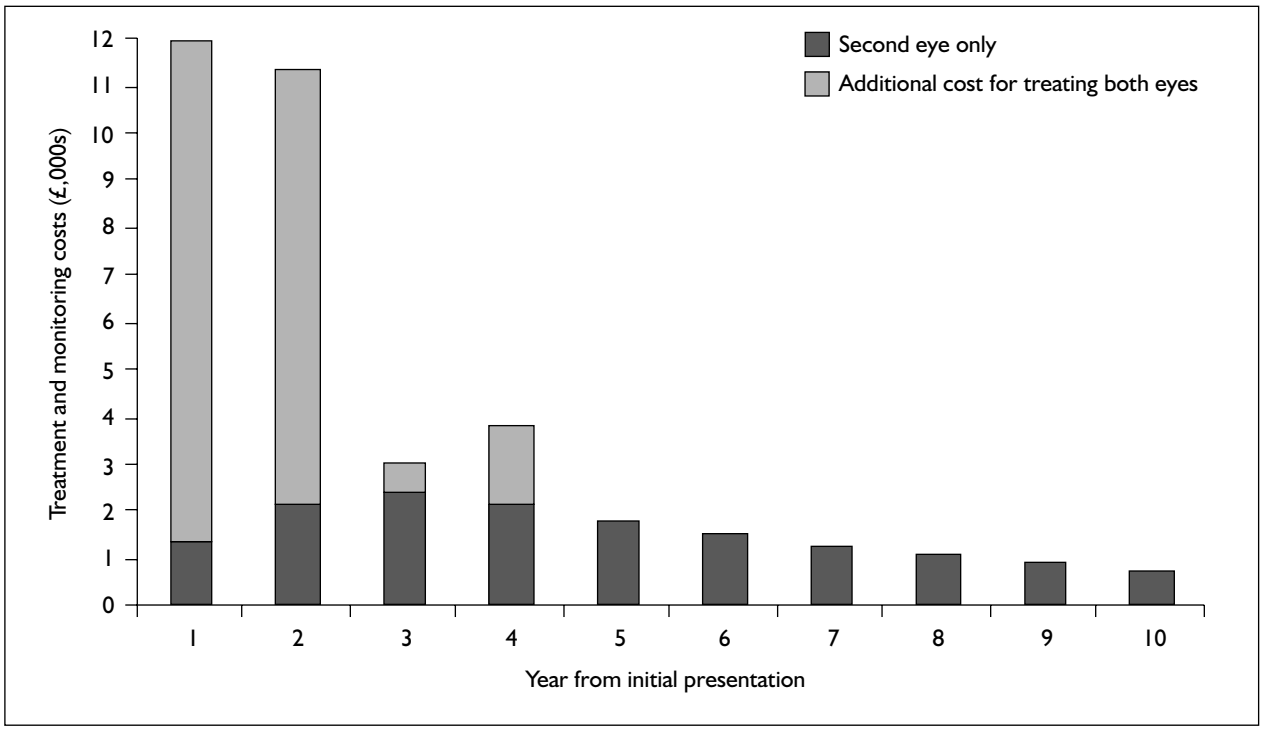

FIGURE A3 *Ranibizumab treatment cost distribution over time for different strategies (assuming monthly assessment and injections for 2 years in each eye); discounted at 3.5%*

TABLE A6 *Ranibizumab treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality; injection costed as a day-case procedure*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 12	Treat both eyes	29,536	14,095	1,366	44,997	28,255
Year 2 = 12	Treat second eye only	0	14,287	2,455	16,741	
Year 1 = 9	Treat both eyes	23,129	11,037	1,366	35,532	21,890
Year 2 = 9	Treat second eye only	0	11,187	2,455	13,642	
Year 1 = 9	Treat both eyes	20,052	9,534	1,366	30,952	18,834
Year 2 = 6	Treat second eye only	0	9,664	2,455	12,119	
Year 1 = 5.6	Treat both eyes	15,867	7,571	1,366	24,805	14,675
Year 2 = 5.6	Treat second eye only	0	7,674	2,455	10,129	
Year 1 = 6.5	Treat both eyes	14,713	6,986	1,366	23,065	13,529
Year 2 = 3.3	Treat second eye only	0	7,081	2,455	9,536	

Alternative assumptions for costs of blindness, treatment cost and frequency of injection with ranibizumab

Question 2 *How would the estimation of cost-effectiveness be affected by alternative assumptions of administration costs as suggested at consultation (e.g. based on the Royal College of Ophthalmologists Commissioning Contemporary Services Guidance, July 2007)*

Deliverable(s)

To produce ICERs from the Assessment Group model using alternative assumptions reflecting the views expressed through consultation with regard to unit costs and resource use assumptions, which include the costs of:

- Unit costs and resource use related to blindness, such as costs of falls and hip fractures.
- Levels of uptake of blind related services. It may be ideal to report a sensitivity analysis on these issues.

TABLE A7 *Ranibizumab treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality; treatment costed using Royal College of Ophthalmologists Commissioning Guidance values*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 12	Treat both eyes	29,859	14,250	1,366	45,475	28,576
Year 2 = 12	Treat second eye only	0	14,444	2,455	16,899	
Year 1 = 9	Treat both eyes	25,121	11,989	1,366	38,476	23,869
Year 2 = 9	Treat second eye only	0	12,152	2,455	14,607	
Year1 = 9	Treat both eyes	22,846	10,877	1,366	35,089	21,609
Year 2 = 6	Treat second eye only	0	11,026	2,455	13,480	
Year 1 = 5.6	Treat both eyes	19,751	9,426	1,366	30,543	18,534
Year 2 = 5.6	Treat second eye only	0	9,554	2,455	12,009	
Year 1 = 6.5	Treat both eyes	18,897	8,993	1,366	29,256	17,686
Year 2 = 3.3	Treat second eye only	0	9,116	2,455	11,570	

TABLE A8 *Ranibizumab treatment costs for alternative treatment strategies for patients presenting with AMD in first eye – accounting for mortality; quarterly monitoring of disease progression in second eye*

No. of injections	Treatment strategy	First eye (£)	Second eye (£)	Monitoring costs (£)	Total (£)	Cost difference (£)
Year 1 = 12	Treat both eyes	22,780	10,870	2,732	36,382	20,714
Year 2 = 12	Treat second eye only	0	11,018	4,649	15,668	
Year 1 = 9	Treat both eyes	18,061	8,618	2,732	29,412	16,027
Year 2 = 9	Treat second eye only	0	8,736	4,649	13,385	
Year 1 = 9	Treat both eyes	15,796	7,512	2,732	26,040	13,777
Year 2 = 6	Treat second eye only	0	7,614	4,649	12,264	
Year 1 = 5.6	Treat both eyes	12,714	6,067	2,732	21,513	10,715
Year 2 = 5.6	Treat second eye only	0	6,149	4,649	10,799	
Year 1 = 6.5	Treat both eyes	11,864	5,636	2,732	20,232	9,870
Year 2 = 3.3	Treat second eye only	0	5,712	4,649	10,362	

- Costs of administering the injections (day-case procedure versus outpatient or an estimate in between based on the Royal College of Ophthalmologists Commissioning Guidance).
- The number of injections used for ranibizumab treatment within its licensed indications. This would require assumptions about the percentage of patients who, despite a reduced frequency of injections, experience the same level of treatment effect as in the ranibizumab studies with monthly injections (MARINA and ANCHOR).

Overview

The following section briefly reviews the evidence, with respect to costs of blindness (and the proportion that each component of blindness costs contributed to total costs), presented in the assessment report and reports sensitivity analyses on key parameters, identified by consultees, as meriting further consideration. This analysis presents the incremental cost per QALY gained under the alternative scenarios.

An important issue to consider here is which costs identified by consultees are associated with AMD (at all levels of vision) or are specific to blindness. For example, the RNIB indicated that people with low vision due to AMD would still attend for clinic visits and optician visits. However, these costs are relevant for all people with AMD and are not specific to those whose vision has deteriorated.

We also present sensitivity analyses using alternative costing assumptions: costing visits using unit costs adopted by the Royal College of Ophthalmologists in their commissioning guidance, and also using a weighted combination

of outpatient and day-case procedure costs for costing the intravitreal injection procedure. Further sensitivity analyses are presented for the reduced-frequency dosage regime with ranibizumab. These analyses present the incremental cost per QALY gained under the alternative scenarios.

Costs of blindness

Annex A1 to this Appendix gives some background on the costs of blindness included in the models developed for the assessment report, indicating the proportion of total costs of blindness which were assumed to be one-off and those which are recurrent costs. The one-off and recurrent costs are further broken down by categories of costs.

Unit costs and resource use related to blindness

The majority of comments related to uptake of services for visual impairment and the assumption that certain costs are one-off, rather than unit costs. The following analyses investigate the sensitivity of incremental cost and ICER to alternative assumptions over the uptake of services in the light of comments from consultees and the evidence offered.

Table A9 reports the variables considered in the sensitivity analysis, the values adopted in the base case, those adopted in the sensitivity analysis and the source for the alternative assumption.

Assumptions in the table that show low-vision rehabilitation and low-vision aids being provided to patients in years after they develop blindness (with the assumption that patients receive new low-vision rehabilitation and new low-vision aids every 2 years) move these components of costs away from being one-off costs only, to where there is initial assessment and service provision, to allow for these to be included also under the recurrent costs attributed to blindness.

The sensitivity analyses presented in *Tables A10–A13* suggest that incremental cost, and hence the ICER, are comparatively insensitive to variation in uptake of services that were suggested as being underestimated at consultation. The incremental cost and ICER were sensitive to alternative assumptions regarding the proportion of blind people receiving community care support. However the values adopted in this sensitivity analysis (25 and 17%) were taken from a study which was not clear on the perspective adopted for costing and which does not report the proportion of domiciliary costs that was funded via social services, rather than funded by service users privately or through allowances. Meads and Hyde[A15] noted, in their discussion of their cost of blindness estimates, that the proportion of blind people receiving community care support may be higher than their 6% estimate, but adopted this as their most likely estimate due to the proportion of service users funding care privately or through attendance allowances.

TABLE A9 *Base case assumption and the assumption adopted in the sensitivity analysis*

	Base case value	Value in sensitivity analysis	Source
Proportion registering blind who were previously registered partially sighted	0	0.45	RNIB
Proportion having annual reassessment by occupational therapist	0	1.00	RNIB
Proportion having annual reassessment by occupational therapist and repeat low-vision rehabilitation each year	0 0	1.00 0.50	RNIB Assumed
Proportion having annual reassessment by occupational therapist low-vision aids each year	0 0	1.00 0.50	RNIB Assumed
Uptake of low-vision rehabilitation	0.11	0.44	Lotery and colleagues[A14]
Uptake of low-vision aids	0.33	0.47	
Proportion receiving community care services (home care)	0.06	0.25	
Proportion receiving community care services (home care)	0.06	0.17	

Pegaptanib-treated cohort compared with usual care

TABLE A10 *Sensitivity analysis for assumptions on uptake of services in costs of blindness for pegaptanib-treated cohort*

Variable	Incremental cost (£)	Incremental QALYs	ICER (£)
Proportion of blind registrations previously registered partially sighted (uptake = 0.45)	8,059	0.26	30,973
Annual reassessment by occupational therapist	8,031	0.26	30,864
Annual reassessment by occupational therapist and low-vision rehabilitation every 2 years	7,994	0.26	30,726
Annual reassessment by occupational therapist and low-vision aids every 2 years	8,008	0.26	30,779
Change cost of low-vision rehabilitation (uptake = 0.44)	8,056	0.26	30,963
Change cost of low-vision aids (uptake = 0.47)	8,061	0.26	30,981
Change cost of community care (home care) (uptake = 0.25)	7,273	0.26	27,951
Change cost of community care (home care) (uptake = 0.17)	7,605	0.26	29,229

Predominantly classic lesions treated with ranibizumab, compared with PDT

TABLE A11 *Sensitivity analysis for assumptions on uptake of services in costs of blindness for patients with predominantly classic lesions treated with ranibizumab for 1 year, compared with PDT*

Variable	Incremental cost (£)	Incremental QALYs	ICER (£)
Proportion of blind registrations previously registered partially sighted (uptake = 0.45)	5,387	0.34	15,629
Annual reassessment by occupational therapist	5,359	0.34	15,546
Annual reassessment by occupational therapist and low-vision rehabilitation every 2 years	5,323	0.34	15,442
Annual reassessment by occupational therapist and low-vision aids every 2 years	5,337	0.34	15,482
Change cost of low-vision rehabilitation (uptake = 0.44)	5,385	0.34	15,621
Change cost of low-vision aids (uptake = 0.47)	5,389	0.34	15,634
Change cost of community care (home care) (uptake = 0.25)	4,603	0.34	13,354
Change cost of community care (home care) (uptake = 0.17)	4,935	0.34	14,315

Predominantly classic lesions treated with ranibizumab, compared with best supportive care

TABLE A12 *Sensitivity analysis for assumptions on uptake of services in costs of blindness for patients with predominantly classic lesions treated with ranibizumab for 1 year, compared with best supportive care*

Variable	Incremental cost (£)	Incremental QALYs	ICER (£)
Proportion of blind registrations previously registered partially sighted (uptake = 0.45)	6,452	0.57	11,402
Annual reassessment by occupational therapist	6,399	0.57	11,309
Annual reassessment by occupational therapist and low-vision rehabilitation every 2 years	6,332	0.57	11,191
Annual reassessment by occupational therapist and low-vision aids every 2 years	6,358	0.57	11,236
Change cost of low-vision rehabilitation (uptake = 0.44)	6,448	0.57	11,395
Change cost of low-vision aids (uptake = 0.47)	6,455	0.57	11,408
Change cost of community care (home care) (uptake = 0.25)	5,003	0.57	8,842
Change cost of community care (home care) (uptake = 0.17)	5,615	0.57	9,923

Minimally classic and occult no classic lesions treated with ranibizumab

TABLE A13 *Sensitivity analysis for assumptions on uptake of services in costs of blindness for patients with minimally classic and occult no classic lesions treated with ranibizumab*

Variable	Incremental cost (£)	Incremental QALYs	ICER (£)
Proportion of blind registrations previously registered partially sighted (uptake = 0.45)	17,299	0.69	25,084
Annual reassessment by occupational therapist	17,245	0.69	25,006
Annual reassessment by occupational therapist and low-vision rehabilitation every 2 years	17,173	0.69	24,901
Annual reassessment by occupational therapist and low-vision aids every 2 years	17,201	0.69	24,941
Change cost of low-vision rehabilitation (uptake = 0.44)	17,292	0.69	25,073
Change cost of low-vision aids (uptake = 0.47)	17,305	0.69	25,092
Change cost of community care (home care) (uptake = 0.25)	15,730	0.69	22,808
Change cost of community care (home care) (uptake = 0.17)	16,394	0.69	23,772

Cost of assessment and treatment as per Royal College of Ophthalmologists Commissioning Guidance

Treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance (reproduced in *Table A14*) need to be adjusted in order to be consistent with NICE methodological guidance for technology appraisal and to allow for the calculation of the cost of an assessment-only visit, that is, without injection. Specifically, we need to remove VAT from drug cost (*Tables A15* and *A16*). This in combination with the 20% overhead applied to all costs (including the post-VAT drug cost) increases the cost per visit by between 18 and 24%, depending on the drug and the type of visit.

Removing VAT on drug costs reduces the cost of a full assessment (which includes FA) including treatment with ranibizumab from £1401.60 to £1190.80 (15% reduction) and reduces the cost of an injection only visit from £1290 to £1079.20 (16% reduction).

Removing VAT on drug costs reduces the cost of a full assessment (which includes FA) including treatment with ranibizumab from £1750.09 to £1438 (18% reduction) and reduces the cost of an injection only visit from £1638.49 to £1326.40 (19% reduction).

For this Appendix, we also need to estimate a cost for clinic attendance, without injection – to be able

TABLE A14 *Costs of treatment with pegaptanib and ranibizumab as reported in Royal College of Ophthalmologists Commissioning Guidance*

Item	Ranibizumab		Pegaptanib	
	Full assessment	Injection only	Full assessment	Injection only
Staffing	230.00	172.00	230.00	172.00
Band 7 management	44.00	£44.00	44.00	44.00
Other drugs	8.00	£8.00	8.00	8.00
Non-pay costs	92.00	£92.00	92.00	92.00
Fundus fluorescein angiography	35.00		35.00	
OCT	14.00	£14.00	14.00	14.00
Intraocular pressure	2.00	£2.00	2.00	2.00
Incidentals	111.00	£111.00	111.00	111.00
PTS	28.00	£28.00	28.00	28.00
Total for visit	**564.00**	**£471.00**	**564.00**	**471.00**
Drug (with VAT at 17.5% added)	894.41	£894.41	604.00	604.00
Sub-total	**1458.41**	**£1,365.41**	**1168.00**	**1075.00**
Overheads at 20%	291.68	£273.08	233.60	215.00
Cost per patient	**1750.09**	**£1,638.49**	**1401.60**	**1290.00**

TABLE A15 *Adjustments to the pegaptanib treatment costs reported in the Royal College of Ophthalmologists Commissioning Guidance for use in the model*

Cost item	Full assessment (£)	Injection only (£)
Non-drug costs (see 'Total for visit' in *Table A14*)	564.00	471.00
Drug costs	514.00	514.00
20% Trust overhead on all costs and VAT (17.5%) on drug costs (see 'Cost per patient' in *Table A14*)	1401.60	1290.00
20% Trust overhead on all costs but no VAT on drug costs	1293.60	1182.00
20% Trust overhead on non-drug costs only, no VAT on drug costs	1190.80	1079.20

TABLE A16 *Adjustments to the ranibizumab treatment costs reported in the Royal College of Ophthalmologists Commissioning Guidance for use in the model*

Cost item	Full assessment (£)	Injection only (£)
Non-drug costs (see 'Total for visit' in *Table A14*)	564.00	471.00
Drug costs	761.20	761.20
20% Trust overhead on all costs and VAT (17.5%) on drug costs	1750.09	1638.49
20% Trust overhead on all costs but no VAT on drug costs	1590.24	1478.64
20% Trust overhead on non-drug costs only, no VAT on drug costs	1438.00	1326.40

to cost the reduced dosage protocols suggested for ranibizumab. One approach to this would be simply to exclude the drug costs for assessment-only visits and use the total of non-drug costs (£564 for full assessment and £471 for injection-only visits). It is likely that other cost items in *Table A14* also relate directly to the injection procedure, but it is not apparent which these may be. We have contacted the team who originally produced these costings. However, they have not been able to rework the costings to estimate the cost of an assessment-only visit in the time available. For the purpose of this Appendix, we have excluded 'Non-pay costs' (£92.00) to derive a cost for a visit where no injection procedure takes place (*Table A17*).

For this Appendix, we have assumed that all patients have a full assessment every 3 months – they have an FA and greater staffing input at these visits. Staff cost (under the heading 'Staffing') is 34% higher on the full assessment visits than for the injection-only visit. This corresponds to FA every 3 months, similar to the protocol for PDT. A sensitivity analysis is presented using full assessment every 6 months.

Pegaptanib-treated cohort compared with usual care

Applying VISION study outcomes without assessment of disease-modifying effect

Incremental costs and ICERs using treatment costs presented in the Royal College of Ophthalmologists

TABLE A17 *Estimates for clinic visit without injection, based on costs in the Royal College of Ophthalmologists Commissioning Guidance*

Cost item	Full assessment (£)	Injection only (£)
Non-drug costs from *Table A14*	564.00	471.00
Non-drug costs (excluding 'Non-pay' costs as an estimate of an assessment-only visit)	472.00	379.00
20% Trust overhead on non-drug costs only (excluding 'Non-pay' costs)	566.40	454.80

Commissioning Guidance, with the adjustments described above, are reported in *Table A18*. Results are presented for each of the scenarios, with regard to the number of injections, included in the deterministic sensitivity analyses in the assessment report (*Table 45*).

A breakdown of the base case costs (8.4 injections in year 1 and 6.9 in year 2) by major categories for the analysis using alternative unit cost assumptions is shown in *Table A19*.

The analyses presented in *Tables A18* and *A19* are based on a schedule of a full assessment every 3 months. A further analysis is presented based on a schedule of a full assessment (which includes FA) every 6 months (*Table A20*), rather than every 3 months.

Including disease-modifying effect for pegaptanib, year 3 only

Table A21 reports incremental costs and ICERs under the assumption that pegaptanib has a disease-modifying effect, reducing the proportion of patients having significant loss of vision (as described in the assessment report) for the year following cessation of treatment.

A breakdown of costs by major categories is shown in *Table A22*. As would be expected, the only category that varies between the three scenarios is 'Administration and monitoring'.

Table A23 reports incremental costs and ICERs using costs presented in the Royal College of Ophthalmologists Commissioning Guidance, but assuming FA occurs every 6 months rather than every 3 months.

TABLE A18 *Applying pegaptanib treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	8,062	0.26	30,986
Base case (day-case procedure)	12,449	0.26	47,845
Royal College of Ophthalmologists costs			
8.4 injections in year 1, 6.9 in year 2	13,180	0.26	50,654
9 injections in year 1, 6.9 in year 2	13,552	0.26	52,084
8.4 injections in year 1, 8 in year 2	13,796	0.26	53,022
9 injections in year 1, 8 in year 2	14,168	0.26	54,452

TABLE A19 *Breakdown of pegaptanib treatment costs for each cohort by major categories, using Assessment Group and Royal College of Ophthalmologists Commissioning Guidance unit costs*

		Drug (£)	Administration and monitoring (£)	Adverse events (£)	PDT (£)	Blindness (£)
Assessment Group (outpatient procedure)	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	4,107	98	404	12,666
Assessment Group (day case)	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	8,493	98	404	12,666
RCOphth	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	9,224	98	404	12,666

RCOphth, Royal College of Ophthalmologists.

TABLE A20 *Applying pegaptanib treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance – full assessment every 6 months*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
8.4 injections in year 1, 6.9 in year 2	12,913	0.26	49,628
9 injections in year 1, 6.9 in year 2	13,343	0.26	51,283
8.4 injections in year 1, 8 in year 2	13,421	0.26	51,581
9 injections in year 1, 8 in year 2	13,852	0.26	53,237

TABLE A21 *Applying pegaptanib treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance – disease-modifying effect in year 3*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	7,710	0.29	26,896
Base case (day-case procedure)	12,097	0.29	42,198
Royal College of Ophthalmologists costs			
8.4 injections in year 1, 6.9 in year 2	12,827	0.29	44,747
9 injections in year 1, 6.9 in year 2	13,199	0.29	46,045
8.4 injections in year 1, 8 in year 2	13,444	0.29	46,897
9 injections in year 1, 8 in year 2	13,816	0.29	48,194

TABLE A22 *Breakdown of pegaptanib treatment costs for each cohort by major categories, using Assessment Group and Royal College of Ophthalmologists Commissioning Guidance unit costs*

		Drug (£)	Administration and monitoring (£)	Adverse events (£)	PDT (£)	Blindness (£)
Assessment Group (outpatient procedure)	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	4,107	98	404	12,314
Assessment Group (day case)	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	8,493	98	404	12,314
RCOphth	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	9,224	98	404	12,314

TABLE A23 *Applying pegaptanib treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance – full assessment every 6 months – with disease-modifying effect in year following cessation of treatment*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
8.4 injections in year 1, 6.9 in year 2	12,560	0.29	43,816
9 injections in year 1, 6.9 in year 2	12,991	0.29	45,319
8.4 injections in year 1, 8 in year 2	13,069	0.29	45,589
9 injections in year 1, 8 in year 2	13,500	0.29	47,092

Including disease-modifying effect for pegaptanib, year 3 onwards

Table A24 reports incremental costs and ICERs assuming pegaptanib has a disease-modifying effect for the remainder of the model time horizon.

A breakdown of these costs by major categories is shown in *Table A25*.

Table A25 reports incremental costs and ICERs using costs presented in the Royal College of Ophthalmologists Commissioning Guidance, but assuming FA occurs every 6 months rather than every 3 months.

Predominantly classic lesions treated with ranibizumab, compared with PDT

Incremental costs and ICERs using treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance, with the adjustments described above, are reported in *Table A27*. Results are presented for each of the scenarios, with regard to the number of injections, included in the deterministic sensitivity analyses in the assessment report (*Table 50*).

A breakdown of the base case (12 injections per year) costs by major categories is shown in *Table A28*.

Predominantly classic lesions treated with ranibizumab, compared with BSC

Incremental costs and ICERs using treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance, with the adjustments described above, are reported in *Table A29*. Results are presented for each of the scenarios, with regard to the number of injections, included in the deterministic sensitivity analyses in the assessment

TABLE A24 *Applying pegaptanib treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance – disease-modifying effect for model time horizon*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	6,941	0.34	20,467
Base case (day-case procedure)	11,328	0.34	33,401
Royal College of Ophthalmologists costs			
8.4 injections in year 1, 6.9 in year 2	12,058	0.34	35,556
9 injections in year 1, 6.9 in year 2	12,430	0.34	36,653
8.4 injections in year 1, 8 in year 2	12,674	0.34	37,372
9 injections in year 1, 8 in year 2	13,046	0.34	38,469

TABLE A25 *Breakdown of pegaptanib treatment costs for each cohort by major categories, using Assessment Group and Royal College of Opthalmologists Commissioning Guidance unit costs*

		Drug (£)	Administration and monitoring (£)	Adverse events (£)	PDT (£)	Blindness (£)
Assessment Group (outpatient procedure)	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	4,107	98	404	11,544
Assessment Group (day case)	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	8,493	98	404	11,544
RCOphth	Usual care	0	220	0	590	15,789
	Pegaptanib	7,388	9,224	98	404	11,544

TABLE A26 *Applying pegaptanib treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance – full assessment every 6 months – with disease-modifying effect in year following cessation of treatment*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
8.4 injections in year 1, 6.9 in year 2	11,791	0.34	34,768
9 injections in year 1, 6.9 in year 2	12,222	0.34	36,038
8.4 injections in year 1, 8 in year 2	12,300	0.34	36,267
9 injections in year 1, 8 in year 2	12,730	0.34	37,537

TABLE A27 *Applying ranibizumab treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance for predominantly classic lesions treated with ranibizumab for 1 year, compared with PDT*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	5,391	0.34	15,638
Base case (day-case procedure)	8,998	0.34	26,102
RCOphth costs (12 injections)	9,195	0.34	26,674
RCOphth costs (9 injections)	6,619	0.34	19,203
RCOphth costs (6.5 injections)	4,473	0.34	12,976
RCOphth costs (5.6 injections)	3,700	0.34	10,735

TABLE A28 *Breakdown of ranibizumab treatment costs for each cohort by major categories, using Assessment Group and Royal College of Opthalmologists Commissioning Guidance unit costs*

		Drug (£)	Administration and monitoring (£)	Adverse events (£)	PDT (£)	Blindness (£)
Assessment Group (outpatient procedure)	PDT	0	0	78	3,845	17,575
	Ranibizumab	8,997	3,316	114	0	14,461
Assessment Group (day case)	PDT	0	0	78	3,845	17,575
	Ranibizumab	8,997	6,923	114	0	14,461
RCOphth	PDT	0	0	78	3,845	17,575
	Ranibizumab	8,997	7,120	114	0	14,461

TABLE A29 *Applying ranibizumab treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance for predominantly classic lesions treated with ranibizumab for 1 year, compared with best supportive care*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	6,457	0.57	11,412
Base case (day-case procedure)	10,065	0.57	17,787
RCOphth costs (12 injections)	10,262	0.57	18,135
RCOphth costs (9 injections)	7,686	0.57	13,584
RCOphth costs (6.5 injections)	5,540	0.57	9,791
RCOphth costs (5.6 injections)	4,767	0.57	8,425

TABLE A30 *Breakdown of ranibizumab treatment costs for each cohort by major categories, using Assessment Group and Royal College of Opthalmologists Commissioning Guidance unit costs*

		Drug (£)	Administration and monitoring (£)	Adverse events (£)	PDT (£)	Blindness (£)
Assessment Group (outpatient procedure)	Best supportive care	0	221	0	0	20,210
	Ranibizumab	8,997	3,316	114	0	14,461
Assessment Group (day case)	Best supportive care	0	221	0	0	20,210
	Ranibizumab	8,997	6,923	114	0	14,461
RCOphth	Best supportive care	0	221	0	0	20,210
	Ranibizumab	8,997	7,120	114	0	14,461

report (*Table 51*) and a breakdown by major cost categories is shown in *Table A30*.

Minimally classic and occult no classic treated with ranibizumab

Incremental costs and ICERs using treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance, with the adjustments described above, are reported in *Table A31*. Results are presented for each of the scenarios, with regard to the number of injections, included in the deterministic sensitivity analyses in the assessment report (*Table 52*) and a breakdown by major cost categories is shown in *Table A32*.

Injection procedure cost based on a combination of outpatient and day-case costs

The Novartis economic model assumed (based on a survey of UK ophthalmologists) that 75% of centres would perform intravitreal injections as day cases and 25% would perform them as outpatient procedures. Responses to the ACD were concerned that costing the injection procedure as a day case was adopting a unit cost at the extreme high end of possible values.

If the day-case procedure cost is £395 (as in the Novartis submission and as used in the Assessment

TABLE A31 *Applying ranibizumab treatment costs presented in the Royal College of Ophthalmologists Commissioning Guidance for minimally classic and occult no classic lesions treated with ranibizumab, compared with best supportive care*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	17,309	0.69	25,098
Base case (day-case procedure)	24,246	0.69	35,157
Royal College of Ophthalmologists costs			
12 injections in year 1, 12 in year 2	24,735	0.69	35,866
12 injections in year 1, 9 in year 2	22,354	0.69	32,414
9 injections in year 1, 9 in year 2	19,779	0.69	28,680
9 injections in year 1, 6 in year 2	17,398	0.69	25,227
9 injections in year 1, 3.5 in year 2	15,413	0.69	22,349
6.5 injections in year 1, 3.5 in year 2	13,268	0.69	19,238

TABLE A32 *Breakdown of total costs for each cohort by major categories, using Assessment Group and Royal College of Opthalmologists Commissioning Guidance unit costs*

		Drug (£)	Administration and monitoring (£)	Adverse events (£)	PDT (£)	Blindness (£)
Assessment Group (outpatient procedure)	Best supportive care	0	220	0	0	13,567
	Ranibizumab	17,314	6,275	193	0	7,313
Assessment Group (day case)	BSC	0	220	0	0	13,567
	Ranibizumab	17,314	13,213	193	0	7,313
RCOphth	BSC	0	220	0	0	13,567
	Ranibizumab	17,314	13,702	193	0	7,313

Group model) and outpatient cost is £90.20 (as in the Assessment Group model), the weighted average cost for intravitreal injection is $(0.25 \times 90.20) + (0.75 \times 395) = £318.80$. This cost has been applied in the Assessment Group model and results are reported below.

Pegaptanib-treated cohort compared with usual care

Applying VISION study outcomes without assessment of disease-modifying effect

Results including those in the assessment report and with the new estimate for procedure cost are given in *Table A33*.

Including disease-modifying effect for pegaptanib, year 3 only

Results including those in the assessment report and with the new estimate for procedure cost, allowing for a disease-modifying effect of pegaptanib in the year following cessation of treatment, are given in *Table A34*.

Including disease-modifying effect for pegaptanib, year 3 onwards

Results including those in the assessment report and with the new estimate for procedure cost, allowing for a disease-modifying effect of pegaptanib for the remainder of the model time horizon, are given in *Table A35*.

Predominantly classic lesions treated with ranibizumab, compared with PDT

Results including those in the assessment report and with the new estimate for procedure cost are given in *Table A36*.

TABLE A33 *Sensitivity analysis on cost of injection procedure (combination of day-case and outpatient procedure cost) for pegaptanib-treated cohort*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	8,062	0.26	30,986
Costed as day case	12,449	0.26	47,845
Costed as per Novartis	11,352	0.26	43,631

TABLE A34 *Sensitivity analysis on cost of injection procedure (combination of day-case and outpatient procedure cost) for pegaptanib-treated cohort*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	7,710	0.29	26,896
Costed as day case	12,097	0.29	42,198
Costed as per Novartis	11,000	0.29	38,373

TABLE A35 *Sensitivity analysis on cost of injection procedure (combination of day-case and outpatient procedure cost) for pegaptanib-treated cohort*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	6,941	0.34	20,467
Costed as day case	11,328	0.34	33,401
Costed as per Novartis	10,231	0.34	30,167

TABLE A36 *Sensitivity analysis on cost of injection procedure (combination of day-case and outpatient procedure cost) for predominantly classic lesions treated with ranibizumab compared with PDT*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	5,391	0.34	15,638
Costed as day case	8,998	0.34	26,102
Costed as per Novartis	8,096	0.34	23,486

Predominantly classic lesions treated with ranibizumab, compared with best supportive care

Results including those in the assessment report and with the new estimate for procedure cost are given in *Table A37*.

Minimally classic and occult no classic treated with ranibizumab

Results including those in the assessment report and with the new estimate for procedure cost are given in *Table A38*.

TABLE A37 *Sensitivity analysis on cost of injection procedure (combination of day-case and outpatient procedure cost) for predominantly classic lesions treated with ranibizumab compared with best supportive care*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	6,457	0.57	11,412
Costed as day case	10,065	0.57	17,787
Costed as per Novartis	9,163	0.57	16,193

TABLE A38 *Sensitivity analysis on cost of injection procedure (combination of day-case and outpatient procedure cost) for minimally classic and occult no classic lesions treated with ranibizumab*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	17,309	0.69	25,098
Costed as day case	24,246	0.69	35,157
Costed as per Novartis	22,512	0.69	32,642

Reduced frequency dosage regime for ranibizumab

Modifications to the model

It was necessary to amend the model to cost the reduced dosage regime for ranibizumab correctly. The formula in the original model assumed that the optometry, OCT and medical assessments would occur less frequently when the number of injections was reduced. This overestimated the saving, through the reduced-frequency dosage regime, since patients should still have monthly assessments, whether or not they have monthly injections. New estimates have been calculated for entries in deterministic sensitivity analysis tables in the assessment report (*Tables 50–52* in the assessment report). The following sections report the impact of the changed formula on results already presented in the assessment report (including the reduced-frequency regime based on the drug and disease model reported in the manufacturer's submission), and then report the ICER for other suggested reduced-frequency dosage regimes.

Predominantly classic lesions treated with ranibizumab, compared with PDT

The effect of change in formula on base case results is zero. The result in the assessment report is an incremental cost of £5391 and incremental QALYs of 0.34 (ICER = £15,638). Results with the new formula are given in *Table A39*.

The effect on sensitivity analysis is reported in the section 'Cost-effectiveness of ranibizumab – deterministic sensitivity analysis' (p. 73). The result in the assessment report is an incremental cost of £2377 and incremental QALYs of 0.34 (ICER = £6897). Results with the new formula are given in *Table A39*.

Predominantly classic lesions treated with ranibizumab, compared with best supportive care

The effect of change in formula on base case results is zero. The result in the assessment report is an incremental cost of £6457 and incremental QALYs of 0.57 (ICER = £11,412). Results with the new formula are given in *Table A40*.

The effect on sensitivity analysis is reported in the section 'Cost-effectiveness of ranibizumab – deterministic sensitivity analysis' (p. 73). The result in the assessment report is an incremental cost of £3444 and incremental QALYs of 0.57 (ICER = £6087). Results with the new formula are given in *Table A40*.

Minimally classic and occult no classic treated with ranibizumab

The effect of change in formula on base case results is zero. The result in the assessment report is an incremental cost of £17,309 and incremental

TABLE A39 *Sensitivity analysis on number of injections (corrected analysis) for predominantly classic lesions treated with ranibizumab compared with PDT*

Strategy[a]	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	5,391	0.34	15,638
9 injections in year 1	2,875	0.34	8,340
6.5 injections in year 1	778	0.34	2,258
5.6 injections in year 1	24	0.34	69

[a] 9 was the figure in the Novartis submission for injections in year 1. 6.5 is based on the 2-year average from the PRONTO study combined with a survey of ophthalmologists' opinions reported in responses to consultation on ACD. 5.6 is the value published in the PRONTO publication.[A13]

TABLE A40 *Sensitivity analysis on number of injections (corrected analysis) for predominantly classic lesions treated with ranibizumab compared with best supportive care*

Strategy[a]	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	6,457	0.57	11,412
9 injections in year 1	3,942	0.57	6,966
6.5 injections in year 1	1,845	0.57	3,261
5.6 injections in year 1	1,090	0.57	1,927

[a] 9 was the figure in the Novartis submission for injections in year 1. 6.5 is based on the 2-year average from the PRONTO study combined with a survey of ophthalmologists' opinions reported in responses to consultation on ACD. 5.6 is the value published in the PRONTO publication.[A13]

QALYs of 0.69 (ICER = £25,098). Results with the new formula are given in *Table A41*.

The effect on sensitivity analysis is reportedin the section 'Cost-effectiveness of ranibizumab – deterministic sensitivity analysis' (p. 77). The result in the assessment report for:

- 12 injections in year 1 and 9 in year 2 is an incremental cost of £14,522 and incremental QALYs of 0.69 (ICER = £21,058).
- 9 injections in year 1 and 9 in year 2 is an incremental cost of £11,510 and incremental QALYs of 0.69 (ICER = £16,689).
- 9 injections in year 1 and 6 in year 2 is an incremental cost of £8723 and incremental QALYs of 0.69 (ICER = £12,649).

Results with the new formula are given in *Table A41*.

Additional sensitivity analyses

Additional sensitivity analyses were requested, including alternative estimates for health state utility with respect to visual acuity. Two alternative sets of utility estimates have been included in this analysis:

- Those developed by SCHARR for the current submission to NICE in support of ranibizumab.[A16] This reference was submitted as Appendix II to the Lucentis NICE submission. These utility values were estimated using the TTO method used to value the EQ-5D.
- Those published by Espallargues and colleagues.[A17]

These are reported in *Tables A42–A45*.

The visual acuity states adopted in the SCHARR study were not the same as those used in the assessment group model. To take account of these differences, we estimated a simple linear regression model using the mean TTO valuation as dependent variable and the mean number of letters read (based on the visual acuity range) as the independent variable.

The utility values reported by Espallargues and colleagues[A17] were estimated using the HUI-3 and valued using data from a Canadian general population sample. The valuations reported by Espallargues and colleagues[A17] start from a lower value [0.50 for a visual acuity range of greater than 6/12 (or 20/40 in feet)].

TABLE A41 *Sensitivity analysis on number of injections (corrected analysis) for minimally classic and occult no classic lesions treated with ranibizumab*

Strategy[a]	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	17,309	0.69	25,098
12 injections in year 1, 9 in year 2	14,982	0.69	21,725
9 injections in year 1, 9 in year 2	12,467	0.69	18,077
9 injections in year 1, 6 in year 2	10,141	0.69	14,704
9 injections in year 1, 3.5 in year 2	8,203	0.69	11,894
6.5 injections in year 1, 3.5 in year 2	6,106	0.69	8,854

[a] 9 injections in year 1 and 6 in year 2 were used in the Novartis submission. 6.5 in year 1 and 3.5 in year 2 are based on the 2-year average from the PRONTO study combined with a survey of ophthalmologists' opinions reported in responses to consultation on ACD.

Pegaptanib-treated cohort compared with usual care

TABLE A42 *Sensitivity analysis on utility values applied for pegaptanib-treated cohort compared with usual care*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Base case		8,062	0.26	30,986
Health state utilities	'Brazier' values	8,062	0.21	38,928
	'Espallargues' values	8,062	0.09	91,712

Predominantly classic lesions treated with ranibizumab, compared with PDT

TABLE A43 *Sensitivity analysis on utility values applied for predominantly classic lesions compared with PDT*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Base case		5,391	0.34	15,638
Health state utilities	'Brazier' values	5,391	0.28	19,491
	'Espallargues' values	5,391	0.15	36,936

Predominantly classic lesions treated with ranibizumab, compared with best supportive care

TABLE A44 *Sensitivity analysis on utility values applied for predominantly classic lesions compared with best supportive care*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Base case		6,457	0.57	11,412
Health state utilities	'Brazier' values	6,457	0.45	14,388
	'Espallargues' values	6,457	0.21	30,241

Minimally classic and occult no classic lesions treated with ranibizumab

TABLE A45 *Sensitivity analysis on utility values applied for minimally classic and occult no classic lesions*

		Incremental cost (£)	Incremental QALYs	ICER (£)
Base case		17,309	0.69	25,098
Health state utilities	'Brazier' values	17,309	0.54	31,966
	'Espallargues' values	17,309	0.28	62,103

Projection of treatment effect

Question 3 *Could the projection of treatment of effect assumed in the Assessment Group model be illustrated graphically [particularly in order to compare the assumptions underlying the model-based 1-year trial data (ANCHOR) in the predominantly classic group versus modelling based on 2-year trial data (in the minimally classic and occult no classic subgroup for ranibizumab and from the VISION study for pegaptanib)]?*

Deliverable(s) (time permitting)

Could the projection of treatment of effect assumed in the Assessment Group model be illustrated graphically [particularly in order to compare the assumptions underlying the model based 1-year trial data (ANCHOR) in the predominantly classic group versus modelling based on 2-year trial data (in the minimally classic and occult no classic subgroup for ranibizumab and from the VISION study for pegaptanib)]?

Graphs 'vision survival', that is, those alive with visual acuity greater than 6/60 over time

Figures A4–A7 illustrate assumptions of treatment effects over the trial durations and projections up to 10 years in the treatment and control cohorts. They show the proportion of the cohort surviving and with visual acuity in the treated eye greater than 6/60.

Extend ranibizumab treatment of predominantly classic lesions to 2 years

The approach to this involves assuming that treatment beyond the first year will maintain stabilisation of visual acuity, but will not lead to further significant improvements. Transition

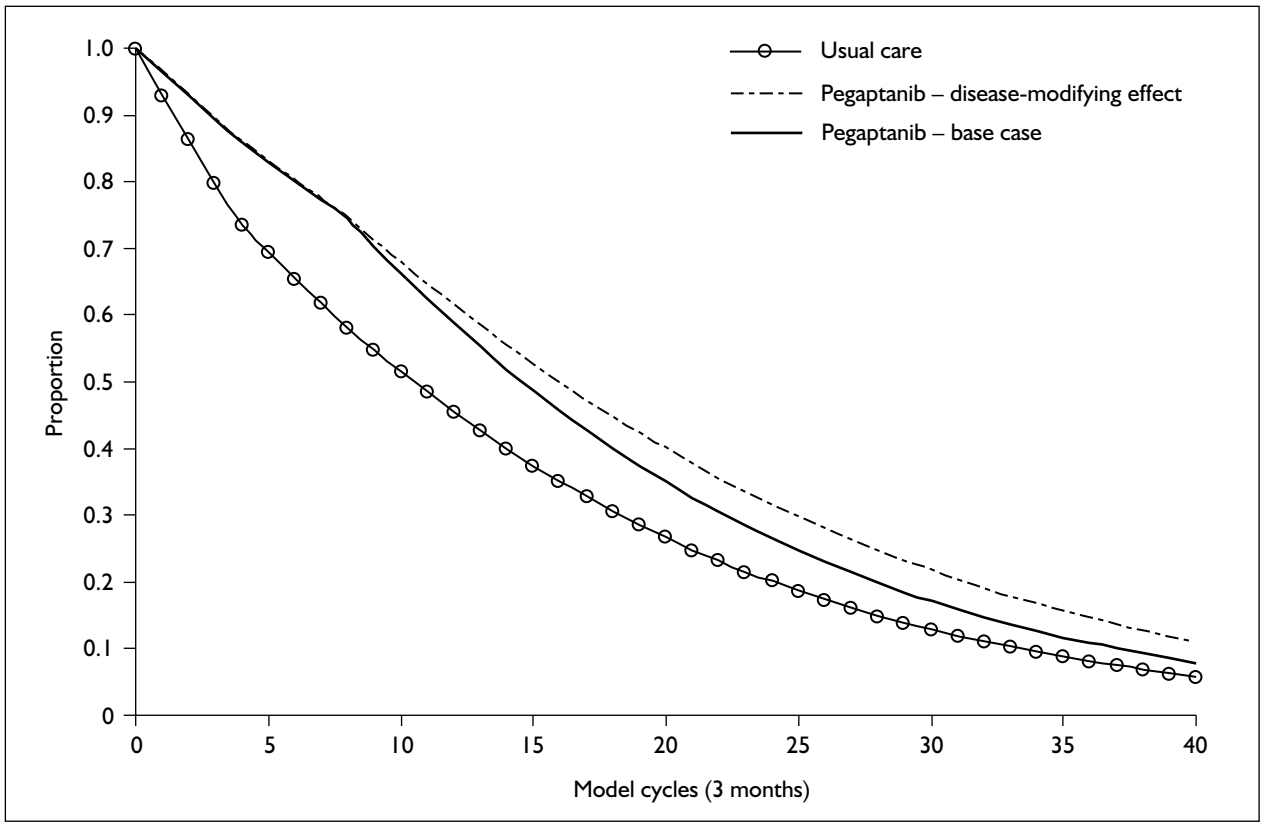

FIGURE A4 *Proportion of cohort surviving and sighted over 10 years, pegaptanib-treated cohort compared with usual care*

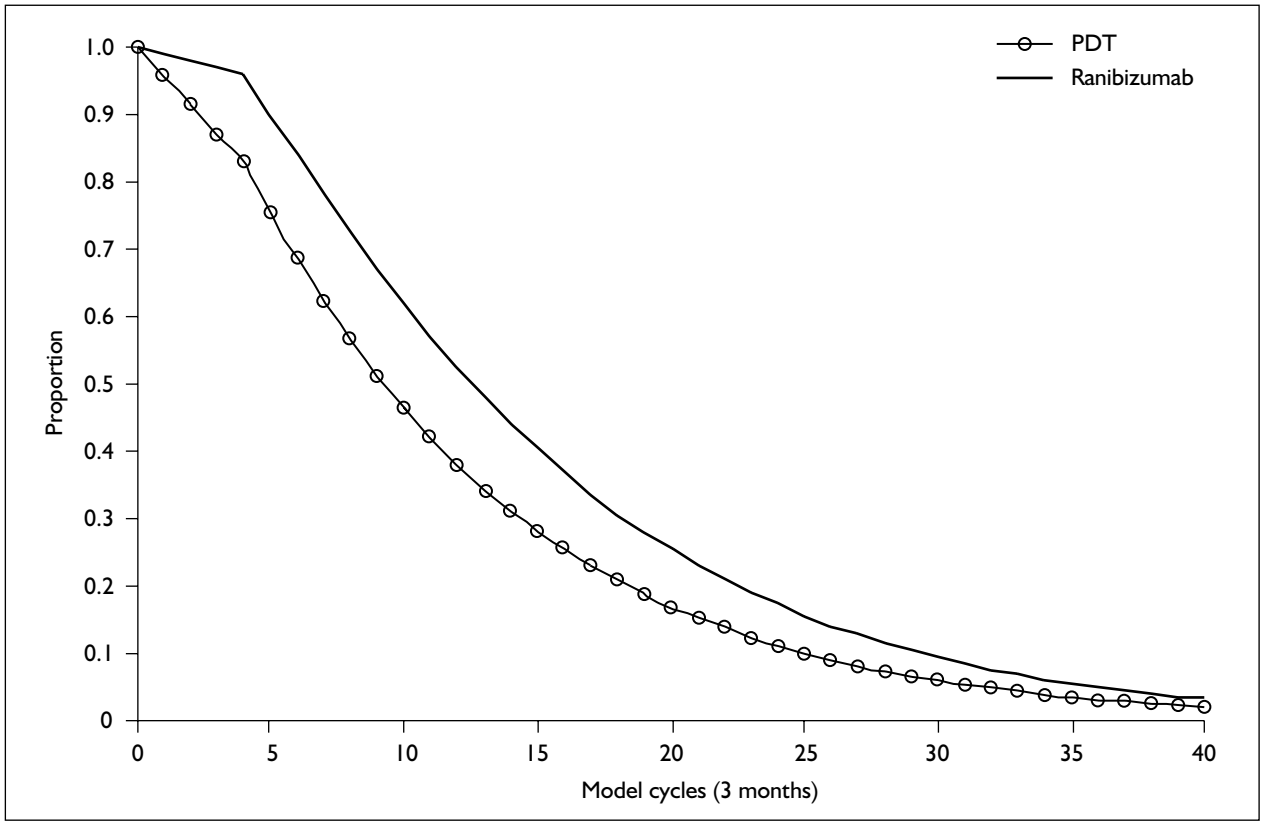

FIGURE A5 *Proportion of cohort surviving and sighted over 10 years, predominantly classic lesions treated with ranibizumab compared with PDT*

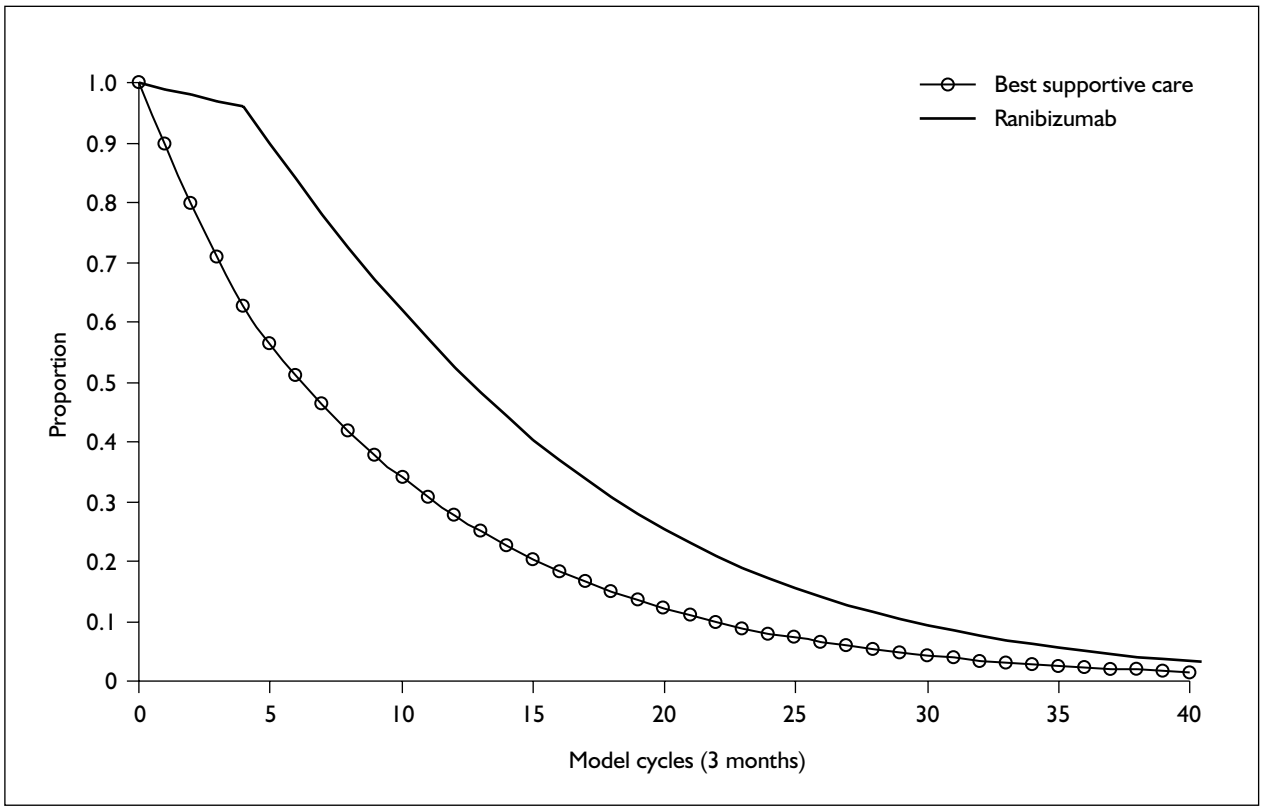

FIGURE A6 *Proportion of cohort surviving and sighted over 10 years, predominantly classic lesions treated with ranibizumab compared with best supportive care*

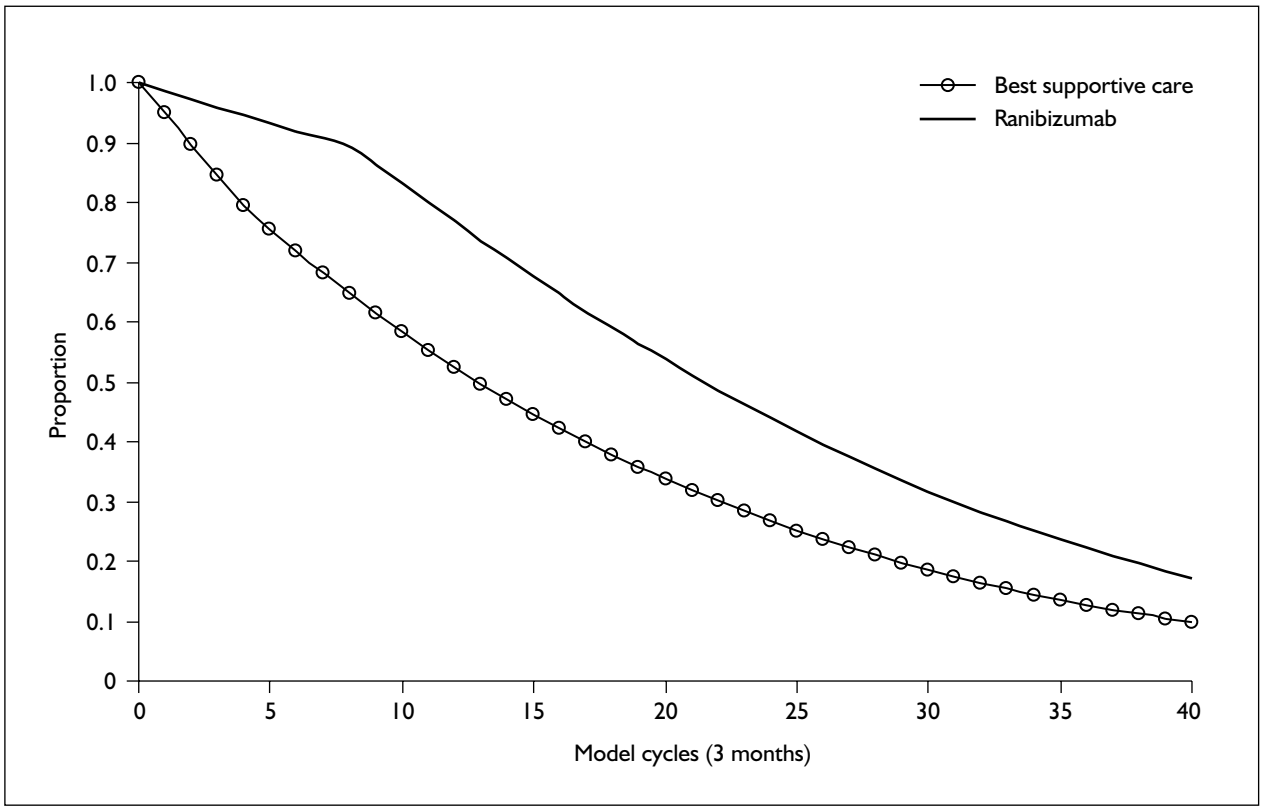

FIGURE A7 *Proportion of cohort surviving and sighted over 10 years, minimally classic and occult no classic lesions treated with ranibizumab*

TABLE A46 *Values used to extrapolate to 2 years of treatment with ranibizumab (predominantly classic lesion)*

	Year 1 (%)	Year 2 (%)
Gaining >3 lines	36.69	4.53
Losing 3–6 lines	2.16	2.16
Losing >6 lines	0.00	0.00

TABLE A47 *Results for second year of treatment with ranibizumab for predominantly classic lesions compared with PDT*

	Costs (£)	QALYs	ICER (£)
PDT	23,455	3.89	
Ranibizumab	35,430	4.45	21,241

probabilities for year 1 are based on the proportions improving or losing vision shown in column 2 of *Table A46*. For year 2, transition probabilities for deterioration of vision are based on the proportions losing vision in column 2, with the probability of gaining vision reverting to the value applied in the best supportive care cohort, derived from the TAP study predominantly classic lesions population.

Predominantly classic lesions treated with ranibizumab for the second year, compared with PDT

Incremental effectiveness increases from 0.34 to 0.56 QALYs in this scenario. The incremental cost becomes £11,975 and the ICER with base case assumptions (i.e. 12 injections per year of treatment) is £21,241 (*Table A47*).

Table A48 shows the breakdown of the total costs (reported in *Table A47*). Clearly, drug and monitoring costs (for ranibizumab) have approximately doubled on adding an extra year of treatment. At the same time, the costs of blindness for ranibizumab have reduced by approximately 20%.

Table A49 reports a sensitivity analysis, assuming equal effectiveness, for the reduced-frequency dosing regime: first that reported in the assessment report of nine injections per year and second based on results reported in consultation (based on the PRONTO study).

Predominantly classic lesions treated with ranibizumab for the second year, compared with best supportive care

Incremental effectiveness increases from 0.57 to 0.94 QALYs in this scenario. The incremental cost becomes £14,467 and the ICER with base case assumptions (i.e. 12 injections per year of treatment) is £15,382 (*Table A50*).

TABLE A50 *Results for second year of treatment with ranibizumab for predominantly classic lesions compared with best supportive care*

	Costs (£)	QALYs	ICER (£)
PDT	20,963	3.51	
Ranibizumab	35,430	4.45	15,382

TABLE A48 *Breakdown of total costs for each cohort by major categories, using Assessment Group unit costs*

	Drug (£)	Administration and monitoring (£)	Adverse events (£)	PDT (£)	Blindness (£)
PDT	0	0	148	7,041	16,266
Ranibizumab	17,330	6,281	220	0	11,598

TABLE A49 *Sensitivity analysis on number of injections (corrected analysis) for 2 years of treatment with ranibizumab for predominantly classic lesions compared with PCT*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	11,975	0.56	21,241
9 injections year 1, 9 year 2	7,129	0.56	12,645
9 injections year 1, 6 year 2	4,798	0.56	8,511
5.6 injections year 1, 5.6 year 2[a]	1,636	0.56	2,903

[a] As reported for year 1 in the PRONTO publication.[A13]

TABLE A51 *Sensitivity analysis on number of injections (corrected analysis)*

Strategy	Incremental cost (£)	Incremental QALYs	ICER (£)
Base case	14,467	0.94	15,382
9 injections year 1, 9 year 2	9,621	0.94	10,230
9 injections year 1, 6 year 2	7,291	0.94	7,752
5.6 injections year 1, 5.6 year 2[a]	4,129	0.94	4,390

[a] As reported for year 1 in the PRONTO publication.[A13]

Table A51 reports a sensitivity analysis, assuming equal effectiveness, for the reduced-frequency dosing regime: first that reported in the assessment report of nine injections per year and second based on results reported in consultation (based on the PRONTO study).

Graphical presentation of vision survival for predominantly classic lesions treated with ranibizumab for 2 years, compared with best supportive care

This is shown in *Figure A8*.

References

A1. Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C. Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2003;**7**(9).

A2. Pieramici DJ, Bressler SB. Age-related macular degeneration and risk factors for the development of choroidal neovascularization in the fellow eye. *Curr Opin Ophthalmol* 1998;**9**(3):38–46.

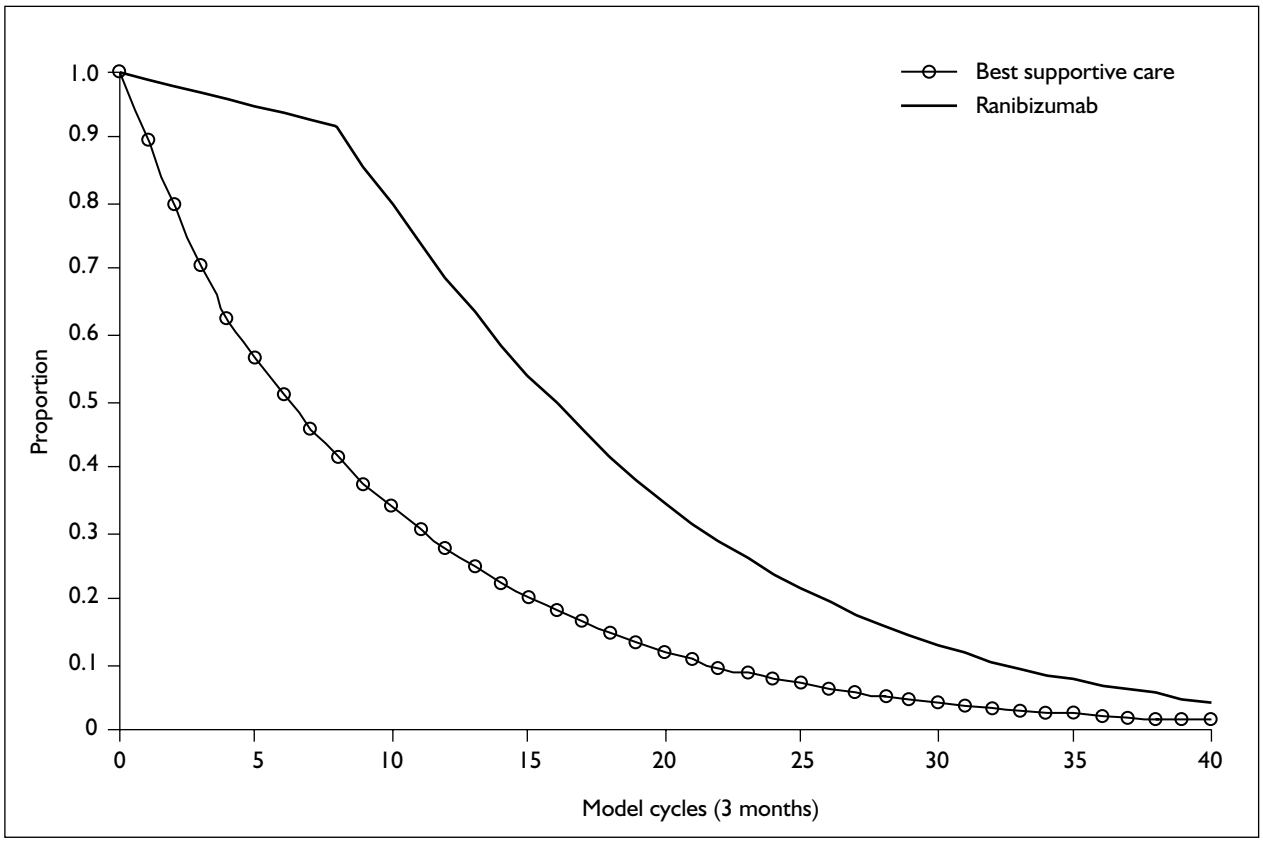

FIGURE A8 *Proportion of cohort surviving and sighted over 10 years, predominantly classic lesions treated with ranibizumab (extrapolation to 2 years) compared with best supportive care*

A3. Macular Photocoagulation Study Group. Risk factors for choroidal neovascularisation in the second eye of patients with juxtafoveal or subfoveal choroidal neovascularisation secondary to age-related macular degeneration. *Arch Ophthalmol* 1997;**115**:741–7.

A4. The Royal College of Ophthalmologists. *Age related macular degeneration. Guidelines*. London: Royal College of Ophthalmologists; 2002.

A5. Gregor Z, Bird AC, Chisholm IH. Senile disciform macular degeneration in the second eye. *Br J Ophthalmol* 1977;**61**:141–7.

A6. Bressler SB, Bressler NM, Fine SL, Hillis A, Murphy RP, Olk RJ, *et al*. Natural course of choroidal neovascular membranes within the foveal avascular zone in senile macular degeneration. *Am J Ophthalmol* 1982;**93**:157–63.

A7. Shrahlman E, Fine SL, Hillis A. The second eye of patients with senile macular degeneration. *Arch Ophthalmol* 1983;**101**:1191–3.

A8. Bressler SB, Bressler NM, Maguire MG, Burgess D, Hawkins BS, Orth DH, *et al*., for the Macular Photocoagulation Study Group. Drusen characteristics and risk of exudation in the fellow eye of argon SMD patients in the Macular Photocoagulation Study. *Invest Ophthalmol Vis Sci* 1989;**30**(Suppl):154.

A9. Schooppner G, Chuang EL, Bird AC. Retinal pigment epithelial tears: risk to the second eye. *Am J Ophthalmol* 1989;**108**:683–5.

A10. Ferris FL, Davis MD, Clemons TE, Lee LY, Chew EY, Lindblad AS, *et al*. Age-Related Eye Disease Study (AREDS) Research Group. A simplified severity scale for age-related macular degeneration: AREDS Report No. 18. *Arch Ophthalmol* 2005;**123**:1570–4.

A11. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, *et al*. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1432–44.

A12. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, *et al*. Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1419–31.

A13. Fung AE, Lalwani GA, Rosenfeld PJ, Dubovy SR, Michels S, Feuer WJ, *et al*. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. *Am J Ophthalmol* 2007;**143**:566–83.

A14. Lotery AJ, Xu X, Zlatava G, Loftus J. Burden of illness, visual impairment, and health resource utilisation of patients with neovascular age-related macular degeneration: results from the United Kingdom cohort of a five-country cross-sectional study. *Br J Ophthalmol* 2007;**91**:1303–7.

A15. Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003;**87**:1201–4.

A16. Brazier JE, Kang K, Carlton J, Czoski-Murray CJ. *General population survey to obtain values for AMD visual impairment states using lenses. Preliminary report*. Sheffield: University of Sheffield, School of Health and Related Research; 2006.

A17. Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA, *et al*. The impact of age-related macular degeneration on health status utility values. *Invest Ophthalmol Vis Sci* 2005;**46**:4016–23.

Annex A1: Cost of blindness in assessment report. Background

We have also included tables illustrating this breakdown of costs for the costs of blindness scenarios reported in the deterministic sensitivity analyses.

Pegaptanib-treated cohort compared with usual care

Costs of blindness for the cohort treated with pegaptanib or receiving usual care are given in the assessment report (*Table 44*) as £12,666 and £15,789, respectively. These are broken down into costs that are assumed to be one-off costs of the transition to blindness (blind registration, provision of low-vision aids and low-vision rehabilitation) and costs that occur in each year of blindness (community care, residential care, treatment for depression and treatment of fractures following accidents). *Table A52* reports the recurring costs of blindness and their proportion of the total estimated costs of blindness. It can be readily seen that, under the assumptions adopted in the assessment report, these recurring costs constitute most of the costs of blindness (99%), with residential care costs constituting the major portion of these costs.

Table A53 reports the one-off costs of blindness – it is clear that these are the minority of costs, under the assumptions adopted in the assessment report. One adjustment to this would be to require some additional (updating) of low-vision aids or low-vision rehabilitation (included in a sensitivity analysis later).

TABLE A52 *Proportion of costs of blindness by type (recurring costs)*

	Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
Pegaptanib	1,005 (7.9)	10,411 (82.2)	429 (3.4)	688 (5.4)	12,533
Usual care	1,254 (7.9)	12,995 (82.3)	536 (3.4)	858 (5.4)	15,643

TABLE A53 *Proportion of costs of blindness by type (one-off costs)*

	Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
Pegaptanib	77 (0.6)	36 (0.3)	20 (0.2)	133
Usual care	85 (0.5)	39 (0.2)	22 (0.1)	146

Table A54 reports the recurring costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 45* of the assessment report.

Table A55 reports the one-off costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 45* of the assessment report.

TABLE A54 *Proportion of costs of blindness by type in sensitivity analyses (recurring costs)*

		Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
High uptake	Pegaptanib	6,700 (14.5)	34,337 (74.4)	552 (1.2)	4,348 (9.4)	45,937
High cost	Usual care	8,362 (14.5)	42,858 (74.4)	689 (1.2)	5,427 (9.4)	57,337
Low uptake	Pegaptanib	240 (9.4)	2,160 (84.8)	66 (2.6)	43 (1.7)	2,510
Low cost	Usual care	300 (9.4)	2,696 (84.9)	83 (2.6)	54 (1.7)	3,133
Medium uptake	Pegaptanib	1,005 (4.8)	18,394 (88.1)	429 (2.1)	879 (4.2)	20,707
High cost	Usual care	1,254 (4.8)	22,959 (88.2)	536 (2.1)	1,098 (4.2)	25,846
Medium uptake	Pegaptanib	240 (3.9)	4,985 (81.1)	429 (7.0)	445 (7.2)	6,099
Low cost	Usual care	300 (3.9)	6,222 (81.1)	536 (7.0)	555 (7.2)	7,613
High uptake	Pegaptanib	6,700 (22.1)	19,435 (64.2)	552 (1.8)	3,397 (11.2)	30,083
Medium cost	Usual care	8,362 (22.2)	24,258 (64.3)	689 (1.8)	4,240 (11.2)	37,549
Low uptake	Pegaptanib	1,005 (17.5)	4,512 (78.5)	66 (1.2)	69 (1.2)	5,652
Medium cost	Usual care	1,254 (17.5)	5,631 (78.6)	83 (1.2)	86 (1.2)	7,054

TABLE A55 *Proportion of costs of blindness by type in sensitivity analyses (one-off costs)*

		Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
High uptake	Pegaptanib	114 (0.2)	79 (0.2)	24 (0.1)	217
High cost	Usual care	125 (0.2)	87 (0.2)	27 (0.0)	238
Low uptake	Pegaptanib	14 (0.6)	14 (0.5)	10 (0.4)	38
Low cost	Usual care	16 (0.5)	15 (0.5)	11 (0.3)	41
Medium uptake	Pegaptanib	114 (0.5)	36 (0.2)	24 (0.1)	173
High cost	Usual care	125 (0.5)	39 (0.1)	27 (0.1)	190
Medium uptake	Pegaptanib	27 (0.4)	14 (0.2)	10 (0.2)	50
Low cost	Usual care	30 (0.4)	15 (0.2)	11 (0.1)	55
High uptake	Pegaptanib	77 (0.3)	79 (0.3)	20 (0.1)	176
Medium cost	Usual care	85 (0.2)	87 (0.2)	22 (0.1)	193
Low uptake	Pegaptanib	41 (0.7)	36 (0.6)	20 (0.3)	97
Medium cost	Usual care	45 (0.6)	39 (0.5)	22 (0.3)	106

Predominantly classic lesions treated for 1 year, compared with PDT

Costs of blindness for cohorts with predominantly classic lesions treated with ranibizumab or PDT are given in the assessment report (*Table 49*) as £14,461 and £17,575, respectively. These are broken down into costs that are assumed to be one-off costs of the transition to blindness (blind registration, provision of low-vision aids and low-vision rehabilitation) and costs that occur in each year of blindness (community care, residential care, treatment for depression and treatment of fractures following accidents). *Table A56* reports the recurring costs of blindness and their proportion of the total estimated costs of blindness. It can be readily seen that, under the assumptions adopted in the assessment report, these recurring costs constitute most of the costs of blindness (99%), with residential care costs constituting the major portion of these costs.

Table A57 reports the one-off costs of blindness – it is clear that these are the minority of costs, under the assumptions adopted in the assessment report. One adjustment to this would be to require some additional (updating) of low-vision aids or low-vision rehabilitation (included in a sensitivity analysis later).

Table A58 reports the recurring costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 50* of the assessment report.

Table A59 reports the one-off costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 50* of the assessment report.

TABLE A56 *Proportion of costs of blindness by type (recurring costs)*

	Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
Ranibizumab	1,147 (7.9)	11,890 (82.2)	490 (3.4)	785 (5.4)	14,313
PDT	1,396 (7.9)	14,466 (82.3)	597 (3.4)	955 (5.4)	17,414

TABLE A57 *Proportion of costs of blindness by type (one-off costs)*

	Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
Ranibizumab	86 (0.6)	40 (0.3)	22 (0.2)	148
PDT	94 (0.5)	43 (0.2)	24 (0.1)	161

TABLE A58 *Proportion of costs of blindness by type in sensitivity analyses (recurring costs)*

		Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
High uptake	Ranibizumab	7,651 (15.2)	39,214 (78.0)	631 (1.3)	2,511 (5.0)	50,006
High cost	PDT	9,309 (15.2)	47,709 (78.1)	767 (1.3)	3,054 (5.0)	60,840
Low uptake	Ranibizumab	274 (9.3)	2,467 (83.4)	76 (2.6)	99 (3.4)	2,916
Low cost	PDT	334 (9.3)	3,001 (83.5)	92 (2.6)	121 (3.4)	3,548
Medium uptake	Ranibizumab	1,147 (4.9)	21,007 (90.0)	490 (2.1)	508 (2.2)	23,152
High cost	PDT	1,396 (4.9)	25,558 (90.1)	597 (2.1)	618 (2.2)	28,168
Medium uptake	Ranibizumab	274 (3.7)	5,692 (75.7)	490 (6.5)	1,004 (13.4)	7,461
Low cost	PDT	334 (3.7)	6,926 (75.8)	597 (6.5)	1,222 (13.4)	9,078
High uptake	Ranibizumab	7,651 (22.1)	22,195 (64.2)	631 (1.8)	3,880 (11.2)	34,356
Medium cost	PDT	9,309 (22.2)	27,003 (64.3)	767 (1.8)	4,720 (11.2)	41,799
Low uptake	Ranibizumab	1,147 (17.5)	5,152 (78.5)	76 (1.2)	79 (1.2)	6,454
Medium cost	PDT	1,396 (17.5)	6,269 (78.7)	92 (1.2)	96 (1.2)	7,853

TABLE A59 *Proportion of costs of blindness by type in sensitivity analyses (one-off costs)*

		Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
High uptake	Ranibizumab	127 (0.3)	88 (0.2)	27 (0.1)	242
High cost	PDT	138 (0.2)	96 (0.2)	29 (0.0)	263
Low uptake	Ranibizumab	16 (0.5)	15 (0.5)	11 (0.4)	42
Low cost	PDT	17 (0.5)	16 (0.5)	12 (0.3)	46
Medium uptake	Ranibizumab	127 (0.5)	40 (0.2)	27 (0.1)	194
High cost	PDT	138 (0.5)	43 (0.2)	29 (0.1)	210
Medium uptake	Ranibizumab	30 (0.4)	15 (0.2)	11 (0.1)	56
Low cost	PDT	33 (0.4)	16 (0.2)	12 (0.1)	61
High uptake	Ranibizumab	86 (0.3)	88 (0.3)	22 (0.1)	197
Medium cost	PDT	94 (0.2)	96 (0.2)	24 (0.1)	213
Low uptake	Ranibizumab	46 (0.7)	40 (0.6)	22 (0.3)	108
Medium cost	PDT	50 (0.6)	43 (0.5)	24 (0.3)	117

Predominantly classic lesions treated for 1 year, compared with best supportive care

Costs of blindness for cohort with predominantly classic lesions treated with ranibizumab or best supportive care are given in the assessment report (*Table 49*) as £20,210 and £14,461, respectively. *Table A60* reports the recurring costs of blindness and their proportion of the total estimated costs of blindness. It can be readily seen that, under the assumptions adopted in the assessment report, these recurring costs constitute most of the costs of blindness (99%), with residential care costs constituting the major portion of these costs.

Table A61 reports the one-off costs of blindness – it is clear that these are the minority of costs, under the assumptions adopted in the assessment report. One adjustment to this would be to require some additional (updating) of low-vision aids or low-vision rehabilitation (included in a sensitivity analysis later).

Table A62 reports the recurring costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 51* of the assessment report.

Table A63 reports the one-off costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 51* of the assessment report.

Minimally classic and occult no classic treated for 2 years

Costs of blindness for cohort with predominantly classic lesions treated with ranibizumab or best

TABLE A60 *Proportion of costs of blindness by type (recurring costs)*

	Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
Ranibizumab	1,147 (7.9)	11,890 (82.2)	490 (3.4)	785 (5.4)	14,313
BSC	1,606 (7.9)	16,648 (82.4)	687 (3.4)	1,100 (5.4)	20,041

TABLE A61 *Proportion of costs of blindness by type (one-off costs)*

	Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
Ranibizumab	86 (0.6)	40 (0.3)	22 (0.2)	148
BSC	99 (0.5)	45 (0.2)	25 (0.1)	169

TABLE A62 *Proportion of costs of blindness by type in sensitivity analyses (recurring costs)*

		Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
High uptake	Ranibizumab	7,651 (15.2)	39,214 (78.0)	631 (1.3)	2,511 (5.0)	50,006
High cost	PDT	10,713 (15.2)	54,907 (78.1)	883 (1.3)	3,515 (5.0)	70,019
Low uptake	Ranibizumab	274 (9.3)	2,467 (83.4)	76 (2.6)	99 (3.4)	2,916
Low cost	PDT	384 (9.3)	3,454 (83.6)	106 (2.6)	139 (3.4)	4,083
Medium uptake	Ranibizumab	1,147 (4.9)	21,007 (90.0)	490 (2.1)	508 (2.2)	23,152
High cost	PDT	1,606 (4.9)	29,414 (90.1)	687 (2.1)	711 (2.2)	32,418
Medium uptake	Ranibizumab	274 (3.7)	5,692 (75.7)	490 (6.5)	1,004 (13.4)	7,461
Low cost	PDT	384 (3.7)	7,971 (75.8)	687 (6.5)	1,406 (13.4)	10,448
High uptake	Ranibizumab	7,651 (22.1)	22,195 (64.2)	631 (1.8)	3,880 (11.2)	34,356
Medium cost	PDT	10,713 (22.2)	31,077 (64.3)	883 (1.8)	5,432 (11.2)	48,106
Low uptake	Ranibizumab	1,147 (17.5)	5,152 (78.5)	76 (1.2)	79 (1.2)	6,454
Medium cost	PDT	1,606 (17.5)	7,214 (78.8)	106 (1.2)	110 (1.2)	9,037

TABLE A63 *Proportion of costs of blindness by type in sensitivity analyses (one-off costs)*

		Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
High uptake	Ranibizumab	127 (0.3)	88 (0.2)	27 (0.1)	242
High cost	PDT	145 (0.2)	101 (0.1)	31 (0.0)	276
Low uptake	Ranibizumab	16 (0.5)	15 (0.5)	11 (0.4)	42
Low cost	PDT	18 (0.4)	17 (0.4)	13 (0.3)	48
Medium uptake	Ranibizumab	127 (0.5)	40 (0.2)	27 (0.1)	194
High cost	PDT	145 (0.4)	45 (0.1)	31 (0.1)	221
Medium uptake	Ranibizumab	30 (0.4)	15 (0.2)	11 (0.1)	56
Low cost	PDT	34 (0.3)	17 (0.2)	13 (0.1)	64
High uptake	Ranibizumab	86 (0.3)	88 (0.3)	22 (0.1)	197
Medium cost	PDT	99 (0.2)	101 (0.2)	25 (0.1)	225
Low uptake	Ranibizumab	46 (0.7)	40 (0.6)	22 (0.3)	108
Medium cost	PDT	53 (0.6)	45 (0.5)	25 (0.3)	123

supportive care are given in the assessment report (*Table 49*) as £13,567 and £7,313, respectively. *Table A64* reports the recurring costs of blindness and their proportion of the total estimated costs of blindness. It can be readily seen that, under the assumptions adopted in the assessment report, these recurring costs constitute most of the costs of blindness (99%), with residential care costs constituting the major portion of these costs.

Table A65 reports the one-off costs of blindness – it is clear that these are the minority of costs, under the assumptions adopted in the assessment report. One adjustment to this would be to require some additional (updating) of low-vision aids or low-vision rehabilitation (included in a sensitivity analysis later).

Table A66 reports the recurring costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 52* of the assessment report.

Table A67 reports the one-off costs of blindness and their proportion of the total estimated costs of blindness in the scenarios reported in the sensitivity analyses in *Table 52* of the assessment report.

TABLE A64 *Proportion of costs of blindness by type (recurring costs)*

	Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
Ranibizumab	578 (7.9)	5,995 (82.0)	247 (3.4)	396 (5.4)	7,217
Best supportive care	1,077 (7.9)	11,160 (82.3)	460 (3.4)	737 (5.4)	13,434

TABLE A65 *Proportion of costs of blindness by type (one-off costs)*

	Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
Ranibizumab	56 (0.8)	26 (0.4)	14 (0.2)	96
Best supportive care	77 (0.6)	35 (0.3)	20 (0.1)	133

TABLE A66 *Proportion of costs of blindness by type in sensitivity analyses (recurring costs)*

		Community care £ (%)	Residential care £ (%)	Depression £ (%)	Fractures £ (%)	Total (£)
High uptake	Ranibizumab	3,858 (15.2)	19,773 (77.9)	318 (1.3)	1,266 (5.0)	25,215
High cost	PDT	7,181 (15.2)	36,806 (78.1)	592 (1.3)	2,356 (5.0)	46,936
Low uptake	Ranibizumab	138 (9.2)	1,244 (83.0)	38 (2.6)	50 (3.3)	1,470
Low cost	PDT	258 (9.3)	2,315 (83.4)	71 (2.6)	93 (3.4)	2,737
Medium uptake	Ranibizumab	578 (4.9)	10,592 (89.8)	247 (2.1)	256 (2.2)	11,674
High cost	PDT	1,077 (4.9)	19,717 (90.0)	460 (2.1)	477 (2.2)	21,731
Medium uptake	Ranibizumab	138 (3.6)	2,870 (75.6)	247 (6.5)	506 (13.3)	3,762
Low cost	PDT	258 (3.7)	5,343 (75.7)	460 (6.5)	943 (13.4)	7,003
High uptake	Ranibizumab	3,858 (22.1)	11,191 (64.1)	318 (1.8)	1,956 (11.2)	17,323
Medium cost	PDT	7,181 (22.1)	20,832 (64.3)	592 (1.8)	3,641 (11.2)	32,247
Low uptake	Ranibizumab	578 (17.4)	2,598 (78.2)	38 (1.2)	40 (1.2)	3,254
Medium cost	PDT	1,077 (17.5)	4,836 (78.6)	71 (1.2)	74 (1.2)	6,058

TABLE A67 *Proportion of costs of blindness by type in sensitivity analyses (one-off costs)*

		Blind registration £ (%)	Low-vision aids £ (%)	Low-vision rehabilitation £ (%)	Total (£)
High uptake	Ranibizumab	82 (0.3)	57 (0.2)	17 (0.1)	157
High cost	PDT	113 (0.2)	79 (0.2)	24 (0.1)	216
Low uptake	Ranibizumab	10 (0.7)	10 (0.7)	7 (0.5)	27
Low cost	PDT	14 (0.5)	13 (0.5)	10 (0.4)	38
Medium uptake	Ranibizumab	82 (0.7)	26 (0.2)	17 (0.1)	125
High cost	PDT	113 (0.5)	35 (0.2)	24 (0.1)	173
Medium uptake	Ranibizumab	20 (0.5)	10 (0.3)	7 (0.2)	36
Low cost	PDT	27 (0.4)	13 (0.2)	10 (0.1)	50
High uptake	Ranibizumab	56 (0.3)	57 (0.3)	14 (0.1)	127
Medium cost	PDT	77 (0.2)	79 (0.2)	20 (0.1)	176
Low uptake	Ranibizumab	30 (0.9)	26 (0.8)	14 (0.4)	70
Medium cost	PDT	41 (0.7)	35 (0.6)	20 (0.3)	96

Annex A2: Visual acuity

Visual acuity data are given in *Table A68*.

TABLE A68 *Visual acuity data*

Visual acuity range	Mean TTO	95% CI
⩾20/50	0.864	0.814 to 0.914
20/60 to 20/100	0.783	0.735 to 0.832
20/125 to 20/160	0.688	0.601 to 0.776
20/200 to 20/400	0.635	0.544 to 0.727
<20/400	0.497	0.416 to 0.577

A visual acuity of ⩾20/50 implies an ability to read 65 letters or more – assuming an upper limit to this range of 20/10, where number of letters reads 100 – giving a median for this visual acuity range of 82.5 letters. Similar median values were estimated for the other visual acuity ranges.
A simple linear regression model was estimated to predict mean TTO valuations for the visual acuity ranges used in the assessment group model – the estimated values are shown in *Table A69*.

TABLE A69 *Estimated utilities for assessment group model*

Visual acuity range	Utility (estimated)
⩾6/12	0.900
⩽6/12 to >6/24	0.786
⩽6/24 to >6/60	0.697
⩽6/60 to >3/60	0.609
⩽3/60	0.518

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We look forward to hearing from you.

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