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

Produced by Southampton Health Technology Assessments Centre

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Rider on responsibility for report

The views expressed in this report are those of the authors and not necessarily those of the NHS R&D HTA Programme. Any errors are the responsibility of the authors.

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DEFINITION OF TERMS 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.

AMD	Age-related macular degeneration
AREDS	Age-related eye disease study
ARM	Age-related maculopathy
BNF	British National Formulary
CI	Confidence interval
CNV	Choroidal neovascularisation
CVI	Certificate of vision impairment
DA	Optic disc areas (measurement of lesion size: DA = 2.54mm^2)
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	Fluoroscein angiography
ICER	Incremental cost-effectiveness ratio
LogMAR	Log_{10} of the minimum angle of resolution
MAR	Minimum angle of resolution
MC	Minimally classic lesion
NEI-VFQ	National Eye Institute Visual Function Questionnaire
OCT	Optical coherence tomography
PC	Predominantly classic lesion
PDT	Photodynamic therapy
QALYs	Quality-adjusted life years
RCT	Randomised controlled trial
RPE	Retinal pigment epithelium
SPC	Summary of Product Characteristics
TAP	Treatment of Age-Related Macular Degeneration with Photodynamic Therapy trial
µm	Micrometer (micron)
VAR	Visual acuity rating
VEGF, VEGF-A	Vascular endothelial growth factor. 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.
VIP	Verteporfin in Photodynamic Therapy trial

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 with verteporfin has been recommended by NICE for those with classic no occult subfoveal CNV and may be used in patients with predominantly classic lesions as part of clinical studies. While 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

To assess the clinical effectiveness and cost-effectiveness of ranibizumab and pegaptanib for subfoveal CNV associated with wet AMD.

Methods

Data sources

Electronic databases 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. Manufacturer submissions to the National Institute for Health and Clinical Excellence 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 though discussion. Inclusion criteria:

- 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/QALY.
- Types of studies: 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 though discussion. The quality of included studies was assessed using criteria by 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.

Results

Number and quality of studies

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). Two published RCTs of ranibizumab were identified, and two additional unpublished RCTs were provided by the manufacturer, comparing:

- 0.3 mg and 0.5 mg ranibizumab versus sham injection in patients with minimally classic or occult lesions (MARINA)
- 0.3 mg and 0.5 mg ranibizumab versus PDT with verteporfin in patients with predominantly classic lesions (ANCHOR)
- A reduced dose frequency regimen of 0.3 mg 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, unpublished)

The quality of the pegaptanib VISION study was generally good. The two published ranibizumab trials and the two unpublished trials were also of good methodological quality.

Summary of benefits and risks

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 mg 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).
- *Subgroup analysis:* A statistically significant difference in mean change in visual acuity was found between all doses of pegaptanib and sham injection for patients with minimally classic or occult with no classic lesions. Only the licensed 0.3mg dose was significantly more effective in reducing visual acuity loss in people with predominantly classic lesions. The publications did not report subgroup analyses of the primary outcome.
- *Anatomical changes:* The 1.0 mg dose had a statistically significant effect on change in size of lesion, change in size of CNV and change in size of leakage, but the 0.3 mg dose

had a significant effect on change in size of lesion only, and the 3.0 mg dose was not statistically significantly different from sham for any of these anatomical measures.

- *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% to 94.5%; 0.5mg: 94.6% to 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). 0.5 mg 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=0.0003) in patients with predominantly or minimally classic lesions. A reduced dosing frequency was [redacted] patients losing less than 15 letters [redacted] compared with sham injection [redacted] 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 [redacted] for patients receiving* 0.5 mg ranibizumab plus PDT compared with PDT plus sham injection (23.8% vs 5.4%, p=0.033). There was [redacted] patients gaining 15 letters or more between ranibizumab and sham injection in the reduced dose frequency study. In the MARINA and ANCHOR trials, ranibizumab patients gained letters of visual acuity (mean 6.5 to 11.3) at 12 months while patients with sham injection or PDT lost about 10 letters (p<0.001). In the PIER study, patients lost on average 1.6 letters (0.3 mg) or 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, 0.3mg: 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. [redacted] patients receiving 0.5mg ranibizumab plus PDT deteriorated to legal blindness compared with PDT plus sham injection [redacted] The difference between* ranibizumab and sham injection was [redacted] in the reduced dose PIER study [redacted]

- *Subgroup analysis:* In the MARINA, FOCUS and ANCHOR trials, the difference in the primary outcome between the ranibizumab groups and the comparator group was statistically significant for each lesion subgroup. In the reduced dose frequency PIER study, the difference between 0.5mg ranibizumab [redacted] versus sham injection [redacted] was [redacted] for the group of patients with [redacted]
- *Contrast sensitivity:* Contrast sensitivity [redacted] in the ranibizumab groups [redacted] in the sham injection [redacted] PDT groups [redacted] The reduced dose frequency PIER study found [redacted] or [redacted] in contrast sensitivity compared with [redacted]
- *Anatomical changes:* The MARINA, [redacted] and ANCHOR trials demonstrated statistically significant differences between 0.3 mg or 0.5 mg ranibizumab and the comparator for the area of CNV, area of leakage from CNV plus intense progressive retinal pigment epithelium staining, or area of classic CNV.
- *Visual function questionnaire scores:* [redacted] results were reported for [redacted] ranibizumab compared with sham injection [redacted] NEI VFQ-25 [redacted], [redacted] and [redacted] A [redacted] in [redacted] was found with [redacted] when compared with PDT. There were [redacted] between ranibizumab and sham injection in the reduced dose PIER study.
- *Adverse events:* Adverse events were common but most were mild to moderate. Serious ocular events were rare in the MARINA and ANCHOR trials. Incidences of severe ocular inflammation varied between treatment arms, and were highest in the 0.5mg ranibizumab groups. The rate of serious ocular adverse events was [redacted] in the ranibizumab plus PDT group compared with [redacted] PDT. Endophthalmitis was reported by very few patients in the active treatment arms of the ranibizumab trials and none in the control arms. The condition occurred in up to 1.4% of 0.5mg dose ranibizumab patients in the ANCHOR trial, and the rate per injection was 0.05% in the MARINA trial. Endophthalmitis occurred in [redacted] of patients across the [redacted] and [redacted] trials [redacted] Very few deaths were reported in the ranibizumab trials, with numbers of deaths being

approximately equal between trial arms. More people died from vascular causes than from non-vascular causes.

Summary of costs

The drug acquisition costs for one year's treatment with pegaptanib was estimated as £4,626, assuming that nine injections are provided during the year at six-weekly intervals as indicated in the Summary of Product Characteristics (SPC) for pegaptanib. The drug acquisition costs for one year's treatment with ranibizumab was estimated as £9,134, assuming that twelve injections are provided during the year, at four-weekly intervals. In addition to drug costs are the costs of administering the injection, repeat vision assessments, fluoroscein angiography for identifying lesions, optical coherence tomography and fluoroscein angiography for monitoring response to treatment, as well as outpatient visits prior to initiation of therapy and for follow-up during treatment. These account for an additional £2,585 for one year's treatment with pegaptanib (36% of total treatment costs) and £3,362 for ranibizumab (21% of total treatment costs).

Further costs of treatment are associated with the management of injection-related adverse events – while the proportion of injections associated with adverse events are low, costs of managing each event range from £1,200 to £2,100. Injection-related adverse events are also associated with significant risks of severe loss of visual acuity.

Summary of cost-effectiveness

With no economic evaluations identified in the systematic review of cost-effectiveness, a model was developed to estimate the cost-effectiveness separately of ranibizumab and of pegaptanib, compared to 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 (short-term analysis) adopted time horizons determined by the available trial data. In this analysis, no attempt was made to extrapolate costs or effects beyond the period of follow-up in clinical trials of ranibizumab and of pegaptanib. The second analysis extrapolated effects of treatment beyond the clinical trials, adopting a time horizon of ten years, the approximate life expectancy for the cohort of AMD patients being modelled.

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

Categories of costs included in the model were drug costs, drug adminstration and patient monitoring while on treatment, management of treatment-related adverse events and co-administration of PDT (if appropriate). 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. These included costs of blind registration, provision of low vision aids and low vision rehabilitation as one-off costs as, well as recurring costs such as community care, residential care and costs of morbidity associated with impaired vision (depression and fractures).

The incremental cost-effectiveness ratio (ICER) for pegaptanib compared to usual care in the short-term model is £163,603. This high ICER arises due to a relatively small QALY gain at two years and because treatment costs are realised in the first two years, whereas the reduction in patients' progression to blindness, which would be expected to lead to reduced use of services for visual impairment, is not apparent over this short time scale. In the longer-term model a larger QALY gain (0.26) is realised. By this stage costs of services for visual impairment comprise the largest proportion of total costs, and while the difference in costs of services for visual impairment between the pegaptanib-treated and usual care cohorts is not large enough to fully offset treatment costs, the ICER is reduced to £30,986.

For ranibizumab we undertook separate analyses for patients with predominantly classic lesions (based on clinical data from the ANCHOR trial}) and for patients with minimally classic and occult no classic lesions (based on clinical data from the MARINA trial. Total costs and the quality adjusted life years 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. The high ICER arises due to relatively small QALY gains (0.04 QALYs and 0.07 QALYs after one year of treatment for patients with predominantly classic lesions in comparison with PDT and best supportive care, respectively) and high incremental costs (approximately £8,000 for the comparison with PDT and £11,500 for the comparison with best supportive care). The QALY gain after two 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 QALY gain at ten years is larger (0.34 and 0.57 for patients with predominantly classic lesions compared with PDT and best supportive care, respectively). The incremental costs

have reduced to £5,391 and £6,457, giving ICERs of £15,638 for the comparison with PDT and £11,412 for the comparison with best supportive care. The QALY gain at ten years for patients with minimally classic and occult no classic lesions is 0.69 QALYs and the incremental cost has reduced to £17,314, giving an ICER of £25,098.

Sensitivity analyses

Deterministic sensitivity analysis showed that the cost-effectiveness estimates in the base case were sensitive to some key assumptions. As discussed above the model time horizon has a large impact on cost-effectiveness of treatment (the longer the time horizon, the more likely the treatment is cost-effective). Visual acuity of the cohort at baseline had an impact in the analysis of pegaptanib (the lower the visual acuity the less likely the treatment is cost-effective), but was less influential on the cost effectiveness estimates for ranibizumab.

Analysis of non-response (patients losing at least 15 letters of visual acuity from baseline) in patients randomised to discontinue pegaptanib after one year of treatment and followed up for a year suggests that pegaptanib may have a disease modifying effect rather than simply treating AMD symptoms. If this effect is included in the model only for the year after treatment stops, the ICER falls to £26,896 – if we assume that the effect persists for the patient's lifetime the ICER falls to £20,467.

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 ten year time horizon (assuming high cost and high uptake) or alternatively could be associated with a 30% to 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, where probabilities of losing or gaining visual acuity, the size of disease modifying effect, health state utility values, cost of outpatient attendances, fluoroscein angiography and optical coherence tomography 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. 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 analyses for ranibizumab (conducted separately for lesion types and alternative comparators) where probabilities of losing or gaining visual acuity, health state utility values, cost of outpatient attendances, fluoroscein angiography and optical coherence tomography 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. That is, the majority of simulations 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 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.

Discussion

We applied the same model, using the same health state utilities and assumptions over resource use at each contact, to estimate cost effectiveness for each drug. Resource use assumptions were developed with advice from clinical experts who advised on the development of this review.

Clinical evidence relevant to each drug has been extracted from good quality RCTs included in the systematic review. Response to treatment was assessed using an accepted measure of significant clinical difference (fifteen letters of visual acuity), to model cost and outcome differences over the time horizons of the clinical trials and over patients' lifetimes. The age of patients in the clinical trials reflect the age-specific incidence and prevalence of AMD reported in epidemiological studies, and would be expected to be broadly representative of patients presenting for treatment.

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.

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 patient is to respond to treatment.

The validity of assumptions underlying our extrapolation from trial results to ten 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). An additional assumption, implicit in our extrapolated analysis, is that the utility associated with visual acuity in the better-seeing eye is constant over time. This may be questioned, given research suggesting that patients adapt 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.

Conclusions

Implications for service provision

Current estimates suggest that around 30% of patients with neovascular AMD are eligible for PDT. The implication of recommendations in interim guidelines on the management and treatment of AMD from the Royal College of Ophthalmologists that intraocular injection of anti-VEGFs should be considered for patients with minimally classic, occult no classic and for predominantly classic subfoveal CNV is that the number of patients eligible for active treatment is likely to increase substantially. One estimate is that patient numbers could increase from 7,000 to 26,000 per year. Workload in ophthalmic services may increase up to six-fold since treatment with anti-VEGFs requires more frequent attendance and monitoring than does PDT.

Many organisations, including the Royal College of Ophthalmolgists 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. Guidelines emphasise the need for a multi-disciplinary team to deliver these treatments, including ophthalmologists experienced in injection procedures, 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 fluoroscein angiography and optical coherence tomography) as well as 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. Bevacizumab (Avastin), which is biologically similar to ranibizumab, is being increasingly used off-label for the treatment of AMD. The US National Eye Institute of the National Institutes for Health announced in October 2006 that it will be funding a new multicentre 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. 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.

1 BACKGROUND

1.1 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 age-related maculopathy (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 that grow between the retinal pigment epithelial cells and the photoreceptor cells in the centre of the retina. 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]

ARM

- Soft drusen ≥ 63 μm (drusen are discrete lesions consisting of lipids deposited under the retina[4])
- Areas of increased pigment or hyperpigmentation (in the outer retina or choroid) associated with drusen
- 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.

Late ARM (AMD): Geographic atrophy or dry AMD

- Any sharply delineated roughly round or oval area of hyperpigmentation, or apparent absence of RPE in which surrounding vessels are more visible than in surrounding areas that must be at least 175 μm

Late ARM (AMD): Neovascular AMD, wet AMD, disciform AMD or exudative AMD

- RPE detachment(s), which may be associated with neurosensory retinal detachment, associated with other forms of ARM
- Subretinal or sub-RPE neovascular membrane(s)
- Epiretinal (with exclusion of idiopathic macular puckers), intraretinal, subretinal or sub-pigment eoithelial scare/glial tissue or fibrin-like deposits
- 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)
- 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 (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 to 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 1.1). However, other demographic, behavioural and medical risk factors have been shown to determine the occurrence of AMD and its neovascular form.

Table 1.1 Odds ratios for selected significant risk factors for neovascular AMD[12]

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

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 leave 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 1 pack of cigarettes smoked per day for a year; Table 1.1). 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 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, beta-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 two 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 two 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 five 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. While 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% CI: 22.5%, 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 Disease 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, USA, Australia and other countries. This section discusses 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 1.2). 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), though 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 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 1.2), 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.

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 to 86 years in Beaver Dam, Wisconsin, USA (Table 1.2), 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 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 1.2).

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. Whilst 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 13788 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 1.2).

Table 1.2 Age specific incidence of AMD (95% confidence intervals (95% CI))

Study	Age Group	Persons	Male	Female
Klaver et al, 2001[5] (Rotterdam, The Netherlands) Design: population-based prospective cohort study (n=4953) Follow-up: 2 years Outcome: age-specific incidence (95%CI) per 1000 person-years	55-64 65-74 75-84 85+ Total	0.0 (0-1.0) 0.75 (0.15-2.2) 3.07 (1.1-6.7) 8.80 (1.8-25.8) 1.22 (0.6-2.1)	1.00	1.37
Van Leeuwen et al, 2003[6] (Rotterdam, The Netherlands) Design: population-based prospective cohort study (n=6418) Follow-up: 5 years Outcome: age-specific incidence (95% CI) per 1000 person-years	55-59 60-64 65-69 70-74 75-79 ≥ 80 Total	0.0 0.2 (0.0-1.1) 0.8 (0.3-1.8) 1.8 (1.0-3.4) 3.9 (2.3-6.6) 6.8 (4.2-11.0) 1.8 (1.3-2.4)	2.0	1.6
Klein et al, 2002[24] (Beaver Dam, USA) Design: population-based prospective cohort study (n=2946) Follow-up: 10 years Outcome: age-specific incidence per 100 persons	43-54 55-64 65-74 75+ Total	0.1 1.0 4.4 9.5 2.1	0.0 1.5 4.6 5.8 1.7	0.1 0.6 4.3 11.3 2.4
Mitchell et al, 2002[25] (Blue Mountains, Sydney Australia) Design: population-based prospective cohort study (n=2335) Follow-up: 5 years Outcome: age-specific incidence per 100 persons	49-60 60-69 70-79 80+ Total	0 0.6 2.4 5.4 1.1	0 0.5 2.4 0 0.7	0 0.8 2.4 8.8 1.4
Bunce and Wormald 2006[26] (England and Wales) Design: Register study (n=32895) Follow-up: 1 year Outcome: Registrations per 100,000	0-15 16-64 65-74 75-84 ≥85 All	0.01 1.01 39.69 251.53 699.02 31.78	0.00 0.91 31.10 208.76 682.94 19.96	0.02 1.10 46.47 275.70 697.37 42.44

The incidence of neovascular AMD was examined by Van Leeuwen and colleagues[6] and Mitchell and colleagues[25] (Table 1.3). 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 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.

Table 1.3 Age specific incidence of neovascular AMD (95% CI)

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

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 to 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 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; 0.57) for people aged 65 to 79 years old 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 1.4). 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 higher prevalence rates at 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 to 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%; 2.23%) in Spain to 4.71% (95% CI: 2.44%; 6.97%) in Greece.

Table 1.4 Age specific prevalence of AMD

Study	Age Group	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 (2.52-4.13)	0.90 (0-2.08) 1.97 (0.77-3.17) 4.07 (1.86-6.27) 6.94 (1.06-12.83) 2.49 (2.07-2.91)	1.03 (0.11-1.96) 2.36 (1.00-3.73) 3.15 (2.02-4.28) 15.00 (9.63-20.37) 4.00 (2.86-5.14)
Buch et al, 2001[37] (Copenhagen, Denmark)	60-64 65-69	0 (0.0-1.6) 0 (0.0-1.5)		

Design: population-based cross sectional study (n=944) Outcome: age-specific prevalence per 100 persons (95% CI)	70-74 75-80 All	0.8 (0.1-3.1) 2.4 (0.9-5.1) 0.85 (0.3-1.7)
Reidy et al, 1998[32] (North London, UK) Design: cross sectional survey (n=13371) Outcome: prevalence per 100 persons (95% CI)	≥ 65	8 (5.8-10.8)

Two studies examined the prevalence of neovascular AMD (Table 1.5).[7,27] Owen and colleagues[27] pooled prevalence rates for neovascular AMD for people aged 65 to 79 years,[28-31,33-36] estimating a prevalence of 1.05% (95% CI: 0.57%; 1.52%). The meta-analysis showed that women had a higher prevalence (1.03%; 95% CI: 0.49%, 1.58%) than males (0.81%; 95% CI: 0.52%; 1.11%). Owen and colleagues[27] noted differences in the prevalence rates between the included studies. Prevalence rates for males aged 65 to 79 years ranged from 1.45% (95% CI: 0.56%; 2.34%) from the Beaver Dam Eye Study[28] to 0.53% (95% CI: 0.14%; 0.92%) in the Rotterdam Eye Study,[33] although 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%; 3.04%) in the Beaver Dam Eye Study[28] to 0.50% (95% CI: 0.18%; 0.83%) in the Rotterdam Eye study.[33] Also Owen and colleagues[27] 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%; 2.86%).

Table 1.5 Age specific prevalence of neovascular AMD

Study	AgeGroup	Persons	Male	Female
Owen et al, 2003[27] Age specific prevalence (%) (95% CI) Design: Systematic review of population-based studies (6 studies, n=22206) Outcome: age-specific prevalence per 100 persons (95% CI)	<50 50-54 55-59 60-64 65-69 70-74 75-79 80-84 85-89 90+	0.0 (0.0-0.18) 0.06 (0.0-0.32) 0.03 (0.0-0.19) 0.26 (0.12-0.49) 0.33 (0.16-0.59) 0.85 (0.55-1.27) 2.29 (1.70-3.02) 4.65 (3.49-6.05) 6.99 (4.73-9.88) 11.27 (6.58-17.65)		
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	 2.29 (1.73-2.86)	0.38 (0-1.01) 1.40 (0.51-2.29) 2.63 (0.78-4.49) 5.56 (0-11.48) 1.69 (1.11-2.27)	0.92 (0.04-1.80) 1.42 (0.34-2.50) 2.17 (0.96-3.37) 10.50 (6.65-14.35) 2.78 (2.09-3.47)

Burden of Disease

Despite the lack of evidence on the epidemiology of AMD and its neovascular form, the information on the incidence and prevalence found provides 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 1.6). 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 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 1.7). 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 cases to 537 cases and for neovascular AMD from 103 cases to 158 cases. Meads and colleagues thought the prevalence of neovascular AMD would be approximately 1946 cases in a standard health authority.

Table 1.6 Estimates of the number of patients with AMD in England and Wales

Study	Age group	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]	Age 55 yrs and over	0.12	14811.6	17774
Van Leeuwen et al, 2003[6]	Age 55 yrs and over	0.148	14811.6	21921
Klein et al, 2002[24]	Age 43 to 84 yrs	0.21	22122.6	46457
Mitchell et al, 2002[25]	Age 49 yrs and over	0.22	18719.5	41183
Neovascular AMD				
Van Leeuwen et al, 2003[6]	Age 55 yrs and over	0.088	14811.6	13034
Mitchell et al, 2002[25]	Age 49 yrs and over	0.2	18719.5	37439
Prevalence				
AMD				
Mitchell et al, 1995[29]	Age 49 yrs and over	1.94	18719.5	72632
Augood et al, 2006[7]	Age 65 yrs and over	3.32	8579.3	284833
Buch et al, 2001[37]	Age 60 to 80 yrs	0.85	9246.5	78595
Neovascular AMD				
Augood et al, 2006[7]	Age 65 yrs and over	2.29	8579.3	196466

Table 1.7 Predicted prevalence of neovascular AMD (in thousands) (95% CI) for 2001 and 2011 in the UK[27]

Age Range	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 Owens and colleagues[27]

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 seven-year cumulative mortality rates of 26% for people with visual impairment compared with a rate of 16% for those without visual impairment.[44] The relative risk of mortality associated with visual impairment was 1.7 (95% CI, 1.2 – 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, Thiagaranjan 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 two years following eye examination, but not over a longer period of time. 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 compared with 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 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 section 4.1.3.

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 one minute of arc (one minute of arc is 1/60th of a degree, 360 degrees 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 get 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 one 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 m, 12 m, 9 m, 6 m, and the smallest letter is 4 m. The outcome is expressed as a pseudofraction, where the numerator describes the chart viewing distance (usually six metres in Europe and 20 feet 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 metres 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 Minimum Angle of Resolution) steps. Normal vision (6/6) equates to a LogMAR of 0, with negative scores for smaller letter sizes (see Table 1.8 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 x 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 and is used in the ranibizumab and pegaptanib trials. The letters in the ETDRS chart area are all square, while the letters of the Bailey-Lovie chart are rectangular.

Table 1.8 Snellen and logMAR equivalents[69,71]

Snellen (metres)	Snellen (feet)	logMAR	VAR	
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. While 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 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 program, 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 opthalmoloscopy 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. 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.

1.2 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 firstly, only 10 to 15% of all neovascular lesions are small enough and sufficiently delineated to be eligible. Secondly, there is at least a 50% chance that leakage will recur during the following two years. Thirdly, 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 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 over-dose of the drug or laser can result in permanent irreversible vision loss.[40] Moreover, while 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 the licensed drug is used for an indication other than the one for which is it labelled. Bevacizumab is a humanised monoclonal antibody against 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 (A. Lotery, 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 or 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. Fluorescein angiography 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 fluorescein angiography (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 Section 1.1 (Burden of Disease) 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] While 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 £4,015 for one year of treatment[86] to between £6,545[85] and £6,666[40] for two years.

Bonastre and colleagues[85] estimated that there would be 4,655 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 two years 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 one year of treatment. Meads and colleagues[40] derived an estimate of £20.1 million, for the first year of treatment for a cohort of 5,000 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 5,000 new cases each year, costs would rise to £33.1 million in year two and £41.3 million in the third year.

As discussed in the previous section, PDT is only recommended for a proportion of patients with 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, see Table 1.9

Table 1.9 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%

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 so 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 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.

1.3 Description of technology under assessment

Summary of interventions

Ranibizumab

Ranibizumab (Lucentis, Genentech, Inc. (US) / Novartis Pharmaceutical Ltd) was approved by the US Food and Drug Administration 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 humanized 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 0.5mg (0.05 mL) by intravitreal injection once a month according to the product prescribing information.[90] A slightly different proposed posology for ranibizumab in the EU and UK has been accepted in principle by the Committee for Medicinal Products for Human Use, whereby treatment is initiated with a loading phase of three monthly injections followed by a maintenance phase in which patients should be monitored for visual acuity on a monthly basis. If the patient experiences a loss of greater than five letters in visual acuity, ranibizumab should be administered. The interval between two doses should not be shorter than one month.[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 intraocular pressure as well as 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 31st 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 0.3mg once every six weeks (9 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 license 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 (A.Lotery, 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 microgram vial of pegaptanib quoted in the current BNF[82] is £514. The recommended frequency of administration at this dosage is every six weeks. This corresponds to nine injections per year giving an annual acquisition cost of £4,626. Since ranibizumab has not received marketing authorisation for the UK there is no quoted price. The best publicly available estimate of the drug acquisition cost is based on a currency conversion from the US price of $1,950. At a current exchange rate of 1 US dollar to 0.5354 pounds sterling the UK cost of ranibizumab would be £1,044 per injection. Assuming that injections are provided monthly, this corresponds to twelve injections per year, at an annual cost of £12,528.

In addition to the drug acquisition are costs of administration of the drugs, since intra-ocular injection requires aseptic procedures beyond those required for a standard outpatient appointment, and patient monitoring. Patients require fluorescein angiography prior to initiation of treatment to type and localise the lesion, and would be expected to have futher fluorescein angiography at least once every six 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 out-patient appointment to assess patients and initiate treatment would be longer than follow-up appointments, the cost of twelve months treatment with pegaptanib would be £7,240 while for twelve months treatment with ranibizumab would cost £15,917 (Table 1.10).

Table 1.10 Cost of first year of treatment with pegaptanib and ranibizumab

	Outpatient		FA	OCT	Drug	Injection procedure	Total
	Initial visit & vision assessment	Follow-up & 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	£ 12,528	£ 1,082.40	£ 15,917

Intra-ocular 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 intra-ocular 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 £1,400 for lens damage to £2,500 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 earlier section on Current Service Cost, the cost of the first year of PDT would be £4,551). Since both drugs are likely to be indicated for all patients with neovascular AMD, rather than the selected sub-groups 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 (six weekly) and ranibizumab (monthly), compared with PDT (three-monthly), ophthalmology departments estimate total workload may increase by six to seven times its current level. This degree of increase in workload has significant implications on demand for specialist imaging services (fluoroscein angiography and optical coherence tomography) and capacity for providing vision assessments.

2 DEFINITION OF THE DECISION PROBLEM

2.1 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 sub-groups

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 fluorescein angiography 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, while 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 photocoagulation therapy 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 (3 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 health care resources consumed in the provision of the interventions – drug acquisition, administration and monitoring costs – as well as consequences of those interventions, such as treatment of adverse effects.

2.2 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.

3 ASSESSMENT OF CLINICAL EFFECTIVENESS

3.1 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.

3.1.1 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 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 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.

3.1.2 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.

3.1.3 Quality assessment

The quality of included RCTs and systematic reviews was assessed using criteria recommended by NHS Centre for Reviews and Dissemination (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.

3.1.4 Inclusion criteria

Patients

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

- Best supportive care.
- For the subgroup of individuals with a confirmed diagnosis of classic with no occult subfoveal wet AMD, photodynamic therapy with verteporfin was also a comparator.
- If insufficient evidence was found using the above comparators, the following comparators were also to be considered:
    - Sham injection (systematic review of clinical effectiveness only)
    - 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 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.

3.1.5 Data synthesis

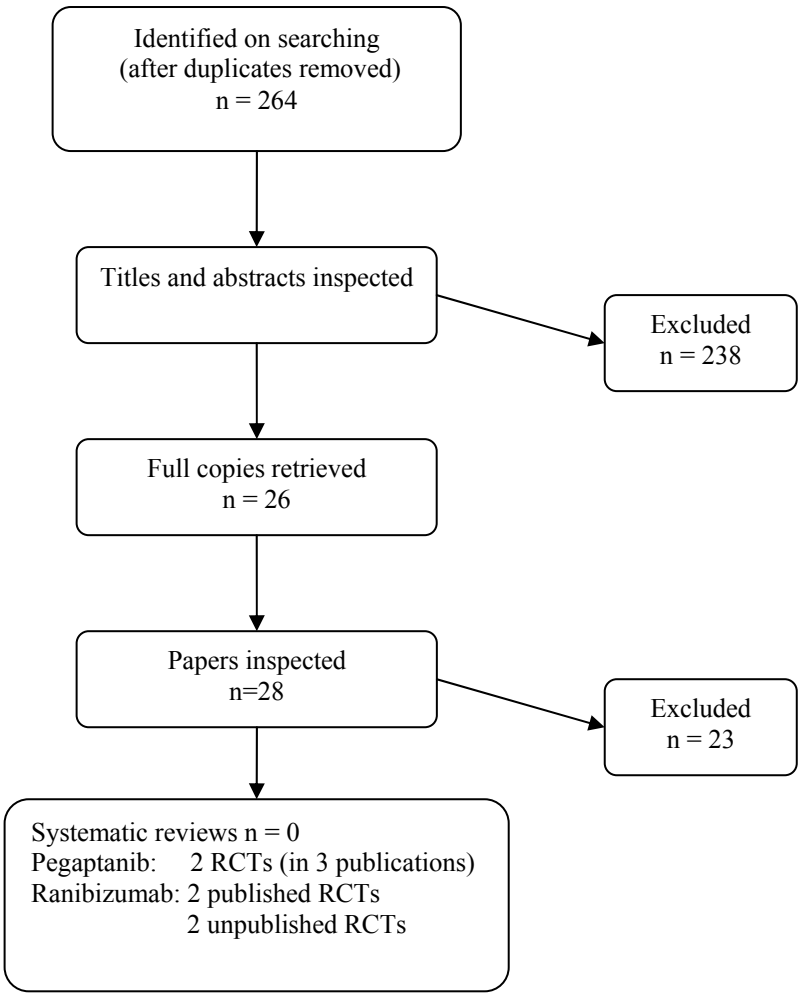
Data were synthesised through a narrative review with tabulation of results of all included studies. Full data extraction forms are presented in Appendix 4. It was not considered appropriate to combine the included RCTs in a meta-analysis due to heterogeneity in the patient groups and comparator treatments.

3.2 Results

3.2.1 Quantity and quality of research available

The number of published papers identified at each stage of the systematic review is shown in Figure 3.1. 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 of the methodology and assessment of the results are listed in Appendix 6. A list of ongoing studies can be seen in Appendix 7.

Figure 3.1 Flowchart of identification of published studies for inclusion in the systematic review of clinical effectiveness



The searches identified three full publications[95,100,101] which reported the combined results of two RCTs of pegaptanib (the VISION study). Two fully published RCTs[96,97] of ranibizumab were identified. In addition, the ranibizumab manufacturers supplied full reports of two unpublished RCTs of ranibizumab, as well as full details and further results for the published RCTs. The key characteristics of the included studies are shown in Table 3.1. 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 can be seen in Appendix 8.

Table 3.1 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. 0.3mg pegaptanib (n=297) 2. 1.0mg pegaptanib (n=305) 3. 3.0mg pegaptanib (n=302) 4. sham injection (n=304) Injections every 6 weeks, total of 9 treatments. Patients re-randomised after 54 weeks 0.3mg: - 0.3mg n=133 - discontinue n=132 1.0mg: - 1.0mg n=133 - discontinue n=131 3.0mg: - 3.0mg n=125 - discontinue n=127 Sham: - 0.3mg n=53 - 1.0mg n=55 - 3.0mg 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%
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; [redacted] *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 [redacted]	1. 0.3 mg ranibizumab monthly for 3 doses, then doses every 3 months [redacted] 2. 0.5 mg ranibizumab monthly for 3 doses, then doses every 3 months	*Target population:* Any lesion type *Angiographic subtype of lesion at baseline* Predominantly Classic

Study	Intervention	Participants
Primary outcomes: mean change in best corrected visual acuity *Length of follow-up:* 12 months (ongoing)	3. Sham injection monthly for 3 doses, then doses every 3 months	Minimally classic Occult with no classic Unclassified
FOCUS RCT, *Primary outcomes:* proportion losing <15 letters; *Length of follow-up:*	1. 0.5 mg ranibizumab* monthly + verteporfin PDT (n=106) 2. sham injection + verteporfin PDT (n=56)	*Target population:* Predominantly classic lesions *Angiographic subtype of lesion at baseline* Minimally classic Occult with no classic Unclassified:

*a lyophilised formulation of ranibizumab was used.

[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. The clinical study report from the manufacturer's submission gives the number of patients in the sham injection group with occult no classic lesions as 151 (63.4%) as in the publication.

The pegaptanib VISION study publications [95,100,101] reported the combined results of two concurrent RCTs (one in the USA and Canada [study 1004], the other at centres worldwide [study 1003]). The studies compared 0.3mg (the licensed dose), 1.0mg and 3.0mg 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 0.3mg 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 two years, study 1003 did not show efficacy for any of the active doses at two years.[102,103] 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.[100]

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 ten or more letters of visual acuity during the second year. Of the 132 patients in the 0.3mg dose randomised to discontinue in the second year, 28 (21%) resumed therapy, at a mean of 73.7 (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 0.3mg and 0.5mg ranibizumab with sham injection. The MARINA trial used monthly injections of ranibizumab, whereas people in the PIER trial received monthly injections for the first three months, followed by a reduced schedule of injections every three months. The ANCHOR trial compared 0.3mg and 0.5mg ranibizumab plus sham PDT with sham injection and active verteporfin PDT. The FOCUS trial compared 0.5mg ranibizumab plus verteporfin PDT with sham injection plus verteporfin PDT. A lyophilised formulation of ranibizumab was used for the [redacted] 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. In the PIER study, which included any lesion type, [redacted] of the patients receiving ranibizumab and [redacted] the patients in the [redacted] group had [redacted] of the patients in the PIER study had [redacted] the inclusion criteria of the FOCUS trial stated

[redacted]There was a [redacted]in the treatment arms for the number of patients whose lesions were classified as [redacted]or[redacted]

The included trials were quality-assessed using standard criteria[99] (Table 3.2). Methodological quality and quality of reporting were generally good in the VISION study,[95] and adequate randomisation would have protected against selection bias.

Table 3.2 Quality assessment of included studies

Study	Randomisation	Concealment of allocation	Baseline characteristics	Eligibility	Blinding of assessors	Care provider blinding	Patient blinding	Reporting outcomes	Intention-to-treat 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]	Ad	Ad	Rep	Ad	Ad	Ad	Ad	Ad	In	Ad
PIER	[redacted]									
FOCUS	[redacted]									

Ad = adequate, In = inadequate, Par = partial, Rep = reported, Un = unknown

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-randomized 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 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 standardized assessment of visual acuity completed at baseline. Three patients in the 0.3mg pegaptanib group, five patients in the 1.0mg group, six patients in the 3.0mg 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 MARINA and ANCHOR trials were of good methodological quality, as were the unpublished PIER and FOCUS trials. The MARINA trial and the other three ranibizumab studies described an adequate method of randomisation which would have protected the studies from selection bias. Baseline characteristics were reported by the published ranibizumab studies and the PIER trial, with similar ocular and demographic characteristics in the trial arms (within studies). In the FOCUS study, mean visual acuity was [redacted] the sham+PDT group than in the ranibizumab+PDT group [redacted] Also, the [redacted] of sham+PDT subjects [redacted] were [redacted] while in the ranibizumab+PDT group the [redacted] of subjects [redacted] were [redacted]. Otherwise, the groups were [redacted] in terms of baseline characteristics.

To protect against bias, outcome assessors, care providers and patients in the published trials and the [redacted] study were masked to treatment, and all injections were performed by separate ophthalmologists who were unmasked to treatment assignment. FOCUS was a [redacted] phase I/II trial. The ranibizumab studies reported appropriate outcome measures, and ITT analysis was used by MARINA and [redacted]. ANCHOR and [redacted] excluded one or more patients with [redacted] 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 vs. 12.6% 0.3mg ranibizumab and 13.8%

0.5mg ranibizumab). 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 0.3mg ranibizumab group and 6.4% of the 0.5mg 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, [redacted] of the sham+PDT arm and [redacted] of the ranibizumab +PDT arm [redacted] primarily due to [redacted] The PIER study [redacted] of [redacted] seen in MARINA, with study and treatment [redacted] (primarily due to [redacted] being [redacted] in the sham injection groups than in the ranibizumab groups.

3.2.2 Assessment of effectiveness

3.2.2.1 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 3.3), or mean change in best corrected visual acuity (PIER) (Table 3.4). Other reported measures of vision change in terms of number of letters gained/lost are also shown in Table 3.3, and Table 3.5 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 1.8).

After the second year of re-randomised pegaptanib treatment, the VISION study[100] reported mean visual acuity from weeks 54 to 102, change in standardized 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 year results are presented below (Table 3.3 - Table 3.5) for the group who continued on 0.3mg 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 3.3) are also shown for those who were randomised to discontinue the 0.3mg 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 0.3mg dose of pegaptanib.

The primary outcome measure for the MARINA and 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 2m. The ranibizumab manufacturers also reported [redacted] but these results are not included here as they were [redacted]. For the ANCHOR and FOCUS studies, [redacted] The primary outcome measure in the PIER study was [redacted]

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 3.3). The difference between pegaptanib doses was not significant for this outcome measure, but a slightly higher percentage of people receiving the 0.3mg or 1.0mg dose of pegaptanib lost fewer than 15 letters compared with the 3.0mg 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 0.3mg pegaptanib for year two (76% vs. 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 0.3mg pegaptanib. So 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 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 0.3mg 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 two 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).[104]

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). In the PIER study, patients received monthly injections for the first three months of the study, but this was then reduced to an injection every three months. Results were not as good in this study as in the MARINA study; approximately 83% of the 0.3mg group and 90% of the 0.5mg group in the PIER study lost fewer than 15 letters, compared with around half of the people in the usual care group.

ANCHOR and FOCUS reported statistically significant differences between 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 0.3mg or 0.5mg 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 0.5mg 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=0.0003).

Table 3.3 Proportion of patients with changes in visual acuity

	No. of patients (%) gaining or losing letters			
Pegaptanib				
VISION study year 1 [95] **Lesion type: all**	**0.3mg pegaptanib (n=294)**	**1.0 mg pegaptanib (n=300)**	**3.0mg 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	p<0.001	p<0.001	p=0.03	
Maintenance or gain ≥ 0 letters	98 (33%)	110 (37%)	93 (31%)	67 (23%)
P value vs. sham	P=0.003	p<0.001	p=0.02	
Gain ≥ 5 letters	64 (22%)	69 (23%)	49 (17%)	36 (12%)
P value vs. sham	p=0.004	p=0.002	p=0.12	
Gain ≥ 10 letters	33 (11%)	43 (14%)	31 (10%)	17 (6%)
P value vs. sham	p=0.02	p=0.001	p=0.03	
Gain ≥ 15 letters	18 (6%)	20 (7%)	13 (4%)	6 (2%)
P value vs. sham	p=0.04	p=0.02	p=0.16	
loss ≥ 30 letters	28 (10%)	24 (8%)	40 (14%)	65 (22%)
P value vs. sham	p<0.001	p<0.001	p=0.01	
VISION study year 2[100] **(Patients re-randomised)**	**0.3mg – 0.3mg (n=133)**	**0.3mg – 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 vs usual care at 102 weeks [104]	p=0.0385			
VISION study year 2 [104] **(Patients re-randomised)**	**0.3mg – 0.3mg (n=133)**		**Sham – discontinue or usual care (n=107)**	
Loss of ≥ 30 letters at 102 weeks	17 (13%)		28 (26%)	
P vs usual care	p=0.0058			
VISION study year 2[100] **(Patients re-randomised)**	**0.3mg – 0.3mg (n=133)**	**0.3mg – 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**	**0.3mg ranibizumab (n=238)**	**0.5mg 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 %	[redacted]	[redacted]	[redacted]	
P value (vs sham)	P<0.0001	P<0.0001		
24 months	219 (92.0%)	216 (90.0%)	126 (52.9%)	
95 CI of the %	88.6%, 95.5%	86.2%, 93.8%	46.6%, 59.3%	
P value (vs sham)	P<0.0001	P<0.0001		
Gain of ≥ 15 letters				
12 months	59 (24.8%)	81 (33.8%)	11 (4.6%)	
95% CI of the %	19.0%[b], 30.3%	27.8%, 39.7%	2.0%, 7.3%	
P value (vs sham)	P<0.0001	P<0.0001		
24 months	62 (26.1%)	80 (33.3%)	9 (3.8%)	
95% CI of the %	20.5%, 31.6%	27.4%, 39.3%	1.4%, 6.2%	
P value (vs sham)	P<0.0001	P<0.0001		
ANCHOR[96] **Lesion type: PC**	**0.3 mg ranibizumab + sham PDT (n=140)**	**0.5mg ranibizumab+ sham PDT (n=139[a])**	**Sham injection + PDT (n=143)**	

	No. of patients (%) gaining or losing letters		
Loss of <15 letters	132 (94.3%)	134 (96.4%)	92 (64.3%)
95 CI of the %	90.4%, 98.1%	93.3%, 99.5%	56.5%, 72.2%
Non-inferiority test vs PDT	P<0.0001	P<0.0001	
Test for treatment difference (vs PDT)	P<0.0001	P<0.001	
Gain of ≥ 15 letters	50 (35.7%)	56 (40.3%)	8 (5.6%)
95% CI of the %	27.8%, 43.7%	32.1%, 48.4%	1.8%, 9.4%
P value (vs PDT)	P<0.0001	P<0.0001	
PIER	**0.3mg ranibizumab**	**0.5mg**	**Sham**
Lesion type: all		**ranibizumab**	
Loss of <15 letters			
95% CI for %			
P value vs sham			
Gain of ≥ 15 letters			
95% CI for %			
P value vs sham			
FOCUS	**0.5mg ranibizumab+PDT**	**Sham+PDT**	
Lesion type: PC/MC			
Loss of <15 letters	(90.5%)	(67.9%)	
95% CI of the %			
p-value			
Gain of ≥ 15 letters			
95% CI of the %			
p-value			

PC=predominantly classic, MC=minimally classic

[a] 1 patient excluded due to

[b] This figure is reported as in the clinical study report provided with the manufacturer's submission.

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 3.3). Statistically significantly more patients in the 0.3mg and 1.0mg pegaptanib groups gained at least five letters (22% and 23%, respectively), compared with 12% of the sham injection group.[95] Gains of at least ten 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 0.3mg, 1.0mg and 3.0mg 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 0.3mg and 1.0mg pegaptanib groups, gains of this magnitude were significantly higher than for the sham injection group (6% and 7% vs. 2%, p=0.04 and p=0.02, respectively). There was no statistically significant difference between the 3.0mg group (4%) and the sham injection group (2%).

The MARINA study found that approximately a quarter of the 0.3mg ranibizumab group and a third of the 0.5mg 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. [redacted] patients in the PIER study gained at least 15 letters of visual acuity, and these were evenly balanced between both ranibizumab arms and the sham injection group.

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 0.3mg ranibizumab group and 40% of the 0.5mg 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 ($p=0.0033$).

Mean change in visual acuity

The mean change in visual acuity, reported as the mean number of letters lost or gained, for people receiving 0.3mg or 1.0mg pegaptanib was approximately half that of people receiving sham injection (Table 3.4). 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 follow-up.[95] People receiving 3.0mg pegaptanib lost an average of 10 letters of visual acuity, which was still significantly fewer letters than those lost in the sham injection group. The VISION study[95] also reported mean loss of visual acuity from baseline to each six-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 0.3mg or 1.0mg, $p<0.05$ at each time point for 3.0mg).

The mean change in standardized 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 3.4).The average decline from baseline to week 102 in people randomised to continue with 0.3mg treatment was 5.88 letters, compared with a decline of 11.24 letters in those who received sham injection for two years or discontinued treatment after a year of sham injections ($p=0.0012$). There was little change between week 54 and week 102 in the group who continued with 0.3mg pegaptanib treatment, with a decline of only 0.6 letters. By contrast, those who discontinued treatment after a year of 0.3mg pegaptanib injections experienced a mean decrease of 3.04 letters ($p=0.0041$). The group who continued for a second year of 0.3mg pegaptanib treatment maintained an average of approximately 44 letters of visual acuity. Those who received 0.3mg 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 two year study lost an average of four letters during the second year.

The MARINA and 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 3.4). 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 ($p<0.0001$).

In the PIER study, patients received monthly injections for the first three months of the study, but this was then reduced to an injection every three months. For the first three 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 0.3mg and 0.5mg 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 0.3mg and 0.5 mg ranibizumab than with sham injection ($p=0.0001$ and $p<0.0001$, respectively). People in the sham injection group lost an average of 16.3 letters by 12 months, compared with 1.6 letters in the 0.3mg ranibizumab group, and 0.2 letters in the 0.5 mg ranibizumab group (Table 3.4).

Table 3.4 Mean changes in visual acuity

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

VA=visual acuity, PC= predominantly classic, MC=minimally classic, LS=least squares

* Data estimated from figure

[a] 1 patient excluded [redacted]

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 3.3) or reached a reduced level of visual acuity the equivalent of legal blindness (Table 3.5), 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 0.3mg pegaptanib group, 43% of the 1.0mg pegaptanib group and 44% of the 3.0mg 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 a third (34%) of those randomised to continue with 0.3mg pegaptanib had a Snellen equivalent of 6/60 or worse, compared with 24% of those randomised to discontinue 0.3mg 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 0.3mg pegaptanib group had deteriorated to the level of legal blindness. By contrast, a further 14% of those who discontinued 0.3mg pegaptanib and 8% more of the control group deteriorated to this level of visual acuity.

The study eyes of approximately [redacted] of the people in the PIER study's ranibizumab groups [redacted] compared with just [redacted] of the people in the sham injection group [redacted] and [redacted] for 0.3mg and 0.5 mg groups, respectively [redacted] A [redacted] proportion of ranibizumab patients in the MARINA trial reached a [redacted] 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 ($p<0.0001$). It is likely that the results from the MARINA trial were better than those in the PIER trial due to the reduced frequency of injections in the latter trial.

Almost all of the people in the ANCHOR trial and approximately [redacted] of those in the [redacted] trial had predominantly classic lesions [redacted].

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 0.3mg ranibizumab and sham PDT and 16% of people receiving 0.5mg ranibizumab and sham PDT. Differences between both ranibizumab groups and the PDT group were statistically significant ($p<0.0001$). [redacted] The [redacted] trial [redacted] found a

[redacted] between people treated with 0.5mg ranibizumab and PDT compared with those receiving sham injection plus PDT[redacted]

Table 3.5 Deterioration to legal blindness (visual acuity 6/60 (20/200) or worse)

	Number of patients (%)			
Pegaptanib				
VISION study year 1[95] **Lesion type: all**	**0.3mg pegaptanib (n=294)**	**1.0 mg pegaptanib (n=300)**	**3.0mg pegaptanib (n=296)**	**sham injection (n=296)**
VA 6/60 or worse	111 (38%)	128 (43%)	129 (44%)	165 (56%)
P value vs. sham	p<0.001	p<0.001	P=0.001	
VISION study year 2[100] **(Patients re-randomised)**	**0.3mg – 0.3mg (n=133)**	**0.3mg – 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**	**0.3mg ranibizumab (n=238)**	**0.5mg 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%, 16.3%	7.6%, 15.7%		36.6%, 49.1%
P value (vs sham)	P<0.0001	P<0.0001		
24 months:	35 (14.7%)	36 (15.0%)		114 (47.9%)
95% CI of the %	10.2%, 19.2%	10.5%, 19.5%		41.6%, 54.2%
P value (vs sham)	P<0.0001	P<0.0001		
ANCHOR[96] **Lesion type: PC**	**0.3 mg ranibizumab + sham PDT (n=140)**	**0.5mg 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%, 29.0%	10.3%, 22.6%		52.1%, 68.2%
P value (vs PDT)	P<0.0001	P<0.0001		
PIER **Lesion type: all**	**0.3mg ranibizumab[redacted]**	**0.5mg ranibizumab[redacted]**		**Sham[redacted]**
VA 6/60 or worse 95% CI for % P value (vs sham)	[redacted]	[redacted]		[redacted]
FOCUS **Lesion type:[redacted]**	**0.5mg ranibizumab+PDT[redacted]**		**Sham+PDT[redacted]**	
VA 6/60 or worse 95% CI of the % P value	[redacted]		[redacted]	

VA=visual acuity, PC= predominantly classic, MC=minimally classic,
[a] 1 patient excluded due to[redacted]

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 0.3mg group and 42.1% of

the 0.5mg 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 0.3mg group and 38.6% of the 0.5mg group ($p<0.001$ for each comparison).

3.2.2.2 Subgroup analysis of visual acuity by lesion type

Lesion type was one of three patient characteristics pre-specified 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 0.3mg pegaptanib dose was significantly more effective than sham injection in reducing visual acuity loss (Table 3.6). The results of multiple logistic-regression analyses found that no factor other than assignment to pegaptanib treatment was significantly associated with response (0.3mg dose, $p<0.001$).[95]

The pegaptanib manufacturer's submission[104] analysed the [redacted]

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 [redacted].

The PIER study reported [redacted] The subgroups of patients [redacted] who were treated with either dose of ranibizumab showed [redacted] compared with the sham injection group. Those who received 0.3mg ranibizumab reported a [redacted] those treated with 0.5mg ranibizumab showed [redacted] Patients without occult CNV formed [redacted]. Patients without occult CNV who received 0.3mg ranibizumab [redacted] People without occult CNV who received 0.5mg ranibizumab [redacted]

[redacted] FOCUS [redacted] of ranibizumab and PDT compared with sham injection and PDT.

Table 3.6 Subgroup analyses of visual acuity by lesion subtype

	Visual acuity outcome (number of letters or proportion of patients)			
Pegaptanib				
VISION study year 1[95]	**0.3mg pegaptanib**	**1.0 mg pegaptanib**	**3.0mg pegaptanib**	**Sham injection**
*Change in VA, no. of letters:**				
Predominantly classic	(n=72)	(n=78)	(n=80)	(n=76)
Mean decrease in VA	7.1	10.2	10.5	14
P vs sham	P<0.05	n/s	n/s	
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	P<0.001	p<0.001	p<0.05	

	Visual acuity outcome (number of letters or proportion of patients)			
Occult with no classic	(n=112)	(n=115)	(n=111)	(n=120)
Mean decrease in VA	9	6	9.5	17
P vs sham	P<0.01	p<0.001	p<0.05	
VISION study year 2[100]	**0.3mg pegaptanib - 0.3mg pegaptanib**		**Sham – discontinue or usual care**	
*Proportion of patients losing <15 letters**				
Predominantly classic				
Year 1	[redacted]		[redacted]	
Year 2				
Minimally classic				
Year 1	[redacted]		[redacted]	
Year 2				
Pure occult				
Year 1	[redacted]		[redacted]	
Year 2				
Ranibizumab				
MARINA[97]	**0.3mg ranibizumab**	**0.5mg ranibizumab**	**Sham**	
Proportion losing <15 letters 12 months:				
Minimally classic CNV	(n=86)	(n=91)	(n=87)	
Response rate n (%)	[redacted] (93%)	[redacted] (91%)	[redacted] (62%)	
95% CI of the %				
P value vs sham	P<0.0001	P<0.0001		
Occult without classic CNV	(n=151)	(n=149[a])	(n=150[a])	
Response rate n (%)	[redacted] (95%)	[redacted]	[redacted] (62%)	
95% CI of the %		(97%)		
P value vs sham	P<0.0001	[redacted]		
		P<0.0001		
24 months:				
Minimally classic CNV	(n=86)	(n=91)	(n=87)	
Response rate n (%)	[redacted] (90%)	[redacted] (89%)	[redacted] (51%)	
95% CI of the %				
P value vs sham	P<0.0001	P<0.0001		
Occult without classic CNV	(n=151)	(n=149)	(n=150)	
Response rate n (%)	[redacted]	[redacted]	[redacted] (54%)	
95% CI of the %	(93%)	(91%)		
P value vs sham	[redacted]	[redacted]		
	P<0.0001	P<0.0001		
ANCHOR	**0.3 mg ranibizumab**	**0.5mg ranibizumab**	**Verteporfin PDT**	
Proportion losing <15 letters				
Occult CNV present	(n=21)	(n=18)	(n=16)	
Response rate n(%)	[redacted]	[redacted]	[redacted]	
95% CI of the %				
P value vs sham				
Occult CNV absent	(n=119)	(n=121)	(n=127)	
Response rate n(%)	[redacted]	[redacted]	[redacted]	
95% CI of the %				
P value vs sham	P<0.0001	P<0.0001		
PIER	**0.3mg ranibizumab**	**0.5mg ranibizumab**	**Sham**	
[redacted]	[redacted]	[redacted]	[redacted]	
Mean (SD)				
95% CI for mean				
P value vs sham				
[redacted]	[redacted]	[redacted]	[redacted]	
Mean (SD)				
95% CI for mean				

	Visual acuity outcome (number of letters or proportion of patients)	
P value vs sham	[redacted]	[redacted]
FOCUS	**R+PDT**	**Sham+PDT**
Proportion losing <15 letters		
Predominantly Classic	[redacted]	[redacted]
Response rate n (%)	[redacted]	[redacted]
95% CI of the percentage	[redacted]	[redacted]
P value	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
95% CI of the percentage	[redacted]	[redacted]
P value	[redacted]	[redacted]

*data estimated from figures, total n per group assumed to be that listed for baseline characteristics
VA= visual acuity
[redacted]The figures given in the clinical study report provided with the manufacturer's submission are:[redacted]
[redacted]These are the exact figures given in the clinical study report provided with the manufacturer's submission. Rounded figures are presented in the publication.[redacted]

3.2.2.3 Change in contrast sensitivity

The pegaptanib VISION study did not report changes in contrast sensitivity. MARINA, ANCHOR and [redacted] reported mean changes in [redacted] 3.7 [redacted] The ANCHOR and MARINA studies also reported [redacted]

Table 3.7 Change in contrast sensitivity

	Mean change in number of letters from baseline		
Ranibizumab			
MARINA	**0.3mg ranibizumab**	**0.5mg ranibizumab**	**Sham (n=238)**
Lesion type: occult/MC	**(n=238)**	**(n=240)**	
Mean change in letters			
Month 12	[redacted]	[redacted]	[redacted]
P value (vs sham)	[redacted]	[redacted]	
Month 24	[redacted]	[redacted]	[redacted]
P value (vs sham)	[redacted]	[redacted]	
ANCHOR	**0.3 mg ranibizumab+**	**0.5mg ranibizumab+**	**Sham injection +**
Lesion type: PC	**sham PDT** [redacted]	**sham PDT** [redacted]	**PDT** [redacted]
Mean change in letters	[redacted]	[redacted]	[redacted]
P value vs (PDT)	[redacted]	[redacted]	
[redacted]	[redacted] **ranibizumab**	[redacted] **ranibizumab** [redacted]	**Sham** [redacted]
Lesion type: [redacted]	[redacted]	[redacted]	

Mean change in letters P value vs (PDT)	[redacted]	[redacted]	[redacted]

3.2.2.4 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 3.8).

The VISION study[95] reported that only the 1.0mg dose of pegaptanib was statistically 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 0.3mg and 1.0mg showed a statistically significantly lower increase in size of lesion than was reported for the sham injection group (1.8 disc areas (DA) vs. 2.5 DA). The highest dose of pegaptanib (3.0mg) showed no statistically significant difference in anatomical changes from baseline compared with the sham injection group. The VISION study[100] reported individual results at two 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 0.3mg pegaptanib group and the usual care group in study 1004 was in lesion size. The continuing 0.3mg 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 (0.5mg dose group) or a decrease in area of CNV of 0.32 DA (0.3mg dose group) between baseline and the end of two years of treatment. By contrast, people in this study who received sham injection experienced an average increase in CNV area of 2.58 disc areas over two 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 months to 24 months. As a result, the difference between each ranibizumab group and the sham group at 24 months (Table 3.8) was somewhat greater than at 12 months. However, differences between groups were statistically significant at both 12 and 24 months ($p<0.0001$).

People in the PIER study received fewer injections than those in the MARINA trial, and [redacted] The mean [redacted] from baseline in

[redacted] for people in the PIER study who were treated with ranibizumab was [redacted] people in the sham injection group [redacted] 3.8 [redacted] People in the ANCHOR trial [redacted] and [redacted] trial 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<0.0001 (ANCHOR) and [redacted].

Treatment with ranibizumab significantly reduced the mean area of leakage from CNV and intensive progressive retinal pigment epithelium (RPE) staining, compared with a mean increase in people in the control group in the MARINA, ANCHOR and [redacted] (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. [redacted] arms of the [redacted] trial experienced [redacted] and [redacted] People who received ranibizumab and PDT experienced an [redacted] compared with an [redacted]

Table 3.8 Anatomical changes from baseline

	Mean (SD) disc areas (DA)			
Pegaptanib				
VISION study year 1[95] **Lesion type: all**	**0.3mg pegaptanib (n=294)**	**1.0mg pegaptanib (n=300)**	**3.0mg pegaptanib (n=296)**	**Sham injection**
Mean change in size of lesion, DA	1.8	1.8	2.5	2.5
P vs. sham	p<0.01	p<0.01	n/s	
Mean change in size of CNV, DA	1.6	1.2	1.8	2.1
P vs. sham	n/s	p<0.01	n/s	
Mean change in size of leakage, DA	1.0	0.5	1.2	1.6
P vs. sham	n/s	p<0.01	n/s	
Ranibizumab				
MARINA[97] **Lesion type: occult/MC**	**0.3mg ranibizumab (n=238)**	**0.5mg ranibizumab (n=240)**		**Sham (n=238)**
Month 12:				
Area of CNV, DA	-0.29 [redacted]	-0.03 [redacted]		1.93 [redacted]
95% CI of mean	-0.55, -0.02	-0.27, 0.21		1.57, 2.29
P value vs sham	P<0.0001	P<0.0001		
Area of leakage from CNV + intense progressive RPE staining, DA	-1.96 [redacted]	-1.88 [redacted]		1.14 [redacted]
95% CI of difference	-2.28, -1.64	-2.18, -1.58		0.68, 1.59
P value vs sham	P<0.0001	P<0.0001		
Month 24:				
Area of CNV, DA	-0.32 [redacted]	0.00 [redacted]		2.58 [redacted]
95% CI of mean	-0.63, -0.01	-0.26, 0.26		2.15, 3.02
P value vs sham	P<0.0001	P<0.0001		
Area of leakage from CNV + intense progressive RPE staining, DA	-2.18 [redacted]	-2.18 [redacted]		0.76 [redacted]

	Mean (SD) disc areas (DA)		
95% CI of difference	-2.52, -1.85	-2.54, -1.83	0.23, 1.29
P value vs sham	P<0.0001	P<0.0001	
ANCHOR[96] **Lesion type: PC**	**0.3 mg ranibizumab + sham PDT (n=140)**	**0.5mg ranibizumab + sham PDT (n=140)**	**Sham injection + PDT (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, -0.37	-0.86, -0.49	0.15, 0.93
P value vs PDT	P<0.0001	P<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, -1.51	-2.38, -1.72	-0.19, 0.83
P value vs PDT	P<0.0001	P<0.0001	
PIER **Lesion type: all**	**0.3mg ranibizumab**	**0.5mg ranibizumab**	**Sham** [redacted]
Area of CNV, DA	[redacted]	[redacted]	[redacted]
95% CI of mean			
P value vs sham			
Area of leakage from CNV	[redacted]	[redacted]	[redacted]
P value vs sham			
FOCUS **Lesion type** [redacted]	**0.5mg ranibizumab+PDT (n=105)**		**Sham+PDT (n=56)**
Area of lesion, DA	[redacted]		[redacted]
95% CI of the mean			
P value			
Area of classic CNV, DA			
95% CI of the mean			
P value			
Area of leakage from CNV + intense progressive RPE staining, DA			
95% CI of the mean			
P value			

P values are change from baseline in treatment group vs. change from baseline in comparator arm.
VA=visual acuity, PC= predominantly classic, MC=minimally classic,

3.2.2.5 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[105] with very limited data presented, and is therefore not discussed further here.

MARINA [redacted] and [redacted] NEI VFQ-25. The full questionnaire comprises 25 questions to assess vision-related functioning and well-being [redacted]

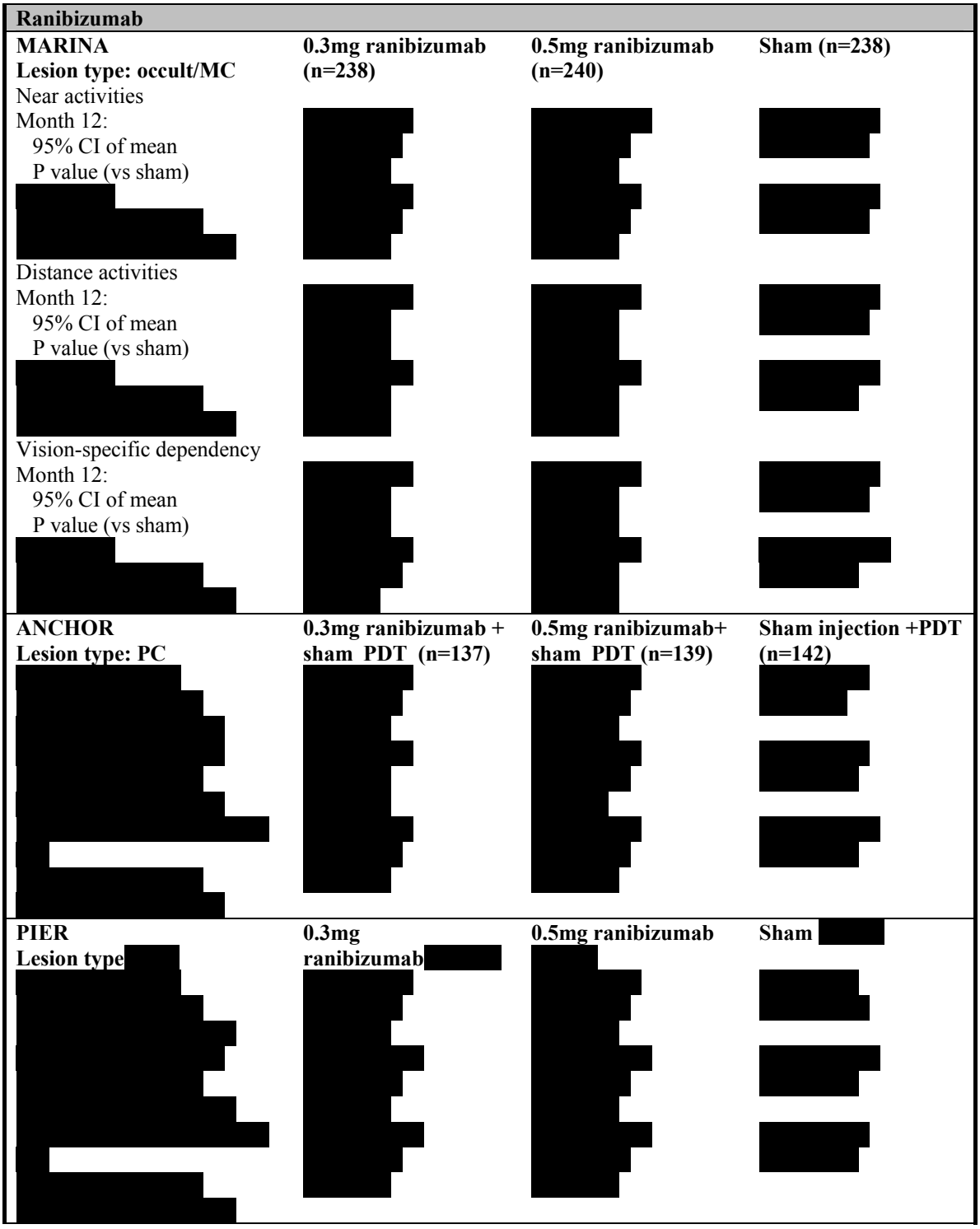
[redacted]MARINA[redacted]
[redacted]NEI VFQ-
25[redacted]
3.9[redacted]

The ANCHOR trial found

[redacted].

Table 3.9 Change from baseline in NEI VFQ-25 scores

	Mean score (SD)



PC= predominantly classic, MC=minimally classic

3.2.3 Compliance with treatment

The pegaptanib manufacturer reported treatment compliance for the full 102 weeks of the 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[104] (Appendix 4).

[redacted]
4[redacted]
[redacted]A [redacted] was observed in the MARINA trial, with at least 89% of patients being treated per protocol during the first year and 76% or more in the second year. A greater number of [redacted]. The ANCHOR trial found that [redacted] ranibizumab or sham injection at each visit. In the [redacted] trial [redacted] ranibizumab subjects [redacted] verteporfin subjects [redacted]

3.2.4 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 3.10 shows adverse events reported for patients in the pegaptanib VISION study.

Table 3.10 Adverse events: pegaptanib VISION study

Adverse Event (AE)	Number of patients (%)				
	VISION study year 1[95]			VISION study year 2[101] (re-randomised) Pts continued with:	
	All doses n=890	Sham n=296	P value	0.3mg (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%	n/s	5 (4)	2 (4)
Death rate	2%	2%	n/s	1 (1)	0
Vascular hypertensive disorders	10%	10%	n/s		
Hemorrhagic AE	2%	3%	n/s		
Thromboembolic events	6%	6%	n/s		
Endophthalmitis	1.3%	0%	nr	0	0
Eye pain	34%	28%	n/s	27 (21%)	9 (18%)
Vitreous floaters	33%	8%	p<0.001	28 (22%)	2 (4%)
Punctuate keratitis	32%	27%	n/s	31 (24%)	14 (27%)
Cataract	20%	18%	n/s	14 (18%)	8 (24%)
Vitreous opacities	18%	10%	P<0.001	13 (10%)	6 (12%)
Anterior-chamber inflammation	14%	6%	P=0.001		
Visual disturbance	13%	11%	n/s	4 (3%)	5 (10%)
Eye discharge	9%	8%	n/s		
Corneal edema	10%	7%	n/s	12 (9%)	4 (8%)
Increased intracocular pressure				26 (20%)	4 (8%)
Lacrimation increased				6 (5%)	6 (12%)
Eye redness				9 (7%)	6 (12%)

n/s = not statistically significant; nr=not reported

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 vs. 8% in sham injection group, p<0.001); vitreous opacities (18% vs. 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 0.3mg 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 one 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 retreated. The rate of retinal detachment in the second year of treatment for those patients who received two years of pegaptanib was 0.15% per injection (4 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 3.11. 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 3.11). In the 24 month MARINA trial, reported rates were highest in the 0.5mg ranibizumab group (20.9%) followed by the 0.3mg group (16.8%) and the sham injection group (12.7%). Rates were lower in the 12 month ANCHOR results; 17.1% in the 0.5mg ranibizumab group; 12.4% in the 0.3mg 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 0.5mg 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 (2 in the 0.3mg group and 3 in the 0.5mg group, approximately 1% overall) and two people in the ANCHOR trial (0.5mg ranibizumab dose group, approximately 0.7% of all ranibizumab patients) [redacted] 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. It is assumed that this is the reason for the discrepancy between the figures in Table 3.11 [redacted] 9 [redacted] 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.

[redacted] patients in the 24 month MARINA trial and the 12 month ANCHOR and [redacted] trials experienced at least one ocular adverse event [redacted] with [redacted] of the 0.3mg ranibizumab group [redacted] % of the 0.5mg ranibizumab group and [redacted] of the sham injection group experiencing at least one ocular adverse event. Intraocular inflammation [redacted]

Conjunctival haemorrhage was the most widely reported ocular adverse effect, but its incidence varied between trials (Appendix 9) [redacted] of the participants [redacted] trial were affected by this condition [redacted] it is not clear whether the PDT procedure or sham/ranibizumab injections were the likely cause. Rates of conjunctival haemorrhage in the other trials were higher in the ranibizumab groups than in the control arms, but people receiving sham

injection still experienced this event in high numbers [redacted] and [redacted] trials [redacted]

Higher proportions of ranibizumab patients than those in the control arms experienced [redacted] (Appendix 9). A post-operative intraocular pressure of 30mmHG or more was reported by higher numbers of ranibizumab patients than those in the control arms (Table 3.11). Some adverse events, such as vitreous detachment and eye irritation, were reported in higher proportions in some ranibizumab trials but not others. Retinal haemorrhage, eye pain and subretinal fibrosis were consistently reported in higher proportions of the control arms than of the treatment arms of [redacted] (Appendix 9).

The overall incidence of ocular serious adverse events was mixed in the four ranibizumab studies (Appendix 9). [redacted] In the FOCUS trial, [redacted] in the ranibizumab plus PDT arm as in the sham injection plus PDT arm. [redacted] patients discontinued the study or treatment due to adverse events. The rate of discontinuation from study or treatment due to adverse events was [redacted]

Severe adverse events were reported between approximately [redacted]% and [redacted]% of the patients in the four trials in Appendix 9. PIER and MARINA reported [redacted], and the FOCUS trial reported a [redacted] The ANCHOR trial had [redacted] Conjunctival haemorrhage was the [redacted]. Increased intraocular pressure and iritis were [redacted]

Selected non-ocular adverse events (not classified as 'severe') are shown in Table 3.11 for the MARINA and ANCHOR studies. Hypertension was reported by 16.1 to 17.2% of patients in the MARINA trial, and by between 2.2% and 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. The incidence of non-ocular serious adverse events was [redacted] (Appendix 10). The MARINA trial reported a [redacted] this study ran for two years, which could explain the [redacted] (Appendix 10).*

Very few deaths were reported in the ranibizumab trials, with numbers of deaths being approximately equal between trial arms (Table 3.11 and Appendix 10). 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, ten due to vascular causes and seven due to nonvascular causes. Seven people died during the first year of the ANCHOR trial, four from vascular causes and three from nonvascular causes.

Table 3.11 Adverse events: ranibizumab MARINA and ANCHOR studies

	Number of patients (%)					
Adverse event (AE)	**MARINA [97] 24 months Lesion type: occult/MC**			**ANCHOR[96]12 months Lesion type: PC**		
	0.3mg (n=238)	0.5mg (n=239)	Sham (n=236)	0.3mg + sham PDT (n=137)	0.5mg + 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 inflamation						
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 ≥ 30mmHg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 40mmHg						
≥ 50mmHg				NR	NR	NR

	Number of patients (%)					
Adverse event (AE)	**MARINA [97] 24 months Lesion type: occult/MC**			**ANCHOR[96]12 months Lesion type: PC**		
	0.3mg (n=238)	0.5mg (n=239)	Sham (n=236)	0.3mg + sham PDT (n=137)	0.5mg + sham PDT (n=140)	Sham + PDT (n=143)
% with cataract	[redacted]			[redacted]		
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)
Nonvascular cause	2 (0.8)	3 (1.3)	2 (0.8)	2 (1.5)	0	1 (0.7)
Nonoccular 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; NR=not reported; MC=minimally classic; PC=predominantly classic; IOP=intraocular pressure

[a] Events were categorized 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.

3.3 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 intention to treat basis. A small number of patients in each arm did not receive study treatment or an adequate baseline assessment, and 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 is based on the combined results of two RCTs (study 1003 and 1004) and data for these are not presented separately.[95] However, it has been noted[102] that the Food and Drug Administration (FDA) Medical Officer Review of the two-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'.[103] 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 US (study 1004) (A. Lotery, 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 (0.3mg, 1.0mg or 3.0mg) 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 0.3mg 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 one year, rather than for the primary outcome (proportion of patients losing fewer than 15 letters). A letter to the Editor of Ophthalmology[102] notes that the data for subgroup analysis of the primary outcome can be found on the FDA website.[106] 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).[106] This is in contrast to the data in the VISION study publication,[95] which demonstrates 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.[106] 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 two published RCTs of ranibizumab, and the manufacturer supplied trial reports for two unpublished studies. The published and unpublished studies were of good methodological quality. Adequate methods of randomisation were used, which would have protected the studies from selection bias. The published trials and the [redacted] trial masked outcome assessors, care providers and patients to treatment, which should have prevented bias in the reporting of results. Whilst the MARINA trial analysed results on an ITT basis, the ANCHOR and [redacted] 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 0.3mg ranibizumab group were more likely to withdraw than those in the 0.5mg 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. One of the trials [redacted] visual acuity outcomes for patients in this trial were [redacted] those in the other studies. 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 be clinically effective for the treatment of AMD, with a greater proportion of patients losing less that 15 letters of visual acuity and patients gaining on average an improvement in vision.

3.4 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 0.3mg 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 one year.
- For all secondary measures of visual acuity, 0.3mg pegaptanib or 1.0mg pegaptanib was statistically significantly better than sham injection after one year of treatment. With the exception of gains in visual acuity of at least 5 letters or at least 15 letters, the 3.0mg pegaptanib dose was also statistically significantly better than sham injection after one 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 0.3mg and 1.0mg 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 0.3mg 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 0.3mg pegaptanib dose was significantly more effective than sham injection in reducing visual acuity loss in people with predominantly classic lesions after one 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 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 one 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 two good quality published RCTs of ranibizumab compared with sham injection[97] or PDT.[96] The manufacturer submitted two additional unpublished good quality RCTs 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 patient with predominantly classic lesions.
- People treated with ranibizumab in the two published and two unpublished RCTs were significantly more likely than those in the comparator arms to lose fewer than 15 letters of visual acuity.
- Between about 25% to 40% of patients receiving ranibizumab [redacted] 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.

[redacted]

- Results from MARINA, ANCHOR and [redacted] 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 three months is insufficient to maintain an average increase in visual acuity.
- The study eyes of people treated with either 0.3mg or 0.5mg ranibizumab in the MARINA and ANCHOR trials [redacted] 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 [redacted] 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.

[redacted]

- [redacted]
- 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 [redacted]. The changes were statistically different from the increases in area found in the comparator group. [redacted]
- [redacted]

[redacted]

- Conjunctival haemorrhage was the most widely reported ocular adverse effect[redacted]. Higher proportions of ranibizumab patients than those in the control arms experienced increased intraocular pressure and vitreous floaters.[redacted]related to use of the study drug. The incidence of non-ocular serious adverse events was reasonably balanced between treatment arms, and these were not generally reported to have been linked to the study drug. 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).

4 ASSESSMENT OF COST-EFFECTIVENESS

Introduction

The aim of this section is to assess the cost-effectiveness of pegaptanib and ranibizumab compared to 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 (Section 4.1.1 to 4.1.3);
- a review of the manufacturer submissions (cost-effectiveness section) to NICE (Section 0);
- presentation of our economic model and cost-effectiveness evaluation (Section 4.2).

As discussed in Section 1.1 (Measurement of disease), 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 in Sections 4.1 and 0 use measurements in feet, therefore these have been converted to metres for consistency (see Table 1.8).

4.1 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 to 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 economic evaluation of treatment for AMD.

4.1.1 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 manufacturer submissions. Three related conference abstracts, by Earnshaw and colleagues,[107-109] 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,[109]
2. cost-effectiveness estimates for pegaptanib and PDT using verteporfin for AMD,[107]
3. a cost-effectiveness analysis to determine the optimal timing of treatment with pegaptanib, based on initial visual acuity.[108]

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 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 less than or equal to 6/60) of 1.5.

The effectiveness of pegaptanib was based on published one-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 two years of efficacy results from the Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP)[10,88,110] and the Verteporfin in Photodynamic Therapy (VIP)[111] trials. To extrapolate outcomes beyond the clinical trials, data from the placebo arms of both trials[10,88,110,111] was used. Utilities applied to life expectancy in each of the model's health states were taken from a published source.[112]

The model used a three 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,[10,88,110] and VIP[111] trials. The method for converting annual proportions to three-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 (though these were not specified), excess costs associated with vision-loss (depression and fracture treatment as well as 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) as well as 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 to usual care, than delaying till disease had progressed, with an estimated incremental cost-effectiveness ratio (ICER) of $49,480.[108]

No incremental analysis was reported for the comparison of pegaptanib with PDT with verterporfin,[107] 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.

4.1.2 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.[40,86,87,113-117] 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.[107-109] The remaining two abstracts are not covered in this review as insufficient detail is reported in the abstracts.[118,119]

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.[116] 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[40,115], or longer[113,114]) or from selected sub-groups of patients within the trial cohort.[87,113-115]

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.[114]

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[40,86,113-115]. Simple models seeking to extrapolate the effectiveness of PDT over

patients' lifetimes have tended to assume that treatment effects observed at two or more years can be projected forward over the patient's remaining life expectancy,[114] though there may be an assumed reduction in effectiveness over time.[115] Two studies[87,117] used a survival function derived from analysis of patient-level trial data for a sub-group 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(98} report "trial-based" (i.e. two year) analyses as well as 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 Moore[86] and Meads and colleagues[40] 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'[87] trial-based analysis for a cohort of patients with initial visual acuity of 6/30. 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[40,86,87,115,117] used the same published health state utility estimates that were derived using the time trade-off method in 72 patents with AMD.[112]

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 section 1.2, 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, though in all cases cost of verteporfin is the major component of the unit cost (ranging from around 70%[86,113] to approximately 80%[40,114,115]).

The evaluations vary as to whether additional health state costs, associated with disease progression, are included. Three studies[113-115] included only direct costs of treatment. Meads and Moore[86] developed costs of blindness based on NHS and Personal Social Services 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 (£8,823 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 two 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.[40,86,116] Two studies reported both "trial-based" and extrapolated analysis.[87,115] 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.

4.1.3 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 classified as A, four studies classified as B, three studies classified as C and the remaining studies classified 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,[61,120-125] poorer contrast sensitivity and colour recognition,[125] severity of disease[126] and severity of visual loss.[65,127] 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.[61,120-123] Berdeaux and colleagues[124] 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[120], 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[123] and the Impact of Vision Impairment (IVI) Questionnaire.[126] 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. Ambrecht and colleagues[127] 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 12 month follow-up.[66,127]

Several studies have identified a strong association between AMD and depression. Forty nine out of 151 (32.5%) patients with AMD and visual acuity of 6/18 or worse in the better-seeing eye enrolled in a randomized 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 amongst 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 as well as 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 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 to 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 SF-36 where some authors have reported

significant associations between SF-36 domains scores and visual impairment [64] and others have not.[61,126]

An alternative approach to estimate the impact of disease is the use of preference-based techniques, such as time trade-off and standard gamble, to derive health state values or utilities. Table 4.1 reports the mean utility values derived using the two methods for ophthalmologists and for patients with visual loss from AMD.[128]

Table 4.1 Mean utility with time trade off and standard gamble for ophthalmologists and for AMD patients

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

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[128] also reported a statistically significant difference between utility values derived using time trade-off and standard gamble methods, for both physicians and patients with AMD. Most typically, utilities obtained with the latter method are higher than those obtained with the time trade-off method. This has been attributed to the greater risk aversion associated with the standard gamble method.[129]

Similar large differences between utility values derived using the time trade-off method from clinicians and patients were reported by Stein and colleagues,[130] 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 4.2, 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 in comparison to 44 for the general public sample and 29 for the clinicians), sex and ethnic makeup between the respondents from the various groups. The values obtained by Stein and colleagues[130] are generally higher than those derived, using the same method and similar respondents, by Brown and colleagues.[128]

Table 4.2 Utility scores in mean and 95% confidence interval by AMD severity

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

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. While 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 fellow eye.

4.1.4 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. See Appendix 8 for more details on each submission and 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.

4.1.4.1 Pfizer submission to NICE:[104] 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 (0.3mg at six 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 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 section 4.1.1.

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. Sub-group 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 two 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 personal social services, 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 (page 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,[131] the requirements of NICE for submissions on cost-effectiveness (reference case)[132] and a suggested guideline for good practice in decision modelling by Philips and colleagues.[133]

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 two years) between pegaptanib and usual care. The model has twelve 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 six weeks, corresponding to treatment intervals for patients receiving pegaptanib and the frequency of assessment of patients' visual acuity in the VISION trial, and a ten year time horizon. The model time horizon is equivalent to a lifetime horizon for patients with a mean age at diagnosis of 77, 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, though 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.[112] These values have been widely used in cost-utility models of treatments for AMD, and were adopted in many of the evaluations of PDT[40,86,87,115] reviewed in section 4.1.2 (and are discussed in our review of research on quality of life in AMD, section 4.1.3).

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 principally relate 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 0.3mg every six weeks for a maximum of two 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 fluoroscein angiography to localise the lesion. The cost per PDT session used in the submission is slightly lower than in 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, so has not biased the evaluation. Also, the cost of an out-patient 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 are the same as in previous UK evaluations.[40,87] The proportion of patients with visual acuity below 6/60 receiving services are 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.[134] Unit costs from different base years (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 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, as well as 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 ususal care in scenario A and a 0.289 QALY gain in scenario B. The incremental cost-effectiveness ratios for the two scenarios are also similar at £15,819 per QALY and £14,202 per QALY for scenario A and scenario B respectively.

The submission concludes that pegaptanib is likely to be a cost-effective treatment, relative to usual care, though 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 Personal Social Services 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 number of pegaptanib treatments over two years estimated in the model in scenario A (12.6) and scenario 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 can be seen in Table 4.3.

Table 4.3 Assessment of Pfizer submission against NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE	?†
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	?‡
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	X*
Discount rate: 3.5% pa for costs and health effects	✓
Notes: † pegaptanib versus "usual care" not best supportive care. Makes sense given the data available ‡ utilities taken from published study using SG and TTO valuations (TTO valuations used in base case) * utilities taken from ARMD patients, not general public	

See Appendix 12 for tabulation of critical appraisal of submission against Drummond and colleagues[131] checklist.

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, though 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 to 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 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 six 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 twelve 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[135] 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 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 (from 1 to 10 lines) and gain (from 1 to 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 (0.3mg, 1mg and 3mg) of pegaptanib. There were sufficient data to estimate models for 1 to 3 line gain and 1 to 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 to those suggested by clinical experts who assisted in the development of this review. In the Pfizer model patients have a single fluoroscein angiogram 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 fluoroscein angiography every six months, though it may be good practice to consider offering fluoroscein angiography every three 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 standard gamble and the time trade-off technique, decrease with declining visual acuity. The mean values, elicited using the time trade-off technique, for each of the visual acuity states reported by Brown and colleagues[112] were used in the base case. Standard deviations were extracted from the study report and used in estimating the parameters 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[135] and were applied to age and sex-specific prevalence of treated depression[136] and annual fracture rates.[137] 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 fluoroscein angiographies, method of monitoring adverse events, costs and probabilities of receiving services for visual impairment, and excluding patients receiving PDT). Only the incremental cost-effectiveness ratio is reported for these sensitivity analyses, so no comment can be made on change 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 (though the difference is small). Exceptions to this were variation 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 three 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 two 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 to partially offset costs of treatment, are around £1,000 at 2 years and around £2,500 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 for parameter values tested (though 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 relatively 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 standard deviation of time trade-off valuations from published study[112]) 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 use of a normal distribution for the number of pegaptanib treatments is likely to produce over-estimates, since the distribution observed in the trial was highly skewed with amedian of 9 treatments and range of 1 to 9 treatments. No patient would be expected to have more than 9 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 sub-group analyses presented in section 3.5 of the submission. Sub-groups examined were defined by patient age, sex, lesion type and lesion size. Very little variation in ICER was reported by these sub-groups, except that the ICER was reduced to £10,940 (£9,454 for scenario B) for patients aged under 75 compared to £18,863 (£17,128 for scenario B) for patient aged 75 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 model. This may over-estimate the benefit associated with pegaptanib treatment.
- The model uses a ten 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 raning from 45 to 75. 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 two years of trial data and one year of data on post-treatment effects to longer time horizons may be questionable.
- The methods for deriving the parameters 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 8 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 optical coherence tomography at each attendance. The reference case assumed the fluoroscein angiography was only performed prior to initiation of treatment, whereas clinical advisors suggested that it may occur every three to six 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 TAR team using the manufacturer's model

Table 4.4 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 incremental cost by around £650 and the ICER rises by around £2,000. Adding in the cost of vision assessments at each attendance increases incremental cost and ICER by the same order of magnitude as for OCT. Assuming that patients have fluoroscein angiography every six 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 £4,000 and the ICER increases to £35,197.

Table 4.4 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
Fluoroscein angiography every six months	£ 6,635	0.298	£ 22,266
Cost injection as day case procedure	£ 10,489	0.298	£ 35,197
Costs as in submission. Utilities from Novartis submission	£ 4,705	0.279	£ 16,863

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). Unpublished utility values developed for the Novartis submission do not show such "steps" in the utility function, in relation to visual acuity. When these 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.

4.1.4.2 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 three 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). Indirect comparison was also used to extrapolate outcomes for patients with predominantly classic lesions beyond the time horizon of the ANCHOR trial. Data from the sham arm of the MARINA trial was used as an estimate of the natural history of disease progression for extrapolating from trial outcomes to a ten-year time horizon for minimally classic and occult no classic lesion types. Two-years of clinical trial data are available for the MARINA study and one-year data is available for the ANCHOR and PIER studies. Resource use estimates in the model were derived from the literature and from [redacted] 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 – one year for patients with predominantly classic lesions (based on the ANCHOR trial) and two years for patients with minimally classic or occult no classic lesions (based on the MARINA trial). For all patients a stopping rule was applied so that patients whose visual acuity declined below 3/60 ceased active treatment with ranibizumab. A lower frequency of dosage (than used in the trials) was assumed in the model, with patients receiving 8 injections in the first year and 6 injections in the second year. This assumption was derived from [redacted] and it was assumed that the treatment effective persisted for up to six months after the end of treatment.

Since (at the time of writing this report) ranibizumab does not have marketing authorization for this indication, there is no unit cost available in the BNF[82] or MIMS[138]. The price of a vial of Lucentis 0.5mg used in the model was based on the manufacturer's target price for the UK of €1,100 (converted at an exchange rate €1 = £0.692, giving a sterling price of £761.20). 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 personal social services 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,[131] the requirements of NICE for submissions on cost-effectiveness (reference case)[132] and a suggested guideline for good practice in decision modelling by Phillips and colleagues.[133]

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) – though 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 and is [redacted] male. 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 by as much as [redacted] health states, 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 three month cycle length and a time horizon of ten years.

The dosing schedule for ranibizumab applied in the model is different from that used in the clinical trials. Both ANCHOR and MARINA trials involved monthly injections, continuing for a maximum of one year in ANCHOR (12 injections) and for a maximum of two years in MARINA (24 injections). For the base case scenario in the economic analysis a schedule of 8 injections in year 1 and 6 injections in year 2 was modelled with the assumption that the same

clinical efficacy would be achieved with this lower dosing frequency. This may be questioned. The [redacted] in both the MARINA and ANCHOR trials showed [redacted] difference between ranibizumab and sham injection group in [redacted] However, [redacted] sh owed [redacted] in the PIER trial. This latter trial used monthly injections for the first three months (the "loading dose") followed by quarterly injections, corresponding to a total of 6 injections over 12 months. The submission argued that [redacted] results from [redacted] using the [redacted] and [redacted] has suggested [redacted] This corresponds to the [redacted] that were assumed in the economic model. The submission included sensitivity analyses on this assumption and these are discussed in the results section of this review.

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 six months following cessation of treatment with ranibizumab. It was assumed that for three 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 three months. After this time the same efficacy as those receiving best supportive care was assumed. The submission does not mention how these post treatment benefits were derived. Simple [redacted] approach was taken to estimate the transition probabilities of those receiving ranibizumab during these two treatment cycles. Howeverm the submission included sensitivity analyses on this assumption and this is discussed in the results section of this review.

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 time trade off exercise prior to insertion of contact lenses that would mimic visual impairment due to AMD. [redacted] A fter this they underwent a vision assessment which was followed by completion of a health

questionnaire and a time trade-off valuation of their changed visual state. The mean age of participants was [redacted] with the oldest being [redacted] An analysis reported with the submission states that [redacted] were found between [redacted] and time trade off values.

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 to best supportive care in 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 incremental cost effectiveness ratios for ranibizumab are variable by lesion type and by comparator. The ICER for patients with predominantly classic lesions are £4,489 per QALY gained for the comparison with PDT (Table 4.5) and £14,781 per QALY gained when compared with best supportive care (Table 4.6). The ICERs are less favourable for occult no classic and minimally classic at around £26,000 per QALY gained (Table 4.8 and Table 4.9). 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 4.7).

Table 4.5 ANCHOR – Predominantly classic lesions: Ranibizumab 0.5mg vs. PDT

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

Table 4.6 ANCHOR – Predominantly classic lesions: Indirect comparison of Ranibizumab 0.5mg vs BSC

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

Table 4.7 PIER - All type of AMD lesions: Ranibizumab 0.5mg vs BSC

	Costs (£)	QALY	Cost /QALY (£)
Ranibizumab	31,323	3.89	

Best supportive care	28,202	3.63	
Incremental	3,120	0.26	12,050

Table 4.8 MARINA – Occult no classic lesions: Ranibizumab 0.5mg vs BSC

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

Table 4.9 MARINA – Minimally classic lesions: Ranibizumab 0.5mg vs BSC

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

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, from twelve to eight injections (the latter including a loading dose of monthly injections for the first three months) in year 1 and from twelve to six injections in year 2, [redacted] 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 later section on Assessment of Uncertainty.

Outline appraisal of the cost-effectiveness analysis undertaken

A summary of the manufacturer's submission compared with the NICE reference case requirements can be seen in Table 4.10.

See Appendix 13 for tabulation of critical appraisal of the submission against Drummond and colleagues[131] checklist.

Table 4.10 Assessment of Novartis submission against NICE reference case requirements

NICE reference case requirements (see detail in NICE report)**:**	Included in Submission
Decision problem: As per the scope developed by NICE	✓
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	✓ (CEA and CUA)
Synthesis of evidence on outcomes: Based on a systematic review	X*
Measure of health benefits: QALYs	✓+
Description of health states for QALY calculations: Use of a standardised and validated generic instrument	✓^
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	✓^
Discount rate: 3.5% pa for costs and health effects	✓
Notes: * The efficacy data inputs were derived from patient level data in clinical studies. However there are no descriptions about the derivation. The inputs for BSC for patients with predominantly classic wet AMD were derived using simple indirect comparison method. + Also included vision year gained as a health benefit measurement. ^ from Brazier, J. Appendix 1 of manufacturer's submission	

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 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 three 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. As the intervention being assessed is indicated for at least [redacted] 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 the transition probabilities between the health states are the mean values that were derived from the patient level data and the impact of treatment duration on transition probabilities was assessed in order to determine which time intervals should be analysed separately. On the basis of this analysis it was reported that the first quarter of AMD treatment, the second to final quarter of the first treatment year, and the second year were identified as requiring separate analysis. A clarification from 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 MLRM were used to assess whether certain time 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.

The resource use assumptions for PDT in the model include an estimate that [redacted]% of patients will receive intravitreal injection of triamcinolone. No reference could be found for this level of use of intravitreal triamcinolone in the clinical trials or in the supporting documents in the submission. This may be an estimate derived from [redacted]This contributed [redacted]% of the total cost of administering PDT, excluding verteporfin, or [redacted]% if the cost of verteporfin is included. A further analysis was undertaken by the TAR team after removing this cost and is reported later in this review.

The cost of administering sham injection to patients in the PDT and best supportive care cohorts were [redacted]as were the costs of [redacted]Since sham injections were administered to these patients in the clinical trials only to ensure treatment blinding and not for any therapeutic purpose it seems inappropriate to include these in the economic model which aims to reflect the clinical practice. A further analysis was undertaken by the TAR team after removing this cost for patients in the PDT or best supportive care cohorts and is reported later in this review. It should be noted that the impact of [redacted]is not taken into account in the submission.

Data inputs

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

It is reported in the submission that pooled data from the MARINA and ANCHOR trials show an approximately [redacted] for patients receiving 0.5mg ranibizumab [redacted] No indication of the statistical significance of this [redacted] was included in the submission. The cost of [redacted] was not included in the model.

As no direct comparison to 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. The equations in the model reveal that [redacted] were applied to the [redacted] in order to estimate [redacted] among the patients with predominantly classic AMD. This method resulted in some of the estimated transition probabilities being smaller than 0 and greater than 1. Where this occurred the values were corrected to 0 and 1, respectively. To avoid this problem the log risk ratio or log odds ratio, rather than risk difference, could be considered when performing indirect comparison.

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 by £[redacted] to £[redacted] 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 time trade off. The valuations were reported for ranges of visual acuity used in the manufacturer's economic model. The valuations elicited by [redacted] and used in the manufacturer's model are consistently [redacted] those derived by Brown and colleagues[112] using the time trade off method in a sample of AMD patients. The health state utilities derived by [redacted] also show a [redacted] the values elicited by Brown and colleagues[112] show a rapid decline between 6/9-6/15 and 6/18-6/30 and a smaller decrease between 6/18-6/30 and 6/60-3/60 (see Table 4.1). The values derived by [redacted] are [redacted] those estimated, using the time trade off method, by Stein and colleagues[130] in AMD patients (see Table 4.2).

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. Parameters included for probabilistic sensitivity analysis are [redacted] and [redacted] at each model cycle. 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 included in estimating the total continuous cost of blindness 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 given that the probability of incremental cost effectiveness ratios for ranibizumab below £30,000 per QALY was predicted to be close or equal to 1 in the submission.

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 4.11.

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 (12 injections) given in both the MARINA and ANCHOR studies. This shows that the main driving factor for incremental cost effectiveness ratios (ICERs) is the number of ranibizumab injections. For the sub-group of patients with predominantly classic lesions the ICERs for all the scenarios are below £30,000 except in the case where the number of ranibizumab injections given in the ANCHOR trial was used. For both the minimally classic and occult no classic subgroups the ICERs are above £30,000 when more than 8 injections in the first year and 6 injections in the second year are assumed. When the number of injections given in MARINA trial are used the ICERs are £55,906 and £56,234.

These results are similar to the those presented by the manufacturer on the sensitivity of cost-effectiveness estimates to assumptions over the number of injection, reported in Tables 3.9 and 3.10 of the submission._Assuming twelve 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 and year 2 of treatment) were both approximately £55,000 per QALY gained.

Since the double-counting error for concomitant treatment cost and the use of intravitreal triamcinolone only applied to PDT, the change in costing assumptions has greatest effect on

the ICER comparing ranibizumab with PDT, which is only relevant for patients with predominantly classic lesions.

Table 4.11 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) Remove 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) to (iii)	1,659	0.20	8,121
Using (iv) as a base case scenario for sensitivity analyses on number of injections per year			
(v) 9 in 1st year+	2,683	0.20	13,135
(vii) 12 in 1st year+	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) 9 in 1st year+	5,241	0.28	19,042
(iii) 12 in 1st year+	8,313	0.28	30,203
+ Injections were assumed in first year only the as observed in ANCHOR trial			
Minimally classic lesions *BSC as comparator*			
As reported in submission	8,494	0.33	25,796
(i) Removing costs a/w 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) 9 in 1st year ; 6 in 2nd year	9,952	0.33	30,227
(iii) 9 in 1st year ; 9 in 2nd year	12,672	0.33	38,488
(iv) 12 in 1st year ; 6 in 2nd year	12,967	0.33	39,384
(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 a/w 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) 9 in 1st year ; 6 in 2nd year	10,616	0.34	30,777
(iii) 9 in 1st year ; 9 in 2nd year	13,450	0.34	38,990
(iv) 12 in 1st year ; 6 in 2nd year	13,731	0.34	39,806
(v) 12 in 1st year ; 12 in 2nd year	19,398	0.34	56,234

4.2 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 compared to 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 personal social services. 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 sub-group with a confirmed diagnosis of classic, no occult subfoveal AMD, PDT with verteprofin. Best supportive care in this group of patients will include blind registration, provision of low vision aids, visual rehabilitation and may also include provision of residential and nursing care as a result of patients' loss of vision.

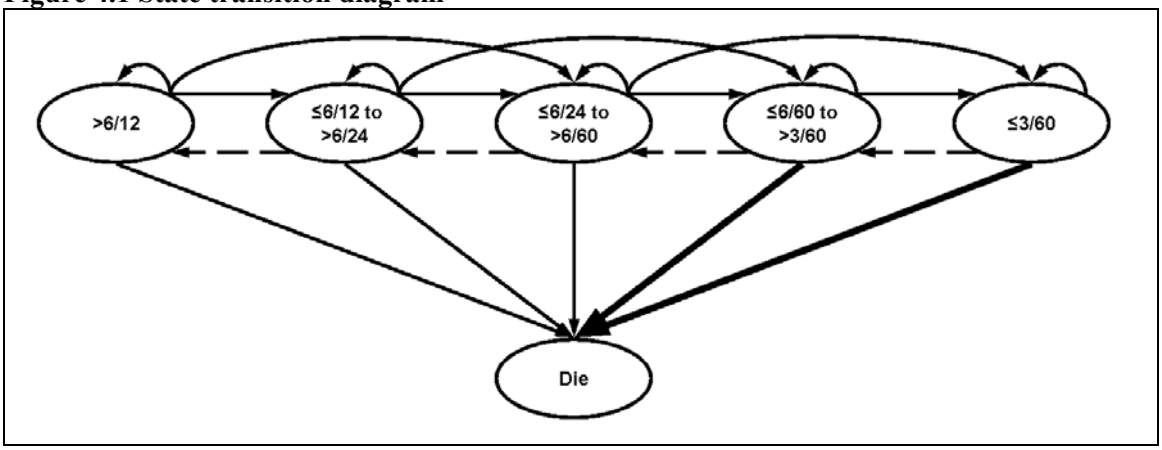
4.2.1 Methods

Model type and rationale for the model structure

The primary outcome in the clinical trials reviewed in Section 3.2 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 proportion of patients gaining 15 letters, losing between 15 and 30 letters and losing more than 30 letters of visual acuity. These endpoints are interpreted clinically as being categories of response (loss of less than 15 letters), intermediate vision loss (loss of 15 to 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 section 4.1, 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 4.1. 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 correspond to approximately three lines (or fifteen letters) of visual acuity, which (as stated in section 1.2 **Outomes**) is generally accepted as a clinically significant difference.

Figure 4.1 State transition diagram



The state transition model indicates that an individual with AMD, in any of the health states defined by visual acuity, may remain at 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 endpoints 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.

While 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 12 month follow-up (6.0% and 2.4% respectively for the PDT and placebo arms). The dotted lines from each visual acuity state to the next higher state indicate the possibility of improvement.

The model adopts a three 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 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 ranibizumab and pegaptanib (Section 3.2) 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 (Section 4.1).

Table 4.12 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 3.3 for Year 1 and Year 2 results from the VISION study).

Table 4.12 Transition probabilities used to model effectiveness of pegaptanib, derived from the VISION study

	Year 1[95]		Year 2[104]	
	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 & 6 lines†	0.0555	0.0626	0.0412	0.0419
Lose at least 6 lines	0.0247	0.0601	0.0169	0.0372

Notes
† not reported in Gragoudas and colleagues[95] or 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 visual acuity) or losing at least six lines, as reported in Table 3.3.

The annual proportion 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,[140] 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 3 lines, losing at least 3 and less than 6 lines and those losing at least 6 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 to 10. Given that treatment with pegaptinib 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[141] in an unpublished analysis of the VISION trial contend that pegaptanib has a disease modifying effect. They showed that patients re-randomised from treatment with pegaptanib at doses 0.3mg, 1mg and 3mg after 54 weeks to discontinuing treatment, continued to experience statistically significant benefit after another 48 weeks compared to those who received the sham treatment throughout the study period (see Table 4.13). Although the study is unpublished and concerns remain about the validity of the analysis, we included a disease modifying effect for pegaptanib through sensitivity analysis in the model.

Table 4.13 Disease modifying effect of pegaptanib

	Relative risk of non-response (95% CI)	p value
All doses pooled	0.70 (0.56, 0.86)	p=0.001
0.3 mg	0.68 (0.51, 0.90)	p=0.008
1 mg	0.62 (0.46, 0.83)	p=0.001
3mg	0.79 (0.61, 1.03)	p=0.09

Adverse events associated with intraocular injection of pegaptanib were reported for the first year of the VISION trial and are discussed in Section 3.2.4 of this report. Three serious adverse events (endophthalmitis, traumatic lens injury and retinal detachment), associated with significant risk of severe loss of visual acuity as well as health care management costs, were identified[95] and their frequencies of occurrence are reported in Table 4.14. The proportion of adverse events, per injection, were treated as the probability of each adverse event occurring, per injection received by patients in the pegaptanib cohort in the model.

Table 4.14 Injection-related adverse events in Year 1 of 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%

This may over-estimate 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.

Table 4.15 and Table 4.16 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 3.3).

Table 4.15 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 & 6 lines†	0.0046	0.0614
Lose at least 6 lines	0.0000	0.0351
Notes † 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 visual acuity) plus the proportion losing at least six lines from 1.		

Table 4.16 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 & 6 lines†	0.0053	0.0648	0.0097	0.0675
Lose at least 6 lines	0.0016	0.0378	0.0032	0.0623
Notes † 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 visual acuity) plus the proportion losing at least six lines from 1.				

The annual proportion of patients in each trial reported as gaining or losing visual acuity were 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.[110]

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 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 6 lines and those losing at least 6 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 to 10.

Adverse events reported in the ANCHOR and MARINA trials are discussed in Section 3.2.4 of this report. The proportion of patients experiencing serious adverse events during the ANCHOR trial are reported in Table 4.17. These annual proportions are converted to cycle probabilities using the density method.[140] The probabilities of experiencing an injection-related adverse event are applied in each model cycle during which treatment by intraocular injection occurs.

Table 4.17 Injection-related adverse events in ANCHOR trial

Adverse event	Events per patient (n=140)
Endophthalmitis	1.43%
Traumatic injury to lens	0.00%
Retinal detachment	0.36%†
Uveitis	0.07%
† one case of retinal detachment in 0.3mg ranibizumab arm – proportion for the model estimated as proportion across both ranibuzamab arms in the trial (i.e. 1/(137+140))	

The proportion of patients experiencing serious adverse events during the MARINA trial are reported in Table 4.18. These are two-year cumulative proportions and are converted to cycle probabilities using the density method.[140] The probabilities of experiencing an injection-related adverse event are applied in each model cycle during which treatment by intraocular injection occurs.

Table 4.18 Injection-related adverse events in 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%

Health state values/ utilities

The health state utilities adopted in the cost-effectiveness model are those reported by Brown and colleagues[112] and derived using the time trade-off 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 seventy two patients using both time trade-off and standard gamble methods. For the time trade-off, 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 4.19 reports the mean time trade-off valuations relevant to health states in our model.

Table 4.19 Health state utilities used in economic model

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

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[112,128] and Sharma and colleagues[142]). The time trade-off valuations reported by Brown and colleagues[112] were adopted in our model as theirs are the most credible published utility values for visual loss associated with AMD, and the time trade-off valuations have been the most widely used in previous cost-utility studies of treatment for AMD[40,86,87,115] (see review in Section 4.1). To test the sensitivity of source of valuations the standard gamble values were used in the sensitivity analysis. The upper and lower confidence limits of the time trade-off 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 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. Secondly, 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 was 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 4.2

All new patients are evaluated in the outpatient department, receiving an extended outpatient appointment for medical assessment, a vision assessment and imaging using fluoroscein angiography and optical coherence tomography (OCT). Those patients proceeding to active treatment are assumed to receive their first drug treatment immediately following their initial out-patient consultation. For subsequent treatments patients are assumed to have a standard out-patient 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 fluoroscein angiography every 3 to 6 months. On discontinuation of treatment (premature termination of treatment or at the scheduled end of treatment) patients are assessed using fluoroscein angiography.

Patients treated with pegaptanib would be seen seventeen times during two years of treatment (the maximum treatment duration in VISION trials). This corresponds to six-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 ranubizumab would be seen twelve times during one year of treatment (the maximum treatment duration in the ANCHOR trial) and twenty four times during two years of treatment (the maximum treatment duration in the MARINA trial). This corresponds to four-weekly visits which was the frequency of treatment in the trials as stated in the Summary of Product Characteristics (SPC). Administration of both drugs is assumed to occur during the patient's hospital attendance for out-patient 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] Ranibizumab does not currently have marketing authorisation there is no unit cost

available, therefore for this evaluation we adopted the target price for the UK indicated by the manufacturer. This is lower than the expected price quoted in section 1.3 (**Anticipated costs**) which was based on a currency conversion form the US price of $1,950.

Drug costs for pegaptanib were calculated for a dosage of 0.3mg administered as an out-patient procedure every 6 weeks for up to two years. A 0.3mg vial of pegaptanib costs £514 and total drug cost for one year of pegaptanib treatment is therefore £4,626 (or £9,252 for a patient receiving the maximum of two years of treatment evaluated in VISION study).

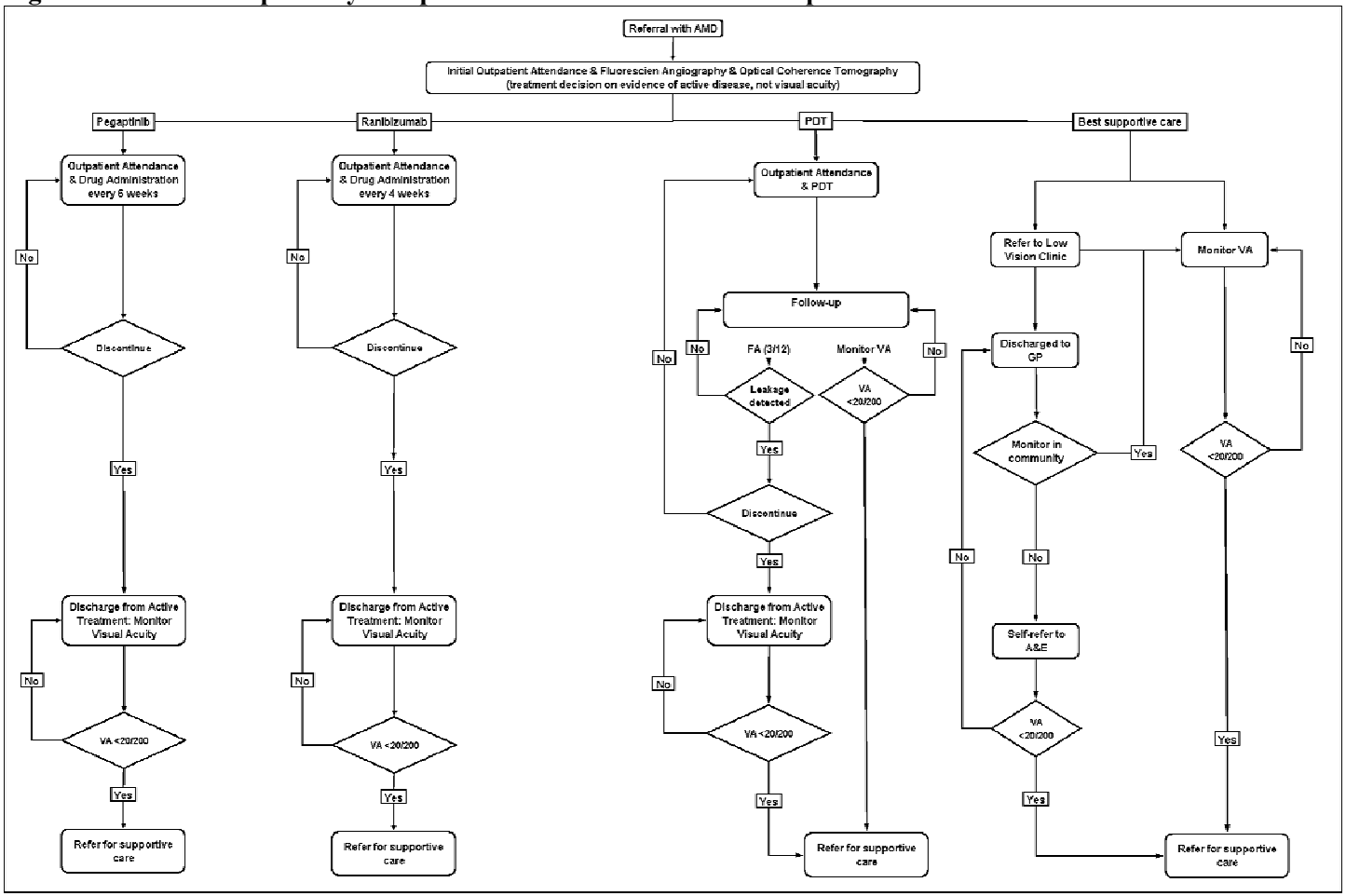
Drug costs for ranibizumab were calculated for a dosage of 0.5mg administered as an out-patient procedure every month for up to one year in analysis using ANCHOR data and up to two years in analysis using MARINA data. The manufacturer's target price for the UK is €1,100, which was converted to sterling at an exchange rate of €1 = £0.692. Therefore a vial of 0.5mg ranibizumab is estimated to cost £761.20 and the total drug cost is £9,134.40 for one year and £18,268.80 for two 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 out-patient visits and treatment with topical steroid. Traumatic lens injury requires cataract extraction, three extended out-patient visits and treatment with topical steroid, while retinal detachment requires cryotherapy with buckle/vitrectomy, three extended out-patient visits, and treatment with topical antibiotic as well as topical steroid. Unit costs and sources are reported in Table 4.20.

Table 4.20 Management costs for injection-related adverse events

Management of adverse event	Unit cost	Source
Endophthalmitis		
Intravitreal tap and injection	£2,077	NHS Reference costs[84]
Extended out-patient visit	£96	NHS Reference costs[84]
Topical steroid	£3.21	BNF[82]
Traumatic injury to lens		
Cataract extraction	£1,119	NHS Reference costs[84]
Extended out-patient visit	£96	NHS Reference costs[84]
Topical steroid	£3.21	BNF[82]
Retinal detachment		
Cryotherapy with buckle/ vitrectomy	£1,725	NHS Reference costs[84]
Extended out-patient visit	£96	NHS Reference costs[84]
Topical steroid	£3.21	BNF[82]
Topical antibiotic	£1.32	BNF[82]

Figure 4.2 Treatment pathways for patients with AMD referred for specialist care



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 equal to or less than 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 have been taken from Unit Costs of Community Care (Curtis and Netten[134]) and NHS Reference Costs[84] as shown in Table 4.21. All costs are expressed as 2005 prices.

Table 4.21 Additional costs associated with vision loss below best corrected visual acuity of 6/60 in better-seeing eye

Services	% receiving services	Unit Cost (£)	Source	Annual cost (£)
Blind registration	95	115	Meads and colleagues[40], Curtis and Netten[134]	109
Low vision aids	33	150	Meads and colleagues[40]	50
Low vision rehabilitation	11	259	Curtis and Netten[134]	28
Community care	6	6,552	Curtis and Netten[134]	393
Residential care	30	13,577	Curtis and Netten[134]	4,073
Depression	39	431	Knapp and colleagues[143]	168
Hip replacement	5	5,379	NHS reference costs, 2005[84]	269
Annual cost is estimated by multiplying unit costs by the proportion of eligible patients estimated as receiving each service.				

Blind registration, provision of low vision aids and low vision rehabilitation are one-off costs associated with loss of vision below 6/60. Unit costs have been estimated using the doctor's sessional fee for completing the Certificate of Vision Impairment and an initial assessment by community occupational therapist (1 hour) for blind registration. Unit costs reported by Meads and colleagues[40] (uplifted to 2005 values) have been adopted for the provision of low vision aids. The cost of an episode of care with a community occupational therapist has been 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, while 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 column 5 of Table 4.21 gives a cost £5,090 for the first year of blindness and £4,903 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% has been applied to future costs and benefits in line with current guidance from NICE.[132] Discount rates of 0% and 6% have been applied in the sensitivity analyses.

Presentation of results

We report findings on the cost-effectiveness of interventions based on 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 ten year time horizon (the approximate life expectancy for patients age 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 quality adjusted life years (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 Table 4.12 to Table 4.16 and for health state costs in Table 4.21. Distributions are also assigned to the health state utilities reported in Table 4.19 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 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 Personal Social Services. This was based on our systematic review of literature on natural history, epidemiology and health-related quality of life in AMD, as well as systematic review of literature on 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 and 50% of whom are male.
- The model has a ten year horizon (the approximate life expectancy for patients age 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 manufatcurer'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%.

4.2.2 Results

4.2.2.1 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 Section 4.2.1. 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 for 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 4.22. Costs and health outcomes in the table have been discounted at 3.5%.

Table 4.22 Cost-effectiveness of pegaptanib against usual care. Base case analysis

	Costs (£)	Life Years	Vision Years	QALYs	Incremental cost per QALY gained
Two 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
Ten year time horizon					
Usual Care	£ 16,600	6.47	3.28	3.89	
Pegaptanib	£ 24,662	6.55	3.99	4.15	£ 30,986

This comparison is based on patients receiving a maximum of two years of treatment with pegaptanib, with the frequency of drug administration as reported over the two years of the VISION study.[95,104] As expected, for the trial-based analysis and for the ten-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 two year time horizon and 0.71 for ten 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 two years and 0.26 at ten years).

There is a large cost difference between pegaptanib and usual care at two 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 incremental cost effectiveness ratio of £163,603. The cost difference is reduced at 10 years (£8,062, with costs for pegaptanib being 49% higher than for usual care). Table 4.23 reports the breakdown of costs at two years and ten years, indicating that all excess costs of treatment are realised in the first two years whereas costs of blindness represent a small proportion of total costs. While the difference between in cost of blindness the pegaptanib-treated and usual care cohorts at ten 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.

Table 4.23 Breakdown of total costs for each cohort by major categories. Base case analysis

	Drug	Administration and monitoring	Managing adverse events	PDT	Blindness
Two year time horizon (no extrapolation beyond trial data)					
Usual Care	£ -	£ 220	£ -	£ 590	£ 1,747
Pegaptanib	£ 7,388	£ 4,107	£ 98	£ 404	£ 820
Ten year time horizon					
Usual Care	£ -	£ 220	£ -	£ 590	£ 15,789
Pegaptanib	£ 7,388	£ 4,107	£ 98	£ 404	£ 12,666

4.2.2.2 Cost-effectiveness of pegaptanib – deterministic sensitivity analysis

We conducted a sensitivity analysis to consider the effect of uncertainty around 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 is 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 4.24 reports the results of the sensitivity analysis. Except for the sensitivity analysis with respect to time horizon, all analyses were conducted using the ten year model. The table is 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.

Table 4.24 Deterministic sensitivity analysis - pegaptinib

		Incremental cost	Incremental QALYs	ICER
Reference case		£ 8,062	0.26	£ 30,986
Structural assumptions				
Time horizon (10 years)	3 years	£ 9,589	0.11	£ 87,428
	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 costs and outcomes)	0% for cost & outcome	£ 7,893	0.29	£ 26,782
	6% for cost & outcome	£ 8,154	0.24	£ 34,029
Baseline cohort characteristics				
Age of cohort at start of simulation (75 years)	-15 years	£ 7,533	0.27	£ 27,537
	-10 years	£ 7,647	0.27	£ 28,108
	+5 years	£ 8,300	0.24	£ 34,040
Proportion of cohort that is male (50%)	40%	£ 8,042	0.26	£ 30,801
	60%	£ 8,062	0.26	£ 30,986
Visual acuity at baseline (6/12 to 6/24)	50% 6/12 to 6/24 and 50% 6/24 to 6/60	£ 8,063	0.22	£ 35,913
	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 out-patient attendance	25 percentile	£ 7,766	0.26	£ 29,846
	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	Standard gamble 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

As shown in Table 4.22, 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 pegaptianib cohort post-treatment as for usual care. An analysis reported in the manufacturer's submission,[104] and submitted for publication 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 three to six 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 three of the ten year model. This reduced the incremental cost by approximately £350 and increased the QALY gain by 0.03, yielding an incremental cost effectiveness ratio of £26,896. Subsequently the relative risk reduction was applied to the transition probabilities for losing visual acuity from year three through to year ten 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 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 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, while a cohort with initial visual acuity of 6/24 to 6/60 produced an ICER of approximately £46,285.

The analyses presented in Table 4.24 have assumed that the intravitreal injection is provided in out-patients, and have used an out-patient 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 4.23 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 4.25, showed wide variation in incremental cost from a situation where pegaptanib was cost saving over a ten 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).

Table 4.25 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

To indicate which variable, costs or uptake, were 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 4.24 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.

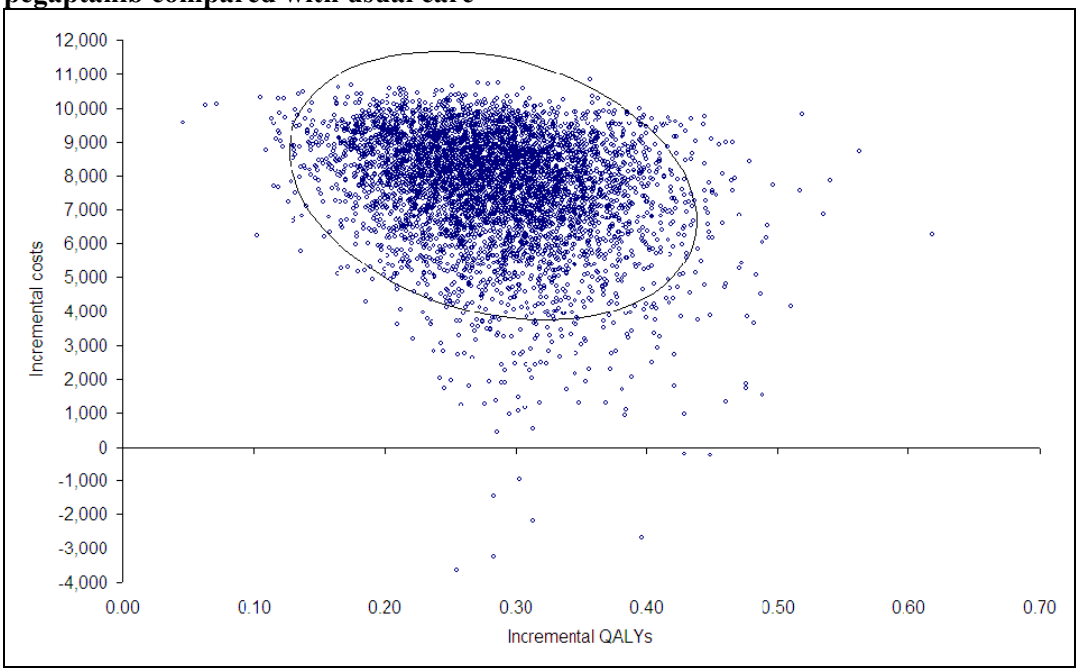
Other parameters included in the sensitivity analysis had comparatively little impact on cost-effectiveness of pegaptinib.

4.2.2.3 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

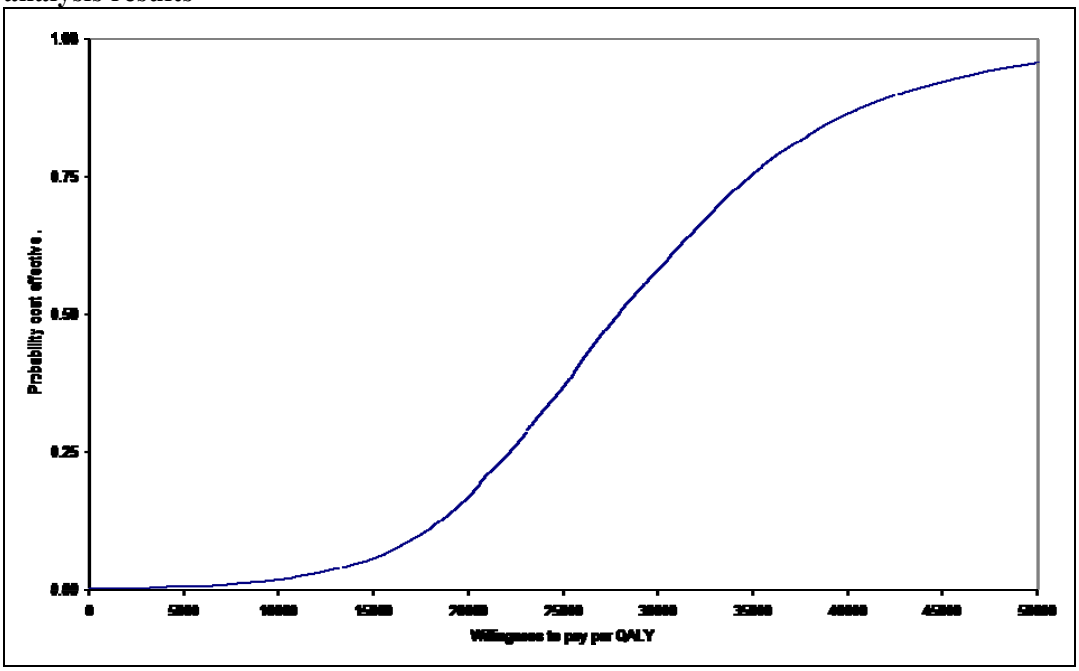
attendances, fluoroscein angiography and optical coherence tomography and costs of services for visual impairment were sampled probabilistically, the majority of simulations produced incremental cost effectiveness estimates that were in the north-east quadrant of the cost-effectiveness map, see Figure 4.3. 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.

Figure 4.3 Cost effectiveness plane – incremental cost and incremental QALYs for pegaptanib compared with usual care



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, see Figure 4.4.

Figure 4.4 Cost effectiveness acceptability curve – pegaptanib probabilistic sensitivity analysis results



4.2.2.4 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 Section 4.2.1. 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 quality adjusted life years 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 4.26. Where relevant, costs and health outcomes in the table have been discounted at 3.5%.

Table 4.26 Cost effectiveness of ranibizumab against PDT or best supportive care. Trial-based analysis

	Costs (£)	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

The analyses presented in Table 4.26 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 one 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 two years, the reported duration of the MARINA trial. Table 4.27 presents the same comparisons for a time horizon of ten 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 a year and consisted of either 12 injections of ranibizumab or the average number PDT treatments observed in the control arm of the ANCHOR trial [redacted]. For patients with minimally classic or occult no classic lesions treatment continued for a maximum of two years and consisted of 12 injections of ranibizumab annually.

Table 4.27 Cost effectiveness of ranibizumab against PDT or best supportive care. Ten year time horizon

	Costs (£)	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

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 ten 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 ten 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 twelve times those for best supportive care, with an absolute difference of £8,245 and £11,495 respectively. These high incremental costs, taken together with the small QALY gains at one year, lead to large incremental cost effectiveness ratios 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 two years and yields an incremental cost effectiveness ratio 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 £5,392 and £6,460 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 4.28 reports the breakdown of costs in the "trial-based" analyses and at the ten year time horizon, indicating that all excess costs of treatment are realised during the first year (ANCHOR trial) or two years (MARINA trial) whereas costs associated with progression to blindness represent a small proportion of total costs in the ranibizumab-treated cohorts. At ten years costs of blindness constitute 24% to 54% of total costs for ranibizumab-treated patients, 82% of total costs for patients with predominantly classic lesions initially treated with PDT and 98% to 99% of total costs for patients in the best supportive care cohorts. The difference in costs of blindness between ranibizumab-treated and comparator cohorts at ten years are £3,113 for patients with predominantly classic lesions in the comparison with PDT and £5,749 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 £6,254. While the difference between cost of blindness in the ranibizumab-treated and comparator cohorts at ten 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 4.27.

Table 4.28 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 (one or two year time horizon)					
Predominantly classic: PDT as comparator					
PDT	£ -	£ -	£ 78	£ 3,845	£ 259
Ranibizumab	£ 8,997	[redacted]	[redacted]	[redacted]	[redacted]
Predominantly classic: Best supportive care as comparator					
BSC	£ -	£ 221	£ -	£ -	£ 712
Ranibizumab	£ 8,997	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic and occult no classic: Best supportive care as comparator					
BSC	£ -	£ 220	£ -	£ -	£ 1,321
Ranibizumab	£ 17,314	[redacted]	[redacted]	[redacted]	[redacted]
Ten year time horizon					
Predominantly classic: PDT as comparator					
PDT	£ -	£ -	£ 78	£ 3,845	£ 17,575
Ranibizumab	£ 8,997	[redacted]	[redacted]	[redacted]	[redacted]
Predominantly classic: Best supportive care as comparator					
BSC	£ -	£ 221	£ -	£ -	£ 20,210
Ranibizumab	£ 8,997	[redacted]	[redacted]	[redacted]	[redacted]
Minimally classic and occult no classic: Best supportive care as comparator					
BSC	£ -	£ 220	£ -	£ -	£ 13,567
Ranibizumab	£ 17,314	[redacted]	[redacted]	[redacted]	[redacted]

4.2.2.5 Cost-effectiveness of ranibizumab – deterministic sensitivity analysis

We conducted a sensitivity analysis to consider the effect of uncertainty around model structure and for variation in certain key parameters that were expected, a priori, to have a strong influence on the cost-effectiveness results. The method we adopted is 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 section 4.2.2.6.

Table 4.29 to Table 4.31 report the results of the sensitivity analysis. Except for the sensitivity analysis with respect to time horizon, all analyses were conducted using the ten 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.

While 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 for PDT for patients with predominantly classic lesions) the pattern of response to change in underlying assumptions is similar in each analysis, and is discussed below.

Table 4.29 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 & outcome	£ 5,078	0.38	£ 13,345
	6% for cost & 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 out-patient 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	Standard gamble 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

Table 4.30 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 & outcome	£ 5,960	0.62	£ 9,575
	6% for cost & 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 out-patient 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	Standard gamble 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

Table 4.31 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 & outcome	£ 16,833	0.79	£ 21,383
	6% for cost & 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 out-patient 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	Standard gamble 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

As anticipated, 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 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 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 model shows higher QALY gains for younger patients and lower incremental costs – this is particularly apparent for patients with minimally 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.

Variation in assumptions regarding intravitreal injections, both their frequency and the cost of the injection procedure, has 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 one year (as observed in the ANCHOR trial), reducing the number of injections from 12 to 9 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 two years (as observed in the MARINA trial), reducing the number of injections in the second year of treatment from 12 to 9 reduces incremental cost by around 16%. Reducing the number of injections in the first year of treatment from 12 to 9 (with a further 9 injections in year 2) reduces incremental cost by around 34% from the value in the reference case. If only 6 injections are given in year 2, following 9 injections in year 1, the incremental cost of ranibizumab treatment, over best supportive care, is 50% of the value in the reference case.

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 one years treatment 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 two years treatment, costing intravitreal injections as day case procedures increased incremental cost by around 40%, with the ICER for increasing from £25,098 to £35,157.

Adopting health state utilities derived from AMD patients by Brown and colleagues[112] using the standard gamble 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 variation in cost-effectiveness estimates. Using high uptake and high unit cost estimates produces a situation where ranibizumab is 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%.

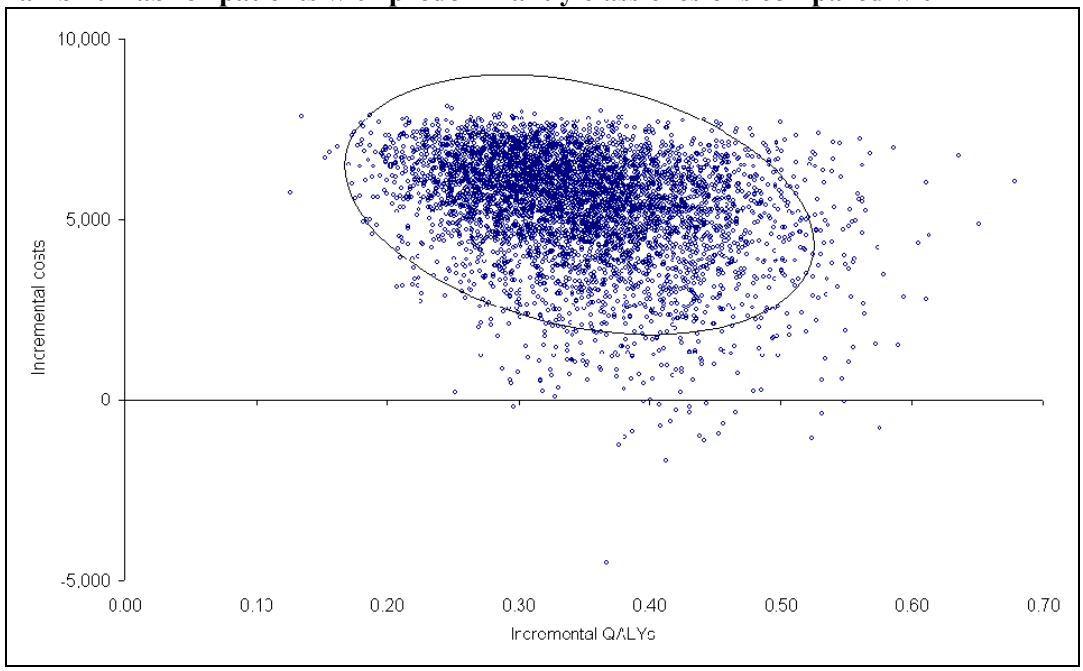
To indicate which variable, costs or uptake, were more influential on cost-effectiveness estimates additional analyses were undertaken using the extreme values for uptake combined with medium cost and extreme values for cost combined with medium uptake. The results shows that the cost effectiveness estimates 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.

4.2.2.6 Cost-effectiveness of ranibizumab – probabilistic sensitivity analysis

In a probabilistic sensitivity analyses for ranibizumab, where probabilities of losing or gaining visual acuity, health state utility values, cost of outpatient attendances, fluoroscein angiography and optical coherence tomography 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, see Figure 4.5, Figure 4.7 and Figure 4.9. 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. Five thousand 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 (see Figure 4.6, Figure 4.8 and Figure 4.10).

Figure 4.5 Cost effectiveness plane – incremental cost and incremental QALYs, ranibizumab for patients with predominantly classic lesions compared with PDT



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 willingness to pay threshold of £30,000 per QALY, see Figure 4.6.

Figure 4.6 Cost effectiveness acceptability curve, ranibizumab for patients with predominantly classic lesions compared with PDT

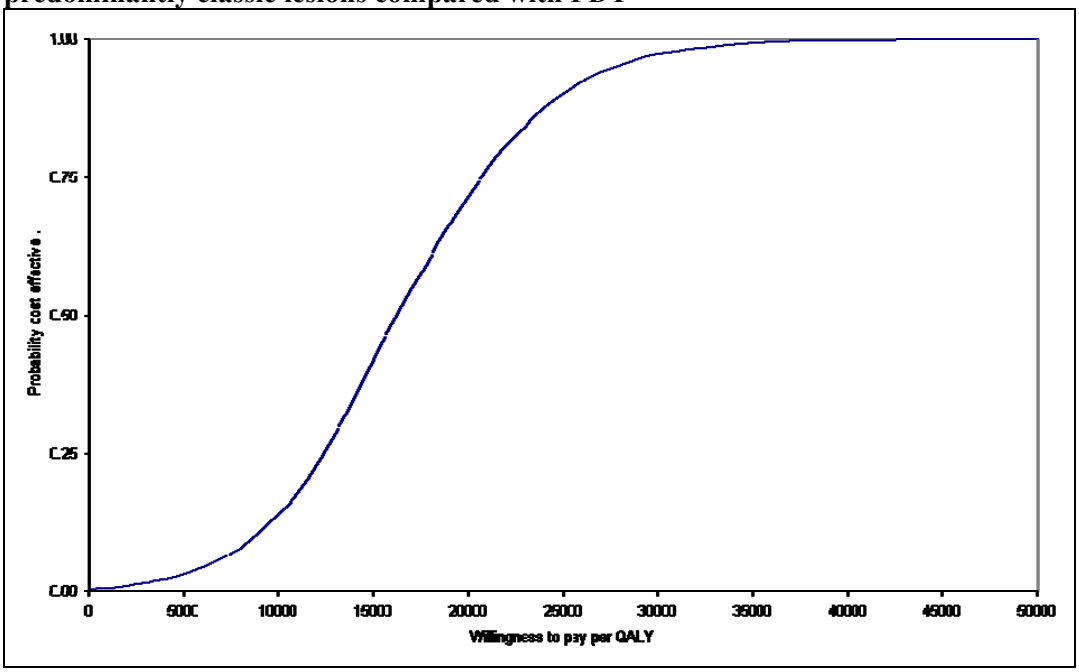
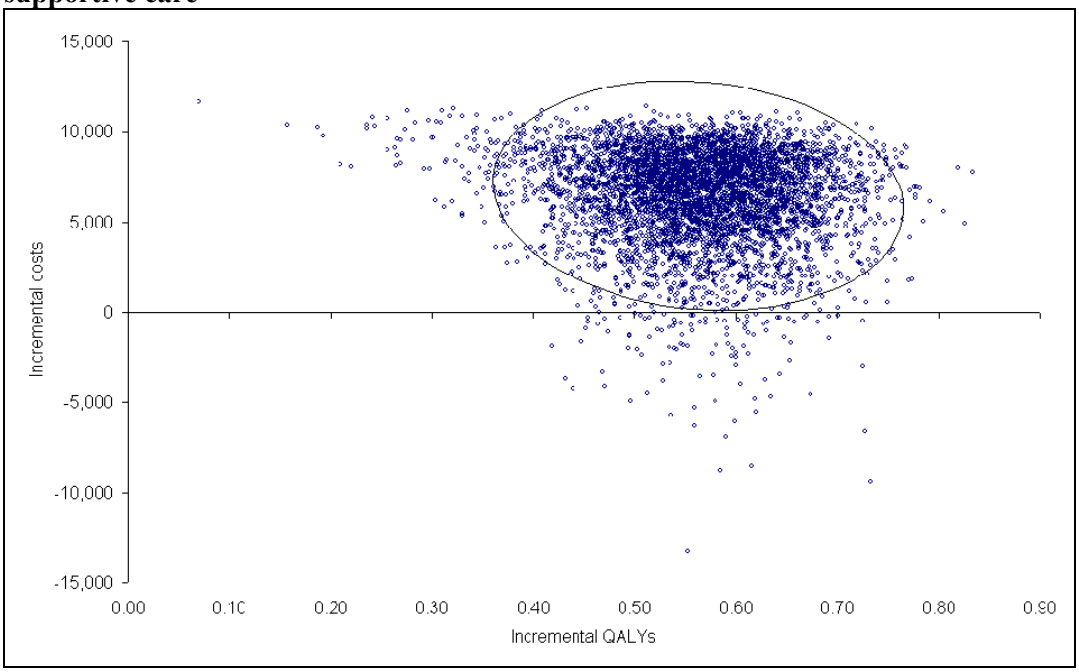


Figure 4.7 Cost effectiveness plane – incremental cost and incremental QALYs, ranibizumab for patients with predominantly classic lesions compared with best supportive care



In this analysis 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, see Figure 4.8.

Figure 4.8 Cost effectiveness acceptability curve, ranibizumab for patients with predominantly classic lesions compared with best supportive care

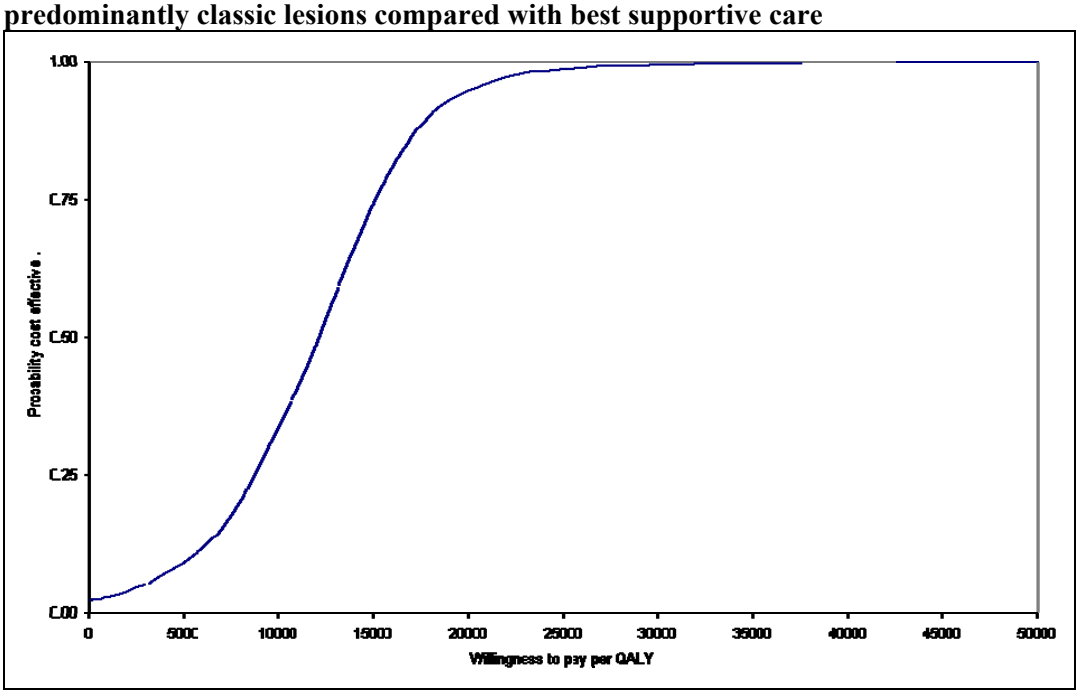
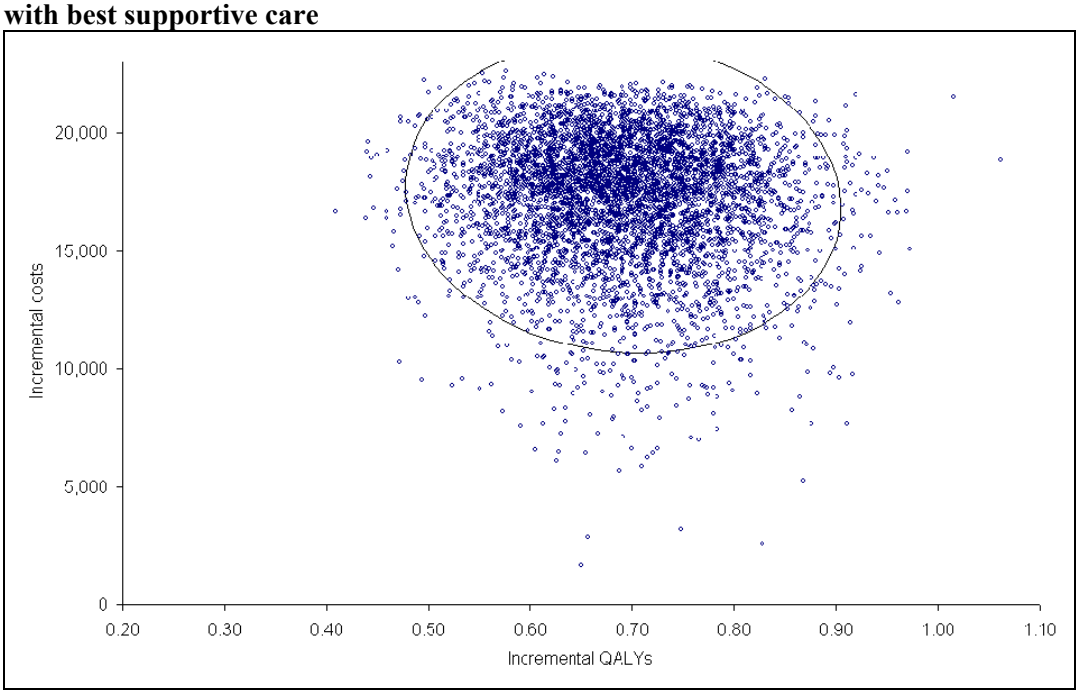
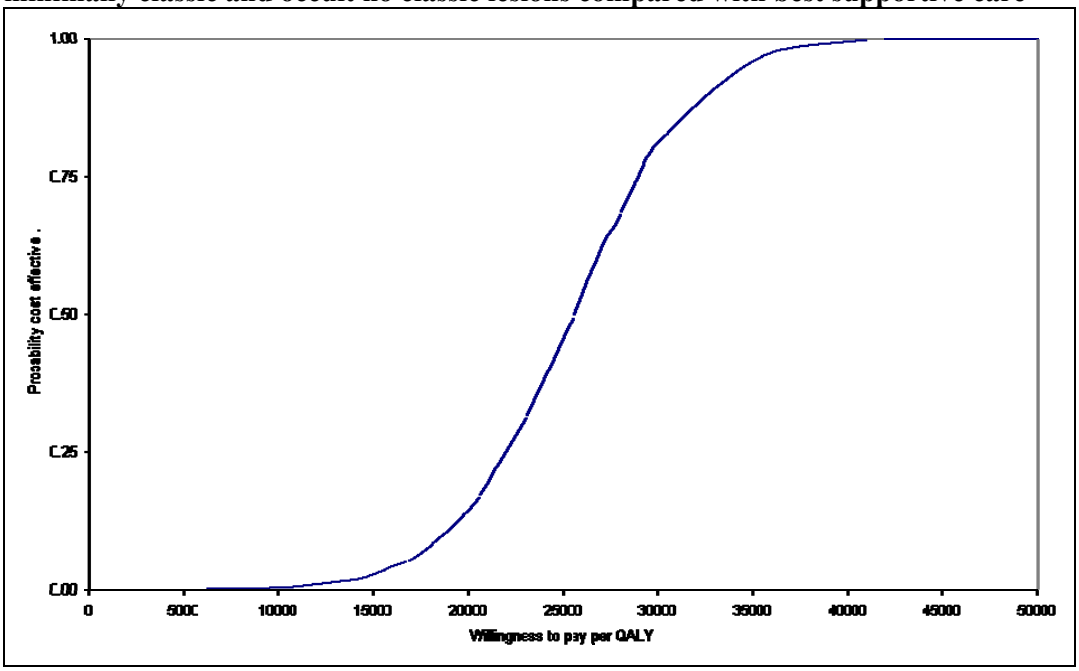


Figure 4.9 Cost effectiveness plane – incremental cost and incremental QALYs, ranibizumab for patients with minimally classic and occult no classic lesions compared with best supportive care



In this analysis 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, see Figure 4.10.

Figure 4.10 Cost effectiveness acceptability curve, ranibizumab for patients with minimally classic and occult no classic lesions compared with best supportive care



4.2.3 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 to 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 focussed primarily on changes in visual acuity. Utility values decline with reduced visual acuity, though when groups other than patients with AMD are included in studies they tend to give lower value 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) to usual care, which consists of best supportive care for all patients as well as PDT for patients with predominantly classic lesions. In the cost utility model health state valuations are based on a published study[112] that has been widely used in previous evaluations of treatment for AMD.
- The QALY gain for the pegaptanib-treated cohort estimated over ten years was 0.298. The cost difference was £4,705, 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 on 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 to best supportive care for patients with all lesion types and additionally to 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 £4,068 (compared with best supportive care), giving ICERs of £4,489 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 £9,125 and £8,494, giving ICERs of £26,454 and £25,796 per QALY gained.
- Limited deterministic sensitivity analyses were undertaken, reporting the incremental cost effectiveness ratios for increasing the number of injections given, up to the values observed in the clinical trials, which increased 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 – while 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 three to six 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 two 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 two years the ICER is high (£163,603).
- The QALY gain after ten years is 0.26 QALYs and incremental cost reduces to around £8,000 giving a lower ICER of £30,986. If pegaptanib is assumed to have a disease modifying effect (analysis submitted for publication included in submission by manufacturer) then 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 one 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 £8,000 for the comparison with PDT and £11,500 for the comparison with best supportive care. The QALY gain after two 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 ten 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 have reduced to £5,391 and £6,457, giving ICERs of £15,638 for the comparison with PDT and £11,412 for the comparison with best supportive care. The QALY gain at ten years for patients with minimally classic and occult no classic lesions is 0.69 QALYs and the incremental cost has 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 variation on 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 are in the range 75-84 (mean age of 76.0 and 77.7 for patients receiving ranibizumab (0.5mg) and PDT, respectively in ANCHOR trial[96] and 77 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 section 1.1, and would be expected to be broadly representative of patients presenting for treatment.

- The proportion 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 (0.5mg) and 45% male for patients receiving PDT[96]). However two thirds of patients in the MARINA were women (63% for patients receiving ranibizumab (0.5mg) and 67% male for patients receiving sham injection[97]). Epidemiological evidence reviewed in section 1.1 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 section 1.1 and also that assumed by Bonastre and colleages,[85] discussed in section 1.2 (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 from different countries. It is difficult to establish the validity of these sources for UK populations where no UK evidence exists, though the pattern of significant increase in incidence and prevalence for ages over 75 and higher proportion of women affected was also suggested in UK register-based studies reviewed in section 1.1.
- The economic evaluations of pegaptanib and ranibizumab discussed and presented in this review have assumed that the majority of treatment is provided in outpatients department 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 outpatients departments, but there is limited experience in providing intravitreal injections and 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 maybe to provide an integrated clinic for AMD patients having intravitreal injections, which would include medical assessments, visual assessments, imaging by optical coherence tomography at each visit and fluoroscein angiography every 3 to 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. The reference case in the manufacturer's submission for ranibizumab adopted a treatment regimen with a reduced frequency of injection, based on monthly injections of three months ("loading dose") and five further injections during the first year of treatment. Reducing frequency of injection in this manner reduces drug and injection procedure costs by [redacted] over the reference case and reduces total cost for a year of ranibizumab treatment by [redacted] The Scottish Medicines Consortium refers to the possibility of restricting pegaptanib treatment to one year.[144]
- 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 fluoroscein angiography prior to treatment, optical coherence tomography and repeat fluoroscein angiography were not included in all protocols, nor were repeat visual assessments for patients undergoing treatment. As far as possible, the economic analyses have used routinely available unit costs estimates – NHS Reference Costs[84] and Unit Costs of Community Care.[134] 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 experience of providing such injections 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.[40,145]

Strengths and limitations

- We have 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' submission to assess their comprehensiveness.
- Clinical evidence relevant to each drug has been extracted from good quality RCTs included in the systematic review. Response to treatment was assessed using an accepted measure of significant clinical difference (fifteen 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 has been 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 similar and there was agreement over the frequency of monitoring of patients (optical coherence tomography and visual assessment at each attendance for injection, and fluoroscein angiography 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 is currently limited data on post-treatment effectiveness of these drugs and no published data on response for patients who have previously been treatment 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 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 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 sections 4.2.2.1 and 4.2.2.4 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 lowh cost).

- The validity of assumptions underlying our extrapolation from trial results to ten 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 ten 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.

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) as well as patient advocacy organisations, such as the AMD Alliance,[146] 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 7,000 to 26,000 (quoted by AMD Alliance[146] attributed to the Royal College of Ophthalmologists). This approximate trebling in patient-load will be compounded by the increased frequency of treatment, from three-monthly attendances with PDT to six-weekly 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 Hositals 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 fluoroscein angiography for patients receiving pegaptanib or ranibizumab (at 3 to 6 monthly) is the same 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 optical coherence tomography, 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.

While AMD predominantly affects people in the older age group, with approximately 90% of prevalent cases in the UK over the age of 70 (see Table 1.7, section 1.1), 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 Personal Social Services perspective as required by NICE.[132] 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[93,94,146] and a concern that patients may feel 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 anticipated workload prove true, this inequity of access to treatment may persist.

6 DISCUSSION

6.1 Statement of principle 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. Two published RCTs (MARINA and ANCHOR) and two unpublished RCTs (PIER and FOCUS) of ranibizumab were also included. The published and unpublished 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%; 0.5mg: 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. 0.5 mg of ranibizumab combined with PDT was found to [redacted] the proportion losing less than 15 letters compared with PDT alone (90.5% versus 67.9%) in patients with predominantly or minimally classic lesions. A study evaluating a reduced dosing frequency (monthly intervals for three months then three monthly up to 12 months) [redacted] found [redacted] losing less than 15 letters [redacted] compared with sham injection [redacted]

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 (0.3mg: 6% vs. sham: 2%, p=0.04). About 25% to 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 [redacted] results were obtained in the [redacted] trial. There was [redacted] in this outcome between ranibizumab and sham injection in the reduced dose PIER study.

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 to 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 1.6 letters (0.3 mg dose) or 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 and ANCHOR [redacted] and [redacted] trials reported that significantly fewer patients deteriorated to legal blindness 12 months after receiving the study drug.

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.[106]

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

reduced dose schedule study, found
was for the subgroup

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. MARINA, ANCHOR and PIER
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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. MARINA and ANCHOR (and and demonstrated statistically significant differences between 0.3 mg 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.

following both doses of ranibizumab compared with sham injection in
were found
at was associated with
a in compared with PDT The reduced dose schedule of ranibizumab
and sham injection.

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. patients receiving ranibizumab in three of the trials experienced the

rate was [redacted] in the [redacted] Rates of [redacted] adverse events were [redacted] ranibizumab and sham injection [redacted] the rate of [redacted] adverse events was [redacted] ranibizumab plus PDT group compared with sham injection plus PDT [redacted] rate of [redacted] with ranibizumab plus PDT may be [redacted] Endophthalmitis was reported by very few patients receiving ranibizumab. The condition occurred in up to 1.4% of 0.5mg dose ranibizumab patients in the ANCHOR trial, and the rate per injection was 0.05% in the MARINA trial. [redacted] occurred in [redacted] of patients across the [redacted] and [redacted] trials [redacted]

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 health and personal social services 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 focussed 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) to 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 twelve 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 two years treatment with pegaptanib and were followed up for ten 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, health state utilities from a published study of valuations by patients with AMD.[112] Costs were estimated based on the number of injections given to patients in the VISION studies, protocols for monitoring patient while on-treatment and on costs of services for visual impairment from a previous UK study.[40,145]

The QALY gain estimated over ten 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 £4,705, and for the alternative stopping rule was £4,109, giving ICERs of £15,815 and £14,202 per QALY gained, respectively. At ten years NHS and Personal Social Services 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 (ICER was greater than £30,000 until the time horizon was over five years) and variation in the costs of blindness. Sub-group analyses were undertaken to examine heterogeneity in the study population. Sub-groups were defined by patient age, sex, lesion type and lesion size. Very little variation in ICER was reported by these sub-groups, except that the ICER was reduced to £10,940 (£9,454 for alternative stopping rule of visual acuity less than 6/60) for patients

aged under 75 compared to £18,863 (£17,128 for alternative stopping rule of visual acuity less than 6/60) for patient aged 75 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 optical coherence tomography, which experts suggested would occur each time patients attended for injection. Clinical experts also suggested that patients would have fluoroscein angiography at least every six months while on treatment, though the frequency may be as high as every three months. When these assumptions are added into the model, while the QALY difference remains unchanged, incremental costs increase to £6,473 and 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 when moving from 6/60 – 3/60 (0.52) to less than 3/60 (0.40). Unpublished utility values developed for the Novartis submission do not show such "steps" in the utility function, in relation to visual acuity. When these utility values are used in the model, while incremental costs remain unchanged, the QALY difference becomes 0.279 and the ICER is little changed, at £16,889.

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 to best supportive care for patients with all lesion types and additionally to PDT for patients with predominantly classic.

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 one year of treatment with ranibizumab and were followed up for ten 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 cohort of patients

received up to two years of treatment with ranibizumab and were followed up for ten years. Patients in the best supportive care cohort received [redacted] once [redacted] had fallen below [redacted]

Clinical outcomes were modelled using patient-level data from the ANCHOR and MARINA trial, health state utilities from an unpublished study of valuations by a sample of members of the general public.[139] Costs were estimated based on a [redacted] observed in the clinical trials [redacted] and [redacted]

The QALY gain estimated over ten 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 £4,068 for the comparison with best supportive care, giving ICERs of £4,489 and £14,781 per QALY gained, respectively.

The QALY gain estimated over ten years for patients with minimally classic lesions was 0.34 and for patients with occult no classic lesions was 0.33. The cost difference was £9,125 and £8,494, giving ICERs of £26,454 and £25,796 per QALY gained.

Limited deterministic sensitivity analyses were undertaken, reporting the incremental cost effectiveness ratios 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 of 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.

Removing costs from the comparator treatments increases the incremental cost of ranibizumab treatment by between £[redacted] and £[redacted] and increases ICERs by [redacted] per QALY gained and £[redacted] per [redacted] None of these changes, by themselves would alter conclusions over the cost-effectiveness of ranibizumab according to conventionally accepted decision thresholds[redacted]

Increasing the number of injections assumed has a large impact on incremental costs and on ICERs. Increasing the number of injections to 12 per year of treatment increases incremental costs for patients with predominantly classic lesions by around £4,000 giving an ICER of £28,176 when compared with PDT and £30,203 when compared with best supportive care. Increasing the number of injections has a greater effect for patients with minimally classic and occult no classic lesions (who receive up to two years of treatment) where incremental costs increase by between £9,500 and £10,000 and ICERs rise to £55,906 and £56,234 for patients with minimally classic and occult no classic lesions , respectively.

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 ten 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 three to six 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 were 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,[112] 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. At the time of writing this report, ranibizumab does not have marketing authorisation for the UK and is not listed in the BNF or Monthly Index of Medical Specialties (MIMS). The dosage of ranibizumab submitted for marketing authorisation by the manufacturer and the manufacturer's target price for the UK have been used in this analysis. Heath 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[40,145], inflated to 2005 prices.

The QALY gain after two 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 anticipated by delaying disease progression in a proportion of patients, are apparent at this time. Given the small QALY gain and high incremental cost at two years the ICER is high (£163,603).

The QALY gain after ten 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 has reduced to around £8,000 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 ten years has 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 ICER, which increases to £47,845. The ICERs are also sensitive to choice of utility values and are particularly sensitive to variation on 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 one 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 £8,000 for the comparison with PDT and £11,500 for the comparison with best supportive care. The QALY gain after two 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 ten 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 have reduced to £5,391 and £6,457, giving ICERs of £15,638 for the comparison with PDT and £11,412 for the comparison with best supportive care. The QALY gain at ten years for patients with minimally classic and occult no classic lesions is 0.69 QALYs and the incremental cost has 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 lesions types and for the different comparators. This 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. 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 variation on 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, fluoroscein angiography and optical coherence tomography 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 was 81%.

6.2 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 has identified all English-language RCTs on ranibizumab and pegaptanib, and has 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.

6.3 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 to make extrapolations beyond the trial data, an indirect comparison against the sham arm of the TAP study was required. Outcomes for the sub-group 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% to 70% increases in incremental cost (low uptake and low unit cost).

6.4 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 endpoint at year one, so were combined for analysis as stated in the study protocol. However, 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 two years.[102,103] 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 [redacted]). This may limit generalisability.
- The off-labelled use of bevacizumab (Avastin) for AMD (see section 1.2) 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 £3.00.[79] However, there is no RCT data on the efficacy of bevacizumab compared with standard treatment nor any long-term safety data, therefore further research is required.

7 CONCLUSIONS

7.1 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 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[146] state, citing the Royal College of Ophthalmologists, that patient numbers could increase from 7,000 (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 six-fold increase in workload (Lotery, A. Southampton University Hopsitals Trust, personal communication, October 2006).

The Royal College of Ophthalmolgists 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 these 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 fluoroscein angiography and optical coherence tomography) as well as provision of clean rooms for performing the injection procedure.

7.2 Suggested research priorities

- This report has established that ranibizumab is clinically effective for delaying vision loss and improving vision in AMD. As discussed in section 1.2 and 6.4, bevacizumab (Avastin), which is biologically similar to ranibizumab, is being increasingly used off-label for the treatment of AMD. There is no long-term data on 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 multicentre 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 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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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 (HRQOL), resource use / costs, and epidemiology / natural history.
- The draft search strategy for Medline can be seen 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 choroidal neovascularisation (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 photodynamic therapy 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, photodynamic therapy with verteporfin is also a comparator.
- If insufficient evidence is found using the above comparators, the following comparators will be considered:
    - Sham injection (systematic review of clinical effectiveness only)
    - Photodynamic therapy 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 randomised controlled trials (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

Refer to Appendix 2 for details of the draft search strategy for Medline. 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,[147] and Drummond and colleagues.[131] For any studies based on decision models we will also make use of the checklist for assessing good practice in decision analytic modelling (Philips and colleagues[133]). Published studies carried out from the UK NHS and PSS perspective will be examined in more detail.

Synthesis of evidence on costs and effectiveness

(a) 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.

(b) 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 Quality Adjusted Life Year (QALY) gained, as well as the cost per vision year gained i.e. for an additional year of visual function, if data permit. The perspective will be that of the NHS and Personal Social Services. 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); and
- 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, 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 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 (PSA). The outputs of PSA 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 is available. The base case results will be presented for the population of 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 8th 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 company submission, provided 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 brackets).

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 - 2006
- 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(R) <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.

Ovid MEDLINE(R) <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>

Searched 25.05.06
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.

Ovid MEDLINE(R) <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

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

Item	Judgement*
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?	

* adequate, inadequate, not reported, unclear

Appendix 4 Data extraction tables

Reference and Design	Intervention	Participants	Outcome measures
VISION study Gragoudas et al. 2004[95] D'Amico et al 2006[101] Chakravarthy 2006[100] CIC info from industry submission [redacted] results [redacted] 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 pharma. and Pfizer	1. intravitreous injection of 0.3mg pegaptanib into 1 eye every 6 weeks, total of 9 treatments 2. intravitreous injection of 1.0mg pegaptanib into 1 eye every 6 weeks, total of 9 treatments 3. intravitreous injection of 3.0mg pegaptanib into 1 eye every 6 weeks, total of 9 treatments 4. sham injection into 1 eye every 6 weeks, total of 9 treatments Pegaptanib pts were then re-randomised (1:1) to either continue or discontinue pegaptanib. Sham pts 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 treatment. *Other interventions used*: pts 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	*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 were included in the worldwide trial. The publication combines both study populations for the analysis data extracted here. Total randomly assigned (N=1208): 1. 0.3mg 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. 0.3mg 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 standardized assessment of visual acuity was not completed at baseline. Total for efficacy analyses (n=1186): 1. 0.3mg n=294 2. 1.0 mg n=300 3. 3.0 mg n=296 4. sham injection n=296 88% (1053/1190) were rerandomised at week 54, and 89% (941/1053) were assessed at week 102. Second year randomisation: 0.3mg – 0.3mg n=133 0.3mg – discontinue n=132 1.0mg – 1.0mg n=133 1.0mg – discontinue n=131 3.0mg – 3.0mg n=125 3.0mg – discontinue n=127 sham – 0.3mg n=53 sham – 1.0mg n=55	*Primary outcome:* Proportion of patients who lost < 15 letters of visual acuity (VA) (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 VA from week 54 to week 102; Kaplan-Meier proportions of the loss of an additional 15 letters from week 54 to week 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 VA; VA 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 treatment.

	classic lesions, although 78% of patients did not receive PDT during the study.	sham – 3.0mg n=57 sham – sham n=53 sham – discontinue n=54 n assessed at week 102: 0.3mg – 0.3mg n=114 0.3mg – discontinue n=117 1.0mg – 1.0mg n=119 1.0mg – discontinue n=122 3.0mg – 3.0mg n=113 3.0mg – discontinue n=109 sham – 0.3mg n=50 sham – 1.0mg n=46 sham – 3.0mg n=52 sham – sham n=51 sham – discontinue n=48 *Sample attrition/dropout*: Approximately 90% completed the study. In all groups, an average of 8.5 injections was administered per patient out of a possible total of 9. *Inclusion/exclusion criteria for study entry*: age ≥ 50 with subfoveal sites of choroidal neovascularisation 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 optic-disk areas (including blood, scar or atrophy, and neovascularisation) were permitted. Additional criteria reported in supplementary paper, not extracted.	

Characteristics of participants: (N/R = not reported)

	0.3mg pegaptanib (n=295)	**1.0 mg pegaptanib (n=301)**	**3.0mg 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 (yrs) n (%)				
50-64	19 (6)	21 (7)	18 (6)	21 (7)
65-74	86 (29)	105 (35)	90 (30)	94 (32)

75-84 ≥ 85	155 (53) 35 (12)	147 (49) 28 (9)	153 (52) 35 (12)	160 (54) 23 (8)
Angiographic subtype of lesion n (%) Predominantly classic (≥ 50% classic CNV) Minimally classic (<50% classic CNV) Occult with no classic	 72 (24) 111 (38) 112 (38)	 78 (26) 108 (35) 115 (38)	 80 (27) 105 (35) 111 (38)	 76 (26) 102 (34) 120 (40)
Size of lesion (±SD), no. of optic-disc areas (=2.54 mm^2)	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 Median (range) Other eye Mean ± SD Median (range)	 52.8 ± 12.6 55 (11-75) 56.2± 27.2 68 (3-85)	 50.7 ± 12.8 52 (19-77) 54.8 ± 27.6 67 (3-85)	 51.1 ± 12.9 53 (14-76) 56 ± 26.4 65 (4-85)	 52.7 ± 13.0 53 (11-77) 55.9 ± 27.0 67 (2-85)
Health status (%) Hypertension Hypercholesterolemia diabetes mellitus cardiac disorders cerebrovascular disease peripheral arterial disease ECG abnormalities	 55 21 10 35 3 3 53			 48 18 7 34 1 3 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) (n/s = not statistically significant)				
Outcomes	**0.3mg pegaptanib (n=294)**	**1.0 mg pegaptanib (n=300)**	**3.0mg pegaptanib (n=296)**	**sham injection (n=296)**
Visual acuity: loss of <15 letters at week 54 n(%) P value vs. sham	206(70) p<0.001	213(71) p<0.001	193 (65) p=0.03	164 (55)
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 (0.3mg of pegaptanib, p=0.03 and p=0.01).				
Maintenance or gain ≥ 1 letters n(%) P value vs. sham	98 (33) 0.003	110 (37) <0.001	93 (31) 0.02	67 (23)
Gain ≥ 5 letters n(%) P value vs. sham	64 (22) 0.004	69 (23) 0.002	49 (17) 0.12	36 (12)
Gain ≥ 10 letters n(%) P value vs. sham	33 (11) 0.02	43 (14) 0.001	31 (10) 0.03	17 (6)
Gain ≥ 15 letters n(%) P value vs. sham	18 (6) 0.04	20 (7) 0.02	13 (4) 0.16	6 (2)
loss ≥ 30 letters n(%) P value vs. sham	28 (10) <0.001	24 (8) <0.001	40 (14) 0.01	65 (22)

Snellen equivalent visual acuity in study eye ≤ 20/200 (legal blindness) **n(%)** P value vs. sham	111 (38) <0.001	128 (43) <0.001	129 (44) 0.001	165 (56)
Mean change in visual acuity (no. of letters) at 54 weeks *	-7.5 <0.002	-6.5 <0.002	-10 0.05	– 14.5
* 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 mg 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)* (*p* compared with sham)				
Lesion type				
Predominantly classic	7.1 P<0.05	10.2 n/s	10.5 n/s	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 optic-disk areas	7.5 P<0.001	8 P<0.001	9 P<0.001	16.5
≥4 optic-disk areas	8.5 P<0.05	6 P<0.001	11 n/s	13.5
* Data estimated from figures. For those receiving pegaptanib at 0.3mg, 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 (0.3mg 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 optic-disc areas)				
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	n/s	
Size of CNV (no. of optic-disc areas)				
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	n/s	p<0.01	n/s	
Size of leakage (no. of optic-disc areas)				
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	n/s	p<0.01	n/s	

Adverse events (year 1)	Pegaptanib (all doses)	Sham injection	P value
Rate of discontinuation due to AE	1%	1%	
Death rate	2%	2%	n/s
Vascular hypertensive disorders	10%	10%	n/s
Hemorrhagic AE	2%	3%	n/s
Thromboembolic events	6%	6%	n/s
Gastrointestinal perforations	0%	0%	n/s
Local or systemic hypersensitivity attributable to pegaptanib	0		
Common ocular adverse events in study eye:			
Eye pain	34%	28%	n/s
Vitreous floaters	33%	8%	p<0.001
Punctuate keratitis	32%	27%	n/s
Cataracts	20%	18%	n/s
Vitreous opacities	18%	10%	P<0.001
Anterior-chamber inflammation	14%	6%	P=0.001
Visual disturbance	13%	11%	n/s
Eye discharge	9%	8%	n/s
Corneal edema	10%	7%	n/s

Reasons for discontinuation due to AE were diverse and were not clustered in relation to a particular system or organ. No further details provided.
No systemic adverse events 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 AE 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 adverse effects on retinal or choroidal vascular beds.
In the second year of the study, the incidence of common ocular adverse events was similar to those reported in year 1. Most adverse events reported in the study eyes were transient, mild-to-moderate in severity, and attributed to the injection procedure itself.

Injection-related AE in 890 pts treated with pegaptanib in the first year of the trial (a total of 7545 injections)

	No. of pts with event (%)	**Events per injection (%)**	**Severe loss of visual acuity (≥ 30 letters) n (%)**
Endophthalmitis	12 (1.3)*	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**

* ¾ of pts with endophthalmitis remained in the trial. The condition was associated with protocol violation in 2/3 of the pts with this condition (most common protocol violation was failure to use an eyelid speculum to prevent bacteria from eyelashes contaminating injection site).
** measurements of visual acuity after the event were not available for one pt.
Because multiple injections are required, the risk of endophthalmitis was 1.3% per patient during the first year of the trials.
In the 374 pts 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 AE 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 (8 injections). Those initially assigned to sham injection were rerandomised 1:1:1:1:1 to continue sham, discontinue sham, or receive 1 of 3 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 one (defined as the loss of ≤ 0 letters between baseline and week 54). DATA FOR THE OTHER DOSE GROUPS AND FOR SHAM-ANY P DOSE GROUP ARE SHOWN IN AN APPX TO THE CHAKRAVARTHY PAPER BUT NOT DATA EXTRACTED

USUAL CARE= all patients in sham group in year 1 rerandomised to continue sham or to discontinue. Studies 1003 and 1004 represent the two RCTs

Visual acuity at baseline and re-randomization (reported separately for the 2 studies)	**0.3mg P – 0.3mg P**		**0.3mg P – 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 VA (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-randomization produced VA 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-randomized population	**0.3mg – 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	**0.3mg P – 0.3mg P (n=133)**	**0.3mg P – discontinue (n=132)**	**Usual care (n=107)**
Change in standardized 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		

LS = least squares				
Progression to legal blindness				
Baseline VA better than 20/200 (n)	111	116	93	
VA 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 (letters) (estimated from graph)				
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	
Responder rates – loss of <15 letters (total n for groups not stated)	**0.3mg – 0.3mg**	**0.3mg - discontinue**	**Sham – any P 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 0.3mg pegaptanib group and the usual care group in study 1004. The continuing 0.3mg 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(%)	**0.3mg pegaptanib (n=133)**	**Usual care (n=107)**		
No. of responders at 102 weeks (<15 letters lost)	78 (59%)	48 (45%)		
P compared with usual care	P=0.0385			
No. with loss ≥ 30 letters (severe vision loss) at 102 weeks	17 (13%)	28 (26%)		
P compared with usual care	P=0.0058			
No. of patients completing the trial (week 102)	106 (33%)	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 pegaptanib 0.3 mg treatment versus usual care (16% versus 27%, respectively). Mean VA in continued 0.3mg pegaptanib group remained stable during the second year, whilst the loss in VA resumed in individuals re-randomised to discontinue				
Adverse events – year 2, n(%)	**0.3mg 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	**0.3mg pegaptanib (n=128)**	**sham (n=51)**		
Eye pain	27 (21%)	9 (18%)		
IOP 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 **Vision blurred** **cataract**	9 (7%) 4 (3%) 14 (18%)	6 (12%) 5 (10%) 8 (24%)
Incidence of Serious Adverse Event (rate/injection) – 2 year results	**Rate (% per injection) (Cohort 1)[1]**	**Rate (% per injection) (All cohorts)[2]**
Endophthalmitis	0%	0.10%
Traumatic cataract (lens injury)	0%	0.02%
Retinal detachment	0.15%	0.17%
1. Cohort 1: All individuals re-randomised to continue on same treatment in the second year n = 374; a total of 2,663 injections of pegaptanib were administered 2. 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 4,091 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 pegaptanib 0.3 mg, and 16.3 of 17 possible treatments were administered to patients receiving usual care. Over the 2-year period, 92% of injections occurred within one week of the scheduled dose of both pegaptanib 0.3 mg and usual care.		
Disease modifying effect (risk of non-response following discontinuation)	**Relative risk of non-response (95% CI)**	**p value**
All doses pooled:	0.70 (0.56, 0.86)	p = 0.001
0.3 mg	0.68 (0.51, 0.90)	p = 0.008
1 mg	0.62 (0.46, 0.83)	p = 0.001
3 mg:	0.79 (0.61, 1.03)	p = 0.09
A year after discontinuation of treatment, pegaptanib still has a highly significant benefit compared to no treatment and this indicates that pegaptanib does not simply treat ARMD symptoms, but targets angiogenesis, the underlying pathologic process. This disease modifying effect represents a significant 30% reduction in the non-responder rate compared with no treatment.		
Subgroup analysis years 1 and 2 – ***estimated from graph***	**0.3mg pegaptanib**	**Usual care**
Responders (<15 letters lost) Predominantly classic Year 1 Year 2 Minimally classic Year 1 Year 2 Pure occult Year 1 Year 2		
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 pegaptanib 0.3 mg on delaying progression to legal blindness at Year 1 was maintained after Years 1&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 1 of 4 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-randomization produced VA 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 endpoint 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 endpoints. Mean changes in visual acuity were analyzed 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 2-sided and unadjusted for multiplicity. Point estimates and confidence intervals 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. But, efficacy results are not ITT, as they exclude 4 patients who did not receive a sufficiently standardized assessment of visual acuity at baseline. Individual and combined analyses of studies 1003 and 1004 reported by Chakravarthy et al. are reported to be ITT, including all patients who were re-randomized at week 54. LOCF for any missing efficacy data. Mean change in VA from week 54 was determined for each treatment visit as a summary measure of treatment trends. These results were confirmed further using a standardized area under the curve, using the trapezoidal rule. Kaplan Meier estimates of proportions with loss of $\geq$ 15 letters after week 54 were calculated for patients continuing with pegaptanib therapy vs. 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 statistically significance in two independent trials.
- Attrition/drop-out: 90% of patients completed the study. 4 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. Dropouts 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 visualization of choroidal new vessels (classic) in the flurorescein 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 optic-disk areas (including blood scar or atrophy and neovascularisation), each of which is 2.54mm^2.
- Inter-centre variability: not reported
- Conflict of interests: Eyetech Pharmaceuticals and Pfizer supported the trials. Gragoudas [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 intention to treat analysis?	inadequate
10. Were withdrawals and dropouts completely described?	partial

Reference and Design	Intervention	Participants	Outcome measures
Chung et al., 2006 (MARINA, FVF2598g) Unpublished United States RCT 96 centres *Setting:* *Funding:* Genentech, Inc*	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. Approx 3 months prior to completion, patients in sham group could cross-over to 0.5mg 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/dropout*: 2 in the sham group and 1 in the 0.5 mg group did not receive any study drug. 12 from 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 disc areas, best corrected visual acuity (using Early Treatment Diabetic Retinopathy Study charts) of 20/40 to 20/320 Snellen equivalent. Only one eye was assessed, if both eyes were eligible, the one with the better visual acuity was selected (unless medical reason for otherwise). *Exclusion criteria:* Prior PDT, external-beam readition therapy or transpoupillary 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	Note: data are extracted for the study's primary and secondary outcome measures and for the TAR's stated outcome measures only. Exploratory efficacy measures not extracted. *Primary outcomes:* Proportion losing fewer than 15 letters (approx 3 lines) in best corrected visual acuity (BVCA) at a test distance of 2 meters 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. Vision-related functioning and well-being: National Eye Institute Visual Function Questionaire-25 (VFQ-25) 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 meters. Proportion losing <15 letters at starting test distance of***meters. Mean change in BCVA. Proportion gaining at least 15 letters. Proportion with Snellen equivalent of 20/200 or worse. Change in Visual Function Questionnaire (VFQ)-25 near activities, distance activities, and vision-specific dependency subscare. Change in total area of CNV. Change in total area of leakage from CNV. *Additional outcomes required by TAR:* Contrast sensitivity [redacted]

		eye,*laser photocoagulation within one 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 disc area 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.	Adherence to treatment (treatment compliance). *Method of assessing outcomes:* BVCA assessed by Early Treatment Diabetic Retinopathy Study chart. CNV assessed by flourescein angiography. Contrast sensitivity [redacted] safety and efficacy. [redacted] *Exploratory efficacy outcomes reported but not extracted:* *First year of treatment:* [redacted]

			[redacted] *For second year of treatment:* [redacted] *Length of follow-up:* 24 months

Characteristics of participants:

	Ranibizumab 0.3mg (n=238)	**Ranibizumab 0.5mg (n=240)**	**Sham (n=238)**
Age yrs, mean (SD), range	77.4 (7.6) 52-95	76.8 (7.6) 52-93	77.0 (6.6) 56-94
Male Female	85 (35.7%) 153 (64.3%)	88 (36.7%) 152 (63.3%)	79 (33.2%) 159 (66.8%)
White Asian or Pacific Islander Hispanic Other	229 (96.2%) [redacted]	232 (96.7%) [redacted]	231 (97.1%) [redacted]
Years since first diagnosis of AMD, Mean (SD), range	[redacted]	[redacted]	[redacted]
Visual acuity at starting test distance 2 meters No. of letters (0-100), Mean (SD), Range ≤ 54	[redacted]	[redacted]	[redacted]

≥ 55	[redacted]	[redacted]	[redacted]
Approximate Snellen equivalent Median 20/200 or worse Better than 20/200 but worse than 20/40 20/40 or better	 [redacted] 35 (14.7%) 176 (73.9%) 27 (11.3%)	 [redacted] 31 (12.9%) 173 (72.1%) 36 (15.0%)	 [redacted] 32 (13.4%) 170 (71.4%) 36 (15.1%)
Visual acuity scores: study eye vs fellow eye Study eye worse than fellow eye	[redacted]	[redacted]	[redacted]
Predominantly classic Minimally classic Occult without classic Missing	1 (0.4%) 86 (36.1%) 151 (63.4%) 0	0 91 (37.9%) 149 (62.1%) 0	0 87 (36.6%) 150 (63.0%) 1 (0.4%)
Total area of lesion (disc areas (DA)) Mean (SD), range) ≤ 4 DA > 4 DA	[redacted]	[redacted]	[redacted]
Total area of CNV (DA), Mean (SD), range	[redacted]	[redacted]	[redacted]
Area of classic CNV (DA), Mean (SD), range	[redacted]	[redacted]	[redacted]
Total area of leakage from CNV plus intense progressive retinal pigment epithelium staining (DA), mean (SD), range	[redacted]	[redacted]	[redacted]
Area of serous sensory retinal detachment or subretinal fluid (DA), Mean (SD), range	[redacted]	[redacted]	[redacted]
Occult CNV present	[redacted]	[redacted]	[redacted]
Any prior therapy for AMD in study eye Laser photocoagulation Medication Supplements Other	140 (58.8%) 13 (5.5%) 1 (0.4%) 134 (56.3%) 3 (1.3%)	139 (57.9%) 14 (5.8%) 3 (1.3%) 127 (52.9%) 3 (1.3%)	135 (56.7%) 22 (9.2%) 3 (1.3%) 121 (50.8%) 8 (3.4%)
Results			
Outcomes	**Ranibizumab 0.3mg (n=238)**	**Ranibizumab 0.5mg (n=240)**	**Sham (n=238)**
Proportion losing <15 letters compared with baseline (starting test distance 2m) n (%) ***Month 12*** 95 CI of the % Difference in % (vs sham) 95% CI of the difference P value (vs sham) ***Month 24*** 95 CI of the % Difference in % (vs sham) 95% CI of the difference P value (vs sham)	 225 (94.5%) [redacted] P<0.0001 219 (92.0%) [redacted] P<0.0001	 227 (94.6%) [redacted] P<0.0001 216 (90.0%) [redacted] P<0.0001	 148 (62.2%) [redacted] 126 (52.9%) [redacted]
Visual acuity at starting test distance of 2 meters, at 24 months			
No. of letters, mean, SD 95% CI of mean Difference in least squares means (vs sham) 95% CI of difference P value (vs sham)	[redacted]	[redacted]	[redacted]

No. of letters change from baseline, mean (SD) 95% CI of mean Difference in least squares means (vs sham) 95% CI of difference P value (vs sham)	5.4[redacted] 3.5, 7.4 [redacted] P<0.0001	6.6[redacted] 4.5, 8.7 [redacted] P<0.0001	-14.9[redacted] -17.3, -12.5
Gain of ≥ 15 letters from baseline, response rate 95% CI of the % Difference in % (vs sham) 95% CI of the difference P value (vs sham)	62 (26.1%) 20.5%, 31.6% [redacted] P<0.0001	[redacted]	9 (3.8%) 1.4%, 6.2%
Snellen equivalent 20/200 or worse, response rate 95% CI of the % Difference in % (vs sham) 95% CI of the difference P value (vs sham) *Approximate Snellen equivalent* 20/200 or worse Better than 20/200 but worse than 20/40 20/40 or better	35 (14.7%) 10.2%, 19.2% [redacted] P<0.0001 35 (14.7%) [redacted]	36 (15.0%) 10.5%, 19.5% [redacted] P<0.0001 36 (15.0%) [redacted]	[redacted] 41.6%, 54.2% 114 (47.9%) [redacted]
12 month data reported but not extracted. Study states that [redacted] (data not extracted).			
Subgroup analysis: proportion losing <15 letters in visual acuity at 24 months compared with baseline (starting test distance 2 metres)			
Minimally classic CNV at baseline Response rate 95% CI of the % Difference in % (vs sham) 95% CI of the difference P value vs sham	[redacted]	[redacted]	[redacted]
Occult without classic CNV at baseline Response rate 95% CI of the % Difference in % (vs sham) 95% CI of the difference P value vs sham	[redacted]	[redacted]	[redacted]
[redacted]			
Change from baseline in VFQ-25 scores at month [redacted]			
Near activities Mean (SD) 95% CI of mean Difference in least squares means (vs sham) 95% CI of difference P value (vs sham)	[redacted]	[redacted]	[redacted]
Distance activities			

Mean (SD) 95% CI of mean Difference in least squares means (vs sham) 95% CI of difference P value (vs sham)	[redacted]	[redacted]	[redacted]
Vision-specific dependency Mean (SD) 95% CI of mean Difference in least squares means (vs sham) 95% CI of difference P value (vs sham)	[redacted]	[redacted]	[redacted]
VFQ-25 data at 12 months reported but not extracted. [redacted]			
Change from baseline in total area of CNV (DA), **at month 24,** mean (SD) 95% CI of mean Difference in least squares means (vs sham) 95% CI of difference P value (vs sham)	-0.32 [redacted] -0.63, -0.01 [redacted]	-0.00 [redacted] -0.26, 0.26 [redacted]	2.58 [redacted] 2.15, 3.02
Change in total area of leakage from CNV + intense progressive RPE staining (DA), **at month 24,** mean (SD) 95% CI of mean Difference in least squares means (vs sham) 95% CI of difference P value (vs sham)	-2.18 [redacted] -2.52, -1.85 [redacted] P<0.0001	-2.18 [redacted] -2.54, -1.83 [redacted] P<0.0001	0.76 [redacted] 0.23, 1.29
12 month data reported but not extracted. The study states that [redacted]			
Change in contrast sensitivity at 24 months, Mean no. of letters P value (vs sham)	[redacted]	[redacted]	[redacted]
Note: Table of data for contrast sensitivity (including standard deviations) [redacted] Study states that [redacted]			
Adherence to treatment (treatment compliance)			
Treatment compliance was [redacted]			

[redacted]

Adverse Effects (safety-evaluable subjects) during 2 yr period	Ranibizumab 0.3mg (n=238)	Ranibizumab 0.5mg (n=239)	Sham (n=236)
Any injection held according to protocol specified criteria	[redacted]	[redacted]	[redacted]
Ocular events: study eye			
All adverse events (a)			
Serious adverse events (b)			
Adverse events led to discontinuation (study or treatment) (c)			
Endophthlamitis			
Intraocular inflammation			
Total			
Serious			
Ocular events: fellow eye			
All adverse events (d)			
Serious adverse events			
Adverse events led to discontinuation (study or treatment)			
Endophthlamitis			
Intraocular inflammation			
Total			
Serious			
Non-ocular events			
All adverse events (e)			
Serious adverse events (f)			
Adverse events that led to discontinuation			
(a) ocular adverse events in study eye (occurring in ≥ 15% in any group or ≥ 5% more frequent in either ranibizumab group)			
Conjunctival haemorrhage			
Macular degeneration			
Eye pain			
Retinal haemorrhage			
Vitreous floaters			
Vitreous detachment			
Eye irritation			
Intraocular pressure increased			
Foreign body sensation in eyes			
Lacrimination increased			
Visual acuity reduced			
Detachment of RPE			
Vision blurred			
Subretinal fibrosis			
Vitritis			
CNV			
(b) Ocular serious adverse events in study eye			

	[redacted]		
(c) Ocular adverse events in study eye leading to discontinuation	[redacted]	[redacted]	[redacted]
Ocular adverse events classified as severe (occurring in ≥ 2 subjects overall) **Study eye** Total Macular degeneration Conjunctival haemorrhage Retinal haemorrhage Visual acuity reduced Eye pain Endophthalmitis Corneal abrasion Eye irritation Intraocular pressure increased Iridocyclitis Vitreous haemorrhage Photophobia Posterior capsule opacification Retinal detachment **Fellow eye** Total Macular degeneration Retinal haemorrhage Cataract Intraocular pressure increased Vitreous haemorrhage CNV Cataract nuclear Visual acuity reduced Cataract subcapsular Eye pain Herpes zoster ophthalmic Vitreous detachment			
Ocular events related to study drug in study eye (Total) Most common: Iritis Intraocular pressure increased Vitritis Vitreous floaters (Others reported, occurred in ≤ 2.5% in any group, not extracted)	[redacted]	[redacted]	[redacted]

Ocular events related to study drug in fellow eye (Total)	[redacted]	[redacted]	[redacted]
Non-ocular events related to study drug, no. of subjects with at least on event	[redacted]	[redacted]	[redacted]
(d) ocular adverse events in fellow eye (occurring in ≥ 10% in any group)	[redacted]		
(e) Non-ocular events			
(f) Non-ocular serious adverse events			
Non-ocular adverse events classified as severe (Total)			
Cataract			
Arterial thromboembolic events, hypertension, non ocular haemorrhage, proteinuria			
Haematology, coagulation, chemistry, urinalysis			
Immunoreactivity			
	Ranibizumab 0.3mg (n=238)	**Ranibizumab 0.5mg (n=239)**	**Sham (n=236)**
Deaths Total Deaths during first year Deaths during second year	[redacted]	[redacted]	[redacted]
Methodological comments • Allocation to treatment groups: [redacted]			

- [redacted]
- Blinding: [redacted]
- Comparability of treatment groups: [redacted]
- Method of data analysis: [redacted]
- Sample size/power calculation: [redacted]
- Attrition/drop-out: [redacted]

General comments

- Generalisability: [redacted]
- Outcome measures: [redacted]
- Inter-centre variability: [redacted]
- Conflict of interests: [redacted]

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 intention to treat analysis?	Adequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and Design	Intervention	Participants	Outcome measures
Sy et al., 2005 (ANCHOR, fvf2587-g) Unpublished, ongoing United States, Europe, Australia RCT 83 centres *Setting:* *Funding:* Genentech, Inc / Novartis Pharma AG	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*:	*Target population:* Primary or recurrent 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/dropout*: 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 (using Early Treatment Diabetic Retinopathy Study charts) of 20/40 to 20/320 Snellen equivalent. Only one eye was assessed, if both eyes were eligible, the one with the better visual acuity was selected (unless medical reason for otherwise). *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 one 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	Note: data are extracted for the study's primary and secondary outcome measures and for the TAR's stated outcome measures only. Exploratory efficacy measures not extracted. *Primary outcomes:* Proportion losing fewer than 15 letters (approx 3 lines) in best corrected visual acuity (BVCA) at a test distance of 2 meters. [redacted] Safety and tolerability *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. Vision-related functioning and well-being: National Eye Institute Visual Function Questionaire-25 (VFQ-25) Size of classic CNV and amount of leakage. *Additional outcomes required by TAR:* [redacted] *Method of assessing outcomes:* [redacted] *Exploratory efficacy outcomes reported but not extracted* [redacted]

		or ≥1 disc area 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.	 *Length of follow-up:* 12 months (study ongoing)

Characteristics of participants:			
	Ranibizumab 0.3mg (n=140)	**Ranibizumab 0.5mg (n=140)**	**Verteporfin PDT (n=143)**
Age yrs, mean (SD), range			
Male Female			
White Black Hispanic American Indian or Alaskan native Other			
Years since first diagnosis of AMD, Mean (SD), range			
Visual acuity at starting test distance 2 metres			

No. of letters (0-100), Mean (SD), Range ≤ 44 ≥ 45	[redacted]	[redacted]	[redacted]
Approximate Snellen equivalent (2 metres) Median 20/200 or worse Better than 20/200 but worse than 20/40 20/40 or better	[redacted]	[redacted]	[redacted]
Visual acuity scores: study eye vs fellow eye Study eye better than fellow eye Study eye worse than fellow eye Study eye same as fellow eye	[redacted]	[redacted]	[redacted]
Predominantly classic Minimally classic Occult without classic	[redacted]	[redacted]	[redacted]
Total area of lesion (disc areas (DA)) Mean (SD), range) ≤ 2 DA >2 to 4 DA > 4 DA	[redacted]	[redacted]	[redacted]
Total area of CNV (DA), Mean (SD), range	[redacted]	[redacted]	[redacted]
Area of classic CNV (DA), Mean (SD), range	[redacted]	[redacted]	[redacted]
Total area of leakage from CNV plus intense progressive retinal pigment epithelium staining (DA), mean (SD), range	[redacted]	[redacted]	[redacted]
Area of subretinal fluid (DA) (aka serous sensory retinal detachment), Mean (SD), range	[redacted]	[redacted]	[redacted]
Presence of occult CNV Absent Questionable Present	[redacted]	[redacted]	[redacted]
Any prior therapy for AMD in study eye Laser photocoagulation Medication Supplements	[redacted]	[redacted]	[redacted]

Results

Outcomes (at 12 months)	**Ranibizumab 0.3mg (n=140)**	**Ranibizumab 0.5mg (n=140)**	**Verteporfin PDT (n=143)**
Proportion losing <15 letters compared with baseline (starting test 2 metres) n (%) 95 CI of the % Difference in % (vs PDT) 95% CI of the difference Non-inferiority test vs PDT Test for treatment difference (vs PDT)	[redacted] 132 (94.3%) [redacted]	[redacted] 134 (96.4%) [redacted]	[redacted] [redacted]
[redacted]			
Visual acuity at starting test distance of 2 metres, at 12 months No. of letters, mean, SD			

95% CI of mean Difference in least squares means (vs PDT) 95% CI of difference P (vs PDT)	[redacted]	[redacted]	[redacted]
No. of letters change from baseline, mean (SD) 95% CI of mean Difference in least squares means (vs PDT) 95% CI of difference P value (vs PDT)	[redacted]	[redacted]	[redacted]
Gain of ≥ 15 letters from baseline, n (%) 95% CO of the % Difference in % (vs PDT) 95% CI of the difference P value (vs PDT)	50 (35.7%) [redacted]	56 (40.3%) [redacted]	8 (5.6%) [redacted]
Snellen equivalent 20/200 or worse, n (%) 95% CI of the % Difference in % (vs PDT) 95% CI of the difference P value (vs PDT) *Distribution, n (%)* 20/200 or worse Better than 20/200 but worse than 20/40 20/40 or better	[redacted] (22.1%) * [redacted]	[redacted] (16.4%) [redacted]	[redacted] (60.1%) [redacted]
[redacted]			
Subgroup analysis: proportion losing <15 letters in visual acuity at 12 months compared with baseline (starting test distance 2 metres)			
Occult CNV present Response rate 95% CI of the % Difference in % 95% CI of the difference P value vs sham	[redacted]	[redacted]	[redacted]
Occult CNV absent Response rate 95% CI of the % Difference in % 95% CI of the difference P value vs sham	[redacted]	[redacted]	[redacted]
Change from baseline in VFQ-25 scores at month*** **Near activities** Mean (SD) 95% CI of mean Difference in least squares means (vs PDT) 95% CI of difference	[redacted]	[redacted]	[redacted]

P value (vs PDT)	[redacted]	[redacted]	
Distance activities Mean (SD) 95% CI of mean Differenc e in least squares means (vs PDT) 95% CI of difference P value (vs PDT)	[redacted]	[redacted]	[redacted]
Vision-specific dependency Mean (SD) 95% CI of mean Difference in least squares means (vs PDT) 95% CI of difference P value (vs PDT)	[redacted]	[redacted]	[redacted]
Change in area of classic CNV (DA), mean (SD) 95% CI of mean Difference in least squares means (vs PDT) 95% CI of difference P value (vs PDT)	[redacted]	[redacted]	[redacted]
Change in total area of leakage from CNV + intense progressive RPE staining (DA), mean (SD) 95% CI of mean Difference in least squares means (vs PDT) 95% CI of difference P value (vs PDT)	[redacted]	[redacted]	[redacted]
Change in contrast sensitivity, no. of letters, mean P value vs (PDT)	[redacted]	[redacted]	[redacted]
[redacted]			
Adherence to treatment (treatment compliance)			
[redacted]			

Adverse Effects (safety-evaluable subjects)	**Ranibizumab 0.3mg (n=137)**	**Ranibizumab 0.5mg (n=140)**	**Verteporfin PDT (n=143)**
Any injection (ranibizumab or sham) held according to protocol specified criteria	[redacted]	[redacted]	[redacted]
Ocular events: study eye All adverse events (a) Serious adverse events (b) Adverse events led to discontinuation (study or treatment) (c) Endophthlamitis Intraocular inflammation Total Serious **Ocular events: fellow eye**	[redacted]	[redacted]	[redacted]

All adverse events Serious adverse events Adverse events led to discontinuation (study or treatment) Endophthlamitis Intraocular inflammation Total Serious **Non-ocular events** All adverse events (d) Serious adverse events (e) Adverse events that led to discontinuation	[redacted]	[redacted]	[redacted]
(a) ocular adverse events in study eye (occurring in ≥ 10% in any group) Conjunctival haemorrhage Macular degeneration Retinal haemorrhage Eye pain Vitreous detachment Subretinal fibrosis Intraocular pressure increased Vitreous floaters Visual acuity reduced Foreign body sensation in eyes Eye irritation	[redacted]	[redacted]	[redacted]
(b) Ocular serious adverse events in study eye	[redacted]		
(c) Ocular adverse events in study eye leading to discontinuation No. with at least one event. Events (all occurred in 1 subject (0.7%))	[redacted]	[redacted]	[redacted]
Ocular adverse events classified as severe (occurring in ≥ 2 subjects overall) **Study eye** Total Conjunctival haemorrhage Eye pain Intraocular pressure increased Retinal haemorrhage Retinal detachment **Fellow eye** Total CNV Macular degeneration	[redacted]	[redacted]	[redacted]
Ocular events related to study drug in study eye (Total) Most common: Intraocular pressure increased Vitritis Iritis (Others reported, not extracted)	[redacted]	[redacted]	[redacted]

Non-ocular adverse events classified as severe (Total)	[redacted]	[redacted]	[redacted]
(d) Non-ocular events	[redacted]		
(e) Non-ocular serious adverse events	[redacted]		
Cataract	[redacted]	[redacted]	[redacted]
Arterial thromboembolic events, hypertension, non ocular haemorrhage, proteinuria	[redacted]		
Haematology, coagulation, chemistry, urinalysis	[redacted]		
Immunoreactivity	[redacted]		
Deaths Total Primary cause of death	[redacted]	[redacted]	[redacted]
Methodological comments • Allocation to treatment groups:* • Blinding	[redacted]		

- [redacted]
- Comparability of treatment groups [redacted]
- Method of data analysis: [redacted]
- Sample size/power calculation: [redacted]
- Attrition/drop-out: [redacted]

General comments

- Generalisability: [redacted]
- Outcome measures: [redacted]
- Inter-centre variability: [redacted]
- Conflict of interests: [redacted]

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 intention to treat analysis?	Inadequate
10. Were withdrawals and dropouts completely described?	Adequate

Reference and Design	Intervention	Participants	Outcome measures
[redacted] PIER [redacted] Unpublished, ongoing [redacted] United States RCT [redacted] [redacted] investigators *Setting:* *Funding:* Genentech, Inc [redacted]	1. 0.3 mg ranibizumab monthly for 3 doses, then doses every 3 months 2. 0.5 mg ranibizumab monthly for 3 doses, then doses every 3 months 3. Sham injection monthly for 3 doses, then doses every 3 months *Duration of treatment:* [redacted] *Other interventions used*: [redacted]	*Target population:* [redacted] *Number of Participants:* [redacted] *Sample attrition/dropout* [redacted] *Main inclusion criteria for study entry*: [redacted] *Exclusion criteria:* [redacted]	Note: data are extracted for the study's primary and secondary outcome measures and for the TAR's stated outcome measures only. Exploratory efficacy measures not extracted. *Primary outcomes:* [redacted] *Secondary outcomes for year one:* [redacted] *Additional outcomes required by TAR:* [redacted] *Method of assessing outcomes:* [redacted] *Exploratory efficacy outcomes reported but not extracted:* [redacted]

			Length of follow-up

Characteristics of participants:

	Ranibizumab 0.3mg	**Ranibizumab 0.5mg**	**Sham**
Age yrs, mean (SD), range			
Male Female			
White Asian or Pacific Islander Hispanic American Indian or Alaskan native Other			
Years since first diagnosis of AMD, Mean (SD), range			
Visual acuity No. of letters (0-100), Mean (SD), Range ≤ 54 ≥ 55			
Approximate Snellen equivalent Median 20/200 or worse Better than 20/200 but worse than 20/40 20/40 or better			
Visual acuity: Study eye worse than fellow eye			
Predominantly classic Minimally classic Occult without classic Cannot classify			
Total area of lesion (DA)			

Mean (SD), range ≤ 4 DA > 4 DA	[redacted]	[redacted]	[redacted]
Total area of CNV (DA) Mean (SD), range	[redacted]	[redacted]	[redacted]
Area of classic CNV (DA), Mean (SD), range	[redacted]	[redacted]	[redacted]
Total area of leakage from CNV plus intense progressive retinal pigment epithelium staining (DA), mean (SD), range	[redacted]	[redacted]	[redacted]
Area of serous sensory retinal detachment or retinal fluid(DA) (aka), Mean (SD), range	[redacted]	[redacted]	[redacted]
Occult CNV present,	[redacted]	[redacted]	[redacted]
Any prior therapy for AMD in study eye Laser photocoagulation Medication Supplements	[redacted]	[redacted]	[redacted]
Results			
Outcomes [redacted]	**Ranibizumab 0.3mg** [redacted]	**Ranibizumab 0.5mg** [redacted]	**Sham** [redacted]
Visual acuity at starting test distance 4 meters *Number of letter change from baseline, mean (SD)* 95% CI for mean Difference in LS means vs sham 95% CI for difference P value vs sham *Number of letters, mean (SD)* 95% CI for mean Difference in LS means vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]
Loss of <15 letters from baseline, n 95% CI for % Difference in % vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]
Gain of ≥ 15 letters from baseline, n (%) 95% CI for % Difference in % vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]

Snellen equivalent 20/200 or worse, n (%) 95% CI for % Difference in % (vs sham) 95% CI of the difference P value (vs sham) *Distribution, n (%)* 20/200 or worse Better than 20/200 but worse than 20/40 20/40 or better	[redacted]	[redacted]	[redacted]
Subgroup analysis: mean change in visual acuity at [redacted] compared with baseline [redacted]			
Occult CNV present Mean (SD) 95% CI for mean Difference in LS means vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]
Occult CNV absent Mean (SD) 95% CI for mean Difference in LS means vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]
Minimally classic CNV Mean (SD) 95% CI for mean Difference in LS means vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]
Occult with no classic CNV Mean (SD) 95% CI for mean Difference in LS means vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]
Predominantly classic CNV Mean (SD) 95% CI for mean Difference in LS means vs sham 95% CI for difference P value vs sham	[redacted]	[redacted]	[redacted]
Change from baseline [redacted]			
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]			

Change in total area of CNV (DA), mean (SD) 95% CI of mean Difference in LS means vs sham 95% CI of difference P value (vs sham)			
Change in total area of leakage from CNV + intense progressive RPE staining (DA), mean (SD) 95% CI of mean Difference in LS means vs sham 95% CI of difference P value (vs sham)			
Change in contrast sensitivity, change in no. of letters, mean P value vs (PDT)			
Adherence to treatment (treatment compliance)			
Adverse Effects (safety-evaluable subjects)	**Ranibizumab 0.3mg**	**Ranibizumab 0.5mg**	**Sham**
Any injection (ranibizumab or sham) held according to protocol specified criteria			
Ocular events: study eye			
Ocular events: fellow eye			

Non-ocular events			
(a) ocular adverse events in study eye			
(b) Ocular serious adverse events in study eye			
(c) Ocular adverse events in study eye leading to discontinuation			
Ocular adverse events classified as severe Study eye			
Ocular events related to study drug in study eye (Total)			
Non-ocular adverse events classified as severe			

(Total)	[redacted]
(d) Non-ocular events	
(e) Non-ocular serious adverse events	
Cataract	
Hypertension, arterial thromboembolic events, non ocular haemorrhage, proteinuria	
Haematology, coagulation, chemistry, urinalysis	
Immunoreactivity	
Deaths	

Methodological comments

- Allocation to treatment groups: [redacted]
- Blinding: [redacted]
- Comparability of treatment groups: [redacted]
- Method of data analysis: [redacted]
- Sample size/power calculation: [redacted]
- Attrition/drop-out: [redacted]

[redacted]

General comments

- Generalisability: [redacted]
- Outcome measures: [redacted]
- Inter-centre variability: [redacted]
- Conflict of interests: [redacted]

Quality criteria for assessment of experimental studies

1. Was the assignment to the treatment groups really random?	[redacted]	
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?		

Reference and Design	Intervention	Participants	Outcome measures
FOCUS Unpublished Phase I/II RCT sites *Setting:* *Funding:* Genentech, Inc	1. R+PDT 0.5 mg ranibizumab* injection 2. sham+PDT sham injection *Duration of treatment:* *a lyophilized formulation of ranibizumab was used *Other interventions used:*	*Target population:* *Number of Participants:* *Sample attrition/dropout:* *Main inclusion criteria for study entry:* *Exclusion criteria:*	*Primary outcomes:* *Secondary outcomes for first treatment year:* *Method of assessing outcomes:* *Length of follow-up:*

Characteristics of participants:			
	R+PDT		**Sham+PDT**
Age yrs, mean (SD), range			
Male Female			
White Hispanic			
Years since first diagnosis of AMD, Mean (SD), range			
Visual acuity (2 metres) No. of letters (0-100), Mean (SD), Range			
Approximate Snellen equivalent Median 20/200 or worse			

Better than 20/200 but worse than 20/40 20/40 or better	[redacted]	[redacted]
Predominantly classic Minimally classic Occult without classic Cannot classify	[redacted]	[redacted]
Total area of lesion (DA) Mean (SD), range	[redacted]	[redacted]
Total area of CNV (DA) Mean (SD), range	[redacted]	[redacted]
Area of classic CNV (DA), Mean (SD), range	[redacted]	[redacted]
Total area of leakage from CNV plus intense progressive retinal pigment epithelium staining (DA), mean (SD), range	[redacted]	[redacted]
Area of serous sensory retinal detachment/ subretinal fluid(DA), Mean (SD), range	[redacted]	[redacted]
Any prior therapies for AMD Laser photocoagulation Photodynamic therapy Medication Supplements Other	[redacted]	[redacted]
Results		
Outcome [redacted]	[redacted]	[redacted]
Loss of < 15 Letters from baseline n (%) 95% CI of the % Difference in % 95% CI of the difference p-value	[redacted]	[redacted]
[redacted]		
Number of letters change from baseline Mean (SD) 95% CI of the mean Mean difference 95% CI of the difference p-value	[redacted]	[redacted]
Gain of ≥ 15 letters from baseline n (%) 95% CI of the % Difference in % 95% CI of the difference p-value	[redacted]	[redacted]

Snellen equivalent of 20/200 or worse n (%) 95% CI of the % Difference in % 95% CI of the difference p-value	[redacted]	[redacted]
Change in the total area of lesion (DA) Mean (SD) 95% CI of the mean p-value**	[redacted]	[redacted]
Change in the area of classic CNV (DA) Mean (SD) 95% CI of the mean p-value	[redacted]	[redacted]
Change in the total area of leakage from CNV + intense progressive RPE staining (DA) Mean (SD) 95% CI of the mean p-value	[redacted]	[redacted]
Change in the area of SSR detachment/ subretinal fluid Mean (SD) 95% CI of the mean p-value	[redacted]	[redacted]
Change in the area of CNV Mean (SD) 95% CI of the mean p-value	[redacted]	[redacted]
Verteporfin PDT Treatment in the Study Eye during the First Treatment Year Subjects retreated with any verteporfin PDT n (%) p-value Number of treatments with verteporfin PDT Mean (SD) Range	[redacted]	[redacted]
Notes [redacted]		
Subgroup analysis	[redacted]	[redacted]
Loss of < 15 Letters from Baseline at 12 Months	[redacted]	[redacted]
N n (%) 95% CI of the percentage Difference in percentages 95% CI of the difference	[redacted]	[redacted]

p-value	[redacted]	[redacted]
Adherence to treatment (treatment compliance) [redacted]		
Adverse Effects (safety-evaluable subjects)	**R+PDT** [redacted]	**Sham+PDT** [redacted]
Ocular (study eye) [redacted]	[redacted]	[redacted]
Ocular (fellow eye)- [redacted]	[redacted]	[redacted]
Non-ocular [redacted]	[redacted]	[redacted]
a) Ocular Adverse Events in the Study Eye [redacted]	[redacted]	[redacted]

d) Ocular Adverse Events in the Fellow Eye [redacted]	[redacted]	[redacted]
Severe Ocular Adverse Events in the Study Eye [redacted]	[redacted]	[redacted]
Ocular Adverse Events Related to Study Drug in the Study Eye [redacted]	[redacted]	[redacted]
b) Serious Ocular Adverse Events in the Study Eye [redacted]	[redacted]	[redacted]
c) Ocular Adverse Events in the Study Eye Leading to Discontinuation of Study or Treatment [redacted]	[redacted]	[redacted]

[redacted]		
Intraocular Cataracts in the Study Eye	[redacted]	[redacted]
Intraocular Cataracts in the Fellow Eye	[redacted]	[redacted]
Adverse Events Potentially Associated with Systemic Anti-VEGF Therapy Total Hypertension Arterial thromboembolic events Haemorrhagic	[redacted]	[redacted]
Notes: [redacted]		
Haematology, chemistry, urinalysis	[redacted]	
Immunoreactivity	[redacted]	
Deaths	[redacted]	

Methodological comments

- Allocation to treatment groups: [redacted]
- Blinding: [redacted]
- Comparability of treatment groups: [redacted]
- Method of data analysis: [redacted]
- Sample size/power calculation:* [redacted]

- Attrition/drop-out:

General comments

- Generalisability:
- Outcome measures:
- Inter-centre variability:
- Conflict of interests:

Quality criteria for assessment of experimental studies

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?	

Appendix 5 List of selected excluded studies

Capone A. Intravitreous pegaptanib sodium (Macugen) in patients with age-related macular degeneration (AMD): Safety and pharmacokinetics. *Investigative Ophthalmology & Visual Science* 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. *Investigative Ophthalmology & Visual Science* 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(4):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(7):815-827.
Reason: not an RCT

Gragoudas ES, Adamis AP, Feinsod M. Pegaptanib and age-related macular degeneration - Reply. *New England Journal of Medicine* 2005; 352(16):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. *Investigative Ophthalmology & Visual Science* 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). *Investigative Ophthalmology & Visual Science* 2005; 46:E-abstract 1393.
Reason: Not an RCT

Rakic JM, Blaise P, Foidart JM. Pegaptanib and age-related macular degeneration. *New England Journal of Medicine* 2005; 352(16):1720-1721.
Reason: letter to editor

Schuman S, Rogers AH, Duker JS, Reichel E, Baumal CR. Six-week outcomes after pegaptanib. *Ophthalmology* 2006; 113(3):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.

(1) 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* 47. 2006.

(2) 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* 47. 2006.

(3) 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* 47. 2006.

(4) 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* 44. 2003.

(5) 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* 47. 2006.

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, randomized, 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 June 2006.

The following records on the ClinicalTrials.gov website would not meet our inclusion criteria (due to lack of 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: 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 Q3 2006.
- PROTECT: phase II open-label combination treatment trial, in patients with occult or predominantly classic neovascular AMD. No control group. Objectives: to evaluate safety of the same-day administration of PDT with verteporfin and an injection of 0.5 mg ranibizumab. Completion date not given.
- EXCITE: phase IIIb randomized, double masked, active-controlled, multicenter study, in patients with subfoveal CNV secondary to AMD. No control group. Objectives: efficacy and safety of ranibizumab administered as 3 consecutive monthly injections of 0.3 mg 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: phase III open-label, multicentre extension study, in patients with subfoveal CNV secondary to AMD. Sham injection control. Objectives: to investigate long-term safety, tolerability and efficacy of multiple intravitreal ranibizumab. Completion date not given.
- SAILOR: phase IIIb single-masked, 1 year multicentre 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 0.3mg and 0.5mg 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: phase IIIb open label multicenter study in patients with subfoveal CNV secondary to AMD. No control group. Objectives: efficacy and safety of ranibizumab administered as 3 consecutive monthly injections followed by PRN re-treatment, in subjects treated with 0.3 mg intravitreal ranibizumab. Completion date not given.

Appendix 8 Critique of industry submissions

Pfizer – Pegaptanib sodium (Macugen)

Pegaptanib is a selective vascular endothelial growth factor (VEGF) inhibitor that specifically targets VEGF16, to suppress pathological neovascularisation. Pegaptanib is indicated for the treatment of neovascular (wet) age-related macular degeneration (AMD). The licensed dose is 0.3mg administered by intravitreal injection once every 6 weeks.

Submitted: 1 report (pp. 80 inc. appendices); 1 spreadsheet containing a cost-effectiveness model; CIC checklist. An unpublished paper by Mills et al. and papers by Chakravarthy et al. and D'Amico et al. 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

1. 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 one safety and effectiveness (Gragoudas and colleagues)
    - Year 2 safety (D'Amico and colleagues)
    - Year 2 effectiveness (Chakravarthy and colleagues)
    - Unpublished analysis of disease modifying effect (Mills and colleagues)

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 (VA). The submission reported year one results for the 0.3mg dose group compared with sham injection, and year two results were reported for those who were re-randomised to continue 0.3mg pegaptanib for two years compared with those who were re-randomised to receive usual care.

Patients losing <15 letters of VA (responders)

Year one results showed a significantly higher proportion of responders in the 0.3mg pegaptanib group than in the control group. Those who continued to receive 0.3mg pegaptanib in the second year were significantly more likely to be classified as responders than those who discontinued 0.3mg pegaptanib treatment after one year.

Maintenance or gain in VA

Significantly more people in the 0.3mg pegaptanib had a maintenance or gain of ≥ 0 letters at the end of year one.

Mean changes in VA

Mean changes in VA were significantly better for the 0.3mg pegaptanib group than for the control group at year one.

Proportion of patients gaining ≥ 5, ≥ 10 or ≥ 15 letters of VA

Significantly more people in the 0.3mg pegaptanib group than those in the sham injection group gained ≥ 5, ≥ 10, or ≥ 15 letters of VA.

Severe vision loss (loss of ≥ 30 letters)

Significantly fewer people who received 0.3mg pegaptanib reported severe vision loss at the end of year one than those who received sham injection. Severe vision loss was also significantly less likely to be reported among those who continued 0.3mg 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 0.3mg and usual care 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 is not currently in public domain)

The manufacturer's submission is primarily based on three published papers. Data from an additional, unpublished paper by Mills and colleagues is included in the manufacturer's submission. The manufacturer supplied the Mills paper at SHTAC's request. It presents academic in confidence analysis of the two year results, which suggest a disease modifying effect of treatment with pegaptanib. This has been considered in the TAR's economic evaluation and highlighted as AIC information. The manufacturer's submission also contains CIC subgroup analyses by lesion type for year 2 data, and these have been added to the TAR report.

The conclusion presented in the submission, i.e. that pegaptanib is significantly more effective than usual care in preserving VA, is supported by the conclusions of SHTAC's systematic review.

Cost-effectiveness

See Section 4.1.4.1 for discussion of the Pfizer cost effectiveness model.

2. Novartis – Ranibizumab (Lucentis)

Ranibizumab is not currently licensed for the treatment of AMD in the UK, although the manufacturer anticipates that it will receive its license during the appraisal process.

Submitted:

1 report (pp. 50); 12 appendices; 1 spreadsheet containing a Markov cost-effectiveness model; CIC checklist. The 12 appendices included the HE final report (pp. 91) and the following trial reports: MARINA 1 year report (pp. 194); MARINA year 2 report (pp. 177); ANCHOR (pp. 198); PIER (pp. 192); FOCUS (pp. 144). 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 and one unpublished RCTs of ranibizumab. A fourth phase I/II RCT (FOCUS) was provided by the manufacturer but not discussed in the submission in any detail. As this met the inclusion criteria for SHTAC's systematic review, it was included in the TAR. The manufacturer's submission refers to meta-analysis of the ANCHOR, MARINA and PIER studies. This is a separate drug and disease model (appendix III) and is not a standard meta-analysis of clinical effectiveness.

RCTs included in the review

- ANCHOR
- MARINA
- PIER (unpublished)
- FOCUS (unpublished) was also briefly discussed, but results weren't tabulated

Summary of key outcome measures

Patients losing <15 letters of VA (responders)

The ANCHOR and MARINA and PIER data are discussed in the submission and the FOCUS study provided by the manufacturer reported the proportion of patients who lost fewer than 15 letters of VA. Results were significantly better for both 0.3mg and 0.5mg doses compared with

sham injection or PDT at one year follow up in the [redacted] ANCHOR [redacted] trial[redacted], and at both years one and two in the MARINA trial.

Mean changes in VA

Results were significantly better for both 0.3mg and 0.5mg doses compared with sham injection or PDT at one year follow up in the [redacted] ANCHOR [redacted] trial[redacted], and at both years one and two in the MARINA trial.

Proportion of patients gaining ≥15 letters of VA

The PIER trial (which had a reduced frequency of injections) reported[redacted]between the ranibizumab groups and the sham injection group. Results were significantly better for both 0.3mg and 0.5mg doses compared with sham injection or PDT at one year follow up in the ANCHOR [redacted] trial[redacted], and at both years one and two 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%. In the comparator groups,[redacted]of sham-injection patients and[redacted]of PDT- patients[redacted]letters from baseline at [redacted]months. This outcome was defined as[redacted]by the CIC study reports, and is therefore not discussed in the SHTAC report. 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 0.3mg or 0.5mg were significantly less likely to deteriorate to legal blindness compared with those in the sham injection or PDT groups at one year follow up in the [redacted]_ANCHOR [redacted] trial[redacted], and at both years one and two in the MARINA trial.

Angiographic changes

Significantly better angiographic changes were reported for both 0.3mg and 0.5mg doses compared with sham injection or PDT at one year follow up in the [redacted] ANCHOR [redacted] trial[redacted], and at both years one and two in the MARINA trial.

Health related quality of life

The PIER trial found [redacted] in health related quality of life measured on the [redacted] scale between people receiving ranibizumab and those receiving sham injections. MARINA and ANCHOR reported significant differences between both the 0.3mg and 0.5mg dose groups and sham/PDT control groups for distant activities, near activities and vision specific dependency subscales. FOCUS [redacted] this outcome.

Adverse events

Adverse events were reported by the trials, and these are discussed in the TAR.

'Added value' of submission

The two published and two unpublished RCTs provided by the manufacturer form the evidence base for ranibizumab AMD treatment. The manufacturer provided a Drug and Disease Model which pooled the placebo groups of the MARINA and PIER trials in order to identify the optimum dosing regimen.

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 0.5mg results in a clinically meaningful improvement of 15 or more letters in over a third of patients. [redacted] this is true of the patients in the two pivotal trials (MARINA and ANCHOR), results [redacted] in the FOCUS trial, which combined ranibizumab with PDT, [redacted] the PIER trial [redacted] It should be noted that patients in the PIER trial had the frequency of dosing reduced from one injection per month to one injection every three months.

1.2 Cost-effectiveness

See Section 4.1.4.2 for discussion of the Novartis cost effectiveness model.

Appendix 9 Ocular adverse events in study eye: CIC information from ranibizumab studies

	Number of patients (%)										
Adverse event (AE)	**MARINA (24 month data) Lesion type: occult/MC**			**ANCHOR Lesion type: PC**			**PIER Lesion type: all**			**FOCUS Lesion type:**	
	0.3mg (n=238)	0.5mg (n=240)	Sham (n=238)	0.3mg + sham PDT (n=140)	0.5mg + sham PDT (n=140)	Sham + PDT (n=143)	0.3mg	0.5mg	Sham	0.5mg +PDT	Sham +PDT
All AE (a)											
Serious AE (b)											
AE led to discontinuation of study or treatment (c)											
Endophthlamitis											
Intraocular inflammation											
Total											
Serious											
Cataract											
(a) Ocular AE[a]											
Conjunctival haemorrhage											
Macular degeneration											
Retinal haemorrhage											
Visual acuity reduced											
Eye pain											

Number of patients (%)												
Adverse event (AE)	**MARINA (24 month data) Lesion type: occult/MC**			**ANCHOR Lesion type: PC**			**PIER Lesion type: all**			**FOCUS Lesion type:**		
	0.3mg (n=238)	0.5mg (n=240)	Sham (n=238)	0.3mg + sham PDT (n=140)	0.5mg + sham PDT (n=140)	Sham + PDT (n=143)	0.3mg	0.5mg	Sham	0.5mg +PDT	Sham +PDT	
Intraocular pressure increased												
Vitreous floaters												
Vitreous detachment												
Subretinal fibrosis												
Vitritis												
CNV												
Eye irritation												
Foreign body sensation in eyes												
(b) Most common ocular serious AE												
Reduced visual acuity Retinal haemorrhage				Rate (in each treatment group) for all ocular serious adverse events lens damage or retinal tears.								
(c) Ocular AE in study eye leading to discontinuation												
Macular degeneration Retinal haemorrhage Visual acuity reduced Iridocyclitis Eye pain Uveitis												
Ocular AE classified as severe (study eye) [b]												

Number of patients (%)												
Adverse event (AE)	**MARINA (24 month data) Lesion type: occult/MC**			**ANCHOR Lesion type: PC**			**PIER Lesion type: all**			**FOCUS Lesion type:**	
	0.3mg (n=238)	0.5mg (n=240)	Sham (n=238)	0.3mg + sham PDT (n=140)	0.5mg + sham PDT (n=140)	Sham + PDT (n=143)	0.3mg	0.5mg	Sham	0.5mg +PDT	Sham +PDT
Total											
Conjunctival haemorrhage											
Eye irritation											
Retinal haemorrhage											
Eye pain											
Visual acuity reduced											
Macular degeneration											
Endophthalmitis											
Corneal abrasion											
Intraocular pressure increased											
Iridocyclitis											
Retinal detachment											
Total											
Intraocular pressure increased											
Iritis											
Vitritis											
Vitreous floaters											
Iridocyclitis											

[a] ocular AE occurring in at least [redacted] in any group in the PIER study, at least [redacted]% in any group or at least [redacted] more frequent in either ranibizumab group in MARINA study,
[b] *occurring in at least 2 subjects overall in Marina and ANCHOR trial

Appendix 10 Non ocular adverse events: CIC information from ranibizumab studies

	Number of patients (%)										
Adverse event (AE)	**MARINA (24 month data) Lesion type: ocuult/MC**			**ANCHOR Lesion type: PC**			**PIER Lesion type: all**			**FOCUS Lesion type:**	
	0.3mg (n=238)	0.5mg (n=240)	Sham (n=238)	0.3 mg + sham PDT (n=140)	0.5mg + sham PDT (n=140)	Sham + PDT (n=143)	0.3mg	0.5mg	Sham	0.5mg + PDT	Sham + PDT
Any injection held according to protocol specified criteria											
Non-ocular events											
All AE											
Serious AE											
AE that led to discontinuation											
Non-ocular events related to study drug											
Non-ocular AE classified as severe											
Deaths											

Appendix 11 Summary of measures reported in studies included in the review of quality of life in AMD

Measure of QoL	*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 summarizing 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, vigor/ activity, confusion/ bewilderment, fatigues/ inertia and anger/ hostility) and a total score that ranges from 0-232.[56,148,149]
▪ 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 (7items) 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 humor, 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. Hospital Anxiety and Depression Scale scores range from 0 to 21 with a higher score representing more symptoms of anxiety ore depression. It is also recommended using categories of 0 to 7, 8 to 10, and 11 or higher to define "noncases", "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]
▪ Short From-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. [61,64,120,126,150]
▪ Short From-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]
▪ Quality of Well-Being (QWB)	A comprehensible measure of health related quality of life 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 quality of life 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	It 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. [126]
▪ MacDQoL	An individualised meadure 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 £) to give a weighted impact score for each domain of between -9 and +3. The use of impact and importance scores enables an estimation of the impact of MD on an individual's QoL, not merely on function. A final item asks the respondents whether MD affects his/her life in any ways not already covered, with a space to write a response for people who reply 'yes'. [125]
▪ National Eye Institute Visual Function Questionnaire (NEI-VFQ)	Three versions of the NEI-VFQ have been published, containing 25 items, 39 items and 51 items. A 51-item questionnaire was originally devised in the US 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. [61,63,120-124,148,151,152]
▪ AMD Self Efficacy Questionnaire	As conceptualized 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. [148]
▪ 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 phone; recognising people nearby; seeing steps, stairs or curbs; reading traffic, store or street signs; doing fine handiwork; writing checks or filling out forms; playing games; playing sports; cooking; watching televisions; 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'. [127]
▪ Daily Living Tasks Dependent on Vision (DLTV)	A 33 item divided into 4 dimensions questionnaire covering tasks relating to visual function, with and without the use of magnification aids, and general aspects of visual health. In 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. [150]
▪ 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]

Measure of QoL	*Description*
▪ 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. [62,112,128,142]
▪ 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.[112,128]

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 0.3mg pegaptinib versus usual care for treatment of patients with subfoveal neovascularisation in better-seeing eye
Is there a clear description of alternatives?	✓	Pegaptinib 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 fellow eye and sub-retinal haemorrhage comprising ≤ 50% total lesion size and total lesion size up to 12 disc areas. 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 pegaptinib, but how does this compare to 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 sub-types of ARMD? Separate analysis of pegaptinib vs supportive care where PDT not appropriate, then supportive care plus PDT vs pegaptinib 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 VA) and valued by utilities for respective health states. Some impact of disease progression on mortality once progression to blindness (VA 6/60). Two base case scenarios presented base on maximum two years of treatment and alternative stopping rules: Scenario A: discontinue when VA falls below 6/96 or for those with severe loss (greater than 6 Snellen lines) at end of Year 1; Scenario B: discontinue when VA 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 personal social services – 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.
Has a lifetime horizon been used for analysis (has a shorter horizon been justified)?	✓	Ten 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	✓	Costs consistent with NHS and PSS perspective. Principally valued

consistent with the perspective employed? *Covered in detail in questions below*		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 pegaptinib reported and incremental cost-effectiveness for pegaptinib vs usual care.
Is sensitivity analysis undertaken and presented clearly?	✓	One-way SA 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 pegaptinib only Use upper and lower limits for NHS and PSS services to visually impaired reported by Meads and colleagues Telephone consultation for monitoring adverse events "accounting for prior PDT" PSA parameters Mean number of administrations of pegaptinib (mean and standard deviation using normal dist^{n}) Transition probabilities (mean, standard error and covariance of VISION survival model parameter estimates – use Cholesky decomposition) Utility weights (beta using mean and standard deviation from published study) Limited SA on costs Maybe do analysis for costs and uptake of NHS and PSS services to visually impaired for each item separately as well as all together Possible SA tests on model structure?

Appendix 13 Critical appraisal checklist of economic evaluation in Novartis submission

Item	Critical Appraisal	Reviewer Comment
Is there a well defined question?	Yes	
Is there a clear description of alternatives?	Yes	▪ 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?	Yes	
Is the correct comparator used?	Yes	▪ Photodynamic therapy (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 (BSC) 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 BSC 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?	Yes	Both cost-effectiveness studies in incremental cost per vision year gained and cost-utility studies in incremental cost per quality-adjusted life year (QALY) gained.
Is the perspective of the analysis clearly stated?	Yes	Both the perspectives of NHS and personal social services in England and Wales.
Is the perspective employed appropriate?	Yes	
Is effectiveness of the intervention established?	Yes	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)?	No	A time horizon of 10 years 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 two 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?	Yes	
Is differential timing considered?	Yes	Both costs and benefits were discounted annually at 3.5%.
Is incremental analysis performed?	Yes	Incremental cost and benefits as well as incremental cost effectiveness ratio for cost per vision year gained and cost per QALY gained.
Is sensitivity analysis undertaken and	Yes	▪ The number of injections per year in the base case scenario

presented clearly?		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

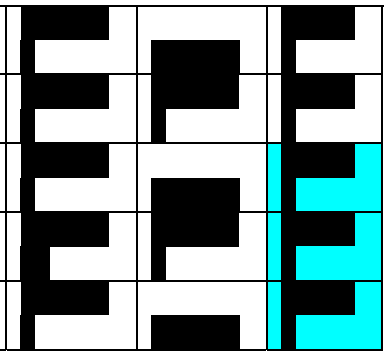
Costs	Distribution	Alpha	Beta	Mean
First OP attendance	Gamma	92.6854	1.0297	95.44
OP follow up	Gamma	114.9876	0.5110	58.76
Fluoroscein angiography	Gamma	96.0365	0.7706	74.01
Ooptical coherence tomography	Gamma	96.0365	0.5296	50.86
Blind registration	Gamma	12.1775	9.4765	115.40
Low vision aids	Gamma	39.4712	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 & <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	[redacted]		
		Lose ≥ 3 & <6 lines	Beta			
		Lose ≥ 6 lines	Beta			
Usual care	Year 1	Gain at least 3 lines	Beta	n = 296	r = 6	0.0203
		Lose ≥ 3 & <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	[redacted]		
		Lose ≥ 3 & <6 lines	Beta			
		Lose ≥ 6 lines	Beta			

Transition probabilities: PC BSC			Distribution	Parameter	Mean
Ranibizumab	Year 1	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
Best supportive care	Year 1	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		

Transition probabilities: PC PDT			Distribution	Parameter	Mean
Ranibizumab	Year 1	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
PDT	Year 1	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		

Transition probabilities: MC OC			Distribution	Parameter	Mean
Ranibizumab	Year 1	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
	Year 2	Gain at least 3 lines	Beta		
		Lose ≥ 3 & <6 lines	Beta		
		Lose ≥ 6 lines	Beta		
Best Supportive	Year 1	Gain at least 3 lines	Beta		

Care		Lose ≥ 3 & <6 lines	Beta	
		Lose ≥ 6 lines	Beta	
	Year 2	Gain at least 3 lines	Beta	
		Lose ≥ 3 & <6 lines	Beta	
		Lose ≥ 6 lines	Beta	