Appendix J: Health economics

Acknowledgements

The methods used to translate NMA outputs into transition probabilities described in J.5.3.3 were based on invaluable advice from the NICE clinical guidelines technical support unit (Nicky Welton, Sofia Dias, Edna Keeney).

Ewen Cummins generously provided expert peer-review of a near-final draft of this document and accompanying health economic model, leading to several important improvements in the analysis and the way it is reported.

All errors that remain are the responsibility of the developers and the guideline committee.

J.1 Introduction

The economic approach to provide evidence to support decision making around a clinical review question begins with a systematic search of the literature. The aim of this is to source any published economic evaluations of relevance to the topic of interest. At this stage it may become apparent that evidence exists in the literature which exactly meets the review question criteria and therefore there is no need for new economic analysis. If this proves not to be the case it may be decided that economic modelling can generate some useful analysis. The aim is to produce a cost–utility analysis in order to weigh up the benefits and harms of comparable interventions. The extent to which this is possible will be driven by the availability of evidence upon which to parameterise the clinical pathway and disease natural history.

A literature search was conducted jointly for all review questions in this guideline by applying standard health economic filters to a clinical search for AMD (Appendix D). A total of 3,163 unique references was returned. This appendix first details the systematic literature reviews undertaken relating to review questions for which any cost-utility analyses (CUAs) were identified. Evidence tables can be found at the end of this appendix (Section J.6). The appendix then provides extensive detail on the new health economic model that was developed for this guideline.

J.2 Risk factors

J.2.1 Strategies to slow the progression of age-related macular degeneration (AMD)

Review question:

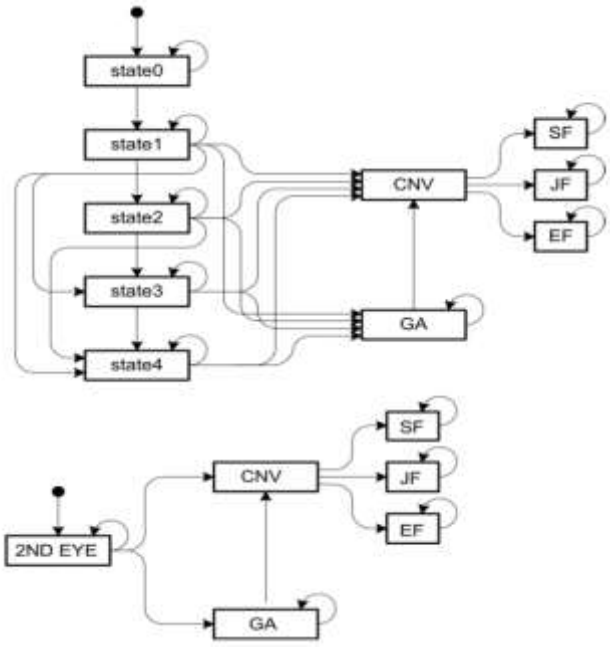
RQ7: What is the effectiveness of strategies to reduce the risk of developing AMD in the unaffected eye or slow the progression of AMD?

Out of the 3,163 unique references retrieved, 2 references were retained for this review question. Health economic modelling was not prioritised for this review question.

J.2.1.1 Vitamin supplementation

Rein et al. (2007) compared the effectiveness of vitamin therapy added to best supportive care with no vitamin therapy using a computerised, stochastic, agent-based model. The model simulated the natural history of AMD and patterns of ophthalmic service use in the United States in a 50-year old cohort. The model ran until patients reached 100 years old or died. It simulated the progression of AMD using data from the Age-Related Eye Disease

Study (AREDS) and generated outcomes of disease progression, years and severity of visual impairment, cost of ophthalmic care and nursing home services, and quality-adjusted life years (QALYs). Costs and benefits were considered from the U.S healthcare service perspective and discounted using a 3% rate. The model is detailed schematically in Figure 1.



States 1–4 refer to VA (see text). CNV=choroidal neovascularisation; EF=extrafoveal; GA=geographic atrophy; JF=juxtafoveal; SF=subfoveal. The model allows for backwards transitions in early/intermediate AMD states, as per AREDS evidence and includes the fellow eye.

Figure 1: Model diagram showing transitions between AMD natural history states

Patients with early and intermediate AMD were categorised into mutually exclusive states numbered 0 to 4 which refer to physiological (not visual) manifestations of AMD pathology. State 0 patients had no large drusen or retinal pigment epithelium (RPE) abnormalities in either eye; state 1 patients had either large drusen in one eye or RPE abnormalities in one eye, with no other symptoms; state 2 patients had large drusen in both eyes, with no RPE abnormalities, RPE abnormalities in both eyes with no large drusen, or large drusen and RPE abnormalities in one eye each; state 3 patients had large drusen in both eyes, with RPE abnormalities in one eye, or RPE abnormalities in both eyes with large drusen in one eye; and state 4 patients had large drusen and RPE abnormalities in both eyes. Following diagnosis, all patients were assumed to have received medical treatment and services recommended by the American Academy of Ophthalmology's preferred practice patterns (2005 – document no longer online).

All individuals with AMD are diagnosed at the point of model entry through routine ophthalmic appointments. The treatment effect was simulated by modifying the transition probabilities between states 1 to 4, using data from AREDS to simulate a 25% relative risk reduction of disease progression among patients taking vitamin supplements, compared with those taking a placebo. Vitamin therapy was assumed to have no impact on backward transitions or transitions from geographic atrophy to choroidal neovascularisation. The model accounts for the cost of routine ophthalmology appointments, medical treatment, vitamin prophylaxis and nursing home care. The base-case results are shown in Table 1.

Table 1: Rein et al. (2007) – base-case cost–utility results

Arm	Cost ($US)			Years of VI & blindness	QALYs	ICER ($/QALY)
	AMD	Nursing home	Total			
Conventional treatment	583.41	265.55	848.96	0.26049	15.6221	-
Vitamin therapy	720.87	216.51	937.38	0.22501	15.6263	-
Incremental	137.46	-40.94	88.42	-0.0355	0.004	21,887

The base-case model produces an ICER of $21,887 per QALY. Incremental QALY gains from vitamin supplementation as a preventative measure appear small; however incremental costs are also relatively minor. In one-way sensitivity analysis, the model outputs were most sensitive to the cost of vitamin supplementation and the discount rate. Doubling vitamin costs from $114 to $228 increased discounted costs per person by $279 (with no corresponding increase in QALYs), resulting in an ICER of $61,683 per QALY. Using the minimum observed prices for vitamins resulted in a slight cost saving, making vitamin therapy dominant.

The analysis assumed that the effectiveness of the vitamin intervention persists over the course of the model, and thus beyond the timeframe of the AREDS evidence. If the effects of the vitamins do in fact wane over time, it is likely the model results would be less favourable for vitamin therapy. The analysis does not consider the impact of non-adherence on the effectiveness of the intervention, either in the base case or the sensitivity analyses.

J.2.1.2 Zeaxanthin supplementation

Olk et al. (2015) conducted an interventional comparative study and cost-effectiveness analysis of zeaxanthin supplement versus no supplement alongside triple combination therapy (PDT + bevacizumab + dexamethasone). The study enrolled 424 participants with 543 eyes with late AMD (wet active).

Patients with classic, minimally classic, and/or occult subfoveal CNV were enrolled. Only eyes with macular blood, sub retinal fluid, and/or retinal oedema with characteristic CNV findings confirmed by fluorescein angiography, optical coherence tomography (OCT) or indocyanine green angiography were included. Eyes with greater than 12 optic disc areas of CNV were excluded. Eyes with less than 20/400 vision were also excluded. The presence of blood was not an exclusion feature unless it covered greater than 12 disc areas.

Patients were treated initially with the consecutive triple therapy without zeaxanthin. Oral zeaxanthin was added to triple therapy on the basis of evidence suggesting its efficacy. Thus, the triple therapy with zeaxanthin cohort participants were all enrolled after the entire cohort without zeaxanthin had already been enrolled and had begun treatment. All patients took a multi-vitamin and an AREDS-I antioxidant regimen throughout the study.

The authors report that time-trade-off (TTO) utility values were used based on the work by Brown et al. (2003). The model runs over a 9-year timeframe, with a mean patient age at baseline of 81 years. It is assumed that zeaxanthin therapy is used continuously over the 9-year period and that its observed effectiveness in terms of categorical VA gains continues over that time, though this assumption is varied in a deterministic sensitivity analysis. Costs include treatment regimens, diagnostic and monitoring tests, ophthalmic evaluation and treatment administration appointments, all from the US healthcare system perspective. The model only considers the disutility associated with intravitreal injection discomfort (1 day) and a small (0.0002) QALY loss associated with the verteporfin infusion for PDT described by Brown (2007).

The model is presented as 3 sub-models based on the number of eyes in which disease occurs. A first-eye model considers that each patient receives therapy in 1 eye, and assumes that no information about the fellow eye is known or has any impact on quality of life or costs.

The second-eye model assumes that untreated disease has caused VA loss in the first-eye, and the disease has become active in the second eye. This approach recognises that the QALY losses of visual impairment in the both eyes are potentially greater than in unilateral disease. The model quantifies the effectiveness of zeaxanthin therapy added to triple therapy based on the interventional study data for quality of life, VA change and development of CNV in the fellow-eye.

Table 2: Olk et al. (2015) – base-case cost–utility results

Zeaxanthin daily + triple therapy	Incremental cost (compared with triple therapy)	Incremental QALY gain (compared with triple therapy)	ICER ($/QALY)
First-eye treated model	$859	0.115	$7,470
Second-eye treated model	$859	0.253	$3,395
Combined-eye model	$859	0.162	$5,302

The model was sensitive to assumptions around the treatment effect over time. The ICER for triple therapy with zeaxanthin ranged from $8,148 per QALY gained when zeaxanthin was used for only the first 2 years to $23,892 per QALY gained when zeaxanthin was used for 9 years, but was assumed to provide no health benefit after 2 years. An additional scenario analysis considered that triple therapy could incur an absolute risk reduction in CNV incidence of 30.3%, calculated by subtracting the 6.3% incidence of CNV in the cohort from the incidence of CNV in the treatment arms of the ANCHOR and MARINA trials. However, it may not be appropriate to combine these incidence rates in this way given the different study designs and protocols. This scenario leads to zeaxanthin dominating triple therapy alone.

J.3 Diagnosis, referral and monitoring

Review questions:

RQ4: What tools are useful for triage, diagnosis, informing treatment and determining management in people with suspected AMD?

RQ5: How do different organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow up influence outcomes for people with suspected AMD (for example correct diagnosis, errors in diagnosis, delays in diagnosis, process outcomes)?

RQ16: How do different organisational models for ongoing treatment and follow up influence outcomes for people with diagnosed neovascular AMD (for example disease progression, time to treatment, non-attendance)?

RQ23b: What strategies and tools are useful for monitoring for people with late AMD (wet active)?

Out of the 3,163 unique references retrieved, 1 reference was included that was relevant for review questions 4 (diagnosis), 23b (monitoring), and 5 and 16 (organisational models). These review questions were not prioritised for health economic modelling.

Mowatt et al. (2014) evaluated the cost effectiveness of a range of organisational models for diagnosing and monitoring neovascular age-related macular degeneration in an HTA systematic review and economic evaluation. The study followed the NICE guidelines for methods of technology appraisals in a Markov model with a 1-month cycle length and an NHS and personal social services (PSS) payer perspective. Costs and QALYs were discounted at 3.5% and uncertainty was explored through deterministic and probabilistic sensitivity analyses. The analysis included diagnostic strategies comprising the use of fundus fluorescein angiography (FFA), OCT, visual acuity (VA) and slit-lamp biomicroscopy (SLB), all interpreted by ophthalmologists to establish the presence or absence of AMD, with

subsequent treatment and monitoring or discharge. The accompanying monitoring strategies were: ophthalmologist interpretation of either (1) OCT alone or (2) VA with SLB and OCT, and (3) nurse- or technician-led OCT and VA with referral to an ophthalmologist for positive or unclear assessments. This third monitoring strategy was included to represent a 'virtual clinic', incorporating other health care professionals in the pathway. Combining diagnosis and monitoring strategies provided nine different organisational models with which to decide on either treatment (monthly ranibizumab injections) or monthly review. The models are summarised in Table 3.

Table 3: Mowatt et al. (2014) – diagnostic and monitoring strategies

Strategy	Diagnostic pathway	Monitoring pathway
FFA & OCT	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear review in 1 month
FFA & Ophthalmologist	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA
FFA & Nurse	FFA interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in a month time; if unclear, arrange for stereoscopic FFA
OCT & OCT	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologists). If positive, treat. If negative or unclear review in 1 month
OCT & Ophthalmologist	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA
OCT & Nurse	OCT alone interpreted by an ophthalmologist. If positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in a month's time; if unclear, arrange for stereoscopic FFA
Ophthalmologist & OCT	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	OCT alone (interpreted by an ophthalmologist). If positive, treat. If negative or unclear review in 1 month
Ophthalmologist & Ophthalmologist	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic	VA, SLB and OCT interpreted together by an ophthalmologist. If positive, treat; if negative, review in a month's time. If unclear, then the ophthalmologist will arrange for stereoscopic FFA

Strategy	Diagnostic pathway	Monitoring pathway
	FFA. If FFA positive, treat and monitor; if negative, discharge	
Ophthalmologist & Nurse	VA, OCT and SLB in all interpreted by an ophthalmologist. If negative, discharge. If positive or unclear, then arrange for stereoscopic FFA. If FFA positive, treat and monitor; if negative, discharge	VA and OCT interpreted by a technician or nurse. If negative, review in a month. If positive or unclear, referral for an ophthalmologist assessment (e.g. SLB and own interpretation of VA and OCT test results). If assessment positive, treat; if negative, review in 1 month; if unclear, arrange for stereoscopic FFA
Note: All patients with active disease at diagnosis/monitoring receive monthly anti-VEGF injection. *Key: FFA, fundus fluorescein angiography; OCT, optical coherence tomography; SLB, slit-lamp biomicroscopy; VA, best-corrected visual acuity.*		

The Markov structure is summarised in Figure 2. Imperfect information at diagnosis and monitoring phases was assumed where possible. OCT sensitivities and specificities were sourced from the authors' systematic review of the tests used in AMD, published in the same study. FFA was assumed to have perfect diagnostic accuracy. Other diagnostic accuracy parameters were obtained from expert opinion.

People who have a true-positive diagnosis in the first model cycle begin the next cycle in the active/treated state and then, conditional on their AMD status (active/inactive) and monitoring assessment, move to other states (e.g. inactive/untreated, inactive/treated, active/untreated). The model assumes that individuals who do not have AMD but subsequently develop active disease are detected by the assigned monitoring strategy. The model also incorporates a natural history of visual acuity change to reflect treatment-related and untreated AMD progression. Transition probabilities between VA states and active/inactive disease were sourced from the MARINA (Rosenfeld et al., 2006), CATT (Martin et al., 2012) and IVAN trials (Chakravarthy et al., 2012), respectively.

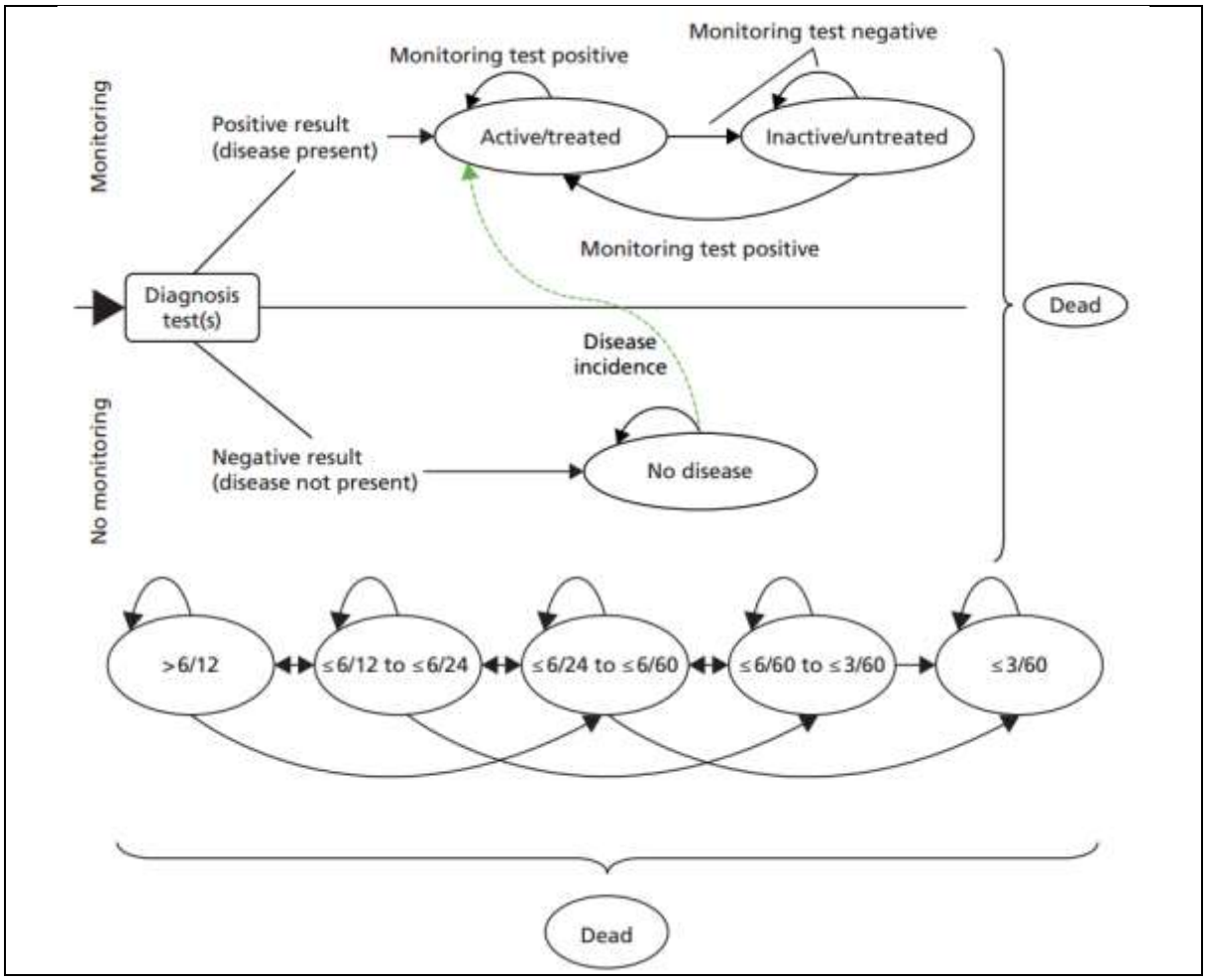


Figure 2: Mowatt et al. (2014) – model schematic

The model uses VA-dependent estimates of utility described by Brown et al. (2000, 2007) which are patient-preference based TTO values. In addition, the adverse event utilities for cataracts, endophthalmitis, glaucoma, retinal detachment and uveitis from Brown et al. (2007) were included, with probabilities of adverse events taken from the CATT study.

Costs of ophthalmologist and nurse visits, FFA, and OCT were sourced from NHS reference costs (2011–12). Treated patients were assumed to receive ranibizumab intravitreal injection at the list price taken from the BNF (issue 65). Costs of profound vision loss/blindness to the NHS & PSS were taken from Colquitt et al. (2008). The model was run with a male-only cohort, as life expectancy data were gender-specific. A sensitivity analysis was run to explore the impact of longer female life expectancy.

The base-case results are given in Table 4. The least costly organisational model is diagnosis using FFA followed by nurse or technician-led monitoring. Diagnosis based on FFA only, followed by ophthalmologist-led monitoring has higher total expected QALYs. However, the strategy is also associated with additional costs, with an incremental cost per QALY gained (ICER) of nearly £50,000. All other strategies were dominated (higher total costs and fewer QALYs) by at least 1 other option.

Table 4: Mowatt et al. (2014) – base-case model results

Strategy	Absolute		Incremental		
	Cost (£)	Effects (QALYs)	Cost (£)	Effects (QALYs)	ICER (£/QALY)
FFA & Nurse	39,769	10.473	-	-	-

Strategy	Absolute		Incremental		
	Cost (£)	Effects (QALYs)	Cost (£)	Effects (QALYs)	ICER (£/QALY)
Ophthalmologist & Nurse	39,790	10.472	21	-0.001	Dominated
OCT & Nurse	41,607	10.465	1838	-0.008	Dominated
FFA & Ophthalmologist	44,649	10.575	4880	0.102	47,768
Ophthalmologist & Ophthalmologist	44,669	10.574	20	-0.001	Dominated
OCT & Ophthalmologist	47,131	10.567	2482	-0.008	Dominated
FFA & OCT	62,759	10.449	18,110	-0.126	Dominated
Ophthalmologist & OCT	62,778	10.449	18,129	-0.126	Dominated
OCT & OCT	67,421	10.442	22,772	-0.133	Dominated

NB: Incremental values compared to last non-dominated treatment option.
Key: FFA, fundus fluorescein angiography; OCT, optical coherence tomography; SLB, sit-lamp biomicroscopy; VA, best-corrected visual acuity.

When plotted on the cost–utility plane of expected costs vs. expected QALYs (Figure 3), the results are clearly clustered according to the 3 monitoring strategies. Ophthalmologist-led monitoring clusters at higher expected QALYs and somewhat higher expected costs than nurse/technician-led monitoring. OCT-only monitoring clusters at higher expected costs and lower expected QALYs than the other 2 monitoring strategies.

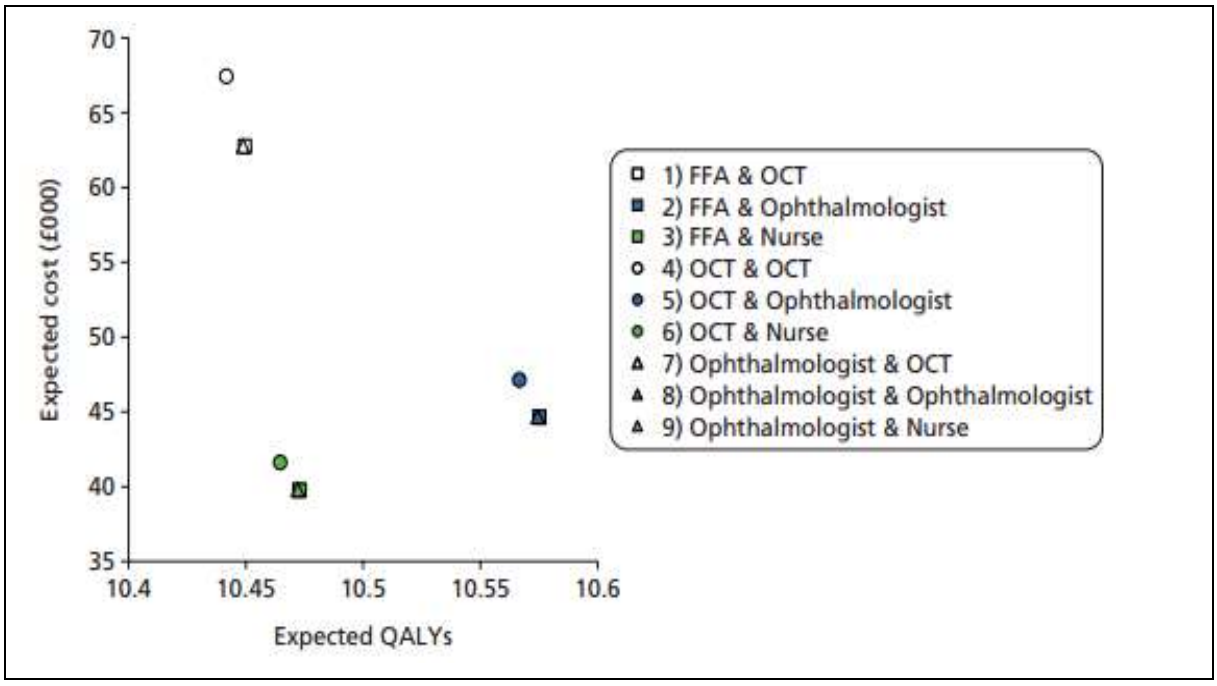


Figure 3: Mowatt et al. (2014) – base-case cost-effectiveness results

A deterministic sensitivity analysis incorporating longer female life-expectancy resulted in more QALYs and higher costs on average, but did not change overall cost effectiveness findings or the ranking of strategies. A probabilistic sensitivity analysis (PSA) was also conducted to explore parameter uncertainty. At a threshold of £20,000 per QALY, FFA followed by nurse-led monitoring has a 57.4% chance of being the optimal organisational model. The next most cost-effective model, FFA followed by ophthalmologist monitoring, has a 21.8% probability of being optimal at the same threshold. Only at QALY values above £50,000 does the FFA then ophthalmologist monitoring strategy become the most likely to be optimal.

The authors note that their economic evaluation was based on limited evidence, particularly on the relative accuracy of OCT compared with FFA. Although OCT sensitivity and specificity data were retrieved from a systematic review of the literature, no such data were available for other tests such that expert opinion was used in place of real data. It is also acknowledged that the modelling of a single eye without consideration of fellow eye status introduces uncertainty to the assessment of strategies that would, in many cases, have implications for both eyes of a patient.

J.4 Pharmacological management

J.4.1 Anti-angiogenic therapies and frequency of administration

Review questions:

RQ 12: What is the effectiveness of different anti-angiogenic therapies (including photodynamic therapy) for the treatment of neovascular AMD?

RQ 18: What is the effectiveness of different frequencies of administration for anti-VEGF regimens for the treatment of neovascular AMD?

Of the 3,163 unique references retrieved, 77 references were included for full-text review for these review questions, and 22 were retained. NICE technology appraisals (TAs) evaluating the use of anti-VEGF therapies and/or PDT were also reviewed in order to identify any cost–utility evidence not captured in peer-reviewed journals.

J.4.1.1 Anti-VEGF studies

Colquitt et al. (2008)

Colquitt et al. (2008) published an economic evaluation and systematic review of ranibizumab and pegaptanib for the treatment of AMD, which served as the Evidence Review Group (ERG) report alongside the NICE TA of the same medicines. The model compares each treatment option with PDT and best supportive care (BSC). Since pegaptanib sodium is no longer used or typically available in the NHS, and is not included in the network meta-analysis developed for our analysis, this review focuses only their evaluation of the cost-effectiveness of ranibizumab compared with PDT and BSC.

The model describes a cohort of patients transitioning between better-seeing eye (BSE) visual acuity states from 6/12 to 3/60 over quarterly cycles (Figure 4). The model uses two time horizons: the first reflecting the 1 or 2 year periods of the clinical trials, and the second a 10-year horizon examining the benefits of treatment beyond the trials, accounting for the majority of remaining life expectancy in a cohort with a mean age of 75 years. The model allows for transitions to occur by VA change, with a maximum possible transition of two VA-related health states in either direction per cycle. The effectiveness of ranibizumab was based on data extracted from 3 clinical trials, stratified by AMD subtype (lesion type). The MARINA trial was used for patients with minimally classic or occult lesions; the ANCHOR trial for patients with predominantly classic lesions. The PIER trial (unpublished at the time of the study), comparing reduced frequency regimen of 0.3 mg and 0.5 mg ranibizumab in patients regardless of lesion type, was also used. In the 10-year analysis, it was assumed that the progression of AMD in the treated cohort would be the same as the BSC cohort following treatment discontinuation at 1 or 2 years.

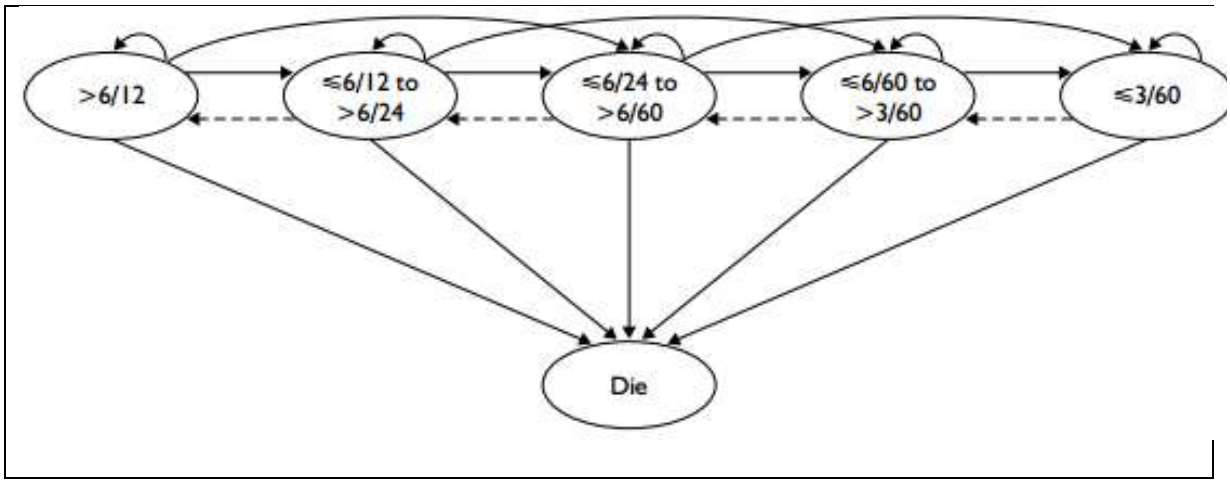


Figure 4: Markov model developed by Colquitt et al. 2008

In addition to the VA-related health states, the model also incorporates a per-cycle probability of adverse events when injections occur (i.e. during the first 2 years of the model, assuming VA remains above 6/12). Adverse events were informed by the ANCHOR and MARINA trials: endophthalmitis, traumatic lens injury, retinal detachment, uveitis, lens damage and retinal tears. The model assumes a 50% higher mortality rate for patients with VA worse than 6/60.

Health state utilities adopted in the model were from the TTO study by Brown et al. (2000), estimated in 72 consecutive patients 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. Patients were asked how many years of their remaining life expectancy they would be prepared to forego to receive a technology that would guarantee permanent perfect vision in each eye. Colquitt et al. note that there is limited evidence on health state utilities in AMD and the majority of published valuations are from the same group of authors.

The cost perspective was the NHS and PSS, as per the NICE reference case. Costs were derived following a consultation with expert ophthalmologists and specialists at Southampton General Hospital Trust on resource use associated with treatment. Unit costs were then applied using NHS Reference Costs. OCT and FFA costs were used for diagnosis and monitoring and that injections were assumed to occur at one-stop clinics, costed as an extended outpatient appointment. Treatment was assumed to occur monthly as per the trials, and was in 1 eye only, with a maximum of 24 injections over 2 years. Costs of managing treatment-related adverse events were included based on practice guidelines. The model also includes costs associated with low vision, taken from the study by Meads et al. (2003). The model used the BNF list price for ranibizumab.

Table 5: Base-case model results from Colquitt et al. 2008

Treatment	Cost	Life-years	Vision-years	QALYs	ICER
Predominantly classic: ANCHOR. PDT as comparator (1-year)					
PDT	4,182	0.98	0.94	0.77	
Ranibizumab	12,427	0.99	0.98	0.81	202,450
Predominantly classic: ANCHOR. PDT as comparator (10-years)					
PDT	21,498	6.43	2.88	3.81	
Ranibizumab	26,888	6.51	3.59	4.15	15,638
Predominantly classic: ANCHOR. BSC as comparator (1-year)					
BSC	933	0.98	0.85	0.74	
Ranibizumab	12,427	0.99	0.98	0.81	160,181
Predominantly classic: ANCHOR. BSC as comparator (10-years)					

BSC	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. BSC as comparator (2-years)					
BSC	1,541	1.89	1.64	1.40	
Ranibizumab	23,902	1.90	1.87	1.54	152,464
Minimally classic and occult (no classic). MARINA. BSC as comparator (10-years)					
BSC	13,787	6.52	3.78	4.10	
Ranibizumab	31,096	6.67	5.19	4.79	25,098

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PDT, photodynamic therapy; QALYs, quality-adjusted life years.

The base-case results are presented in Table 5. Results are presented for a 1 or 2 year time horizon informed by the trial data used and a 10-year time horizon. The 2-year time horizon effectively ignores any life-long benefits of treatment and minimises the impact of discounting. It assumes by design that people only benefit while on treatment and that treatment stopping results in a rapid decline to the natural history state of AMD that would have prevailed having never received treatment. The 10-year time horizon includes the 2-year treatment costs and also longer term savings in costs associated with low vision. The difference between low vision costs in the ranibizumab and comparator cohorts at 10 years does not fully offset the costs of treatment with ranibizumab. However, the increased proportion of total costs accounted for by visual impairment and low vision over time, and the associated QALY gain, yield lower ICERs.

Deterministic sensitivity analysis suggests that ICERs are less favourable for older patients, though poorer initial VA had little effect on cost-effectiveness estimates. Costing the injection procedure as a day case rather than an outpatient procedure caused large increases in the ranibizumab ICER (which for patients with predominantly classic lesions increased to £26,102 for the comparison with PDT and £17,787 for the comparison with BSC, and for patients with minimally classic and occult no classic lesions the ICER increased to £35,157). The ICER is also sensitive to the choice of utility values and the cost of low vision. PSA shows a 72% probability of ranibizumab being cost-effective for patients with predominantly classic lesions (compared with PDT) at a QALY value of £20,000, and 97% at a QALY value of £30,000. For the comparison with BSC, the equivalent figures are 95% and 99%, respectively. For patients with minimally classic and occult (no classic) lesions, 15% of probabilistic analyses had an ICER of less than £20,000 per QALY and 81% were less than £30,000 per QALY.

Following the publication of the Colquitt et al. analysis, the same model framework has been updated with local costings from Spain (Hernandez-Pastor et al. 2008), Greece (Athanasakis et al. 2012) and Germany (Neubauer et al. 2010), yielding with similar conclusions favouring ranibizumab at 10-year time horizons. An HTA monograph of aflibercept treatment for AMD based on the ERG report from NICE TA 294 is in progress.

Claxton et al. (2016)

Claxton et al. (2016) developed a two-eye patient-level simulation model for the treatment of wet AMD. The primary objective of the study was to present the feasibility of patient simulation modelling in AMD, where the majority of previous models are Markov models. However, the backdrop to this objective was a CUA comparing pro re nata (PRN) aflibercept with ranibizumab injections. In their model, a simulated patient first received 1 treatment and experienced their individual journey through the model, then returned to the start and received the other treatment.

Baseline patient characteristics were obtained from the EXCITE study, a trial of alternative ranibizumab regimens (mean age 76 years; mean VA of 56 letters and 55 letters; 18.5% of patients with bilateral wet AMD). Clinical effectiveness evidence from baseline to year 2 was

obtained from the IVAN trial for ranibizumab, and the relative effectiveness of aflibercept was informed by a NMA (with the aflibercept comparison informed by the VIEW study). The primary effectiveness outcome was the mean change in VA over 2 years, from which the authors estimated monthly VA change. Monthly VA change was assumed to be normally distributed, with treated patients experiencing a random draw from the distribution each month, independent of previous months.

Treatment was discontinued in the first 2 years if the VA of an eye dropped below 35 letters, or according to trial discontinuation data (aflibercept 0.68% per month [VIEW], ranibizumab 0.41% per month [IVAN]). Treatment was permitted for a maximum of 5 years, with the VA of treated eyes assumed to stay at a constant level between month 24 and month 60. Trial discontinuation probabilities remained constant during this time. After discontinuation, the VA of an eye progressed based on natural history data. Unaffected fellow eyes experienced normal vision loss, but could develop neovascular AMD at any time (0.8% to 1.4% probability per month). The model had a lifetime horizon. Mortality was informed by UK national life tables, with increased mortality for people with visual impairment (Christ et al. 2008).

Quality of life was informed by 5 regression models from a simulation contact lens study (Czoski-Murray et al. 2009): utility as a function of the BSE only, the worse-seeing eye (WSE) only, both eyes separately, both eyes with an interaction term, and with a coefficient for blindness. Resource use and costs were modelled from an NHS and PSS perspective (2014 prices), including drug costs, outpatient administration, OCT monitoring, and low vision (informed by Meads et al. [2003]). Adverse events were not included. Costs and outcomes were discounted at a rate of 3.5% per year.

The base-case model simulated 200,000 patients. The PSA simulated 10,000 patients each with 100 sets of sampled model input parameters. In both the base-case and probabilistic analyses, ranibizumab PRN was associated with lower total costs and higher QALYs than aflibercept PRN, regardless of which of the 5 utility regression models was used (Table 6). Base-case QALYs using the 2-eye utility models ranged from 5.009 to 5.165 for ranibizumab and 4.968 to 5.122 for aflibercept. Incremental costs remained close to £31,400 per patient on ranibizumab and £39,700 per patient on aflibercept. Probabilistic analyses showed the differences in costs and QALYs between treatments to be statistically significant. Ranibizumab had a probability in excess of 95% of being considered cost-effective, compared with aflibercept, at all QALY valuations.

Table 6: Base-case and probabilistic model results from Claxton et al. 2016

Utility model used	Mean cost (2014£)		Incremental cost (95% CI)	Mean QALYs		Incremental QALYs (95% CI)
	Rani.	Aflib.		Rani.	Aflib.	
Base-case analysis						
BSE only	31,361	39,745	-8384	5.772	5.728	0.044
WSE only	31,362	39,736	-8374	4.406	4.364	0.042
2 eyes, no interaction	31,351	39,700	-8349	5.165	5.122	0.043
2 eyes, with interaction	31,386	39,746	-8360	5.085	5.044	0.041
2 eyes, with blindness term	31,366	39,713	-8347	5.009	4.968	0.041
Probabilistic analysis						
BSE only	32,450	39,597	-7168 (-7669 to -6667)	5.739	5.693	0.046 (0.038—0.065)
WSE only	32,539	39,563	-7016 (-7492 to -6540)	4.460	4.424	0.035 (0.027—0.043)
2 eyes, no interaction	32,732	39,577	-6846 (-7273 to -6419)	5.158	5.109	0.049 (0.040—0.057)

2 eyes, with interaction	33,270	40,071	-6811 (-7244 to -6379)	5.096	5.057	0.039 (0.029—0.049)
2 eyes, with blindness term	33,116	39,172	-6051 (-6474 to -5628)	5.160	5.122	0.039 (0.029—0.049)

Key: Aflib, aflibercept; BSE, better-seeing eye; QALYs, quality-adjusted life years; Rani, ranibizumab; WSE, worse-seeing eye.

Dakin et al. (2014)

Dakin et al. (2014) conducted a within-trial cost–utility analysis alongside the IVAN study. The analysis compared 0.5 mg ranibizumab with 1.25 mg bevacizumab, both as continuous monthly and PRN regimens. The model drew on trial data from 610 patients aged ≥50 years with untreated AMD in one eye, across 23 secondary care ophthalmology clinics in England. The time horizon was 2 years, matching the trial follow-up duration. PRN dosing consisted of a loading phase of monthly injections for 3 months, followed by further courses of the same duration if monitoring indicated a need for retreatment. To account for interactions within a factorial trial design (i.e. differences in costs and/or quality of life between ranibizumab and bevacizumab according to treatment regimen), mean costs and QALYs were reported for four pairwise comparisons, comprising each combination bevacizumab or ranibizumab and continuous or discontinuous (PRN) treatment.

The main driver of cost-effectiveness between the 2 interventions was assumed to be the price differential, therefore a cost-minimisation approach was proposed unless the magnitude of QALY gain for ranibizumab treated patients was 0.05 or more QALYs. The cost difference between continuous and PRN treatment was anticipated to be smaller, therefore a cost–utility analysis was used for this comparison.

Costs were from the NHS perspective, with standard reference costs used for OCT and FFA imaging and a microcosting approach for the costs of injection and monitoring consultations (based on surveys of 13 trial centres). Staff, clinic overheads, facility and equipment costs were also derived from the surveys. The ranibizumab price reflected the BNF list price (2011), and the price of bevacizumab was obtained from the within-trial provider. Resource use data and unit costs were combined to estimate quarterly costs of drug acquisition and administration, monitoring consultations, and hospitalisations, ambulatory consultations and medication changes for serious adverse events.

Adverse events were categorically subdivided using a mixed model approach, with model selection based on Akaike's Information Criterion resulting in four categories of event:

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

Mixed models were also used to estimate the time over which utility decrements due to serious adverse events occurred, and generate linear slopes of recovery of EQ-5D utility following an adverse event. This approach allowed for the inclusion of sequential adverse events, which were rare in the trial but did occur for some patients.

Total costs and QALYs for each participant were combined using linear regression models to estimate mean totals in each study arm. In the base-case model, there were no statistically significant differences in QALY outcomes for patients in any of the 4 arms. However, drug costs differed substantially between the continuous and discontinuous treatment arms as a

consequence of the different number of injection over 2 years (means of 22 and 13 injections on continuous treatment and PRN respectively). Although continuous treatment required 6 fewer monitoring visits than PRN, drug administration and monitoring costs were higher with continuous treatment (mean difference: £130 per patient), with no significant difference between ranibizumab and bevacizumab. Overall, continuous ranibizumab cost £14,989 per patient more than continuous bevacizumab over the 2-year trial period. The model predicted that switching from ranibizumab to bevacizumab would have a ≥99.9% probability of being cost saving.

Table 7: Total costs, QALYs and Net benefits for each comparator in Dakin et al

Strategy	Total costs	Total QALYs	Total net benefits
PRN bevacizumab	£3002 (2601 to £3403)	1.584 (1.538 to 1.630)	£28,683 (£27,707 to £29,658)
Continuous bevacizumab	£3601 (£3259 to £3943)	1.604 (1.563 to 1.845)	£28,480 (£27,548 to £29,412)
PRN RBZ	£11,500 (£10,798 to £12,202)	1.582 (1.530 to 1.634)	£20,142 (£18,963 to £21,321)
Continuous ranibizumab	£18,590 (£18,258 to £18,922)	1.608 (1.565 to 1.651)	£13,576 (£12,769 to £14,383)
Difference: rani. vs. beva.	Continuous £14,989 (£14,522 to £15,546) Discontinuous £8,498 (£7,700-£9,295)	Continuous: 0.004 (-0.046 to 0.054) Discontinuous: -0.002 (-0.064 to 0.060)	Continuous -£14,904 (-£15,995 to -£13,813) Discontinuous -£8541 (-£9939 to -£7144)
Difference: PRN vs. Continuous	Rani.£7,090 (£6,337 to £7,844) Beva. £599 (£91 to £107)	Rani. 0.026 (-0.032 to 0.085) Beva. 0.020 (-0.032 to 0.071)	Rani. -£6566 (-£7861 to -£5271) Beva. -£203 (-£1372 to £967)

Key: Beva, bevacizumab; PRN, pro re nata (treat as needed); QALYs, quality-adjusted life years; Rani, ranibizumab.

Sensitivity analyses suggested that the model was robust to deterministic variation in parameter estimates. However, assuming that FFA is only conducted at baseline and not at any subsequent monitoring consultation; measuring quality of life using the Health Utilities Index (HUI-3) rather than EQ-5D; and using unadjusted Kaplan-Meier estimates of the probability of surviving at any point in time to account for censoring, rather than excluding differences in deaths that were unrelated to study medication, changed the conclusion that continuous bevacizumab is not cost-effective compared with PRN bevacizumab. A threshold analysis of cost suggested that ranibizumab would need to be discounted by 91% of its list-price to become a cost-effective treatment option.

Elshout et al. (2014)

Elshout et al. (2014) evaluated the cost-effectiveness of aflibercept, ranibizumab and bevacizumab for the treatment of neovascular AMD. A patient-level, VA-based, 2-eye model was developed. Data on effectiveness were derived from RCTs (CATT, MARINA). Utility and resource utilisation were assessed in interviews with AMD patients and clinical experts. Costs were based on standard health care cost prices in the Netherlands. Time horizons were 2 years for the analysis based on trial data and 5 years in a scenario analysis extrapolating from the 2-year data. A societal perspective was employed, with costs discounted at 4% per annum, and benefits at 1.5% in accordance with Dutch standards for cost-effectiveness analysis.

Utility values were informed by an unpublished cross-sectional study by the authors in which 184 patients in Eindhoven with AMD were asked to complete the HUI-3 questionnaire. The results of this study were used to generate a linear regression model between HUI-3 scores

and utility so that for each Early Treatment Diabetic Retinopathy Study (ETDRS) letter lost a utility loss could be derived. Utility was based upon the BSE only, although the model does allow for the development and treatment of AMD in the fellow-eye. Baseline VA was calculated from the trials, with fellow-eye acuities derived stochastically using an assumed triangular distribution based on the VA of eyes in the general population. The rate of AMD development in fellow-eyes was derived from a systematic review of AMD natural history and parameterised at 5% per annum (Wong et al. 2008)

The model included costs of medical visits, OCT and FFA imaging, fundus photography, drug costs per injection and also costs for ocular adverse events (endophthalmitis, retinal detachment, lens injury and bleeding). Low vision aids, low vision service provision and the cost of patients moving house as a result of their AMD (it is not clear how this was derived) are included and apportioned to visual acuity states.

Table 8: Base-case results from Elshout et al. 2014

Treatment	Schedule	Study	2 years		5 years	
			QALYs	Cost	QALYs	Cost
Aflibercept	1x/2 months	VIEW 1&2	1.02	17,963	2.15	36,030
Bevacizumab	PRN	ABC	1.01	8,427	2.16	19,367
		CATT	1.02	12,664	2.17	26,746
	1x/month	CATT	1.01	13,021	2.15	30,520
Ranibizumab	PRN	CATT	1.01	19,919	2.16	45,491
	1x/month	MARINA	1.01	31,706	2.15	74,837
No treatment	-	Review of literature	0.96	3,298	1.96	9,530

Key: PRN, pro re nata (treat as needed); QALYs, quality-adjusted life years.

Cost–utility ratios (not shown) were calculated for each strategy relative to providing no treatment. The authors concluded that there was little difference in the QALY gains across treatment options, but substantial differences in costs. The reduced frequency of injections reduces the costs of aflibercept compared to ranibizumab. The treatment interval between aflibercept injections would need be 15-38 weeks in order for its costs to approximate PRN bevacizumab.

Fletcher et al. (2008)

Fletcher et al. (2008) present a simple decision tree model to estimate the cost–utility of treating wet AMD with each of ranibizumab, PDT and pegaptanib compared with BSC. The analysis was in a US setting. The effectiveness of each treatment over 2 years was derived from categorical VA gains and losses reported in clinical trials (ranibizumab: MARINA and PIER; PDT: TAP; pegaptanib: VISION; BSC: TAP). Utility values associated with BSE VA were estimated using a regression analysis from a previous TTO study (Sharma et al. 2000). Disutilities were also included for adverse events associated with treatment. Costs included investigations, treatments and monitoring ('Current Procedural Terminology' standard prices) and low vision (Meads et al. 2003). Administration costs were excluded, assumed to be equivalent across treatments. BSC was assumed to incur the cost of an initial investigation followed by quarterly monitoring. Outcomes in year 2 were not discounted.

ICERs were reported for each intervention relative to BSC, with no fully incremental analysis. No total or incremental cost or QALY results were presented. In the main scenario – treated eye with VA of 53 letters, fellow eye with VA of 0 letters – ranibizumab delivered by the regimen in the PIER study has the lowest ICER ($626,938 per QALY). The PIER study regimen is a 3-month loading phase then treatment once every 3 months. The authors cite a US cost-effectiveness threshold of $50,000 per QALY. An analysis simulating bevacizumab,

by assuming a $50 treatment cost, equal effectiveness and disutility in 2% of patients due to thromboembolic adverse events, the ICER is $104,748 per QALY compared with BSC.

ICERs were not reported for alternative scenarios designed to reflect different presenting eyes and baseline VA levels. It appears the same VA gain or decline is assumed to apply regardless of the level of baseline VA. The authors do state that it is not cost effective to treat an eye that is significantly worse-seeing than its fellow eye. No analysis of parameter uncertainty is reported.

Ghosh et al. (2016)

Ghosh et al. (2016) developed a 2-eye, individual patient model to evaluate the cost-effectiveness of ranibizumab compared with aflibercept, where ranibizumab is given in a "treat and extend" protocol (TREX). TREX regimens involve treating patients on a monthly basis until disease activity is determined to be no longer detectable, at which point the retreatment interval is increased by 2-week steps. This extension is reversed if VA declines or disease activity is detected. Unlike a PRN regimen, patients are not required to undergo monitoring visits between treatments, which may reduce costs and improve capacity at eye clinics as the treatment interval lengthens for some patients.

The authors developed a NMA of randomised controlled trials to parameterise the relative effectiveness of ranibizumab TREX and aflibercept. Adverse events were not included in the model, based on the similarity in adverse event rates observed in the VIEW trials. Mean monthly VA change for ranibizumab TREX was modelled stochastically using its mean effectiveness relative to ranibizumab PRN from the NMA, and the mean monthly VA for ranibizumab PRN was estimated stochastically using data from the IVAN trial. Mean monthly VA change for aflibercept was then estimated stochastically using the relative effectiveness of ranibizumab TREX versus aflibercept, with the distribution derived from the NMA. This means that the VA change over time is modelled as a continuous variable, as opposed to being represented as a series of categorical "states" as Markov models have typically done previously.

In the base-case analysis, patients are treated for up to 2 years in accordance with the trial data. Post-treatment discontinuation VA change was derived from 2 studies of healthy adult eyes (Elliott et al. 1995, Frisen and Elliott et al. 1981). The cost perspective was the NHS and PSS. The number of treatments and monitoring visits were taken from the costing templates for NICE TA 294 for aflibercept, and from the LUCAS trial for TREX ranibizumab. Resource use costs were taken from NHS Reference Costs for the treatment procedure, OCT scan, and outpatient consultant-led ophthalmology clinic follow-up. Costs of low vision described by Meads et al. (2003) were applied as in other models. The base-case analysis assumed all patients were treated in 1-stop clinics. Treatment was terminated if VA in any treated eye fell to <35 ETDRS letters.

Utilities were modelled based on the regression model developed using simulation contact lenses described by Czoski-Murray et al. (2009), assuming a correlation between eyes and considering health-related quality of life (HRQL) to be dependent on the VA of both eyes. A hazard ratio was applied to background mortality rates to model increased premature death in patients with low vision.

Table 9: Base-case results from Ghosh et al. 2016

Treatment	Total Costs	Total QALYs	Incremental Costs	Incremental QALYs	ICER
Ranibizumab TREX	£29,282	4.69	-£19,604	1.058	-

Aflibercept	£48,887	3.63	-	-	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adjusted life years.					

Several scenario analyses were undertaken. Varying the proportion of patients attending 1-stop vs. 2-stop treatment clinics, the discount rate applied to the treatments, the number of injection and monitoring visits, the baseline VA, and the treatment duration all resulted in ranibizumab TREX dominating aflibercept. Removing low vision costs resulted in an ICER of £1,417 per QALY gained, and setting the relative effectiveness to zero gave an ICER of £1,168, or £4,911 if the list price of aflibercept is reduced by 50%.

Hurley et al. (2008)

Hurley et al. (2008) evaluated the cost-effectiveness of ranibizumab in the Australian health care system, with particular focus on the impact of therapeutic assumptions in the post-treatment phase. A single-eye model was developed in which the BSE was treated. In the base-case scenario, ranibizumab effectiveness observed in the 2-year MARINA trial (0.5 mg arm) was assumed to apply for the first 4 years after starting treatment, with patients experiencing VA decline from years 5 to 10, parameterised by studies of geographic atrophy progression. A further scenario in which the treatment effect is assumed to be sustained after treatment discontinuation (i.e. patients maintain their VA until death), and another in which the treatment effect is assumed to decline each year after discontinuation, are also considered and are described in Table 10.

Table 10: Scenarios used in Hurley et al. (2008)

Settings	Base-case scenario	Sustained effect Scenario	Non-Sustained effect scenario	No treatment
Years 1 & 2	Results of MARINA 0.5 mg arm	As for base-case	As for base-case	Results of MARINA, sham arm
Years 3 & 4	Year 2 MARINA data, 0.5 mg ranibizumab arm.	As for base-case	Year 2 MARINA data, sham arm	Year 2 data from MARINA, sham arm
Years 5 to 10	Year 5 to 10 progression rates of the geographic atrophy form of age-related macular degeneration	No further transitions (neither increasing nor decreasing visual acuity)	Year 2 MARINA data, sham arm, progression rates decreasing by 40% each year	Year 2 MARINA data, sham arm, progression rates decreasing by 40% each year
Ranibizumab dosing regimen	One dose monthly for the first 2 years, then every 3 months until end of Year 4. No ranibizumab thereafter.	Three doses at monthly intervals, then every 3 months until the end of Year 2. No ranibizumab thereafter.	One dose monthly for the first 2 years. No ranibizumab thereafter.	N/A

The model incorporates 2 prices for ranibizumab: the wholesale acquisition price of $1,950 (US) and the estimated price of an aliquoted dose of bevacizumab set at $50 (Steinbrook, 2006). A fixed administration cost, assumed to be $250, was added to drug costs. Other costs in the model were categorised as: medical care directly relating to AMD, non-eye related medical care, and caregiver costs. Clinical costs and resource use were calculated based on the average annual cost per patient with neovascular AMD not treated with PDT in Medicare data (n = 6,558). Non-eye related costs were based on the excess annual medical costs that could be attributed to VA loss in a cohort of 24,000 Medicare recipients. Caregiver costs were based on a study by Schmier et al. (2006) which assessed the patient-reported

use of caregiving at different levels of VA, using the AMD Health and Impact Questionnaire and the Daily Living Tasks Dependent on Vision Questionnaire in a sample of 803 AMD patients. Annual costs for caregiving ranged from $225 to $47,086 depending on VA.

Table 11: Base-case results from Hurley et al. (2008)

Scenario	Ranibizumab treatment	No ranibizumab treatment	Incremental Cost	ICER
Base-Case				
Ranibizumab (list price)	205,800	238,00	-32,500	Dominant
Ranibizumab (bevacizumab price)	147,100	238,300	-91,100	Dominant
Sustained effect scenario				
Ranibizumab (list price)	144,400	238,300	-93,800	Dominant
Ranibizumab (bevacizumab price)	125,500	238,300	-112,700	Dominant
Non-Sustained effect scenario				
Ranibizumab (list price)	209,800	238,300	-28,500	Dominant
Ranibizumab (bevacizumab price)	164,800	238,300	-73,500	Dominant

Key: QALY, quality-adjusted life year.

The ICER results in Table 11 were sensitive to the inclusion or exclusion of caregiver costs. Excluding caregiver costs results in ICERs of $91,900 (list price) and $5,600 (bevacizumab price) in the base-case; $20,300 in the sustained effect scenario (wholesale price – if the price is that of bevacizumab it remains dominant); and $86,900 (list price) and $5,000 (bevacizumab price) in the non-sustained-effect scenario. A deterministic sensitivity analysis showed that, when caregiver costs were included, ranibizumab was cost-saving beyond 6 years, even at the wholesale price. Ranibizumab reached a threshold cost-effectiveness of $50,000 per QALY at about $1,000 per dose over 10-years, $300 per dose over 4-years and just less than $50 over a 2-year time horizon.

Panchmatia et al. (2016)

Panchmatia et al. (2016) developed a 2-eye cost–utility model to compare aflibercept (2 mg), delivered every 8 weeks following a 3-month loading phase, with ranibizumab regimens. The Markov state-transition model consisted of 5 VA-related health states (>80 letters; 65-79; 50-64; 20-49; and <20), and a death state. Baseline data were obtained from the VIEW trials. Treatments were given to the BSE for up to 2 years, however a lifetime horizon was taken for a cohort with mean age 77 years. Patients were able to discontinue treatment due to VA decline and due to non-adherence. After discontinuation due to this or reaching 2 years, vision loss was assumed equal to natural history. While receiving treatment, transition probabilities were informed by the VIEW trial data (for aflibercept, and for ranibizumab monthly for 1 year followed by PRN). Transition probabilities for patients on ranibizumab PRN (following a 3-month loading phase) were informed by observational data from the Swedish Macular Registry. A further scenario was explored, using data from the CATT study, to explore the relative cost-effectiveness of ranibizumab given by the regimen used in CATT.

Direct costs were included for treatment, administration, monitoring, low vision and endophthalmitis. Endophthalmitis was the only adverse event included, based on discussions with local clinical experts. A partial societal perspective was taken, with the inclusion of the cost of carers' time spent accompanying people to hospital. Costs were presented in 2012 Swedish Krona. Utility weights were informed by the Czoski-Murray et al. (2009) regression model. All outcomes were discounted at a rate of 3% per year.

Table 12: Base-case results from Panchmatia et al. 2016

Treatment	Total Costs, SEK [£]	Total QALYs	ICER, SEK [£]
Ranibizumab PRN	573,570 [£51,218]	4.41	
Aflibercept	578,360 [£51,646]	4.58	26,787 [£2,392]
Monthly ranibizumab (VIEW)	686,598 [£61,326]	4.59	20.4m [£1.81m]

Note: Estimates in pounds sterling provided to aid interpretation of SEK costs. Conversion is an estimate using the spot exchange rate as of 7 November 2016.
Key: ICER, incremental cost-effectiveness ratio; PRN, pro re nata (treat as needed); QALYs, quality-adjusted life years; SEK, Swedish Krona.

Several scenario analyses were undertaken. Aflibercept was reported to dominate a strategy of treating with ranibizumab as per the CATT study regimen. Varying the estimates of aflibercept effectiveness in 1-way sensitivity analysis saw the aflibercept ICER vs. ranibizumab range from dominating to 160,000 SEK. The ICER was also sensitive to the number of injections given on ranibizumab PRN. PSA suggested that aflibercept had an ICER of less than 500,000 SEK per QALY gained compared with both ranibizumab regimens.

Patel at al. (2012)

Patel et al. (2012) undertook a cost–utility analysis using a single-eye Markov model to evaluate the cost-effectiveness of bevacizumab and ranibizumab from a US payer perspective. Rather than using a matrix of states defined by VA, the model had a simplified structure with 4 states: “stable vision”, “worsening vision”, “vision improvement” and death. Transition probabilities between states were derived from the effectiveness data reported in ANCHOR and MARINA for ranibizumab, and observational studies and the Veterans Affairs San Diego Healthcare System (VASDHS) for bevacizumab. Although the clinical evidence used to parameterise effectiveness contained a mixture of PRN and continuous treatment, all patients in the model were assumed to receive continuous monthly injections. The transition probabilities for the bevacizumab arm were derived by weighting the mean averages of clinical probabilities of gaining or losing *n* lines of visual acuity.

Resource utilisation and direct costs were estimated using the ‘Centers for Medicare and Medicaid Services and the Veterans Affairs’ Decision Support System. Costs comprised appointments, imaging (OCT, FFA and fundus photographs), prophylactic antibiotics, and drug acqusition, for treatment of the BSE only. Utility values were informed by Brown et al. (2000), condensed in order to fit the chosen model tructure. It is not clear how the utility weights map on to model states that describe a general directional change in VA, rather than an explicit level of VA. A hypothetical cohort of 1,000 patients was simulated through the model for 20 years. Univariate and probabilistic sensitivity analysis were performed on all costs, transition probabilities and utility values.

Table 13: Base-Case results from Patel et al. 2012

Treatment	Basic		Incremental		ICER
	Cost	QALY	Cost	QALY	
Bevacizumab	$30,349	21.60	-	-	Dominant
Ranibizumab	$220,649		$190,300	-3.48	Dominated

Key: ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life year.

Bevacizumab was found to be dominant compared with ranibizumab. The base-case ICER was sensitive to the cost of study medications, with break-even points of $44 for ranibizumab

and $2,666 for bevacizumab. PSA revealed a 95% probability of bevacizumab being more cost-effective than ranibizumab at a value of $50,000 per QALY.

Raftery et al. (2007)

Raftery et al. (2007) adapted previous models that were developed to explore the cost-effectiveness of PDT to do the same for treatment with either ranibizumab or bevacizumab. The single-eye model uses VA-defined states, with utilities derived from Brown et al. (2000). Patients entered the 10-year model at 75 years of age. They started in the second-least severe state to allow improvement in VA to occur. Two groups of patients were modelled; those gaining and those losing VA, based on data from licensing trials. Treatment was administered to the BSE. Treatment frequency was also based on the licencing trials, with treatment duration dependent on the subtype of neovascular AMD: monthly treatment was given for 1 year in the cohort with predominantly classic disease, and for 2 years in minimally classic and occult cases. After treatment, disease progression for untreated patients was applied. The most severe states (visual acuity worse than 6/60) had an annual cost based on the cost of severe vision loss. Patient mortality reflected UK averages for the relevant ages, with a 50% increased mortality risk assumed for the worst VA states. The model simulated a hypothetical cohort of 1,000 patients with a cycle length of 3 months.

NHS and PSS costs of treatment administration, monitoring and low vision were taken from NHS Reference Costs and Meads et al. (2003). All included costs and utilities were discounted at 3.5%. The model does not account for the costs or QALY impact of adverse events and assumes, in the base-case, that there is no difference in these between treatments. A sensitivity analysis applied the adverse event incidence data from MARINA to ranibizumab, and a doubled rate for bevacizumab. In the absence of published trial evidence on bevacizumab at the time, the model assumed the relative effectiveness of bevacizumab compared with ranibizumab to be given by a ratio of between 0.1 and 0.9 (units not stated).

The authors did not present disaggregated cost and QALY results. Instead they presented cost-utility ratios of ranibizumab vs. bevacizumab at varying levels of efficacy and price ratios (10, 25 and 39) for the two subgroups (PC and MC/OC lesions). These results suggested that the relative efficacy of bevacizumab compared to ranibizumab would need to be 0.4 for a ranibizumab ICER of £31,092 per QALY gained. For ranibizumab to achieve an ICER below £20,000, relative bevacizumab efficacy would need to be 0.65 and 0.85 where ranibizumab is 25x and 10x the price, respectively. Applying a doubled rate of serious ocular events in the bevacizumab group did not change these results for either cohort. Results for ranibizumab in the minimally classic and occult patients were marginally less favourable than in predominantly classic patients, because of the 2 year treatment horizon.

Stein et al. (2014)

Stein et al. (2014) compared the cost-effectiveness of bevacizumab and ranibizumab for newly diagnosed neovascular macular degeneration using data from the CATT study. The single-eye model incorporated both ranibizumab and bevacizumab according to monthly or PRN schedules, delivered to treat AMD in the BSE.

Direct medical costs of managing neovascular AMD were based on Centres for Medicare and Medicaid Services (CMS) items in Michigan (2011) and included the costs of eye-care provider visits; ancillary testing (OCT and FFA); interventions; treatment of side effects; and associated with severe vision loss when VA remained ≤20/200. For pharmaceutical products the drug cost, professional fee, and facility fee reimbursed by CMS were included. The cost of all drugs paid for outside the CMS office setting was calculated by using Red Book data from 2012. All costs were adjusted for inflation to 2012 dollars. The number of office visits and injections for each therapeutic regimen was taken from the CATT trial. Utilities associated with VA in the BSE were obtained from Brown et al. (2003).

Adverse events were based on the broadest categorical descriptions from CATT, and included endophthalmitis, venous thromboembolism (VTE), myocardial infarction (MI), cerebrovascular accident (CVA) and death from vascular complications. Utility losses for adverse events were sourced from various published studies identified through a literature review. MI, CVA, and endophthalmitis were assumed to have both short-term complications, expressed in costs and utility losses, and potential long-term complications (blindness from endophthalmitis, sequelae from MI and CVA) incurring lifetime cost and QALY losses. Cardiovascular and cerebrovascular events also increased the probability of premature mortality in an age-specific manner derived from life-table data. A diagram of the model is given in Figure 5.

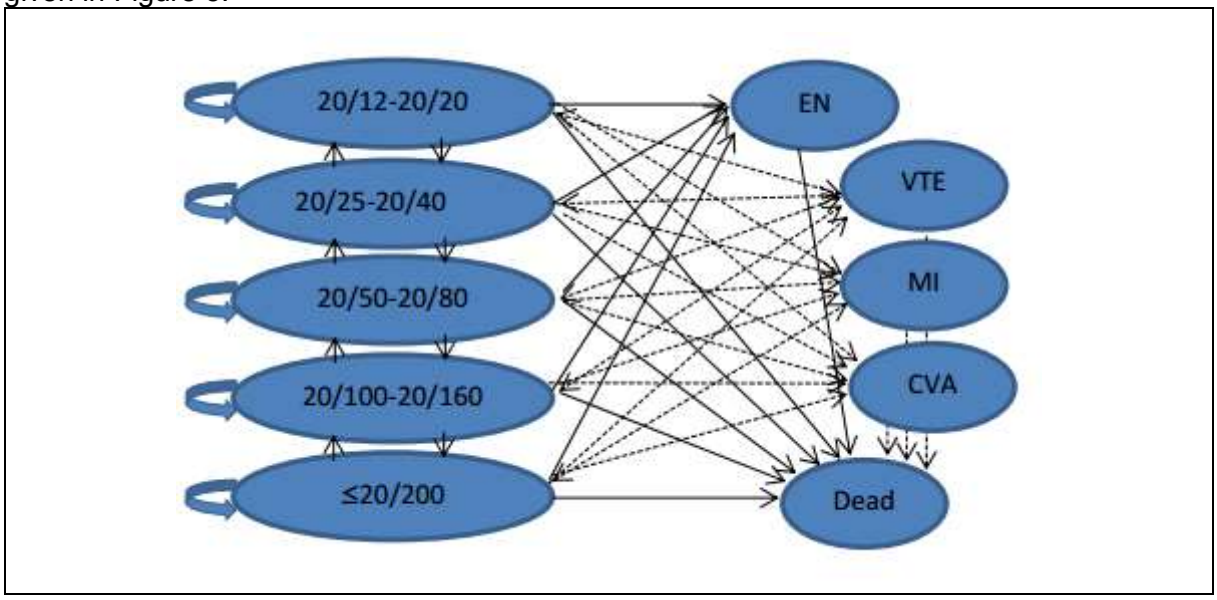


Figure 5: Markov model of VA and adverse event states proposed by Stein et al. (2014)

In the base-case analysis, The ICER of monthly bevacizumab versus PRN bevacizumab was $242,357 per QALY gained. The ICER of monthly ranibizumab compared with PRN bevacizumab was $10,708,377 per QALY gained. PRN ranibizumab was dominated by monthly bevacizumab, because monthly bevacizumab had lower expected costs and higher expected QALY gains.

Table 14: Base-case results from Stein et al.

Treatment	Cost (2012$)	QALYs	ICER
PRN bevacizumab	65,267	6.60	-
Monthly bevacizumab	79,771	6.66	242,357
PRN ranibizumab	163,694	6.64	Dominated
Monthly ranibizumab	257,496	6.68	10,708,377

Key: ICER, incremental cost-effectiveness ratio; PRN, pro re nata (treat as needed); QALYs, quality-adjusted life years.

Deterministic sensitivity analysis suggested that base-case results were robust to changes in parameter values, with only extreme values and assumptions resulting in results that favoured ranibizumab. In a treshold analyses, the annual risk of serious vascular events with bevacizumab would have to be at least 2.5 times higher than was observed in CATT for PRN ranibizumab to have an ICER below $100,000 per QALY gained. Even if every patient receiving bevacizumab experienced a VA decline by 1 category (e.g. from '20/25-20/40' to '20/50-20/80') after 2 years and every patient receiving ranibizumab maintained their level of VA, PRN ranibizumab would have an ICER of $97,340 per QALY gained.

Vottonen & Kankaanpää (2016)

Vottonen & Kankaanpää (2016) developed a 2-eye Markov model to compare the costs and QALYs of aflibercept, ranibizumab and bevacizumab. The model was composed of five VA-related health states. The 'best' state involved 1 eye having wet AMD, but no visual impairment in either eye. Patients in the other 4 VA states have diagnosed wet AMD in both eyes, with varying degrees of visual impairment. The model also contained a death state. An 8-year time horizon was selected, reported to represent the total treatment duration that can be expected. The model assumes that patients are treated for the entire duration. Two-year data from the CATT and VIEW studies were used to inform treatment effectiveness (transition probabilities not reported). The authors state that transition probabilities are extrapolated beyond year 2 by assuming stability. Disease develops in the second eye in 9.5% of patients per year.

Injection frequencies were informed by treatment protocols for continuous regimens (aflibercept, ranibizumab) and derived from CATT for PRN regimens (ranibizumab, bevacizumab). Ocular AEs were included from the trial evidence. Direct costs were diagnosis, treatments and administration, low vision rehabilitation, adverse events and monitoring, with monitoring assumed to only occur when useful for informing treatment decisions. A hospital perspective was taken for costs (2013 euros), which were discounted at a rate of 3% per year. VA-related utility weights were obtained from Brown et al. (2000). The authors do not report whether or not health outcomes were discounted. Base case results were obtained by simulating 1,000 patients through the model.

Table 15: Base-case results from Vottonen & Kankaanpää, 2016

Treatment	Total Costs	Total QALYs	ICER vs. aflibercept
Aflibercept	€39,921	6.888	-
Bevacizumab monthly	€9219	6.870	€1.8m *
Bevacizumab PRN	€16,784	6.862	€928,040 *
Ranibizumab monthly	€147,322	6.880	Dominated
Ranibizumab PRN	€95,505	6.873	Dominated

** Note: ICERs derived from negative incremental QALYs and costs should be interpreted as the opportunity gain accrued by foregoing each 1 QALY lost by adopting the less effective strategy. Key: ICER, incremental cost-effectiveness ratio; PRN, pro re nata (treat as needed); QALYs, quality-adjusted life years.*

The analysis suggests that aflibercept is not cost effective compared with bevacizumab, but is cost effective compared with ranibizumab. The authors estimate that the cost of aflibercept would have to be €128 per vial for it to be considered equivalent to bevacizumab. Four scenario analyses were presented; results were not sensitive to variation in the costs of low vision or adverse events, to extending the time horizon to 10 years, or to removing cost discounting. No measures of uncertainty in the base-case results or cost-effectiveness acceptability analysis were reported.

Wu et al. (2016)

Wu et al. (2016) developed a single-eye Markov model to evaluate the relative cost-effectiveness of ranibizumab, bevacizumab, PDT and usual care (no active treatment) in China. A Markov model was constructed, consisting of five VA-related health states defined by Snellen VA ranges (from '>20/40' to '≤20/400'). Baseline data were obtained from two Chinese PDT trials. The cohort had a mean age of 73.6 years. The model was a lifetime analysis, with outcomes discounted at a rate of 3% per year.

Effectiveness data were obtained for 1 year and 2 year time points for ranibizumab (ANCHOR, MARINA) and PDT (TAP, VIP). Usual care effectiveness was informed by the sham arms of MARINA, TAP and VIP. An indirect comparison was performed to compare the alternative strategies. The authors assumed that transition probabilities were defined by an

underlying exponential distribution, in order to estimate 3-month transitions from the annual data. Different AMD subtypes were modelled based on the relevant clinical evidence. The CATT study was used to estimate a relative risk between bevacizumab and ranibizumab. Treatments were assumed to be given for no longer than 2 years, with transition probabilities from year 2 for the usual care cohort applied to all arms from year 3 until the end of the model or death. Quality of life was informed by BSE utility weights from Brown et al. (2000).

The model included direct costs (2012 US dollars). Ranibizumab dosing and number of injection were from ANCHOR and MARINA, and bevacizumab was assumed to have the same posology. PDT treatment frequency was from VISION. Treatments were assumed to be delivered at outpatient appointments. Other costs included serious adverse events, monitoring, low vision costs and related non-medical costs, all derived from local health systems directly or costed using national sources.

Table 16: Base-case results from Wu et al. 2016

AMD subtype Treatment	Total costs	Total QALYs	ICER vs. usual care	Authors' comment
Predominantly classic				
Usual care	$8,619	3.97	-	-
PDT	$18,293	4.19	$44,333	Dominated
Ranibizumab	$29,468	4.55	$36,089	Not cost eff.
Bevacizumab	$9,233	4.46	$1,258	Cost effective
Minimally classic				
Usual care	$8,664	4.10	-	-
PDT	$18,289	4.19	$112,992	Dominated
Ranibizumab	$29,480	4.31	$102,828	Not cost eff.
Bevacizumab	$9,243	4.26	$3,803	Cost effective
Occult, no classic				
Usual care	$8,595	3.90	-	-
PDT	$18,240	4.01	$91,424	Dominated
Ranibizumab	$29,465	4.26	$58,790	Not cost eff.
Bevacizumab	$9,228	4.21	$2,066	Cost effective

Key: AMD, age-related macular degeneration; ICER, incremental cost-effectiveness ratio; PDT, photodynamic therapy; QALYs, quality-adjusted life years.

Although the authors do not present ICERs from a fully incremental analysis, the statements for each intervention in the 'Authors' comment' column reflect the results of a fully incremental analysis.

PSA determined that bevacizumab is likely to be cost-effective for any AMD subtype when the value of 1 QALY exceeds approximately $2,000. Neither PDT nor ranibizumab had any likelihood of being the cost-effective strategy at QALY values up to $10,000. A number of deterministic sensitivity analyses were presented, which had little impact on the ICER of bevacizumab compared with usual care (the only results shown). One sensitivity analysis suggested that treatment may be more cost-effective in patients with higher baseline VA.

Yanagi et al. (2016)

Yanagi et al. (2016) developed a single-eye Markov model, composes of 5 VA health states and a death state. The purpose of the model was to estimate the cost-effectiveness of aflibercept relative to ranibizumab monthly, ranibizumab PRN, pegaptanib, PDT and BSC, in the Japanese health care setting. The baseline cohort of patients was informed by the VIEW studies, with a mean age of 77 years and a mixture of mild, moderate and severe visual impairment. The base-case model took a lifetime horizon by ceasing after 12 years, selected as the life expectancy from age 77 in Japan. No mortality was applied for this duration.

Clinical effectiveness estimates were obtained from VIEW for the aflibercept arm – a loading phase following by 2-monthly injections – and the monthly ranibizumab arm. The probability of gaining (and losing) 15 or more letters after 2 years was equated with the 2-year transition probability of moving up (and down) by 1 model health state. An unpublished manufacturer-sponsored indirect comparison was conducted to inform the relative effectiveness of other comparators. Aflibercept was associated with the highest 2-year probability of gaining 15 letters (26.2%) and lowest probability of losing 15 letters (4.3%). BSC had a lower probability of losing 15 letters (6.5%) than both pegaptanib (17.4%) and PDT (26.9%).

Quality of life was informed by a Japanese time-trade-off study into the relationship between BSE VA and quality of life (Yanagi et al. 2011), though the authors had to adapt the study results to fit their health states. Costs included drugs, monitoring and adverse events (2016 ¥). The societal cost of family time spent caring for people with low vision was included. We have therefore excluded these societal costs from our reporting of results below. All costs and QALYs were discounted by 2% per year.

Base-case results, excluding pegaptanib and societal costs, and re-ordering as a fully incremental analysis, are presented in Table 17. Aflibercept produces the highest total QALYs, and has an ICER of ¥2,221,089 per QALY gained compared with BSC. The typical cost-effectiveness threshold in Japan is ¥5,000,000 per QALY gained. Both ranibizumab strategies are dominated by aflibercept, with its lower total cost driven by lower treatment costs, while PDT is extendedly dominated. The study also estimated that PRN ranibizumab produces a higher number of QALYs than monthly ranibizumab, despite having a lower probability of gaining 15 letters (and only slightly lower probability of losing 15 letters). Sensitivity analyses were conducted by the authors, but only for analyses including the societal costs that we have excluded, and only as head-to-head comparisons of aflibercept compared with each alternative. With this in mind, the outcomes do not change compared with the base-case model results. Alibercept is estimate to be more than 80% likely to be cost effective in each head-to-head comparison (relative to a threshold QALY value of ¥5,000,000).

Table 17: Base-case results from Yanagi et al. (2016)

Model arm	Total		Incremental		
	Costs ¥	QALYs	Costs ¥	QALYs	ICER
BSC	38,316	6.09	-	-	-
PDT	1,228,615	6.41	1,190,299	0.32	Ext. Dominated
Aflibercept	1,837,398	6.90	1,799,082	0.81	2,221,089
PRN ranibizumab	2,216,172	6.88	378,774	-0.02	Dominated
Monthly ranibizumab	2,953,548	6.87	1,116,150	-0.03	Dominated

Key: BSC, best supportive care; ICER, incremental cost-effectiveness ratio; PDT, photodynamic therapy; PRN, pro re nata (treat as needed); QALYs, quality-adjusted life years.

TA 155

For NICE TA 155, the manufacturer of ranibizumab submitted a cost–utility model; however thorough details of the model are not publicly available. The ERG that reviewed the manufacturer's model described it as a 10-year Markov model with 5 VA-related health states, separately analysing different AMD subtypes and using the ANCHOR, MARINA, PIER and TAP studies to inform efficacy as appropriate (Colquitt et al., 2008). Effectiveness was tapered over the 6 months after discontinuation (maximum treatment duration 2 years). The base-case ICER for ranibizumab in eyes with predominantly classic lesions, from the manufacturer's submitted model, was reported to be £4,489 per QALY gained compared with PDT, with 100% of probabilistic ICERs under £30,000. Compared with BSC, ICERs were

£14,781 (96% < £30,000), £26,454 (59%) and £25,796 (57%) in predominantly classic, occult no classic and minimally classic lesions respectively.

Colquitt et al. (2008) also developed their own economic model, which was published as a Health Technology Assessment and has been described above.

TA 294

For NICE TA 294, the manufacturer of aflibercept submitted a single-eye cost–utility model comparing 2-monthly aflibercept with PRN ranibizumab. The Markov model submitted was based on 5 VA-related health states, defined by worsening, improving or maintained VA in 15-letter ranges. The model took an NHS and PSS cost perspective, with outcomes discounted at a rate of 3.5% per year. Costs were from routine UK sources. The cost of injections included confidential patient access scheme discounts, however publicly available results are available based on published list prices. Administration was assumed to occur at an outpatient appointment, with half of injections occurring at a 1-stop visit, half at a 2-stop visit. Injection frequencies were derived from SPCs. The cost of low vision was included based on Meads et al. (2003). Effectiveness data were derived from the VIEW trials and an indirect comparison conducted by Kleijnen Systematic Reviews, as VIEW did not compare aflibercept with ranibizumab PRN. Effectiveness was characterised by relative risks (RRs) of maintaining and improving VA in year 1 and in year 2. Eyes were assumed to maintain stable vision for years 3 to 5. During this time period, treatment of the second eye was permitted if it developed wet AMD. From year 6 all treatment ceased (in both eyes) and a gradual decline in VA associated with BSC was applied. Quality of life inputs were obtained directly from EQ-5D data from the VIEW-2 trial, however these are confidential and are therefore not publicly available.

Table 18: Base-case results from manufacturer submission for TA 294 (without patient access scheme)

Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Aflibercept	£25,009	7.767	-	-	-
Ranibizumab	£28,615	7.758	£1,396	-0.010	Dominated
Key: ICER, incremental cost-effectiveness ratio; QALYs, quality-adhjusted life years.					

Aflibercept was estimated to be dominant over ranibizumab in the base-case, and this was also the case in all iterations of PSA and all deterministic sensitivity analyses submitted.

The ERG for TA 294 (Cummins et al.) reviewed the submitted analysis, and revised the model to produce an ERG analysis. The ERG felt that treatment of the second eye had not been implemented satisfactorily, and so reverted to single-eye analysis, but presented separate results where this was the BSE and the WSE. The RR estimates used were revised, because the ERG interpreted the RRs from the two-year data to represent the RR of maintaining or improving VA from baseline to year 2. This differed from the manufacturer's interpretation, which was that these RRs reflected differences from year 1 to year 2. The ERG also made minor adjustments to unit costs.

Table 19: Base-case results from ERG (Cummins et al.) revised model for TA 294 (without patient access scheme)

Treated eye Treatment	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
BSE model					
Aflibercept **Ranibizumab**	£19,075 £20,714	6.692 6.719	£1,639	0.027	£61,653

WSE model					
Aflibercept **Ranibizumab**	£19,075 £20,714	8.014 8.018	£1,639	0.004	£399,140

Key: BSE, better-seeing eye; ICER, incremental cost-effectiveness analysis; QALYs, quality-adjusted life years; WSE, worse-seeing eye.

The ERG model revisions suggested that aflibercept does not dominate ranibizumab. Ranibizumab was associated with additional QALYs, at an ICER of £61,653 per QALY gained in the BSE model and £399,140 per QALY gained in the WSE model. These results were highly sensitive to the RR parameters. The point estimates of the RRs were not statistically significant (that is, the limits of the 95% confidence intervals were either side of the 'no effect' value of 1). Varying them to their lower and upper confidence interval limits saw the BSE model ICER go from £15,139 to aflibercept dominating. In the WSE model ICERs varied from £99,148 to aflibercept dominating.

J.4.1.2 PDT Studies

This chapter is focused on anti-VEGF medicines; however the NMA of treatment options and regimens which feeds into the new health economic model includes PDT as a comparator. This was primarily because no large synthesis of treatment evidence encompassing PDT and anti-VEGF injections has been undertaken to date, and the existing health economic analyses of PDT were published before the widespread adoption of anti-VEGF as the first-line treatment for AMD. A review of the published PDT cost–utility analyses is therefore included in this chapter.

Grieve et al. (2009)

Grieve et al. (2009) used data on verteporfin PDT use collected from patients attending 45 NHS ophthalmology units, and 15 units which collected data on self-reported use of services, to generate a cost–utility analysis of PDT compared with BSC. The economic model assumed that the BSE of patients was treated, though VA in both eyes was modelled. The decision to retreat was based on the TAP study and the UK VPDT cohort study. No mortality was modelled over the 2-year time horizon.

Costs for verteporfin PDT treatment, monitoring (FFA), follow-up and low vision assessments were taken from NHS reference costs and the BNF. The model incorporates significant PSS costs, in a more comprehensive manner than any other published CUA for AMD, drawn directly from the UK 'VPDT Cohort Study' database. These costs include social services, day centre use, nursing home stays, residential care use, sheltered housing, and anti-depressant use. The comparator arm of BSC was costed according to expert opinion, with an assumption that untreated patients would have 1 to 1.5 low vision assessments each year. The effectiveness of PDT relative to placebo was informed by TAP. QALYs were derived from patients surveyed in the UK VPDT study using the SF-6D instrument and a VA measurement in ETDRS letters.

In the base-case model, utility gains from PDT over BSC were small relative to the incremental costs involved. The ICER for PDT was £170,000 per QALY ganed over the 2 years of treatment.

Hopley et al. (2004)

Hopley et al. (2004) developed single-eye CUA models to assess the cost-effectiveness of PDT relative to placebo. The clinical effectiveness of PDT was taken from TAP. Costs were from the Australian Medicare Benefits Schedule (2003). Treatment frequency and costs were based on the TAP study protocol, with an average of 3.3 treatments in year 1, 2.2 in year 2, and 1.3 in year 3 as per the TAP extension study. It was assumed that, as per the 3 year

TAP extension study, the differential in VA between treated and untreated (placebo) eyes could be maintained for as long as treatment continues. QALY gains and losses were related to categorical VA ranges (Brown et al, 2000). Costs for PDT treatment include an initial consultation, FFA, treatment with verteporfin and administration of the PDT laser, and subsequent consultation appointments. Costs were reported in 2003 £ (following a PPP conversion from A$), and all outcomes were discounted at 6% per annum.

Two scenarios were evaluated:

Scenario 1

- Reasonable initial VA of 6/12 in the BSE
- Predominantly classic CNV in that eye
- Poorer vision in the fellow-eye (worse than 6/24)

Scenario 2

- Poor initial VA of 6/60 in the BSE
- Predominantly classic CNV in that eye
- Poorer vision in the fellow-eye (counting fingers and worse)

The base-case ICERs for PDT in scenario 1 and 2 were £31,607 and £63,214 per QALY gained, compared with placebo, respectively. These results suggesting that PDT is less cost effective in patients with poor VA compared with patients with better VA.

Meads et al. (2003)

Meads et al. (2003) evaluated the cost–utility of verteporfin PDT relative to placebo from an NHS and PSS perspective using data from the TAP and VIP studies. The single-eye decision tree model had a 2-year treatment duration and time horizon, with costs derived from a systematic review of PDT costing studies. Utilities were based on Brown et al. (2000). Insufficient data were available to simulate categorical changes in VA over time for treated and untreated eyes in each arm.

The analysis results indicate that PDT has an ICER of between £151,000 and £182,000 compared with placebo. Varying the cost of PDT treatment had some effect on the ICER, though the model was most sensitive to the estimates of effectiveness. In a 'best-case' scenario, with optimistic assumptions regarding effectiveness data, high utility scores, low net costs and the highest possible cost of low vision, the ICER for PDT compared with placebo was £47,000 per QALY gained.

Meads & Moore (2001)

Meads & Moore (2001) evaluated the cost–utility of verteporfin compared with placebo from an NHS and PSS perspective. The effectiveness evidence used in the evaluation was taken from TAP. The relationship between VA and quality of life was informed by the Brown et al. (2000) TTO study. PDT costs were disaggregated into the costs of one typical treatment, with cost items obtained from NHS Reference Costs. An NHS Trust (University Hospital Birmingham) also provided local costs for comparison.

The total cost for one verteporfin PDT treatment was estimated to be £1,181. Assuming each patient receives 3.4 treatments in the first year, the average cost of treatment per patient was estimated to be £4,015. The ICER of PDT compared with the placebo was £137,138 per QALY gained. When low vision costs were included in the analysis, the ICER was £120,095.

Smith et al. (2004)

Smith et al. (2004) used individual patient-level data from TAP to develop a single-eye cost–utility model comparing PDT with no treatment. The no treatment arm was informed by the sham (placebo) arm of TAP. The Markov model contained 15 VA-related health states, separated by Snellen 'drops' from best (20/40) to worst (<20/800) VA, and a death health state. A Weibull function was fitted to 'time to worsening VA' data, with adjustment for patient characteristics, and this was used to estimate the probability of transition to the next worst VA state. Health state utilities were derived from Brown et al. (2000). Health outcomes were discounted by 2% per year.

Treatment costs, including the drug and procedure, were obtained from national UK sources. A "government" perspective included costs associated with low vision (and a further scenario broadened this by including income transfers to people with severe low vision). Costs were discounted at a rate of 6% per year.

In a 2-year 'within trial' analysis, the treatment costs only perspective produced a PDT ICER of £89,464 per QALY compared with placebo in patients with a starting VA of 20/40. In patients with initial VA of 20/100, the ICER was £411,553. From the broader perspective, ICERs were £75,580 and £285,867 respectively. In a 5-year extrapolation, the treatment costs only perspective produced PDT ICERs of £38,088 per QALY compared with placebo (starting VA of 20/40) and £68,882 (starting VA of 20/100). From the broader perspective, ICERs were £8,823 and £29,797 respectively.

TA 68

For NICE TA 68, the manufacturer of verteporfin submitted a cost–utility model; however thorough details of the model are not publicly available. The ERG reviewed the manufacturer's model, describing it as a 1-eye Markov model based on TAP, with 18 possible VA-related health states, and treatment limited by whether the patient was classified as a responder or non-responder after 6 months. VA was assumed to remain stable beyond year 2, reportedly based on stable VA in longer term TAP data. Base-case ICERs from the manufacturer's submission ranged from £70,492 per QALY gained over 2 years to £14,754 in a lifetime analysis.

Meads et al. (2003) also developed their own economic model, which was published as a Health Technology Assessment and has been described above. The TA committee requested a subgroup analysis looking at patients with classic (no occult) lesions. In this subgroup the ICER ranged from £10,000 to £57,000 per QALY gained, with a £26,000 ICER when the majority of VA changes were assumed to occur in the first year after treatment initiation. The committee considered these ICERs when evaluating the evidence, ultimately recommending PDT in people with classic (no occult) lesions.

J.4.2 Treatment in people presenting with visual acuity better than 6/12 or people presenting with visual acuity worse than 6/96

Review questions:

RQ 10: What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity better than 6/12?

RQ 25: What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity worse than 6/96?

Of the 3,163 unique references retrieved, 2 references were retained for these review questions. Both studies contained CUAs related to treating people with presenting VA better than 6/12. One reference also presented an analysis related to relating people with presenting VA worse than 20/400, and therefore worse than 6/96.

Butt et al. (2015)

Butt et al. (2015) presented a CUA comparing treating wet AMD in people with presenting VA better than 6/12 (immediate treatment) with waiting until their VA falls to 6/12 (delayed treatment). Patients were assumed to be treated with monthly ranibizumab. A 2-year, single-eye Markov model was developed, with 5 VA health states:

- 6/6 to >6/12
- 6/12 to 6/24
- 6/24 to 6/60
- 6/60 to 3/60
- <3/60

Data were obtained from a national, observational AMD database (Tufail et al., 2014), which tracked UK patients who were treated with ranibizumab. Using these data meant that the study was representative of typical practice, rather than using treatment effects from trial settings. On the delayed treatment arm, after a time spent in the '6/6 to >6/12' state, patients were distributed between the <6/12 states based on untreated fellow-eye data. This meant that the majority of patients moved to '6/12 to 6/24' (43%) or '6/24 to 6/60' (39%). A small proportion of patients (3%) moved directly to '<3/60'. Direct costs were informed by the NICE costing template published for TA 294 (2012 £). Quality of life was related to VA using the Brown et al. (2000) TTO utility weights.

The central estimates of total costs from 10,000 Monte Carlo simulations were £7,460 for delayed treatment and £8,470 for immediate treatment (Table 20). Total QALY estimates were 1.35 and 1.59, respectively. Incremental costs and QALYs were £1,010 and 0.24, producing a mean ICER for immediate treatment of £4,252 per additional QALY compared with delayed treatment. Immediate treatment was reported to have an ICER of £20,000 or less in over 90% of PSA simulations.

Table 20: Base-case model results from Butt et al. (2015)

Strategy	Total outcomes		Incremental outcomes		
	Costs	QALYs	Costs	QALYs	ICER
Delayed treatment	7,460	1.35	-	-	-
Early treatment	8,470	1.59	1,010	0.24	4,252

One-way sensitivity analyses were presented, using alternative utility weights (Brown et al., 2000, standard gamble values); accruing only drug costs; extending the time horizon to 5 years; and reducing the baseline cohort age from 78 to 60 years. The ICER of early treatment relative to delayed treatment remained low in all scenarios.

Sensitivity analysis around the drug cost – which may have simulated alternative treatments (assuming equal effectiveness) or the confidential patient access scheme discount for ranibizumab – was not presented. A lower treatment cost would have reduced the ICER associated with early treatment, as the QALY gains associated with immediate treatment would have been accrued at a lower incremental cost.

Wu et al. (2016)

Wu et al. (2016) developed a single-eye Markov model to evaluate the relative cost-effectiveness of ranibizumab, bevacizumab, PDT and usual care (no active treatment) in China. The analysis is detailed in Section J.4.1.1. Briefly, the lifetime model was composed of 5 VA-related health states defined by Snellen VA ranges (from '>20/40' to '≤20/400'). Effectiveness data were obtained for 1 year and 2 year time points for ranibizumab (ANCHOR, MARINA) and PDT (TAP, VIP). Usual care effectiveness was informed by the sham arms of MARINA, TAP and VIP. The CATT study was used to estimate a RR between

bevacizumab and ranibizumab. Different AMD subtypes were modelled using the relevant clinical data. The model included direct costs (reported in 2012 US dollars), and quality of life was informed by BSE utility weights from Brown et al. (2000). All outcomes were discounted by 3% per year.

ICERs were presented graphically, stratified by presenting VA (see Figure 6), separately for each active treatment compared with usual care. However, numerical ICERs for each level of presenting VA were not reported. The following baseline VA ranges were evaluated this way:

A. >20/40
B. 20/40 to >20/80
C. 20/80 to > 20/200
D. 20/200 to >20/400
E. ≤20/400

Group A is equivalent to VA better than 6/12, and is therefore relevant to Review Question 10. In these patients, the ICERs display little systematic variation when treating people with presenting VA >20/40 and people with lower levels of VA, regardless of the particular treatment used.

All patients in Group E will possess VA worse than 6/96, relevant to Review Question 25. It is also possible that some patients in Group D will possess VA worse than 6/96. The ICERs in these groups, of each treatment compared with usual care, are higher than in better presenting VA groups for patients with occult/no classic AMD. This suggests that active treatments are less cost-effective in people with occult/no classic disease and low presenting VA. In other AMD subtypes, there appears to be little systematic variation between treating people with presenting VA ≤20/400 and higher levels of VA. Stratification by baseline VA was itself a sensitivity analysis; no further sensitivity analyses (deterministic or probabilistic) were presented for these ICERs.

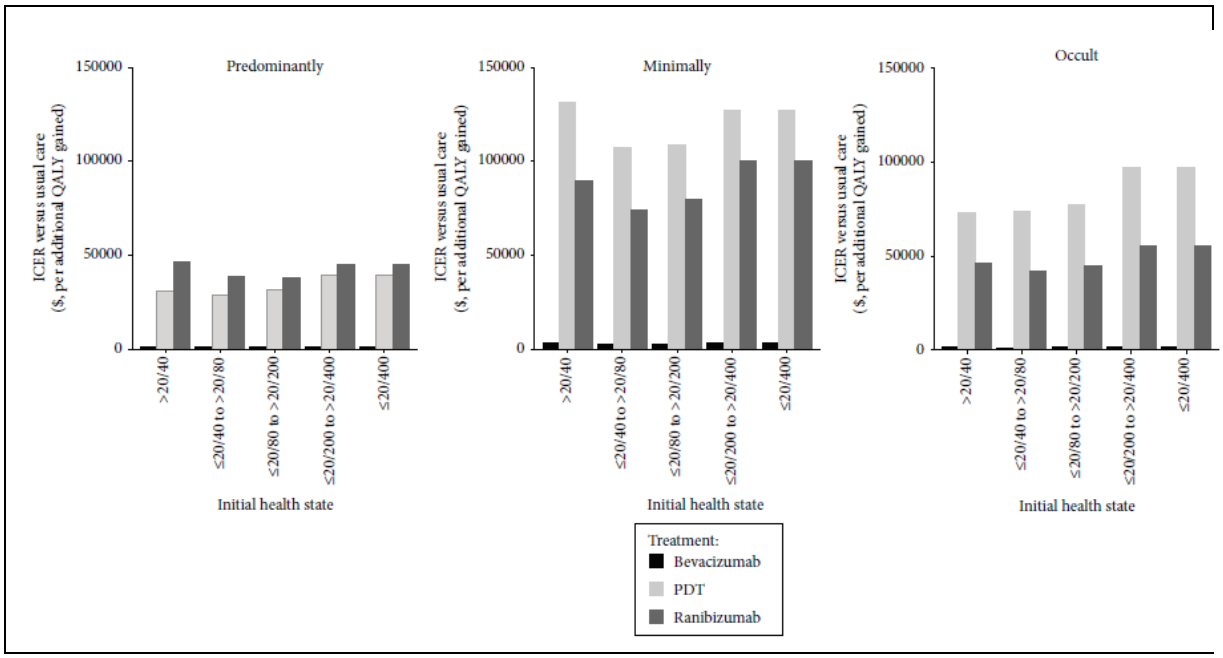


Figure 6: ICERs for treatments compared with usual care presented graphically by Wu et al. (2016)

J.5 New cost–utility model

J.5.1 Decision problem

We developed an economic model with a view to supporting a number of review questions with economic evidence for this guideline. The review questions (RQs) supported by the model, listed in Table 21, were all identified as either high or medium priorities for economic analysis by the guideline committee.

Table 21: Research questions incorporated by new economic modelling

RQ 10	What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity better than 6/12?
RQ 12	What is the effectiveness of different anti-angiogenic therapies (including photodynamic therapy) for the treatment of neovascular AMD?
RQ 18	What is the effectiveness of different frequencies of administration for anti-VEGF regimens for the treatment of neovascular AMD?
RQ 25	What is the effectiveness of treatment of neovascular AMD in people presenting with visual acuity worse than 6/96?

A systematic review was undertaken to identify and review all existing cost–utility evidence for the RQs in this guideline. A literature search was conducted jointly for all RQs by applying standard health economic filters to a clinical search for AMD. A total of 3,163 unique references was returned. For review questions 12 and 18, a total of 75 references were ordered for full-text review. Economic evaluations developed for previous NICE TAs in AMD were also reviewed. This led to 20 studies being included as relevant. For review questions 10 and 25, 2 studies were reviewed in full. Both were deemed to be relevant and were included.

The results of this review for RQs 12 and 18 and for RQs 10 and 25 are provided in sections J.4.1 and J.4.2, respectively. Briefly, we appraised the applicability and quality of included studies. The majority of studies identified as relevant to RQs 12 and/or 18 had the limitation of being single-eye analyses, which implicitly assume that the treated eye is the BSE, and that the fellow eye remains the WSE and untreated. This assumption biases in favour of treatment, by incurring costs only for the treatment of eyes that stand to provide the biggest improvement to quality of life. No studies conducted an adequate exploration of the distinction between treating AMD in the BSE only and treating AMD in whichever eye has it, regardless of its VA relative to the other eye. Only 2 CUAs were identified as relevant to RQs 10 and/or 25; one considered only treatment with ranibizumab, while the other was from the perspective of the Chinese healthcare system. It was therefore felt that a new economic analysis, supporting all of these questions simultaneously, would provide the guideline committee with useful additional evidence.

J.5.2 Methods

J.5.2.1 Modelled population(s) and intervention(s)

The new model seeks to support 4 review questions simultaneously (see Table 21). The modelled population – people with late AMD (wet active) – is consistent with the review protocols for all review questions. The interventions and comparators included in the model are comprehensive, population-level treatment strategies including several features that capture each of the 4 review questions. It does not make a simple comparison of, say, one pharmacological agent with another; rather, we compare treatment strategies that include a

choice of treatment, a treatment frequency, and decision rules about which eyes should be treated. More detail is provided in Section J.5.2.3.

J.5.2.2 Model structure

We built a patient-level Markov ('microsimulation') model with a cycle length of 1 year and a lifetime horizon. The cycle length is consistent with typical outcome reporting points in the effectiveness trials (year 1 and year 2). Our model is a '2-eye' model. This means that the treatment and VA of both eyes are explicitly modelled simultaneously, in contrast to the majority of previous, 'single-eye' models, which were limited by implicitly assuming that the treated eye is the BSE, and that the fellow eye remains the WSE and untreated. In single-eye models the fellow eye is typically ignored, implicitly assumed to be blind. This does not reflect clinical reality, in which both eyes can and do develop neovascular AMD, making a 2-eye model fundamentally more appropriate. The majority of previous models in AMD have been Markov cohort models. We favour a microsimulation approach for its ability to handle the vast number of potential health state transitions required for a complete 2-eye model (our structure would have required 1,081 unique health states; see below). A cohort model constructed for this purpose would become unwieldy to the point of being entirely impractical, but a microsimulation provides a computationally more efficient method of obtaining the same results.

Visual acuity health states

The Markov structure allows simulated patients – or, more accurately, each of their eyes – to transition between discrete health states. One set of states is defined by best-corrected VA of the eye, measured by the number of ETDRS letters read. The model uses 6 VA 'ranges', from the best state of VA >85 letters to the worst state of VA ≤25 letters (Table 22). This structure is similar to several previous economic models (Colquitt et al. 2008, Stein et al. 2014, Panchmatia et al. 2016), though there is variation in the exact ranges used across models. For example, the highest VA state in our model (>85 letters or >6/6) has often been omitted from previous models, with those patients included by a broader 'VA >6/12' state.

Transitions between our VA states are informed by annual transition probabilities. Transition probabilities are derived from a network meta-analysis (NMA) which uses the mean change in VA reported in clinical trials. The methods and results of the NMA are detailed in Section J.5.3.3. By using a mean VA change treatment effect obtained from the NMA for each treatment, and assuming it to be normally distributed, it is possible to estimate the probability that an eye gains any given number of letters. This assumption was also made in a recent cost–utility analysis of aflibercept and ranibizumab (Claxton et al. 2016), which cites evidence from the VIEW trial that mean changes in VA are approximately normally distributed. We use this assumption to estimate the probability of transitioning between our different VA health states. We weight these probabilities according to the baseline VA of an eye, as detailed in Section J.5.3.3.

Approaching transition probabilities in this way represents a departure from previous Markov models in AMD. Previous models have largely used the widely-reported trial outcomes of the proportion of patients gaining or losing ≥15 or ≥30 letters, and have assumed that those probabilities are equivalent to the probability of transiting between 15-letter health states. Implicitly, this means that an eye must gain at least 15 letters to move up or down by 1 health state. In reality, some eyes will only need a few letters to move up into the next health state, e.g. going from 53 letters (state '55-41') to 56 letters (state '70-56'). Other eyes will need to gain at least 15 letters to move up, e.g. going from 41 letters to 56 letters. Similarly, some eyes could gain 29 letters and still only move up by one 15-letter state, e.g. going from 41 letters (state '55-41') to 70 letters (state: '70-55'). Because we assume that, on average, an eye has the midpoint VA in a particular range, it follows that the probability of moving up (or down) by 1 health state is the probability of gaining (or losing) between 7.5 and 22.5 letters. Similarly, based on the average patient within each VA state, the probability of moving up or

down by 2 health states is represented by the probability of gaining (or losing) more than 22.5 letters.

At any given time, a living patient in our model is simultaneously situated in 2 VA health states: 1 for each eye. This means there is a total of 36 unique combinations of VA health states. The VA changes in 1 eye are assumed to be independent of the other eye.

Treatment-related health states

Alongside these VA-range states is a second level of health states, defined by where an eye is in the treatment pathway. Each eye with late AMD (wet active) at baseline has 5 potential treatment-related states (Table 22): pre-treatment (AMD present), year 1 of treatment, year 2 of treatment, subsequent treatment, and post-treatment. The 'pre-treatment' state will contain eyes that are not treated despite the presence of late AMD (wet active). This will only be the case when the prevailing population-level treatment strategy makes that eye ineligible for treatment. For example, it could be the WSE in a scenario where only BSEs are to be considered for treatment, or it could have VA >6/12 in a scenario where eyes with VA >6/12 are not treated (these strategies are described in detail in Section J.5.2.3).

For treated eyes, the distinct health states for different years of treatment is made to accurately incorporate differences in treatment effects and injection frequencies over time; in particular, the clinical evidence suggests that the majority of VA gains are experienced in the first year of treatment. If a patient presents with unilateral late AMD (wet active), the unaffected fellow eye will start the model in an additional treatment-related state: no AMD. This health state can only ever be occupied by fellow eyes, as all patients are assumed to enter the model with late AMD (wet active) present in at least 1 eye.

At any given time, a living patient in the model is simultaneously situated in 2 treatment-related health states: 1 for each eye, with each eye assumed to be independent of the other. This means there is a total of 30 unique combinations of treatment-related health states. There is also a 'dead' state, in which patients remain if they die.

Table 22: Modelled health states

First eye (100% have AMD at baseline)	Fellow eye (potentially AMD-free at baseline)
Health states defined by visual acuity	
VA > 85 ETDRS letters	VA > 85 ETDRS letters
85-71 letters	85-71 letters
70-56 letters	70-56 letters
55-41 letters	55-41 letters
40-26 letters	40-26 letters
≤ 25 letters	≤ 25 letters
Health states defined by AMD or treatment status	
-	No AMD
Pre-treatment, AMD present	Pre-treatment, AMD present
First year of treatment	First year of treatment
Second year of treatment	Second year of treatment
Subsequent years of treatment	Subsequent years of treatment
Post-treatment (discontinued)	Post-treatment (discontinued)
Other states	
Dead	

Figure 7 and Figure 8 provide schematic depictions of the 2 components of our model structure: first the VA states, then treatment-related states. Each patient is modelled with 2 eyes, and each eye is simultaneously in 2 states: 1 from both of the structures shown.

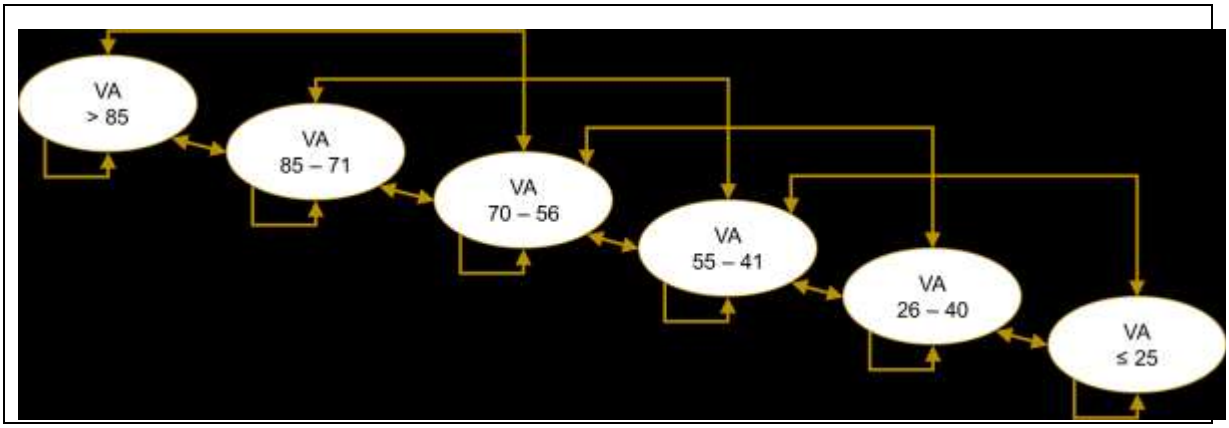
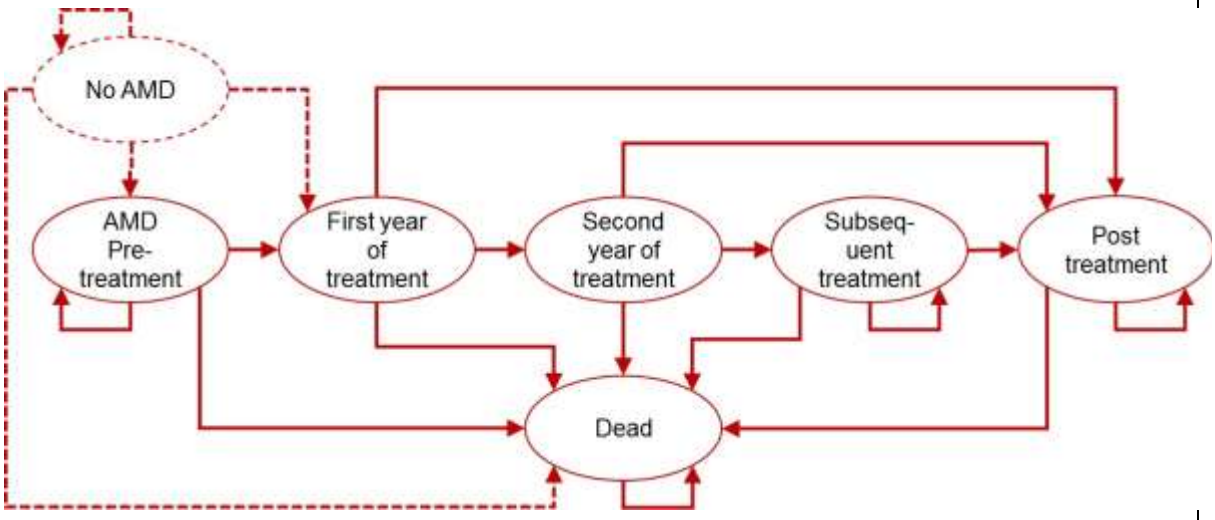


Figure 7: Visual acuity health states and transitions for one eye



Note: Dashed lines indicate health states and transitions that only a fellow eye with no AMD can experience.

Figure 8: Treatment-related health states and transitions for one eye

With 36 VA-related health state combinations, 30 treatment-related state combinations and 1 death state, the model contains a total of 1,081 unique health state combinations. The number of transition probabilities required for this many health states renders a typical cohort Markov model computationally impractical. In our microsimulation approach, 1 patient is simulated through the Markov structure at a time, and the average health state occupancy from all patient simulations is obtained. This significantly improves the computational efficiency of the model, while retaining the simplicity of the Markov structure and comparability with previous models.

In contrast to some patient-level state-transition models, our model does not calculate costs and utilities for each simulated patient; as noted above, the simulation is only used to calculate average state occupancy over time, and the costs and effects related to that average profile are calculated as in a standard state-transition model. Costs and utilities will differ by health state. For example, an eye in the 'year 1 of treatment' state will incur the cost of a treatment, whereas an eye in the 'post-treatment' state will not. A patient whose eyes

are in the VA-states of '>85' and '85-75' will have different quality of life than a patient whose eyes are both in the VA state of '≤25'.

J.5.2.3 Interventions

As introduced in Section J.5.1, the model seeks to answer a number of questions for this guideline simultaneously. Doing so means comparing the health and resource outcomes of different broad strategies that include:

- A treatment: anti-VEGF therapy, or PDT, or sham injections
- A treatment regimen (e.g. continuous monthly, or loading phase then PRN)
- A threshold level of VA above which an eye with AMD will not commence treatment
- A threshold level of VA below which an eye with AMD will not commence treatment
- A population-level strategy of treating either the BSE only or any eye that has AMD.

Results are therefore presented to indicate the cost–utility of a comprehensive, population-level intervention strategy, treating each unique combination as a different unique strategy within the pool of available options. This approach is conceptually and analytically superior to the alternative of 'piecewise' decision making (see Tappenden et al. 2012, 2013). Ultimately, different combinations of each of the aspects of treatment listed above multiply to produce 161 unique treatment strategies. Our base-case analysis comprises 137 of these strategies. The following sections describe each component in turn.

Treatment choice

The model includes 4 different active treatments for comparison: aflibercept (2 mg), bevacizumab (1.25 mg), ranibizumab (0.5 mg) and photodynamic therapy (PDT). A 'sham injections' arm is also included to model a strategy that provides no active treatment. While bevacizumab was included in the scope of this guideline, it is recognised that it is not licensed for intraocular use for late AMD (wet active). Pegaptanib was also included in the scope of this guideline; however the guideline committee advised that it is neither routinely used nor available, and was therefore not relevant for inclusion in the model. Similarly, the committee advised that some doses that have been explored in trials of aflibercept (0.5 mg) and ranibizumab (0.3 mg; 2 mg) are neither used nor available, and are therefore not included.

Treatment frequency

It is not possible to choose a particular treatment without also selecting a dosing regimen for that treatment; hence, RQs 12 and 18 are intrinsically linked. In the base-case analysis, 4 potential dosing regimens are included for aflibercept, with 6 for each of ranibizumab and bevacizumab. One PDT regimen is included. This means, including the no treatment arm, there are 18 unique drug and regimen combinations compared in the base-case analysis (Table 23). When a patient is being treated in both eyes, we assume that the same drug and regimen is used for each eye.

One alternative regimen for treatment with anti-VEGF therapies is included in scenario analyses – dosing by a 'PRN and extend' (PRNX) protocol. This is not included in the base-case due to a scarcity of clinical evidence. It is connected to the our network meta-analysis by 1 study with a small sample size (see Section J.5.3.3).

Table 23: Interventions included in the model

Treatment regimen	Anti-VEGF therapies			PDT
	Aflibercept 2 mg	Bevacizumab 1.25 mg[a]	Ranibizumab 0.5 mg	
1-monthly	Base case	Base case	Base case	
2-monthly	Base case	Base case	Base case	
3-monthly		Base case	Base case	Base case
2-monthly then PRN [b]	Base case			
As needed (PRN) [c]		Base case	Base case	
3-month loading phase then PRN		Base case	Base case	
Treat and extend [d]	Base case	Base case	Base case	
PRN and extend [e]	Scenario	Scenario	Scenario	
a) Bevacizumab is not licensed for intraocular use for late AMD (wet active).				
b) The VIEW regimen is composed of 2-monthly injections for 1 year followed by PRN injections. This regimen is unique to aflibercept.				
c) PRN regimens involve routine clinic appointments for monitoring, which are used to inform whether treatment is required at that appointment or not. If treatment is not required, the next opportunity to receive treatment is at the next scheduled monitoring appointment.				
d) Treat-and-extend (TREX) regimens involve a routine treatment schedule initially. The treatment interval may be extended if the clinician feels it is possible to do so while maintaining stable visual and/or anatomic outcomes.				
e) PRN and extend (PRNX) regimens, like PRN regimens, require monitoring to inform whether treatment is required at that time. However, unlike PRN, the interval between monitoring appointments may be extended if the clinician feels it is appropriate to do so. Clinical expert advice from the guideline committee has informed us that PRNX often occurs in clinical practice.				

Details of the different dosing regimens are provided in Section J.5.3.5 (see Table 35).

We recognise that a number of regimens in Table 23 are not used in practice, and in some cases have not been explored in clinical trials (e.g. aflibercept PRNX, ranibizumab 2-monthly). However, our method of estimating relative effectiveness has made it possible to simulate a world in which such regimens are available, thus allowing us to include them in the model. While PRNX dosing is omitted from our base-case analysis, some other regimens included with little or no comparative effectiveness data – e.g. bevacizumab given every 2 months – have individual components (agent: bevacizumab; dosing: 2-monthly) that are well-connected within the network, providing ample data to estimate the effectiveness of those components used together. The resulting point estimates are much more certain than for PRNX, which is only loosely connected to the wider network, by 1 data point. The precise methods and results of our NMA) which estimates the relative treatment effects associated with each component of a treatment (drug, treatment frequency, use of a loading phase, and the use of discontinuous regimens), are provided across a separate appendix for this guideline and Section J.5.3.3 of the present appendix.

Our base-case analysis contains all drugs listed in Table 23, as well as PDT and no treatment. Two alternative sets of results are also provided, the first of which excludes bevacizumab strategies. This restriction reflects that bevacizumab is not licensed for the treatment of AMD. An analysis containing only licensed anti-angiogenic therapies is therefore useful information to inform the situation where bevacizumab is not available due to its licensing status. However, there has been extensive clinical research into the use of bevacizumab as a treatment for AMD, it is widely used outside the UK, and the guideline committee advised that there are circumstances where it is currently considered in the NHS. As such, we still primarily present 'full' base-case results including bevacizumab.

The third set of results includes only those regimens in the model that are included on product labels. This further restriction reflects that a number of our treatment strategies have been simulated by our NMA, despite not being used in practice or, in some cases, in clinical trials. The guideline committee felt that an analysis comparing regimens commonly used in current practice, which are the regimens listed on the product labels, would be valuable. This analysis therefore contains only the following comparators:

- Aflibercept: 2-monthly treatment for 1 year, then PRN (VIEW trial regimen) Ranibizumab: Loading phase then PRN
- Ranibizumab: Monthly treatment
- Ranibizumab: Treat-and-extend
- PDT
- No active treatment (sham injections)

Note: aflibercept treat-and-extend is included on its label after a first year of treatment, however, this is not included in the economic model (a purely treat-and-extend regimen, from treatment initiation, is simulated in earlier results).

Treating AMD when VA is >6/12 or <6/96

Current guidelines recommend that treatment is initiated when VA declines to 6/12 (70 letters) or worse, such that the treatment of late AMD (wet active) in an eye with VA better than 6/12 is not recommended as cost effective. Treatment is also not recommended in eyes with VA of 6/96 (25 letters) or worse. A potential population-level treatment strategy could have different initiation strategies, at both the upper level (i.e. do not treat eyes until VA declines to some threshold) and the lower level (i.e. do not treat eyes with presenting VA of less than some threshold). The following potential threshold combinations will therefore be presented:

- Current practice (treat if VA is between 26 and 70 letters)
- Extend eligibility to treat eyes with VA better than 6/12 (i.e. remove the upper threshold, treat if VA is >25 letters)
- Extend eligibility to treat eyes with VA of 6/96 or worse (i.e. remove the lower threshold treat if VA is ≤70 letters)
- Extend eligibility to treatment eyes with any level of VA (i.e. remove both thresholds).

In any analysis where it is not otherwise stated, the thresholds used will match current practice, such that eyes will only be eligible for treatment if their VA is between 70 letters and 26 letters.

Treating the better-seeing eye or any eye

Another potential population-level treatment strategy decision is whether to treat only AMD that occurs in BSEs, or to treat AMD in whichever eye has it, regardless of whether it is the better or WSE. Treatment of only BSEs was initially recommended as an outcome of NICE TA 155, but became a key subject of the appeal hearing that followed the initial guidance (NICE, 2008). It is a theoretically important decision problem, firstly because loss of vision in the BSE has been shown to be a much more prominent determinant of quality of life than visual impairment in the WSE (Scanlon et al. 2015), and because economic analysis is fundamentally about exploring the cost-effectiveness of the next possible incremental step. As such, comparing treating AMD in any eye with no treatment, regardless of the specific therapy and frequency, misses an interim strategy of treating only 1 eye.

Previous cost–utility models have failed to deal with this distinction explicitly, instead exploring strategies that treat AMD in either the BSE or in any eye, but never comparing those 2 decisions as competing strategies themselves. Our analysis including both as

potential components of our broad, population-level strategies for treating AMD. It is not feasible that treating only the WSE would ever be cost-effective compared with a strategy of treating only the BSE, given the relative impact on a person's quality of life of VA in the better-seeing and WSEs. Given the importance of the BSE compared with the WSE, it is logical that the '1 eye' strategy we explore should be the treatment AMD in the BSE only.

J.5.2.4 Model outcomes

The model uses a patient perspective for outcomes, and an NHS and PSS perspective for costs, in line with the manual for developing NICE guidelines (2014). The primary health outcome estimated by the model is the number of QALYs achieved by each strategy, combining the number of years alive with HRQL experienced during that time. The other key model outcome is the total cost incurred by each strategy. If one strategy has higher costs than another, but provides no extra QALYs – or provides fewer QALYs than another, but no cost saving – then it is *dominated* and is not considered to be cost-effective use of resources. The model uses the incremental QALYs and incremental costs of all remaining (non-dominated) strategies to produce the primary outcome of the model – the incremental cost-effectiveness ratio (ICER), a combined measure of net benefit.

An ICER should be compared with the opportunity cost of allocating limited resources to something else in the NHS. For example, adopting a strategy that has an incremental cost of £20,000 compared with not doing so will require £20,000 of additional funding. This will divert £20,000 from other uses within the health care system which is, in general, considered to lose 1 QALY elsewhere (NICE, 2014). Therefore, adopting the new strategy should generate *at least* 1 additional QALY compared with not doing so, in order to offset the 1 QALY foregone elsewhere in the system. The value of this opportunity cost becomes the 'maximum acceptable ICER', a threshold value with which our model's ICERs should be compared. A credible ICER below this threshold would typically be considered to represent a cost-effective use of NHS resources, as the number of QALYs gained at least offset the QALYs foregone by diverting resources from other uses (NICE, 2014).

As noted in Section J.5.2.3, the model can compare the health and cost outcomes associated with 160 different, unique treatment strategies, plus 1 strategy of no treatment. Interpreting the ICERs of such a large number of alternatives can be difficult, as many strategies are typically dominated; their ICERs are omitted and so the implications of their incremental QALY and costs results might be ignored. Given this, we also present results as net health benefit (NHB). NHB converts the monetary value of a cost into an equivalent number of QALYs, based on the opportunity cost of one QALY (e.g. £20-30,000). This effectively relabels a given cost as the number of QALYs that amount of money could 'buy' for the NHS. Alternatively, it can be interpreted as showing the net balance of the QALYs gained by a course of action and the QALYs lost from elsewhere in the system by diverting resources to fund this strategy. The NHB and is calculated as follows:

NHB = Total QALYs of Strategy – (Total Cost of Strategy / Opportunity Cost of 1 QALY)

With this approach, no strategies are removed from the analysis, even if they are dominated. All strategies will have a NHB value, being the overall QALYs gained by the system as a whole if that strategy is adopted, which may be easier to interpret when a large number of alternatives are available. Furthermore, interpreting different NHB figures is simple: if strategy X has a higher NHB than strategy Y, then we can say that strategy X is cost effective compared with strategy Y at the specified value of 1 QALY. It follows that the strategy producing the highest NHB figure is always the optimal strategy from those being compared. NHB and ICERs are essentially different ways of coming to the same conclusion; decision making based on NHB will always lead to the same outcome as decision making based on ICERs.

J.5.2.5 Key assumptions

There are a number of assumptions built into the economic model which need to be considered when interpreting the results generated. These are summarised in Table 24.

Table 24: Key assumptions of new cost–utility model

Interventions

- Treatments that are not routinely available have been excluded from the analysis:
  - Aflibercept 0.5 mg
  - Pegaptanib sodium
  - Ranibizumab 0.3 mg
  - Ranibizumab 2 mg
- 'Treat as needed and extend' (PRNX) regimens are not included in the base-case analysis, as it is connected to the network of evidence by a single, small sample trial.

Network meta-analysis

- The relative effects on visual acuity of different aspects of treatment are independent of each another.
- Each potential treatment includes 6 components: a drug; a treatment frequency; the potential use of a loading phase; the use of PRN treatment; the use of PRNX treatment; and the use of TREX treatment. Our NMA estimates an independent treatment effect associated with each of these components.
  - For example, the effect that can be attributed to ranibizumab is the same regardless of whether it is given monthly of every 2 months. The dosing frequency has its own relative effect parameter.
  - Similarly, the effect that can be attributed to TREX regimens is the same regardless of whether the drug being given this way is aflibercept, ranibizumab or bevacizumab. Each drug will have its own relative effect parameter.
  - This allows the model to simulate what some treatment options might look like, even though they might not presently exist in clinical reality (e.g. ranibizumab given every 2 months).

Treatment effects

- The mean change in visual acuity is characterised by a normal distribution, from which it is possible to estimate the probability of gaining or losing any given number of letters
- For the 'average' eye, the probability of moving up (or down) by 1 health state (15-letter range) is equal to the probability of gaining (or losing) between 7.5 and 22.5 letters. Here, the 'average' eye is defined as having the midpoint VA in any given 15-letter range (e.g. 48 letters in the state '55-41').
- Similarly, the probability of moving up (or down) by 2 health states is equal to the probability of gaining (or losing) more than 22.5 letters.
- A movement of 2 health states is the maximum permissible transition in any 1 model cycle (year). For example, an eye cannot move from state '85-71' to '40-26' in one cycle.
- Transition probabilities are weighted by baseline visual acuity according to observational treatment response data (Buckle at al. 2016). This reflects a ceiling effect in eyes with good baseline acuity, and a floor effect in eyes with poor baseline acuity.

Long-term effects

- Two sets of relative treatment effects have been estimated: from year 0 to year 1, and from year 1 to year 2. The relative effects from year 1 to year 2 are assumed to persist over time. For example, the relative effect attributed to aflibercept in year 2 is assumed to hold in future years of treatment
- The relative effect of using a loading phase ceases after year 2.
- After year 2, eyes still receiving treatment experience visual acuity change consistent with the 3-year ARMD database, which shows a decline of 2.5 letters per year in patients treated with PRN ranibizumab. Relative treatment effects are applied to this 2.5-letter decline for each intervention according the relevant year 2 NMA coefficients.

- Eyes still receiving treatment with PDT after 2 years will experience a 3.7-letter decline each year as per SEVEN-UP (i.e. long-term effects are equivalent to anti-VEGF therapies).
- Eyes on the sham injections arm will be subject to 'year 1 to year 2' annual transition probabilities for the remainder of the simulation duration beyond year 2.

Treatment discontinuation

- An NMA was developed to predict treatment discontinuation using the same methodology as for treatment effects (i.e. a relative effect for each component of treatment).
- There is no enforced cap on treatment duration.
- Eyes with treatment discontinued experience visual acuity change consistent with the sham injection arms of clinical trials.
- No second-line therapies are simulated, in reflection of recommendations made elsewhere in this guideline.

Adverse events

- The adverse event rates of ranibizumab, aflibercept and bevacizumab are the same, with the exception of gastrointestinal disorders, which are more likely to occur in patients treated with bevacizumab.
- PDT has a different adverse event profile, composed of back pain, injection site reactions, photosensitivity and temporary acute vision loss.
- Treatment appointments are associated with a 100% utility loss for 1 day, to account for anxiety in the days preceding treatment and discomfort in the days following an injection. This occurs in 50% of patients (varied from 0% to 100% in sensitvity analysis)

AMD and visual acuity at presentation

- At presentation, at least 1 eye has late AMD (wet active). The proportion of patients with bilateral AMD at baseline is informed by observational UK data from Liverpool and Sheffield provided by committee members.
- The baseline visual acuity of all eyes is informed by observational UK data from Liverpool and Sheffield provided by committee members.

Unaffected fellow eyes

- The visual acuity in non-neovascular fellow eyes of people with unilateral late AMD (wet active) remains constant, unless the eye becomes neovascular.
- An unaffected fellow eye will remain in the same 15-letter health state for the model duration if the eye never develops late AMD (wet active).
- The rate of neovascularisation is informed by the UK AMD database data on second-treated eyes: 42.0% after 3 years, which gives an annual probability of 16.6%.
- Upon neovascularisation, the visual acuity distribution for fellow eyes is estimated using the distribution of unilateral eyes from the observed UK data modified according to data on the likelihood of earlier recognition in fellow eyes.

Number of injections

- The number of injections per year is not widely reported in the clinical trials, therefore this information been estimated for some regimens. Where there are no data for a type of regimen, the following assumptions are made:
  - For bevacizumab regimens, missing data are assumed to be proportionally equivalent to the observed ranibizumab data.
  - For PRN regimens, missing data are assumed to have a constant proportion compared with monthly treatment. A loading phase is associated with 0.2 extra injections per year, on average.
  - For 2 or 3 monthly regimens, missing data are assumed to be half and one-third of the data for monthly treatment respectively.
  - For injections in year 2, missing data are assumed to have a constant proportion relative to year 1 data as observed in the ranibizumab evidence.
  - For TREX regimens in year 2, missing data are assumed to have a constant proportion relative to year 1 data as PRN.

Long-term treatment

- Patients can receive treatment beyond year 2.
- The constant number of treatments required is calculated relative to the 3-year ARMD data for ranibizumab PRN, showing 3.7 injections per year. The propotional difference between a regimen and ranibizumab PRN in their year 2 injection requirement is assumed to be maintined into year 3 and therafter.
- For all interventions, the number of treatments required per year beyond year 3 remains constant. This is based on stable injection frequency over time reported in long-term ranibizumab PRN evidence (Gillies et al. 2015).

Treatment appointments

- All treatment appointments occur in an outpatient clinic.
- All treatments are 'one-stop' appointments, where monitoring and treatment occur at the same time. In people with bilateral late AMD (wet active), both eyes are treated at the same appointment.
- The cost of the administration is obtained from NHS reference costs. The cost estimated the IVAN study investifators using a micro-costing approach were judged to be too low by the guideline committee.
- The cost of administration in patients who are treated in both eyes is 1.5 times the administration cost of treating 1 eye.

Monitoring appointments

- Monitoring occurs at the same appointment as treatment, in a '1-stop' clinic.
- Monitoring is performed by an OCT examination. A fluorescein angiography is used a maximum of once per eye, to confirm a diagnosis of neovascular AMD in that eye.
- An OCT is performed at every treatment appointment.
- Additional monitoring visits are required for patients receiving PRN and PRNX treatment, because these regimens will involve some appointments at which the clinician decides that treatment is not needed. The number of additional monitoring appointments is calculated by the total number of visits in the SALUTE trial (for years 1 and 2) then the ARMD dataset (for years 3+), minus the number of injections given in that year.
- The cost of an OCT is the same when monitoring unilateral and bilateral neovascular AMD.
- The cost of monitoring is obtained from NHS reference costs, rather than the micro-costing exercise that was performed alongside the IVAN trial.

Quality of life

- The quality of life of modelled patients is dependent on visual acuity, age and adverse effects from treatment (e.g. injection-related anxiety, pain and complications).
- The impact of visual acuity on quality of life is predominantly associated with the better-seeing eye, informed by a regression model from a UK simulation contact lens study (Czoski-Murray et al. 2009).
  - The impact of a change in visual acuity on quality of life is adjusted by a scaling factor of 0.3 to inform the impact of the same change in visual acuity in the worse-seeing eye.

J.5.3 Model parameters

J.5.3.1 General approach

Identifying sources of parameters

The relative effectiveness of different interventions included within the model was informed by a NMA described Section J.5.3.3 which was itself informed by RCTs included in the clinical review (see Appendix E). The meta-regression provides estimates of the mean change in VA attributable to each drug, dosing regimen, and the presence of an initial loading phase. With this, we are able to simulate any intervention that can be described through this 'catalogue' of items; that is, the drug used, the regimen by which that drug was

given, and whether or not an intensive initial loading phase was used. Additional covariates specified whether the regimen was delivered in PRN, PRNX and TREX regimens, included to capture the impact of these 'discontinuous treatment' regimens.

Modelling in this way possesses the underlying assumption of an equivalent treatment effect associated with each covariate, independent of the other covariates. For example, there is a fixed relative effect attributable to 'PRN-ness', consistent regardless of the drug used. Similarly, the effect specifically attributable to 'aflibercept' is consistent, regardless of whether a loading phase was used. As described in J.5.3.3, this additive approach was arrived at following extensive exploration of alternative NMA model structures, including those that estimated separate effects for each treatment.

With the exception of treatment effect parameters, clinical model inputs were identified through informal searches that aimed to satisfy the principle of 'saturation' (that is, to 'identify the breadth of information needs relevant to a model and sufficient information such that further efforts to identify more information would add nothing to the analysis' [Kaltenthaler et al. 2011]). We conducted searches in a variety of general databases, including Medline (via PubMed) and the Cochrane Database of Systematic Reviews. Where suitable evidence could not be identified, model parameters were also sought from the guideline committee directly. Clinical parameters informed by these searches and committee discussions included adverse event rates and long-term treatment effects.

When searching for quality of life, resource use and cost parameters, the systematic review of economic analyses for anti-angiogenic treatments was typically the first source of evidence considered, alongside economic evaluations conducted for previous NICE TAs in AMD (TA 68, TA 155 and TA 294). During the review, we also retrieved articles that did not meet the formal inclusion criteria, but appeared to be promising sources of evidence for our model. We studied the reference lists of articles retrieved through any of these approaches to identify any further publications of interest. Other databases that were considered, designed for this purpose, were the Cost-Effectiveness Analysis Registry and the NHS Economic Evaluation Database (NHS EED).

In cases where there was paucity of published literature for values essential to parameterise key aspects of the model, data were sought from unpublished sources. In our model, the distribution of eyes by level of VA at baseline, and the proportion of patients presenting with bilateral late AMD (wet active), were informed this way. Further details are provided below.

J.5.3.2 Cohort parameters and natural history

Epidemiological parameters were required to inform the following model inputs:

- Cohort age and gender
- The distribution of eyes by VA at baseline
- The relationship between baseline VA and treatment effect
- The rate at which AMD develops in the fellow eye
- VA outcomes in the long-term.

Age and gender at baseline

The age and gender of the cohort are required by the model to calculate the mortality rate for a given patient. A patient's HRQL is also dependent on their age. These data were sourced from the large, observational, UK AMD database, which holds data on 11,135 patients treated with ranibizumab in a total of 12,951 eyes (Tufail et al, 2014). The mean age of these patients was 79.7 years (range: 55–101), and 36.6% of the sample was male.

Visual acuity at baseline

The model requires a distribution of patients across VA-related health states at baseline. This should attempt to present a reasonable reflection of the expected VA profile of people with AMD at diagnosis. A simplifying assumption would be to assumption all patients have the same level of VA at baseline (e.g. 6/12), however this is known to be uncharacteristic of practice (Zarranz-Ventura et al. 2014).

No published data were identified to inform the proportion of patients in each of our 15-letter VA health states at baseline. We therefore sought unpublished data and, through guideline committee members, obtained data from two UK patient samples (Royal Liverpool and Broadgreen University Hospitals Trust and Sheffield Teaching Hospitals NHS Foundation Trust). Data included the presenting VA of eyes affected by late AMD (wet active), stratified by whether the eye was unilaterally affected (Liverpool data only, N=198 eyes) or one of a pair of bilaterally presenting neovascular eyes. For both datasets, we calculated the proportion of presenting eyes in each of our 15-letter VA health states. In our model, all patients are assumed to possess late AMD (wet active) in at least 1 eye at baseline (meaning all patients are potentially eligible for treatment in at least 1 eye).

The VA of unilaterally neovascular eyes was informed by the Liverpool data. For bilaterally neovascular eyes, we took an unweighted mean average of the 2 datasets (Table 25). The use of an unweighted average reflects that they represent 2 distinct samples from different parts of the country, whereas a weighted average would make our baseline population more representative of the larger Liverpool dataset. In patients with bilateral disease, the VA of each eye is drawn separately, and independently, from the bilateral distribution in Table 25.

The distributions suggest that the VA of unilaterally neovascular eyes tends to be worse than the VA of bilaterally neovascular eyes. The guideline committee were satisfied that this is clinically plausible; people are less likely to recognise the vision in 1 eye worsening if they possess better vision in their unaffected fellow eye, meaning the affected eye will have declined further by the time they seek medical advice and present at hospital.

The fellow eye at baseline

No published data were identified regarding the proportion of patients who present with bilateral late AMD (wet active). This model parameter was therefore also obtained from the observational data from Liverpool and Sheffield. An unweighted average of the 2 datasets was calculated, again to reflect that they represent two distinct samples from different parts of the country. The resulting figure is 7.3% of patients (Liverpool: 20/218; Sheffield: 3/55). The guideline committee had hypothesised that the proportion patients presenting with bilateral disease was around 10%, and were satisfied that the data figure was close to their estimate and plausible. This value therefore informs the proportion of patients with late AMD (wet active) in both eyes at the start of the model. As described above, the presenting VA profile of each of these eyes is drawn independently from the observational UK data distribution in Table 25.

Observational data regarding the presenting VA of non-neovascular fellow eyes were obtained from both the Liverpool (N=156 eyes) and Sheffield (N=52 eyes) sites. These were converted into the proportion of eyes in each of our 15-letter VA health states and, as with neovascular eyes, an unweighted average of the 2 datasets was calculated (see Table 25). The resulting distribution was used as our baseline distribution of VA in non-neovascular fellow eyes, drawn independently of VA in the eye with late AMD (wet active). It suggests that unaffected fellow eyes of people presenting with unilateral late AMD (wet active) typically possess better VA than the eye with late AMD (wet active), which the guideline committee deemed to be clinically plausible.

Table 25: Distribution of presenting eyes by visual acuity from UK observational data

		Unilateral late AMD (wet active)		Bilateral late AMD (wet active) Liverpool & Sheffield
		Affected eye Liverpool data	Fellow eye Liverpool & Sheffield	
VA at diagnosis of AMD	≥85	1.01%	5.77%	1.25%
	85-71	15.15%	69.87%	31.25%
	70-56	29.80%	15.71%	42.50%
	55-41	29.29%	4.81%	15.00%
	40-26	15.66%	3.85%	7.50%
	≤25	9.09%	0.00%	2.50%

Developing neovascular AMD in the fellow eye

Fellow eyes that do not have late AMD (wet active) at baseline are subject to a risk of neovascularisation over time. Data from the UK AMD database are used to inform this model parameter. The study reports that 42.0% of fellow eyes developed AMD over 3 years, in patients whose fellow eye VA was ≥20/200 at baseline (Zarranz-Ventura et al. 2014). The equivalent rate in all patients is 22.6%; however, this includes people whose fellow-eye VA was <20/200 at baseline. Given the observational nature of the dataset, participants with this level of visual impairment are likely to have extensive disease history, and potentially treatment history predating the use of anti-VEGF therapies.

A number of alternative long-term studies report rates of AMD development in fellow eyes. The UK AMD database value was preferred to these much older and/or smaller studies; however their results are reasonably consistent with our 42% figure at year 3. Finger et al. (2014) presented approximately 45% of fellow-eyes developing CNV at year 3. The Submacular Surgery Trials Research Group (2004) reported a rate of around 40% over 3 years when a number of risk factors are present. The Macular Photocoagulation Study Group (1997) reported a rate of 28% over 3 years.

Upon developing AMD, we assume that a fellow eye can move into any VA-range health state in the model (similar to a previous CUA [Butt et al., 2015]). The distribution of these eyes between VA states, upon diagnosis, is informed by our distribution of first-treated eyes, adjusted to account for the higher likelihood of fellow eyes having VA ≥6/12 due to being diagnosed earlier. First-treated eyes are 17% likely to have VA of 6/12 or better, compared with 47% of second-treated eyes, based on data from the UK AMD database (Zarranz-Ventura et al. 2014). The difference was re-estimated on a probit scale, and was then applied on our VA distribution of unilaterally presenting neovascular eyes (Liverpool data, N=198), thereby estimating the equivalent distribution of fellow eyes when they develop late AMD (wet active). The resulting distribution is shown in Table 26, and is relatively similar to the distribution of bilaterally-affected eyes by VA in Table 25.

We identified no published evidence regarding the progression of VA in non-neovascular fellow eyes, and the guideline committee were not aware of any such data. The model therefore assumes that the VA of non-neovascular eyes remains constant (i.e. in the same 15-letter state) until the eye develops late AMD (wet active).

Table 26: Estimated distribution of previously unaffected fellow eyes at the time of diagnosis of late AMD (wet active)

		At diagnosis of late AMD (wet active)
VA at diagno	≥85	7.44%
	85-71	38.22%

sis of AMD	**70-56**	32.49%
	55-41	15.92%
	40-26	4.58%
	≤25	1.34%

Long-term visual acuity

Randomised evidence in the anti-VEGF and PDT clinical trials is typically 1 to 2 years in duration. Previous cost–utility models have approached the lack of long-term evidence in various ways, such as assuming treatment ceases after 2 years (Colquitt et al. 2008; Ghosh et al. 2016; Raftery et al. 2007), or that all patients sustain their level of VA beyond 2 years (Stein et al. 2014). These approaches are likely to provide inaccurate estimates of longer-term differences in costs and health outcomes between treatments. Treatment does not necessarily stop after 2 years, meaning there are long-term cost implications. Furthermore, the available longer-term observational evidence suggests that VA does not remain constant over time (Rofagha et al. 2013).

Given this, it is necessary to extrapolate beyond the typical 1 to 2 years of comparative evidence using available natural history data. For this, we use VA data from the third year of treatment in an observational UK dataset following people being treated with ranibizumab PRN (the ARMD database; Tufail et al. 2014). Alternative long-term VA data sources are used in sensitivity analyses. Our methods of applying long-term VA data are detailed in Section J.5.3.3.

Mortality

Mortality is modelled using National Life Tables for England and Wales (2013–15). The model looks up the relevant annual probability of mortality given the patient's age and gender. An increased mortality risk is included for patients with low vision, informed by a structural equation model developed using a dataset of recorded deaths in the US (Christ et al., 2008). The effect of having severe visual impairment – defined as being blind in both eyes – on mortality hazard, relative to no visual impairment, is characterised by a hazard ratio of 1.54 (95% CI: 1.28, 1.86). In the model, this hazard ratio is applied to patients whose VA is ≤25 ETDRS letters in both eyes. The equivalent hazard ratio for people with some visual impairment (but not blindness in both eyes) is 1.23 (95% CI: 1.16, 1.31). In the model, this is applied to patients whose VA is less than 55 ETDRS letters in at least 1 eye.

J.5.3.3 Treatment effects

Network meta-analysis

Relative effectiveness inputs to the economic model were obtained from an NMA, full methods and detailed outputs of which are provided in Appendix G. The key effectiveness outcomes used by the NMA were mean differences (MDs) in VA from baseline to 1 year and from baseline to 2 years. These data were extracted from RCTs identified in the clinical evidence review. A single model with a bivariate normal likelihood was used to synthesise the 1-year and 2-year outcomes simultaneously. A correlation structure between 1-year and 2-year effects was assumed, informed by the RCT data.

Each intervention for which data were extracted could be defined by 2 distinct features: its 'agent' and its 'characteristics'. For example, the ANCHOR, CATT and MARINA studies included monthly ranibizumab treatment arms; here, the agent was ranibizumab, and its characteristic was the frequency of injections (one per month). Defining interventions this way meant we had treatment effects associated with 7 unique agents and 5 characteristics (Table 27).

Table 27: Agent and characteristic nodes used in the NMA

Agent (treatment)	Characteristic (treatment frequency)
Aflibercept 2.0 mg	Loading phase (presence of)
Aflibercept 0.5 mg	PRN regimen
Bevacizumab 1.25 mg	PRNX regimen
PDT	Frequency of continuous treatment regimen
Ranibizumab 0.5 mg	TREX regimen
Ranibizumab 2.0 mg	
Sham injections	
Note: neither aflibercept 0.5 mg nor ranibizumab 2.0 mg are included as comparators in the economic model, following the advice of the guideline committee (see Secton J.5.2.3). However these trials provide informative data, such that retaining them in the NMA provided a superior model fit.	

We employed a meta-regression approach to estimate the relative effect on mean VA change that can attributed to each of these features. We assume that the relative effect of each characteristic is shared between different agents; for example, the effect associated with using a PRN regimen is the same regardless of which agent is used this way. Monthly ranibizumab (0.5 mg) was selected to be the reference treatment for the analysis, as it is the best-connected active treatment in the network. The meta-regression therefore provides 1-year and 2-year parameters for each agent listed in Table 27 relative to ranibizumab 0.5 mg, and similarly, parameters for each characteristic relative to continuous monthly dosing. Adding the parameters for any combination of agent and characteristics – for example, bevacizumab with a loading phase following by PRN treatment – provides an estimate of the effect on mean VA change of that intervention, relative to monthly ranibizumab (0.5 mg), at years 1 and 2.

As shown in the schematic in Section J.5.2.2, the economic model requires treatment effect estimates for both year 1 and year 2 of treatment. The second of these – the effect specifically attributable to continuing treatment for a second year – is not widely reported in the trial literature, which is why our NMA utilises ‘baseline to year 1’ and ‘baseline to year 2’ outcomes. Doing so allows us to subtract the 1-year results from the 2-year results, thereby estimating the proportion of the overall effect that is attributable to treatment in year 2.

Baseline synthesis

Before undertaking the meta-regression, a baseline synthesis was conducted to inform the absolute effectiveness of the reference treatment: monthly ranibizumab 0.5 mg. This analysis is also detailed in Appendix G. Like the relative effects synthesis, year 1 and year 2 mean changes for monthly ranibizumab (0.5 mg) were estimated in a single synthesis with a bivariate normal likelihood. The resulting reference mean change from baseline to 1-year is +8.2 letters at year 1. The accompanying standard deviation (13.7) was not obtained from the synthesis model itself; the model produces a measure of variance that focuses in on its own estimated mean effect, making it closer to a standard error than the representative standard deviation required. There is no clear rationale for favouring any 1 trial included in the baseline synthesis as being more representative than the others, therefore the standard deviation is the pooled value of all included RCTs.

The 2-year treatment effect estimated by the synthesis model is a mean change of +7.6 letters. To estimate the effect of continuing treatment into year 2, as is required by the economic model, the 1-year effect can be subtracted from this value. Doing so provides a reference VA change during year 2 of -0.7 letters. The only trial in the baseline synthesis that provides a standard deviation around a mean change in year 2, from a cohort of participants who continued ranibizumab treatment, is the CATT study. The standard deviation from this study (11.1) is therefore applied to our reference year 2 mean change of -0.7 letters.

Meta-regression results

The relative effect prameters obtained from the meta-regression are presented in Table 28. Aflibercept 0.5 mg and ranibizumab 2.0 mg are not included in the economic model, and as such the parameters for these agents are not presented.

The synthesis model was only able to produce year 1 coefficients for PRNX and treatment frequency, owing to a lack of 2-year evidence to inform these relative effects. The economic model therefore assumes that the relative effects of these characteristics in year 2 are equal to the estimated year 1 coefficients. Comparing the coefficients for characteristics with both year 1 and year 2 estimates suggests that this is likely to be a reasonable assumption, as the point estimates are generally similar and well within the 95% confidence intervals of each other.

The treatment frequency coefficient should be interpreted as the relative effect of extending the interval between treatments by 1-month for a continuous regimens. For example, the coefficient for aflibercept is added once to obtain the effect of 2-monthly aflibercept relative to monthly, and twice to obtain the effect of 3-monthly aflibercept relative to monthly. This coefficient is negative, meaning effectiveness is reduced by extending the interval between injections. In estimating the relative effect of each additional month between treatments, bevacizumab and ranibizumab data were pooled. Doing so produced the optimal model fit, determined by comparison of deviance information criterion statistics (see appendix G). This means bevacizumab and ranibizumab are assumed to share a common relative effect associated with extending treatment intervals, which has biological plausibility as they are similar monoclonal antibodies.

To estimate the coefficients for a loading phase – a 3-month period of monthly treatment during treatment initiation – the evidence synthesis used data on PRN regimens only. This is a limitation of the synthesis. It was not possible to disentangle the use of loading phases from 2-monthly and 3-monthly continuous regimens (monthly regimens contain a loading phase by design). All 3-monthly continuous treatment arms in the RCTs did include a loading phase. This means 2 additional injections were provided relative to a 3-monthly regimen without a loading phase, with injections at ‘month 0’, ‘month 1’ and ‘month 2’ prior to commencing 3-month intervals. The synthesis model therefore impliclty grants a loading phase ‘boost’ to the effectiveness of 3-monthly regimens. It also does this to the effectiveness of 2-monthly regimens, though here the boost will be less pronounced; firstly because not all 2-monthly treatment evidence included a loading phase, and secondly because in this instance using a loading phase means adding just 1 additional injection (at ‘month 1’). The implication of this is that the effectiveness penalties that we estimate for extending treatment intervals are likely to be underestimated, and the economic model carries this effect forward beyond year 1. However, underestimating this penalty is not expected to significantly impact upon the economic model outcomes, given that the year 1 relative effect coefficient for a loading phase is among the smallest coefficients in Table 28.

Table 28: Meta-regression coefficients used to inform relative treatment effectiveness

Parameter	Year 1 coefficient (95% CI)	Year 2 coefficient (95% CI)
Agent vs. ranibizumab 0.5 mg		
Aflibercept 2.0 mg	-1.981 (-4.767, 0.805)	-0.859 (-2.312, 0.594)
Bevacizumab 1.25 mg	-0.396 (-1.569, 0.777)	0.132 (-0.872, 1.135)
PDT	-20.166 (-23.735, -16.597)	0.207 (-1.621, 2.035)
Sham	-18.947 (-22.098, -15.796)	-3.628 (-5.239, -2.017)
Characteristic vs. monthly treatment		
Loading phase	0.136 (-1.970, 2.241)	0.519 (-1.499, 2.538)
PRN regimen	-1.467 (-3.115, 0.182)	-0.426 (-2.213, 1.360)
PRNX regimen	4.456 (-3.876, 12.788)	No coefficient

Parameter	Year 1 coefficient (95% CI)	Year 2 coefficient (95% CI)
TREX regimen	-1.285 (-3.625, 1.054)	-3.068 (-9.550, 3.415)
Treatment interval +1 month, aflibercept	-0.840 (-3.248, 1.568)	No coefficient
Treatment interval +1 month, bevacizumab or ranibizumab	-1.524 (-2.800, -0.249)	No coefficient
Note: The reliance of PRNX clinical evidence on a single trial with a small sample is evident in the wide confidence intervals around their relative effect coefficients.		

A case can be made for simulating the treatment effects of only those regimens that have been clinically trialled, rather than taking our approach of estimating the relative effect attributable to each potential agent and characteristic of an intervention. However, we do feel that our approach is more informative, given that many trialled regimens possess little to no evidence beyond 1 to 2 years of follow up. Further, simulating only those treatment strategies with direct evidence produced an inconsistent result whereby bevacizumab delivered every 2 months was, on average, more effective than bevacizumab delivered monthly. All other dosing frequencies follow the expected, clinically plausible dose–response pattern, whereby more frequent dosing produces better visual outcomes. The bevacizumab data artefact is resolved when, as per our chosen NMA method, all data are pooled to provide a relative effect attributable specifically to each component of treatment, including different dosing regimens. Were this inconsistency to remain, the economic model would show 2-monthly bevacizumab treatment to dominate monthly bevacizumab, which would lack clinical validity.

From NMA to transition probabilities

The coefficients from the NMA described above are used to estimate a mean change in ETDRS letters achieved by each possible intervention. For example, the treatment strategy of aflibercept delivered through a loading phase followed by PRN dosing will use the NMA coefficients for aflibercept, presence of a loading phase and PRN dosing to estimate its treatment effect (MD) relative to monthly ranibizumab. With our model possessing a Markov structure of discrete VA health states, it was necessary to estimate how those mean change treatment effects map onto transition probabilities between different states.

To do this, we assume that all mean changes in VA are characterised by a normal distribution. This assumption has been made by other researchers (e.g. Elshout et al. 2012; Claxton et al. 2016).

Upon making this assumption, it is possible to calculate the probability of gaining or losing any number of letters for a given mean change. For example, a treatment providing a mean VA change of +3 letters will be associated with some probability of gaining (and losing) 15 letters.

More formally, the probability that change lies between cut-point c and (c+1) is estimated as follows. Let m be the mean change observed with the reference treatment (which, in our network, is monthly ranibizumab), and s the SD of change on that treatment (calculated as the pooled SD of all studies contributing to our baseline syntheses of monthly ranibizumab, and assumed the same for all treatments). Then,

$$p(change < X_c) = \Phi\left(\frac{X_c - m - d_{Ak}}{s}\right)$$

where d_{Ak} is the mean difference (MD) for the treatment in question compared with treatment 1 and Φ indicates the cumulative distribution of the standardised normal distribution $N(0,1)$. Consequently,

$$p(X_c < change < X_{c+1}) = \Phi\left(\frac{X_{c+1} - m - d_{Ak}}{s}\right) - \Phi\left(\frac{X_c - m - d_{Ak}}{s}\right)$$

The probabilities of gaining and losing 15 and 30 letters or more are often reported in clinical trials. Previous cost–utility models have often used those data directly, and have made the assumption that the probability of gaining, for example, 15 letters or more, is equivalent to the probability of moving up into the next 15-letter health state. We show, below, that this is conceptually incorrect, and so use the above method of deriving the probability of gaining or losing any number of letters from a given mean change to estimate transition probabilities slightly differently. We assume that the VA of an eye is, on average, situated in the middle of its current 15-letter VA range. This assumption is common of previous analyses. However, if the average eye has a VA in the middle of its 15-letter range, the probability of moving up (or down) into the next VA state is the probability of gaining (or losing) *between 7.5 and 22.5 letters* – not the probability of gaining (or losing) 15 or more letters.

To validate taking this approach, we conducted a simulation exercise to explore the impact of defining the probability of moving by one 15-letter health state as (1) equal to the probability of gaining 15 letters (as per previous models), and (2) equal to the probability of gaining 7.5 to 22.5 letters (as per our approach). We generated 100,000 eyes with baseline VA sampled from a plausible distribution: VA(LogMAR) ~ Gamma(2.145, 0.242). Next, we applied a VA change to each eye, drawn from a normal distribution with a mean of 5 letters and SD of 10 letters. The resulting VA of each eye was grouped into our 15-letter VA health states, providing the 'true' final distribution of eyes. We compared this with the distributions estimated through dissecting the normal distribution, as described above; first at gains and losses of ≥30 letters and 15 to 30 letters (as per previous models), then at losses and gains of ≥22.5 letters and 7.5 to 22.5 letters. In each case, the estimated probabilities of moving up and down by 1 state and 2 states were applied to the baseline VA distribution, to produce predicted distributions of eyes following the VA change. The results of this exercise show that using our interpretation of how to estimate transition probabilities produces a much more plausible final distribution of eyes, following a given mean VA change, than the widely-used alternative (Figure 9). In this simulation, the assumption made in previous cost–utility models – that a gain of 15-or-more letters equates to moving up one 15-letter health state – produces a final distribution of eyes that differs markedly from the 'true' distribution. It predicts the number of eyes with VA above 85 letters to be more than double the 'true' number, and the number of eyes with VA ≤25 letters to be less than half the expected amount.

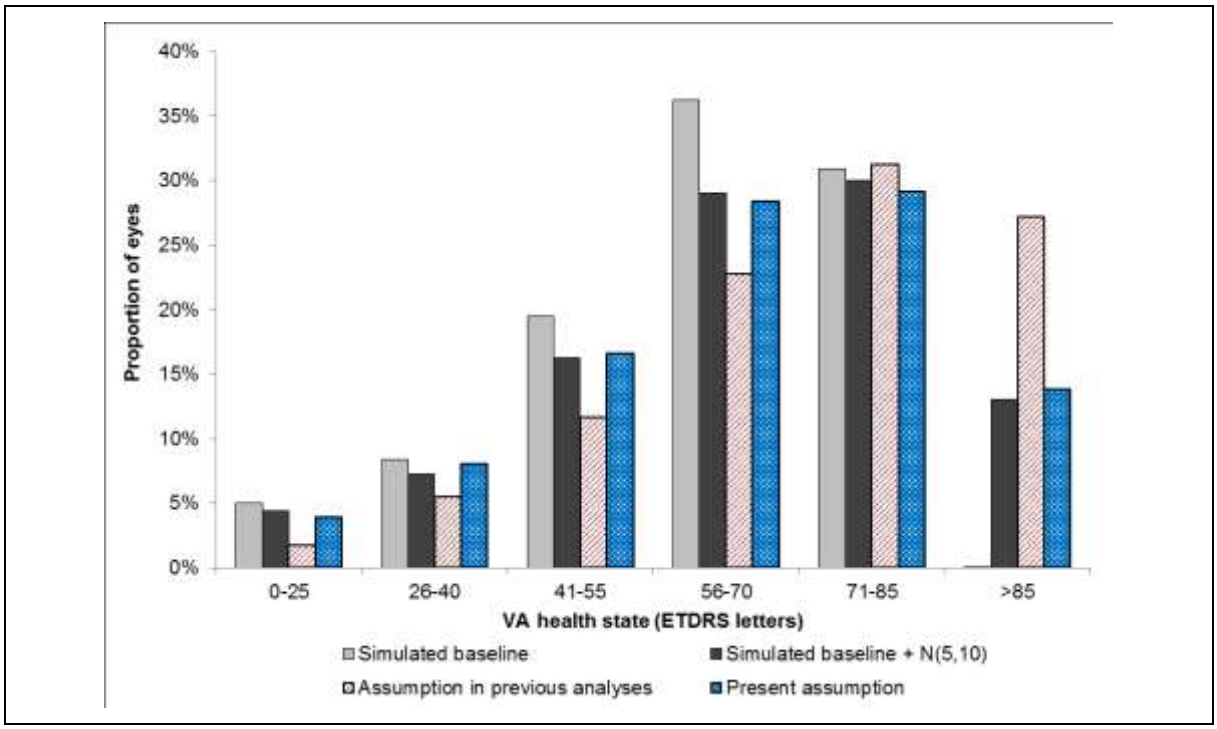


Figure 9: Simulation comparing different assumptions regarding the number of letters required to move up or down by one 15-letter health state

Given the above, in order to map onto our model health states the normal distribution underlying any given mean change is dissected as shown in Table 29.

Table 29: Transitions between VA health states and corresponding section of the normal distribution around the mean change

Model transition required	Probability density from normal distribution
VA worsening by 2 health states	Probability of a loss of ≥ 22.5 letters
VA worsening by 1 health state	Probability of a loss of 7.5 to 22.5 letters
VA remains in the same health state	Probability of a change of -7.5 to +7.5 letters
VA improves by 1 health state	Probability of a gain of 7.5 to 22.5 letters
VA improves by 2 health states	Probability of a gain of ≥ 22.5 letters

The probabilities are converted to odds, from which transition probabilities associated with the required model transitions in Table 29 are calculated, for each treatment strategy. The maximum permissible transition in any year is up or down by 2 VA states, which represents a structural model simplification. However, the probability of moving by 3 states in any one year – thereby gaining or losing at least 37.5 letters – will be negligibly small as mean treatment effects are of much smaller magnitudes. These extreme movements are therefore not captured in the model, with eyes restricted to moving by a maximum of 2 VA states in any 1 year.

We recognise that assuming mean VA changes to be normally distributed represents an important clinical assumption. This assumption was also used in a recent CUA comparing aflibercept and ranibizumab, where the authors present that the probabilities of ≥15-letter VA gains and losses from the VIEW-1 trial are consistent with assuming 1-year mean VA change is normally distributed (Claxton et al., 2016). Given this, we feel it is a justifiable simplification that allows us to estimate transition probabilities that seem sensible, particularly given the absence of alternative evidence regarding the probability of gaining or losing 7.5 and 22.5 letters. Further, we acknowledge that a consequence of our approach to estimating transition

probabilities is that we cannot use results of the 'probability of categorical VA change' synthesis NMA (see Section J.5.3.3) to inform the economic model. We would need such an NMA to be based on the probability of gaining 7.5 and 22.5 letters, but those outcomes are not reported in clinical trials. For this reason, we can only use our mean change NMA (based on mean differences) to inform the economic model.

Impact of initial VA on treatment effects

Treatment effectiveness has been shown to be related to the starting VA of the treated eye (Tufail et al. 2014; Buckle et al. 2016). Eyes with worse VA are observed to respond better to treatment, with a higher mean improvement and higher probability of gaining ≥15 letters than eyes with better initial VA. This is likely to be caused by a ceiling effect, whereby eyes with better initial VA have less potential for VA improvement, whereas eyes with worse initial VA have greater capacity to improve, and less potential to decline.

This effect is captured in the economic model using 1-year data from Buckle et al. (2016). The data show the proportions of patients gaining and losing at least 15 letters after 1 year of treatment with ranibizumab PRN, stratified by starting VA. We have extracted the numerical proportions from these figures (Table 30). These are used to weight our transition probabilities between VA states by the initial distribution of patients between VA states, to reflect that the probability of VA change is dependent on initial VA. First, by assuming that mean changes are normally distributed, as described above, the estimated mean VA change for each comparator – derived using our evidence synthesis and NMA results – are converted into a probabilities of gaining and losing <7.5 letters, 7.5 to 22.5 letters and ≥22.5 letters. These are the probabilities of staying in the same VA health state; moving up or down by 1 state; and moving up or down by 2 states, respectively. The probabilities are converted to odds, and it is these odds that are weighted to adjust for starting VA, using the Buckle et al. evidence. This is performed using the following formula:

$$o_{ref} = \frac{o}{\left(\frac{\sum_{i=1}^{i=x} R_i n_i}{\sum_{i=1}^{i=x} n_i} \right)},$$

where o represents the expected odds of gaining or losing <7.5 letters, 7.5 to 22.5 letters or ≥22.5 letters (informed by our evidence synthesis); R represents the odds ratios of gaining/losing VA from Buckle et al. for i different categories of initial VA; and n represents the number of eyes in each of i initial VA categories. This therefore represents the expected odds across the whole cohort divided by the weighted average of the odds ratios for the different VA categories. The number of eyes in each category (n_i) is informed by the starting cohort used in the model, informed by data from NHS Trusts in Liverpool and Sheffield. Ideally, the clinical trials used to inform the evidence synthesis would be used to inform the baseline distribution of eyes, however these data are not reported, and our "real life" observational data are likely to provide a good estimate.

The above equation is only required to estimate the weighed odds of VA change for one VA state (the reference category in the underlying data), because the odds ratios derived from Buckle et al. can then be used to estimate the equivalent odds of change for all other VA states. In our model, the '56-70 letters' state is the reference state to which the above equation is applied. The resulting weighted odds of VA change are then multiplied by the relevant odds ratio (Table 30) to produce the weighted odds for all other VA states.

Table 30: Weighting the odds of VA change by initial VA – inputs derived from Buckle et al. (2016)

	Initial VA			
	>70 letters	**70-55 letters**	**54-40 letters**	**39-23 letters**
Gaining ≥15 letters				
Buckle (2016)	NR	11.0%	20.6%	28.8%
Odds ratio	-	1.000 (ref)	2.105	3.283
Odds	-	0.113	0.238	0.372
Probability	-	10.2%	19.2%	27.1%
Losing ≥15 letters				
Buckle (2016)	9.2%	9.6%	12.1%	6.7%
Odds ratio	0.950	1.000 (ref)	1.289	0.675
Odds	0.102	0.107	0.138	0.073
Probability	9.3%	9.7%	12.2%	6.8%

This way, mean VA gains are weighted towards eyes with lower baseline VA, as per the clinical evidence. Similarly, the estimated odds of losing VA are weighted by the Buckle et al. data on vision loss stratified by baseline VA. These data have some appearance of the opposite effect to the vision gains data, with worse eyes at baseline having less potential to lose vision than better eyes (a 'floor effect'), though this is much less pronounced. We have restricted our use of the Buckle et al. data to 1 year based on the pattern typical in clinical evidence whereby the majority of VA change occurs in the first year of treatment (Gillies et al. 2015; Tufail et al. 2014; Rosenfeld et al. 2006).

The impact of removing the dependence of treatment effects on initial VA is explored in sensitivity analysis.

Approximations required

Using the Buckle et al. data to weight our NMA-derived odds of gaining and losing letters required a number of approximating assumptions. Firstly, the Buckle data only report the likelihood of gaining and losing ≥15 letters (stratified by initial VA). We have assumed that the odds ratios derived from these data can be applied to the odds of gaining or losing 7.5 to 22.5 letters, which is equivalent to moving up or down by 1 VA health state in the economic model. This approximation allows the odds ratios to fit with our chosen economic model structure. We also apply the same odds ratios to the odds of gaining or losing ≥22.5 letters, which is equivalent to moving up or down by 2 VA health states in the economic model. This is because the Buckle study does not report on the likelihood of gaining or losing a larger number of letters (e.g. ≥30). Effectively, this means we interpret the 'gain of ≥15 letters' data as gaining ≥7.5 letters, and the 'loss of ≥15 letters' as losing ≥7.5 letters.

Secondly, the VA categories into which the Buckle et al. data are stratified do not correspond perfectly with the VA health states used in the economic model. To resolve this, we have assumed that some of the Buckle VA categories can be extended to include additional economic model VA states. The proportion of eyes gaining ≥15 letters is stratified into baseline VA groups of 55–70, 40–54 and 23–39 letters, which does not capture the 2 economic model states with the highest VA (>85 letters and 71–85 letters). We assume that the odds ratios derived for the 55-70 group can also apply to eyes in these 2 states (see Table 31). Buckle et al. stratified the proportion of eyes losing ≥15 letters is stratified into baseline VA groups of >70, 55–70, 40–54 and 23–39 letters, meaning there is an additional 'high VA' group compared with the 'VA gain' stratification. Here, we assume that the odds ratios derived for the >70 letters group can also apply to eyes with VA >85 letters (Table 31). The first approximation may overestimate the likelihood of VA improvement by eyes with VA of 71–85 letters or >85 letters, as the observed ceiling effect suggests they have less

potential to improve than eyes with VA of 55-70 letters. The second approximation may underestimate the likelihood of VA decline by eyes with VA of >85 letters, as these will have greater potential to decline than eyes with VA of 55-70 letters (though evidence of this floor effect is weaker than the aforementioned ceiling effect).

Similarly, the lowest VA category into which the Buckle data are stratified is 23–39 letters (for both VA gains and losses). We assume that this is sufficiently similar to the 26–40 letters VA state in the economic model, and apply its derived odds ratios to this state. We also assume that these odds ratios can apply to eyes in the lowest-VA state in the economic model (≤25 letters; see Table 31). This approximation potentially underestimates the likelihood of VA improvement by eyes with VA ≤25 letters (given the observed a ceiling effect), and overestimates the likelihood of VA decline in those eyes (if there is a floor effect).

Table 31: Mapping the Buckle et al. data onto the economic model VA health states

Outcome of interest	Buckle baseline VA stratification groups	Economic model VA states
Probability of gaining ≥15 letters	55-70 letters	>85 letters 71-85 letters 56-70 letters
	40-54 letters	41-55 letters
	23-39 letters	26-40 letters ≤25 letters
Probability of losing ≥15 letters	>70 letters	>85 letters 71-85 letters
	55-70 letters	56-70 letters
	40-54 letters	41-55 letters
	23-39 letters	26-40 letters ≤25 letters

Treatment discontinuation (NMA)

The rate of treatment discontinuation for each comparator in the economic model is also informed by an NMA. The key outcome used for this was the proportion of trial participants who had discontinued treatment at 1 year. Discontinuation rates are not as well reported by clinical trials as efficacy outcomes, meaning evidence of discontinuation in year 2 is particularly weak. For this reason, our synthesis of discontinuation rates used only 1-year data.

The synthesis model had a binomial likelihood with a logit link, such that the resulting coefficients are estimates of the relative odds of discontinuation on a log-scale. The reference intervention remains monthly ranibizumab; its log(odds) of 1-year discontinuation are -2.331, which equates to a probability of 8.9%. The economic model applies the log(odds) ratios produced by the synthesis model (Table 32) to this reference value directly, from which a 1-year probability of discontinuation is calculated for each comparator. The resulting values are applied in the model for all years, including beyond year 1, such that the probability of discontinuing any particular treatment remains constant over time.

Table 32: Meta-regression coefficients used to inform treatment discontinuation

Parameter	Log(odds) ratio (95% CI)
Baseline log(odds), ranibizumab monthly	Log(odds): -2.331 (-2.719, -1.943)
Agent vs. ranibizumab 0.5 mg	
Aflibercept 2.0 mg	-0.608 (-0.608, 0.683)
Bevacizumab 1.25 mg	0.133 (0.133, 0.157)

Parameter	Log(odds) ratio (95% CI)
PDT	1.072 (0.299, 1.845)
Sham injections	1.157 (0.411, 1.903)
Characteristic	
Loading phase vs. no loading	-0.404 (-1.107, 0.229)
PRN vs. monthly	0.074 (-0.454, 0.603)
PRNX vs. PRN with loading	0.567 (-0.744, 1.878)
TREX vs. monthly	1.737 (-1.073, 4.548)
Treatment interval +1 month, aflibercept	0.377 (-0.365, 1.119)
Treatment interval +1 month, bevacizumab or ranibizumab	0.010 (-0.311, 0.331)

Long-term effects

As discussed in Section J.5.3.2, no comparative trial data exist beyond 2 years of follow-up. To inform long-term VA changes, the model uses the ARMD database evidence in its base-case (Tufail et al. 2014). The observational study provides a mean change in VA from the end of the second year of follow-up to the end of the third year of follow-up among people receiving ongoing treatment with ranibizumab PRN, in graphical form. The empirical number of letters lost was estimated from the figure to be 2.5 letters per year, declining in an approximately linear fashion (Figure 10).

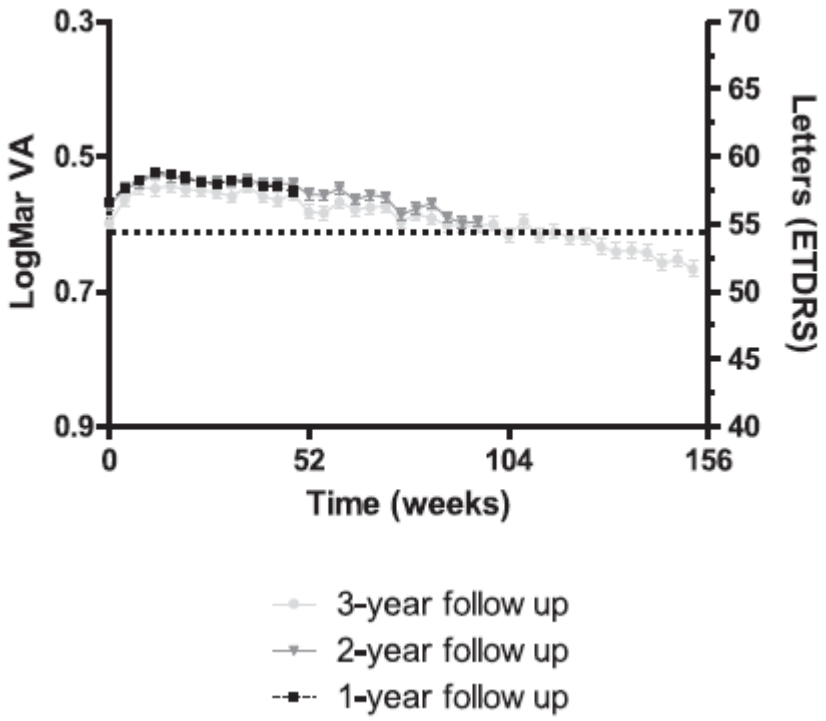


Figure 10: Change in ETDRS letters over time in the UK Age-Related Macular Degeneration (UK ARMD) database (Tufail et al. 2014)

For each simulated treatment, the mean annual VA decline from year 3 onward varies from this 'base' figure of 2.5 letters according to the estimated difference between that treatment and PRN ranibizumab in the NMA based on second-year RCT data. This is because the guideline committee advised that most of the relative treatment effects from year 1 to year 2 (see Section J.5.3.3) can reasonably be expected to be sustained in the longer term. This

means that the relative treatment effect from year 1 to year 2 of, for example, monthly treatment, persists from years 2 to 3, from years 3 to 4, and so on. Although the relative effect remains constant over time, it is applied to a different 'baseline' VA at the start of each year, as VA continues to change over time. The exception to this is the treatment effect attributable to using a loading phase, which is only applied to outcomes from baseline to year 2. The committee advised that they would not expect to observe a sustained differential effect associated with an initial loading phase. Additionally, the number of injections per year, in year 3 and thereafter, is anchored on the mean in the ARMD data, to ensure that long-term effectiveness data are consistent with resource use data. The number of injections is 3.7 per year for ranibizumab PRN. For other interventions it is proportional to this number, based on second-year RCT data (see Section J.5.3.5).

The ARMD data were selected as the reference rate of long-term VA decline while on treatment over 2 alternative observational data sources: the SEVEN-UP study (Rofagha et al. 2013) and the Gillies et al. (2015) data. The rationale for this decision was because the ARMD study provides UK data, like the Gillies et al. evidence, and has the largest number of observations. Clinical experts on the committee advised that the mean annual decline of 2.5 letters derived from the ARMD data was the most reflective of practice, compared to the other 2 estimates of 3.7 letters (SEVEN-UP) and 0.7 letters (Gillies et al. 2015). These alternative sources of data are used in sensitivity analyses, however.

Estimating long-term VA outcomes this way means a 'base' loss of 2.5 letters per year is applied, and the annual mean decline associated with each intervention relative to 2.5 letters is calculated using the year 2 treatment effect NMA coefficients. The mean change is then mapped onto probabilities of categorical VA changes using the normal distribution, z-score methodology described in Section J.5.3.3. A limitation to this approach is that it is unclear what the error bars presented in the ARMD study around long-term VA decline represent; taken literally, they produce very large standard deviations, not in-keeping with those in the wider evidence base. While we can use the estimated standard deviation of the mean change per year in the necessary for the z-score calculations, it was deemed preferable to use the standard deviation reported in the CATT study (the only trial that reports a standard deviation of mean VA change from year 1 to year 2). The standard deviation used is therefore 11.1, for patients on ranibizumab monthly. We adopt this as the standard deviation of the mean annual decline of 2.5 letters for our z-score calculations. The resulting probabilities of gaining or losing 7.5 to 22.5 letters and >22.5 letters are used to estimate transition probabilities between our 15-letter VA health states.

We sought alternative evidence to inform the long-term effectiveness of treatment with PDT, and of natural history for the sham injections arm, given the superiority of anti-VEGF treatment over these alternatives. We felt that anchoring the long-term effectiveness of PDT to ranibizumab PRN, from the ARMD data, would overstate its effectiveness. However, the only long-term evidence for PDT – a 5-year follow-up of the TAP trial – suggests that the VA of eyes continuing to receive PDT plateaus after 2 years (Kaiser et al. 2009). Using this assumption in the model would mean that ongoing treatment with PDT is more effective than treatment with anti-VEGF therapies (which would be anchored to the ARMD decline of 2.5 letters per year). This implies that the only benefit of anti-VEGFs is the VA gains made in the first 2 years of treatment. The guideline committee felt this to be uncharacteristic of clinical reality. As such, the model does use the long-term ranibizumab PRN data to anchor the long-term VA of eyes continuing to receive PDT. It is unclear, given the long-term results from the TAP trial, whether this is an optimistic or pessimistic view of PDT effectiveness. With respect to sham injections, the year 1 transition probabilities are repeated indefinitely to produce a stable natural history projection of VA.

The long-term VA of patients who have discontinued treatment is estimated in the model using the year 1 NMA coefficient for the sham arm. Given the NMA coefficient for the relative effectiveness of sham injections, this means these patients experience more rapid long-term VA decline than patients who continue to receive treatment (results presented in Figure 13).

A number of scenario analyses have been performed to explore the impact of different assumptions to extrapolate beyond the available randomised data. These include:

- Assuming that only 1-year RCT data exist, such that the second year relative effects and number of injections have to be extrapolated, and ocular adverse events and long-term treatment effects are re-estimated, using only 1-year data.
- Ceasing the 'year 1 to year 2' relative treatment effects beyond year 2. In this scenario, after 2 years, eyes on all active treatment arms experience an annual decline in VA of 2.5 letters, as per ranibizumab PRN from the ARMD database (Tufail et al. 2013).
- A scenario that expands upon this further, by assuming equal VA decline following year 2, like above, as well as equal rates of treatment discontinuation. This scenario also applies an equal number of injections and monitoring visits per year for all arms (all set equal to ranibizumab PRN). This scenario therefore removes any differential effects and costs beyond the available randomised data.
- Assuming that VA declines more rapidly than is observed in the ARMD data. The alternative inputs were obtained from an observational study of treated eyes (SEVEN-UP; Rofagha et al. 2013), which reported a decline of approximately 3.7 letters per year from 65 patients followed up 7.3 years after their initial ranibizumab injection. This decline in VA of 0.7 letters per year becomes our 'anchor' decline in this scenario. Additionally, the number of injections of ranibizumab PRN becomes 2.0 per year (after year 2), in this scenario, reflecting the SEVEN-UP data (see Section J.5.3.5).
- Assuming that VA declines less rapidly than is observed in the ARMD data. The alternative inputs were obtained from an observational Australian study of treated eyes (Gillies et al. 2015), which reported a decline of approximately 3.3 letters over a 5 year period, after the first 2 years of treatment (extracted from a figure in the publication). This equates to decline in VA of 0.7 letters per year, which becomes our 'anchor' decline in this scenario. Additionally, the number of injections of ranibizumab PRN becomes 4.9 per year (after year 2), in this scenario, reflecting the Gillies et al. data (see Section J.5.3.5).
- Applying NMA relative effect estimates for sham injections after treatment year 1, rather than the base-case assumption of repeating year 1 effects.

J.5.3.4 Adverse events

Previous CUAs that have attempted to capture ocular adverse events have shown them to have a negligible impact on results (e.g. Dakin et al. 2014, Raftery et al. 2007, Vottonen et al. 2016). This is not surprising, as safety evidence suggests that there is little difference in ocular complication rates across anti-VEGF therapies (see Guideline Chapter 10). To reflect this in our model, ocular adverse event rates associated with anti-VEGF therapies (Table 33) are applied to aflibercept, ranibizumab and bevacizumab equally. The ocular adverse events included in the model were those reported as serious events in a Cochrane systematic review of ranibizumab and bevacizumab (Solomon et al. 2014), and were validated with the guideline committee. Event rates were parameterised for the model using 2-year data from this review. The guideline committee also advised that occurrence of stroke should also be captured. Stroke data were reported in the Cochrane review, with no statistically significant difference between ranibizumab and bevacizumab.

There is no evidence of a different ocular or stroke safety profile for aflibercept, therefore the same ocular adverse event rates are used in the model for treatment with aflibercept. It is likely that including equal event rates this way will have only a very small impact on incremental costs and QALYs between anti-VEGF treatments (better treatments will cause patients to remain on treatment for longer, and therefore at risk of adverse events for longer). However, as a significant reduction in ocular events was identified for PRN regimens compared with continuous regimens (RR: 0.31, 95%CI [0.13, 0.78]; see Chapter 10). The impact of applying this relative risk for PRN and PRNX regimens on cost–utility results was explored in a scenario analysis.

The Cochrane review found evidence that treatment with bevacizumab causes a small but statistically significant increased risk of gastrointestinal events compared with ranibizumab. Although the guideline committee did not agree that a gastrointestinal event risk associated with bevacizumab is true of clinical practice, it agreed that it was appropriately conservative to assume the risk is genuine. Therefore, the only difference in adverse event rates between anti-VEGF therapies in our model is the rate of gastrointestinal events experienced by patients treated with bevacizumab (Table 33). However, a scenario analysis was performed in which the annual probability of experiencing endophthalmitis while receiving treatment with bevacizumab was increased. This scenario was included to explore the extent to which its ocular event profile might impact on its cost-effectiveness outcomes, given a recent report (Messori, 2017) and because bevacizumab is not currently licensed for the treatment of AMD.

The guideline committee advised that PDT is associated with a very different safety profile to anti-VEGF therapies, with PDT patients at risk of a different set of events, including photosensitivity and infusion-related back pain. For our model, event rates for these AEs (Table 33) were parameterised using 2-year data from a Cochrane systematic review comparing PDT with placebo (Wormald et al. 2007).

For all adverse events, the published event rates are converted to annual probabilities by the model, and patients on treatment in either or both eyes experience each event according the annual probability of that event for the relevant treatment.

Table 33: Adverse event data and annual probabilities used in the model

Adverse event	Pooled 2-year data (Events / N)	Annual probability in model
Treated with anti-VEGF therapy		
Cataract	2 / 610	0.16%
Endophthalmitis	11 / 1185	0.47%
Gastrointestinal event	37 / 882 (bevacizumab) 14 / 913 (ranibizumab)	2.13% (bevacizumab) 0.77% (aflibercept, ranibizumab)
Retinal detachment	1 / 610	0.08%
Retinal tear	4 / 610	0.33%
Stroke [a]	25 / 1795	0.70%
Treated with PDT		
Infusion-related back pain	49 / 958	2.59%
Injection site reaction	85 / 714	6.14%
Skin photosensitivity	15 / 627	1.20%
Temporary acute vision loss	14 / 714	0.99%

Note: a) A minor limitation is that the probability of stroke only occurs for patients on treatment with anti-VEGF therapy, with no background incidence for patients off treatment or on the PDT or sham injection arms. No placebo-controlled RCTs were identified that provided sufficient detail of stroke incidence on the control arm to adjusted for background risk of stroke.

J.5.3.5 Resource use

The primary resource use requirements included in the model fall into one of three categories: treatment-related, vision-related and adverse event-related.

Treatment-related resource use

Treatment-related resource requirements include the therapies themselves, administration of treatment, and ongoing monitoring of a patient's condition. The model assumes that all treatments are administered at '1-stop' appointments; that is, any monitoring required (such

as OCT or VA examinations) can occur on the same day as an injection. Treatment of both eyes is also assumed to occur on the same day in patients who require 2-eye treatment, for all active treatments (including PDT). Following advice from the guideline committee, 2-eye treatment requires double the drug cost (except in the case of verteporfin where 1 vial is sufficient), and 50% higher treatment administration costs due to additional time spent preparing the patient and reviewing images.

– Appointments

In the base-case analysis, all treatment-related hospital appointments are assumed to occur in an outpatient clinic setting. This assumption was based on feedback from the guideline committee, who advised that people with late AMD (wet active) are now routinely treated as outpatients, often in specific wet AMD clinic sessions.

The economic analyses conducted for NICE TA 294 used Hospital Episode Statistics (HES) data to estimate the proportion of wet AMD treatment visits conducted as outpatient procedures and the proportion conducted as day case admissions. A weighted average of outpatient and days procedures obtained from HES records across the following OPCS codes:

- C79.4: Injection in vitreous body NEC
- C89.3: Injection of therapeutic substance in posterior segment of eye NEC

These are general codes that will include procedures that are not treatment of wet AMD. It is not possible to derive further granularity than this from the HES data; however the observed trend over time is one of intraocular injections increasingly being performed in outpatient settings. This, in addition to the guideline committee's advice that wet AMD treatments are routinely delivered in outpatient clinics, means we have adopted the TA 294 method as a scenario analysis only. In this scenario the outpatient and day case unit costs are weighted by the most recently available HES data (2014-15; see Table 34).

Table 34. Hospital Episode Statistics from 2010-11 (used in TA 294 manufacturer model) to 2014-15.

Procedure setting	HES dataset				
	2010-11	2011-12	2012-13	2013-14	2014-15
Outpatient	44.9%	52.4%	54.6%	59.6%	63.2%
Day case	55.1%	47.6%	45.4%	40.4%	36.8%

Proportions were calculated as the total number of C79.4 *and* C89.3 *procedures delivered as outpatient procedures and as day case procedures, divided by total number of procedures.*

A further cost scenario analysis is included in which the outpatient clinic is non-consultant led, to explore whether using nurse-led clinics has an important influence on cost–utility outcomes.

– Number of injections

Years 1 and 2

The number of treatments given determines the overall amount of treatment-related resources required. The mean number of treatments given per year for each regimen was directly informed by the trial evidence for that treatment (where a mean and measure of variance were provided), or was estimated based on the available evidence. The mean number of treatments delivered in year 1 and year 2 of treatment, data sources, and any assumptions made, are presented in Table 35.

Table 35: Mean number of treatments per year

Treatment and regimen	Year 1		Year 2	
	No.	Source	No.	Source
Aflibercept				
Monthly, continuous	11.9	VIEW 1 & 2 [a]	11.4	Same ratio relative to Year 1 as observed in ranibizumab evidence
Every 2 months, continuous	7.0	VIEW 1 & 2 [a]	5.3	Same frequency as year 1 minus 3x 1-monthly loading doses
Every 2 months for 1 year, then as needed (PRN)	7.0	VIEW 1 & 2 [a]	5.0	VIEW 1 & 2 [a, b]
Treat and extend (TREX)	8.8	Same ratio relative to PRN treatment as observed in ranibizumab evidence	7.3	Same ratio relative to year 1 as PRN
PRN and extend (PRNX)	6.3	Same ratio relative to PRN treatment as observed in ranibizumab evidence	5.1	Same ratio relative to year 1 as PRN
Bevacizumab				
Monthly, continuous	11.6	CATT, IVAN	11.0	CATT, IVAN [c]
Every 2 months, continuous	5.8	Half as frequent as year 1 monthly	5.5	Half as frequent as year 1 monthly
Loading phase then every 3 months, continuous	5.9	3 loading doses then one-third as frequent as monthly	3.7	One-third as frequent as year 2 monthly
PRN	7.5	Barikian (2015), CATT [d]	6.6	Barikian (2015), CATT [e]
Loading phase then PRN	7.7	Barikian et al. (2015) [f]	5.3	Barikian (2015), CATT, IVAN [g]
TREX	8.9	LUCAS	9.2	LUCAS
PRNX	6.6	Same ratio relative to PRN treatment as observed in ranibizumab evidence	5.7	Same ratio relative to year 1 as PRN
PDT				
Verteporfin PDT every 3 months	2.9	VIM, VIO [h]	1.5	ANCHOR, VIM, VIO, VIP [i]
Ranibizumab				

Treatment and regimen	Year 1		Year 2	
	No.	Source	No.	Source
Monthly, continuous	11.4	CATT, EXCITE, HARBOR, IVAN, TREND [j]	10.9	CATT, IVAN, EXCITE, HARBOR, TREX-AMD [k]
Every 2 months, continuous	5.7	Half as frequent as year 1 monthly	5.4	Half as frequent as year 2 monthly
Loading phase then every 3 months, continuous	5.5	EXCITE	3.6	One-third as frequent as year 2 monthly
PRN	6.9	CATT	5.7	CATT
Loading phase then PRN	7.0	GEFAL, HARBOR, IVAN, MANTA, SALUTE, Subramanian et al. [l]	5.6	Barikian (2015), IVAN [m]
TREX	8.4	LUCAS, TREND [n]	8.1	LUCAS, TREND, TREX-AMD [o]
PRNX	6.0	SALUTE	5.0	Same ratio relative to year 1 as PRN
No active treatment				
Sham injections (no treatment)	0.0	N/A	0.0	N/A

a) Pooled VIEW 1 and VIEW 2 data from Schmidt-Erfurth et al. (2014)

b) VIEW year 2 data are from week 52 to week 96. VIEW study protocols state that participants were monitored every 4 weeks, therefore additional treatment could theoretically have been administered if follow up continued to week 104 (2 years). As such, the 52 to 96 week number of injections in VIEW have been inflated by (48/40) to estimate number of injections for the full year.

c) Sample size-weighted 2-year mean from CATT and IVAN minus 1-year mean from CATT

d) Sample size-weighted 1-year mean from Barikian et al. (2015) and CATT

e) CATT 2-year mean minus the 1-year mean derived using Barikian et al. (2015) and CATT 1-year.

f) Barikian et al. (2015) estimate that a loading phase leads to an additional 0.2 injections, on average, for PRN bevacizumab in year 1 compared with not having a loading phase.

g) IVAN 2-year mean minus the 1-year mean derived using Barikian et al. (2015) and CATT 1-year.

h) Sample size-weighted 1-year mean from VIM and VIO.

i) Sample size-weighted 2-year mean from ANCHOR, VIM, VIO and VIP minus sample size-weighted 1-year mean from VIM and VIO

j) Sample size-weighted 1-year mean from CATT, EXCITE, HARBOR, IVAN and TREND

k) Sample size-weighted 2-year mean from CATT, IVAN and TREX-AMD minus sample size-weighted 1-year mean from CATT, EXCITE and HARBOR

l) Sample size-weighted 1-year mean from GEFAL, HARBOR, IVAN, SALUTE and Subramanian et al. (2010)

m) IVAN 2-year mean minus the 1-year mean derived using Barikian et al. (2015)

n) Sample size-weight 2-year mean from LUCAS and TREND

o) Sample size-weighted 2-year mean from LUCAS and TREX-AMD minus sample size-weighted 1-year mean from LUCAS and TREND

Long-term (year 3 onward)

For long-term treatment – that is, injections received beyond year 2 of treatment – the mean number of injections per year for each regimen is estimated, given the absence of comparative evidence beyond year 2. For continuous regimens (monthly, 2-monthly and 3-monthly) we assume that the each treatment was intended to be given the scheduled number of times (12, 6 and 4 injections, respectively). The *actual* number of injections given is estimated by adjusting the intended number to reflect imperfect adherence to continuous, routine injections. Pooling the monthly ranibizumab and bevacizumab arms of the IVAN study – selected because it is a UK study with 2 years of monthly injection data – produces an estimated 21.8 injections over 2 years. This is 91% of the intended total of 24 injections (i.e. 1 per month). Therefore, for all continuous regimens, the number of injections given long-term is assumed to be 91% of the intended number of injections per year (see Table 36).

Table 36: Long-term number of treatments per year – continuous regimens

Regimen [a]	Injections intended	Adherence to appointments	Injections given
Monthly, continuous	12	(21.8 / 24) = 91% [b]	10.9
Every 2 months, continuous	6		5.5
Every 3 months, continuous	4		3.6

a) Same value used for aflibercept, bevacizumab, ranibizumab and PDT.

b) Informed by the IVAN study (pooled continuous ranibizumab and bevacizumab arms); IVAN study selected as it is a UK study, and is therefore more likely to reflect adherence to injections in the NHS than the CATT study.

For the long-term injection requirement of discontinuous regimens, the approach described above was not possible, as there is no obvious intended number of injections per year for PRN, TREX or PRNX protocols. Instead, the number of injections per year for these regimens was estimated relative to ranibizumab PRN. This is because the main source of long-term VA decline used in the model, the ARMD database, provides a value of 3.7 injections per year for eyes receiving ranibizumab PRN in year 3 of treatment (Tufail et al. 2014). Using these data ensures long-term outcomes and injection frequencies are modelled in a consistent manner.

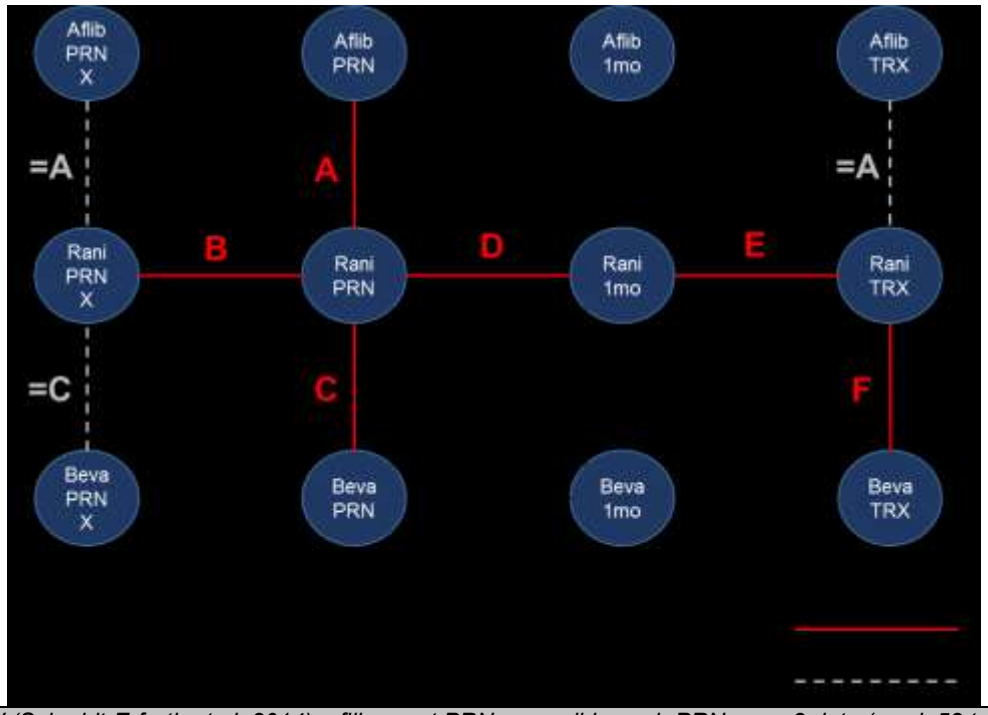
To link all other discontinuous regimens with the estimate for ranibizumab PRN, we used a piecewise network of randomised comparisons that provide 2-year, or 2nd year, injection data. The network of evidence providing these data (Figure 11) shows that most discontinuous regimens are linked to ranibizumab PRN. For these, using the data provided by each study, it was possible to estimate proportionally how many more, or fewer, injections each regimen required compared with ranibizumab PRN (Table 37). For example, the multiplier for ranibizumab monthly, versus ranibizumab PRN, is 1.78 (informed by the CATT study), meaning the monthly regimen required 78% more injections than PRN. In the TREX-AMD study, ranibizumab given in a treat-and-extend manner required 27% fewer injections than ranibizumab monthly. The presence of ranibizumab monthly in this trial links it to the CATT study, making it possible to estimate the number of ranibizumab TREX injections relative to ranibizumab PRN: 1.78 * 0.73 = 1.30 (i.e. 30% more injections). Bevacizumab TREX is linked to the network via the LUCAS study, in which it required 15% more injections than ranibizumab TREX. The presence of ranibizumab TREX in this trial links it to the network via the TREX-AMD study; therefore bevacizumab TREX is estimated to require 1.78 * 0.73 * 1.15 = 1.49 injections compared with ranibizumab PRN (49% more). For regimens that were not linked to ranibizumab PRN at all (e.g. aflibercept TREX), the network was completed using the most appropriate data from elsewhere in the network (see Figure 11).

While a full network meta-analysis would have been superior to this method, it was not feasible due to a general lack of injections data, with mixed reporting of variance in particular.

This piecewise approach does preserve the randomisation of each head-to-head comparison.

With an estimate of the number of injections required relative to ranibizumab PRN for each discontinuous regimen, and using the ARMD database estimate of 3.7 injections per year for ranibizumab PRN, it was possible to estimate how many injections each regimen required relative to that 3.7. Note that this approach was not taken for continuous regimens, however, which were only included here to inform the network of randomised evidence. Their long-term injection requirements were estimated as described earlier (see Table 36).

The resulting number of injections per year for each regimen is assumed to remain constant for the duration of an eye's long-term treatment in the model. This assumption is validated by a long-term observational study of 1,212 eyes, which shows that injection frequency remains stable from year 2 to year 7 (Gillies et al. 2015).



A. VIEW (Schmidt-Erfurth et al. 2014): aflibercept PRN vs. ranibizumab PRN, year 2 data (week 52 to week 96).
B. SALUTE (Eldem et al. 2015): ranibizumab PRNX vs. ranibizumab PRN, 1-year data only (note: this regimen is only used in a scenario analysis).
C. CATT (Martin et al. 2012): ranibizumab PRN vs. bevacizumab PRN, 2-year data.
D. CATT (Martin et al. 2012): ranibizumab PRN vs. ranibizumab monthly, 2-year data.
E. TREX-AMD (Wykoff et al. 2017): ranibizumab monthly vs. ranibizumab TREX, 2-year data.
F. LUCAS (Berg et al. 2016): ranibizumab TREX vs. bevacizumab TREX, year 2 data.

Figure 11: Piecewise network of randomised year 2 or 2-year injections data

Table 37: Long-term number of treatments per year – discontinuous regimens

Treatment and regimen	Link to ranibizumab PRN in network [a]	Injections relative to ranibizumab PRN	Injections per year
Ranibizumab			
• PRN [b]	N/A	1.00	**3.7**
• TREX	D–E	(22.4 / 12.6) * (18.6 / 25.5) = 1.30	* 3.7 = **4.8**
• PRNX [c]	B	(6.0 / 6.6) = 0.91	* 3.7 = **3.4**

Treatment and regimen	Link to ranibizumab PRN in network [a]	Injections relative to ranibizumab PRN	Injections per year
Aflibercept			
• PRN	A	(4.2 / 4.6) = 0.91	* 3.7 = **3.4**
• TREX	No link	(22.4 / 12.6) * (18.6 / 25.5) * (4.2 / 4.6) = 1.18 [d]	* 3.7 = **4.4**
• PRNX	No link	(6.0 / 6.6) * (4.2 / 4.6) = 0.83 [e]	* 3.7 = **3.1**
Bevacizumab			
• PRN [b]	C	(14.1 / 12.6) = 1.12	* 3.7 = **4.1**
• TREX	D–E–F	(22.4 / 12.6) * (18.6 / 25.5) * (9.2 / 8.0) = 1.49	* 3.7 = **5.5**
• PRNX	No link	(6.0 / 6.6) * (14.1 / 12.6) = 1.02 [f]	* 3.7 = **3.8**

a) See Figure 11.
b) Comparison of bevacizumab and ranibizumab monthly and PRN provided by CATT and IVAN studies, however, data used here are from CATT only. This is because PRN in the IVAN study included a 3-month loading phase, which would have caused an underestimation of the difference in injections between PRN and monthly regimens in the long term.
c) Only 1-year randomised data available for PRNX (SALUTE study; Eldem et al. 2015).
d) No data. Values are from the ranibizumab TREX calculation, adjusted to reflect the difference between aflibercept and ranibizumab PRN in the VIEW study (Schmidt-Erfurth et al. 2014).
e) No data. Values are from the ranibizumab PRNX calculation, adjusted to reflect the difference between aflibercept and ranibizumab PRN in the VIEW study (Schmidt-Erfurth et al. 2014).
f) No data. Values are from the ranibizumab PRNX calculation, adjusted to reflect the difference between bevacizumab and ranibizumab PRN in the CATT study (Martin et al. 2012).

Scenario analyses

A scenario analysis has been included in the model that standardises the number of injections required across different treatments for any given regimen. For example, in the base-case model 2-monthly continuous regimens of ranibizumab and bevacizumab require a different number of injections, despite theoretically being the same dosing regimen. This difference is plausible; the clinical evidence suggests that bevacizumab may be very marginally less effective than ranibizumab, which may lead to more injections being given on average. This scenario analysis explores the impact of ignoring our estimated differences in the number of injections shown in the tables above. The scenario instead assumes that a particular dosing regimen always requires the same number of treatments regardless of the therapy being used (Table 38).

Table 38: Scenario analysis – no difference in the treatment requirement for different therapies provided according to the same dosing regimen

Dosing regimen	Year 1		Year 2		Year 3	
	No.	Source	No.	Source	No.	Source
Monthly, continuous	11.6	Mean of 1-monthly regimens for which data are available	10.9	Mean of 1-monthly estimates for year 2	10.9	Planned injections (12) * adherence (91%)
Every 2 months, continuous	5.8	Half as frequent as 1-monthly value	5.5	Half as frequent as 1-monthly value	5.5	Planned injections (6) * adherence (91%)
Every 3 months, continuous	5.9	A loading phase, then one-third as frequent as 1-monthly value	3.6	One-third as frequent as 1-monthly value	3.6	Planned injections (4) * adherence (91%)
Every 2 months for 1 year, then PRN (aflibercept only)	5.8	Equal to 2-monthly continuous in year 1	5.7	Equal to PRN value	3.7	Equal to PRN value

Dosing regimen	Year 1		Year 2		Year 3	
	No.	Source	No.	Source	No.	Source
PRN	7.2	Mean of PRN regimens for which data are available	5.7	Mean of PRN estimates for year 2	3.7	ARMD database (Tufail et al. 2014)
Loading phase then PRN	7.4	PRN + 0.2 (Barikian et al. 2015)	5.7	Equal to PRN value	3.7	Equal to PRN value
TREX	8.5	Mean of TREX regimens for which data are available	8.6	Mean of TREX estimates for year 2	4.9	Mean of TREX estimates for year 3
PRNX	6.0	SALUTE	4.7	Same ratio relative to year 1 as PRN	3.4	Mean of PRNX estimates for year 3

An additional scenario analysis has been explored, introduced in Section J.5.3.3, in which all anti-VEGF treatments are effectively assumed to be equivalent after year 2 (i.e. beyond the observed randomised trial data). In this scenario, all anti-VEGF treatments are assumed to have long-term effectiveness and discontinuation rates equal to ranibizumab PRN. We therefore assume that they also require the same number of injections as ranibizumab PRN beyond year 2 (3.7 per year), thereby removing any differential effects and costs beyond the available randomised data.

– Monitoring

In the base-case analysis, monitoring consists of an OCT examination. We assume that an OCT occurs at every treatment appointment, following advice from the guideline committee. The committee advised that many clinics will perform an OCT as standard when they have the opportunity to do so (that is, the patient is at the clinic for their treatment), even if the patient is on a continuous treatment regime, such that the OCT will not necessarily affect treatment decision making. The exception to this occurs in year 1 of treatment, where the cost of an FFA examination is also incurred, as we assume that an FFA would have been required to confirm the diagnosis. The committee advised that treating 2 eyes at the same appointment requires no additional monitoring resources compared with treating one eye.

Our base-case model inputs have patients on PDT receiving 2.9 injections per year in year 1 followed by 1.5 injections per year thereafter. This means that assuming an OCT occurs only when treatment is given would underestimate monitoring costs for PDT, as its SPC states that patients should be evaluated every 3 months. As such, for PDT, we assume that patients who are on treatment are monitoring by OCT 4 times per year.

Assuming that an OCT occurs only when an injection is given would also underestimate monitoring costs for patients on PRN and PRNX treatment regimens. This is because these regimens use monitoring to inform whether or not the patient needs treatment; therefore, monitoring may occur without an injection being administered.

One RCT (SALUTE) was identified that provides a head-to-head comparison of PRN and PRNX (both ranibizumab; Eldem et al. 2015). This found that PRN and PRNX regimens were associated with medians of 13 and 10 total clinic visits during 1 year respectively (excluding screening visits). Using these medians and the ranges reported, we estimated corresponding means of 12.7 and 10.1. The observational UK AMD database (Tufail et al. 2014) also provides an estimate of the total number of appointments required by patients on ranibizumab PRN in year 1, 2 and 3, including those over and above the number of injections received (Table 39).

Using the data sources described above, monitoring on PRN and PRNX regimens in the model for years 1 and 2 is informed by the SALUTE data. These inputs are calculated as the total number of visits per year from the relevant arm of the SALUTE study, minus the number

of injections required by that regimen in each year. This gives the number of monitoring-only visits required for each PRN and PRNX regimen in years 1 and 2. From year 3 onwards, VA outcomes and injection frequencies in the model are informed by the ARMD database. To make the long-term annual monitoring requirement consistent with this, the number of injections required is subtracted from the mean number of appointments in the ARMD dataset in year 3, for each regimen. The SALUTE and ARMD data for the number of visits required on ranibizumab PRN and PRNX regimens are assumed to apply equally to aflibercept and bevacizumab.

Note that PRN and PRNX patients are still assumed to receive an OCT when they do receive treatment (see Table 39), as the OCT will have informed the decision to treat. These data are used in the model to ensure the cost of OCTs that lead to no treatment being provided is captured.

Table 39: Mean number of monitoring-only visits per year (PRN and PRNX)

Reason for visit	Mean number required		
Observational data (Tufail et al. 2014)	Year 1	Year 2	Year 3+
Total clinic visits	9.2	8.2	8.2
Injections	5.7	3.7	3.7
SALUTE data (Eldem et al. 2015)	Year 1		
Total clinic visits, PRN	12.7		
Injections, PRN	6.6		
Total minus injections, PRN	6.1		
Total clinic visits, PRNX	10.1		
Injections, PRNX	6.0		
Total minus injections, PRNX	4.1		
Difference: PRN - PRNX	2.0		

Monitoring forms part of a broader scenario analysis explored, in which all anti-VEGF treatments beyond year 2 are assumed to be equivalent. In this scenario, all anti-VEGF treatments are assumed to have long-term effectiveness, discontinuation rates and injection requirements equal to ranibizumab PRN. We therefore assume that they also require the same number of monitoring-only appointments as PRN treatment beyond year 2. This scenario therefore removes any differential effects and costs beyond the available randomised data.

A separate scenario analysis, specific to monitoring, is also explored in which OCT examinations are not used for monitoring patients who are on continuous treatment regimens. This is consistent with a previous CUA by Dakin et al. (2014), in which monitoring was only required when it could inform treatment decisions. On a continuous treatment regimen, for example a monthly anti-VEGF injection, there might not be any treatment decision to make – treatment is continuous – rendering an OCT unnecessary. In this scenario, one OCT is still assumed to be necessary to confirm diagnosis in all patients (alongside an FFA). For discontinuous treatment regimens, such as PRN injections, a treatment decision must be made at each appointment. As such, an OCT is assumed to continue to be necessary at each appointment on PRN and PRNX regimes.

– Low vision resources

Vision-related health care resources are included in the model, required when a patient's VA reaches a threshold level of impairment. Previous CUAs have almost exclusively used estimates of the uptake of different low vision resources collated by Meads et al. (2003), originally from various sources. This defines the proportion of people who register as sight impaired (94.5%), the uptake of low vision aids (33%) and low vision rehabilitation (11%),

and the use of services to treat vision-related depression (39%) and hip replacements due to falls (5%). It provides estimates of the use of PSS resources, namely the use of community care by home care workers (6%) and entry into residential care (30%). It also provides estimates of the use of some non-NHS/PSS resources due to severe sight impairment: housing benefit and council tax benefit (45%), social security (63%) and tax allowances (5%).

In our model, low vision resources are required when VA in the BSE is 25 letters or fewer, according to the relevant level of uptake listed above, with the exception of low vision aids. The guideline committee advised that, in practice, low vision aids are used by all patients with VA of approximately 60 letters or fewer in their BSE. As the model is composed of health state VA letter ranges, this is applied by assuming that one-third of patients whose BSE is in the 55-70 letters state will use low vision aids, and that all patients with worse VA will do so. Like previous models, blindness registration is assumed to be a one-off cost (even if a patient's sight recovers to >25 in the model).

– Adverse events

Resource use associated with adverse events was assumed to reflect the health care required to treat that event. Resources are assumed to be required on a one-off basis except in the case of stroke, which has an ongoing resource requirement. Differential resource use due to adverse events was not expected to be a major driver of model results.

J.5.3.6 Costs

The costs of individual units of resource use items included in the model are obtained from a number of standard sources. These include:

- NHS Reference Costs, as the source of unit costs for inpatient and outpatient procedures as well as hospital stay information.
- The Personal Social Services Research Unit (PSSRU) Unit Costs of Health and Social Care report, for costs for both community and hospital-based healthcare staff, and health care price inflation indices.

– Treatment costs

The list prices per vial of aflibercept and ranibizumab are ranibizumab are £816 and £551, respectively (BNF). Both drugs are provided to the NHS in accordance with a patient access scheme (PAS), a commercially sensitive discount to the list price. In the analyses presented here, list prices of aflibercept and ranibizumab have been used. This ensures that the electronic model can be made available alongside this document, providing transparency and allowing for critical appraisal of its assumptions and calculations, without compromising PAS confidentiality. A descriptive summary of results when PAS prices are used is provided in Section J.5.6.4. The unit cost of one dose of bevacizumab – which is aliquoted from a much larger vial size – is estimated to be £49 (Chakravarthy et al. 2015).

Table 40: Treatment unit costs

Treatment	*Unit cost per vial /dose*	*Source*
Aflibercept	£[redacted]	PAS price
	£816.00	List price, BNF
Bevacizumab	£49.00	Chakravarthy et al. (2015)
PDT	£135.96	NHS Reference Costs 2014-15: Outpatient procedure code for Major Vitreous Retinal Procedures, 19 years and over, with CC Score 0-1

Treatment	*Unit cost per vial /dose*	*Source*
Ranibizumab	£[redacted]	PAS price
	£551.00	List price, BNF
Verteporfin	£850.00	List price, BNF

– Other costs

The unit costs of all other health care resources detailed in Section J.5.3.5 are shown in Table 41. These are multiplied by the requirement for that resource to estimate a total cost. Like previous models, we assume that 30% of residential care is funded privately by the patient, and is therefore deducted from the total cost of this care where required. Non-NHS/PSS resources associated with low vision are not included in the base-case analysis.

Table 41: Other unit costs

Cost category/item	*Unit cost*	*Source (NHS Reference Costs 2014-15 unless stated otherwise)*
Administration		
Consultant led outpatient attendance	£88.59	Consultant led non-admitted follow-up (ophthalmology): WF01A.
Non-consultant led outpatient attendance (scenario analysis)	£58.69	Non-consultant led non-admitted follow-up (ophthalmology): WF01A.
Day-case admission (scenario analysis)	£637.19	Day case procedure code for Minor Vitreous Retinal Procedure: BZ87A.
Administration cost multiplier for treatment of 2 eyes	1.50	Guideline committee advice
Diagnosis / monitoring		
FFA	£153.22	Weighted average of diagnostic imaging codes for Contrast Fluoroscopy Procedures: RD30Z, RD31Z and RD32Z.
OCT	£115.52	Outpatient procedure code for Retinal Tomography: BZ88A (ophthalmology).
NHS/PSS low vision resources	Per year	
Depression	£2,478.95	McCrone et al. (2008), inflated to 2015/16 prices using PSSRU (2016) HCHS inflation indices (2006/07: 249.8; 2015/16: 297.0).
Hip replacement	£5,777.80	Meads & Hyde (2003), inflated to 2015/16 prices using PSSRU (2009) and PSSRU (2016) HCHS inflation indices (1999/00: 188.6; 2015/16: 297.0).
Low vision aids	£214.69	
Low vision rehabilitation	£323.30	
Home care worker	£8,361.70	
Registration as sight impaired (one-off cost)	£153.40	
Residential care (less 30% privately funded)	£22,859.20	
Other low vision resources	Per year	
Housing and council tax benefit	£2,714.40	Meads & Hyde (2003), inflated to 2014-5 prices using PSSRU (2009) and PSSRU (2016) HCHS inflation indices (1999/00: 188.6; 2015/16: 297.0).
Social security	£3,029.84	
Tax allowances	£502.35	
Anti-VEFG adverse events		
Cataract	£850.84	Weighted average of non-elective short stay and day case codes for Phacoemulsification

Cost category/item	Unit cost	Source (NHS Reference Costs 2014-15 unless stated otherwise)
		Cataract Extraction and Lens Implant: BZ34A, B and C.
Endophthalmitis	£1,608.15	See below
Proportion requiring vitrectomy	18.31%	Kamalarajah et al. (2004)
Urgent vitrectomies	38.46%	Kamalarajah et al. (2004)
1 or more revisions	17.95%	Kamalarajah et al. (2004)
2 revisions	5.13%	Kamalarajah et al. (2004)
Requiring vitreous tap	100.00%	Committee guidance
No. outpatient visits required	5.5	Committee guidance
Elective vitrectomy	£751.55	Weighted average of elective and day case procedures: BZ84A, BZ84B.
Urgent vitrectomy (nonelective)	£3,953.40	Weighted average of nonelective long-stay procedures: BZ84A, BZ84B.
Vitreous tap	£680.23	Weighted average of procedures: BZ87A
Outpatient attendance	£88.59	Consultant led (ophthalmology): WF01A
Additional drugs (Amikacin)	£45.83	EMIT
Gastrointestinal event	£431.28	Weighted average of non-elective short stay and day case codes for Abdominal Pain (FZ90A and B) and for Non-Malignant Gastrointestinal Tract Disorders (FZ91A to M).
Retinal detachment	£1,825.06	See below.
Prop. requiring nonelective vitrectomy.	75.00%	Committee guidance
No. outpatient visits required	2.0	Committee guidance
Elective vitrectomy	£687.08	Weighted average of day case procedures: BZ84A, BZ84B.
Urgent vitrectomy (nonelective)	£1,968.15	Weighted average of non-elective procedures: BZ84A, BZ84B.
Outpatient attendance	£88.59	Consultant led (ophthalmology): WF01A
Retinal tear	£713.23	Weighted average of non-elective short stay and day case codes for Major Vitreous Retinal Procedures: BZ84A, BZ84B.
Stroke – event cost	£4,128.62	NICE CG 181 (Lipid modification)
Stroke – annual, post-event	£156.39	NICE CG 181 (Lipid modification)
PDT adverse events		
Infusion-related back pain (immediate)	£0.89 (1 course NSAIDs)	NHS Electronic Drug Tariff (Part VIIIA Category M)
Injection site reaction	£0.00 (treated during procedure)	Assumption to avoid double-counting
Skin photosensitivity	£1.98 (1 course of topical corticosteroid)	NHS Electronic Drug Tariff (Part VIIIA Category M)
Temporary acute vision loss	£0.00 (no direct cost)	Assumption

In their CUA alongside the IVAN trial, Chakravarthy et al. (2015) undertook extensive micro-costing work to estimate the cost of administering ranibizumab and bevacizumab. Twelve of the trial centres responded to a cost questionnaire. The responses had mean injection costs of £60.65 as part of 1-stop clinics and £60.93 as standalone appointments. The guideline committee advised that these costs were unrealistically low; therefore they are not used in the present analysis, but are included in a scenario analysis, alongside the micro-costed estimate for an OCT (£71.83).

As per the NICE reference case, all costs beyond year 1 are discounted at a rate of 3.5% per year.

J.5.3.7 Quality of life

We reviewed the measurement of HRQL in AMD in both single-eye and bilateral economic models that have been submitted in NICE TAs and/or published in the literature. Consideration was also given to TAs of medicines indicated for use in AMD where the appraisal is for another condition but the methods used could be translated to an AMD model.

Better-seeing eye and worse-seeing eye relation to HRQL

There is usually differential VA and visual function (VF) between an individual's eyes. Typically, the eyes are categorised into the BSE and the WSE on the basis of this dichotomy. In the ANCHOR and MARINA trials of ranibizumab in AMD, the differentiation of BSEs and WSEs was categorised by VA alone.

This has been criticised because VA is only one dimension of vision, and patients may report good VA on measurement but also experience problems with glare, contrast sensitivity, and stereopsis for example (Hirneiss, 2014). Despite this, there remains a need to establish the better and worse seeing eyes. This is because treatments for AMD may be limited to 1 eye at a time, and it is intuitive that if the vision related aspects of patients quality of life are mostly determined by their BSE function, that this eye should be prioritised for treatment because expected benefits would be greater than making improvements to the WSE. It is self-evident that this becomes more complex as the dichotomy in VA/VF between the BSE and WSE narrows. In many studies, after the BSE is established, an assumption is made that the WSE is of no importance with regard to HRQL and is ignored. Other studies have reported that the HRQL of the patient is in fact a product of the vision in both the BSE and WSE. For example, a recent article by Scanlon et al. (2015) argued that a weighted combination of the visual acuity in the BSE and WSE should be used when relating visual acuity to HRQL and that valuable data was missed when only 1 eye was considered.

HRQL in technology appraisals for AMD

– Czoski-Murray et al. (2009)

Czoski-Murray et al. (2009) used contact lenses to simulate 3 AMD severities and quantify the health utility associated with these states. The lenses contained a central scotoma of varying size, designed to represent 3 visual acuities: 20/80 (reading limit); 20/200 (legal blindness), and 20/500 (the state that patients with untreated AMD will reach). A random sample of 2,000 addresses across six postcodes in Sheffield yielded 77 respondents, and 47 actual attendees at interview for the study. In order to ensure adequate statistical power, a further 66 participants were recruited from the network of colleagues and household members of those 47 initial attendees. The mean age of the final 108 enrolees was 32 (SD 12.5 years). Most were in good health with a mean TTO at baseline of 0.960 (SD 0.109, 0.30-1) although 23% reported unspecified long-term illness. Overall, the participants had excellent vision. An OLS linear regression showed that the order in which the contact lenses were applied did have a significant impact on the recorded utility values ($F_{6,306} = 3.44$, $p =$

0.003) particularly when the milder lens was used first. Therefore, adjustments were made for the ordering effect using the results from the regression analysis.

Participants in the study completed selected questions from the VF-14, the HUI-3 and the EQ-5D for comparative purposes. TTO values were recorded through the direct elicitation method. Crucially, the participants wore the contact lens during the valuation exercise and interviews, removing any problems with recall. The final model allows for TTO utility to be calculated for any given logMAR visual acuity score. Butt et al. (2016) critiqued the study, noting the limitations of using contact lenses to provide participant members of the general public with an idea of what living with AMD is like. Wearing contact lenses to simulate AMD for up to 2 hours cannot simulate the effects of living with long-term AMD with continued visual acuity decline. However, alternative approaches to informing participants about a condition typically involve simply describing health states, using vignettes or a validated generic tool such as the EQ-5D. We feel Czoski-Murray's attempt at informing participants represents a step forward from these approaches, with respondents likely to be better informed – albeit not perfectly informed – after using simulation contact lenses compared with hearing a health state description. An unexplored alternative is the elicitation of TTO values directly from people with AMD.

The Czoski-Murray model has been used in NICE TAs for ranibizumab and aflibercept, and a recent CUA by Ghosh et al. (2016). TA 155 used a pre-publication version of the model in a single eye cost–utility model. No consideration of the relationships between eyes and HRQL in patients undergoing ranibizumab treatment was included in the model.

– TA 294 – aflibercept (first-line) in AMD

For TA 294, which considered the use of aflibercept as a first-line intervention for AMD, the manufacturers presented a two-eye model in the appraisal submission, which uses EQ-5D data collected during the VIEW-2 trial to describe HRQL in the following combinations of visual acuity:

- None/None
- None/Mild
- None/Moderate
- None/Severe
- None/Counting Fingers
- Mild/Mild
- Mild/Moderate
- Mild/Severe
- Mild/Counting Fingers
- Moderate/Moderate
- Moderate/Severe
- Moderate/Counting Fingers
- Severe/Counting Fingers
- Severe/Severe
- Counting Fingers/Counting Fingers

The data remain commercial/academic in confidence, so the utility values associated with these states are not available. In the cost–utility model submitted by the manufacturer a modified version of the data collected in VIEW-2 is used, and applied to a matrix of 30 states composed of the combinations of visual acuity (based on ETDRS letters) in the first (treated) and fellow eye.

– Other AMD cost–utility analyses

The majority of cost–utility analyses of AMD treatment options have used earlier studies by Brown et al. (2000, 2003) or Sharma et al. (2000) to inform estimates of HRQL. A recent study by Elshout et al. (2014) used the HUI-3 instrument applied to a cohort of patients with late AMD (wet active), but EQ-5D and VFQ-25 data collected during the large anti-VEGF trials remains commercial and academic in confidence and this in part explains a potential reason for the reliance on older studies of HRQL in the literature. Problematically, some of these studies report patient preferences and are not compatible with the NICE reference case.

– Technology appraisals in other conditions

Although not an appraisal of aflibercept in AMD, TA 346 presents a model that accounts for the HRQL as a function of VA in both eyes. The appraisal considered the use of aflibercept for the first-line treatment of diabetic macular oedema (DMO). Given that AMD can affect both eyes, and that aflibercept is also used in AMD, the approach to HRQL is presented here.

The manufacturer submitted a 2-eye model with health states that represent the visual acuity in the better- and WSEs. EQ-5D data were collected from patients during the VIVID and VISTA trials. A relationship between the reported utilities derived using the UK EQ-5D tariff and VA in both the better and WSEs was developed using OLS regression. The model equation is detailed in the TA submission, but the coefficients for the equation are currently academic in confidence:

$$y_i = \alpha + \beta_1 (\text{log of BCVA of BSE}) + \beta_2 (\text{log of BCVA of WSE}) + \beta_3 (\text{age}) + \beta_4 (\text{baseline BMI}) + u_i$$

However, the VIVID/VISTA derived utility values are not used in the base-case analysis. Rather, the utility estimates taken from the Czoski-Murray contact lens simulation study were applied, weighted to account for the differential impact on HRQL of a change in visual acuity in the worse seeing-eye compared to the BSE.

$$\Delta WSE = \Delta Both\ eyes * \left(\frac{1}{1 + \left(\frac{1}{x\%} \right)} \right)$$

where x is the % impact on utility of a change in the WSE compared with the BSE.

In TA 237 (ranibizumab for DMO), the manufacturer's submission details a single-eye model which uses OLS regression to predict EQ-5D derived utility values from ETDRS assessed visual acuity. The observed EQ-5D and VA data used to validate the model were collected as part of the RESTORE trial, and are redacted in the submission. The impact of treatment of the fellow eye on vision-related quality of life was not measured in the clinical trials for ranibizumab.

HRQL in the model

– Visual acuity

In the base-case of our health economic analysis, we employ the Czoski-Murray et al. (2009) study results, in the same way that it was used in manufacturer submission for TA 346, presented above. The contact lens study reported a regression model (below) in which utility

is dependent on a person's bilateral VA. A scale factor used in previous TAs (TA 294, TA 346) is used to inform the HRQL impact of the WSE relative to the BSE.

Equation 1: Czoski-Murray et al. (2009) utility regression model, used to inform VA-related HRQL in the cost–utility model

*Utility = 0.860 – 0.001 * age in years – 0.368 * BSE VA*

The widely used scaling factor, used to estimate the impact of changes in WSE VA on utility, is 0.3, meaning visual impairment in the WSE has a smaller effect on HRQL than the same degree of impairment in the BSE. The ERG for NICE TA 346 (aflibercept for diabetic macular oedema) suggested that this factor should be 0.4285, and we adopt this alternative value in scenario analysis.

We use the regression model and scaling factor to estimate an age-adjusted utility weight for each VA-health state in our model. To do so, we make the simplifying assumption that the average VA of an eye in a particular VA-range is approximated by the midpoint of that range. For example, an eye in the VA-state '85 to 71' is assumed to have an actual VA level of 78. Due to the age coefficient, a unique matrix calculating utility by VA in each eye can be estimated for any age. An illustrative example, for a patient aged 79.1 years (the baseline age of our cohort), is presented in Table 42. The equivalent matrix for all ages used in the model are calculated and shown in the executable model. The importance of the BSE compared with the WSE is evident through the larger utility decrements by moving from left to right (BSE getting worse) with those moving from top to bottom (woWSEgetting worse).

Table 42: Vision-related utility weights for an individual aged 79, derived from Czoski-Murray et al. (2009)

		Better-seeing eye VA					
		≥85	***85-71***	***70-56***	***55-41***	***40-26***	***≤25***
Worse-seeing eye VA	***≥85***	0.839					
	85-71	0.814	0.729				
	70-56	0.788	0.706	0.618			
	55-41	0.763	0.678	0.593	0.508		
	40-26	0.737	0.652	0.567	0.483	0.398	
	≤25	0.702	0.618	0.533	0.448	0.363	0.247

While we acknowledge the critique by Butt et al. (2016), and that the primary purpose of the Czoski-Murray study was to assess its methodological feasibility, we also recognise the scarcity of utility values estimated for people with AMD. We feel that their attempt at informing the general public using contact lenses before eliciting TTO values represents a step forward relative to other utility studies in AMD, which have instead used descriptions of health states known to be suboptimal at capturing the impact of visual impairment. Furthermore, having HRQL depend on VA in both eyes is suited to the economic model developed for this guideline, as it is a two-eye model in which both eyes can have, and be treated for, AMD.

A scenario analysis is included that uses the utilities reported by Brown et al. (2000), elicited by the time trade-off technique from a cross-section of 72 AMD patients in the US. The study reported utility weights by Snellen VA in the BSE (Table 43), which have been used widely in previous cost–utility analyses. There are notable gaps between the 5 VA ranges includes in the Brown study, likely to have been caused by the low number of participants (for example, there might have been no participants with VA of 6/48 [20/160]). Furthermore, the Brown et al. VA ranges are inconsistent with the VA health states in our model.

Table 43: Brown et al. (2000) health states utilities

VA range	*Equivalent as Snellen /6*	*Continuous (assuming midpoint of gaps)*	*Utility weight*
1. 20/20 to 20/25	6/6 to 6/7.5	6/6 to 6/8.25	0.89
2. 20/30 to 20/50	6/9 to 6/15	6/8.25 to 6/16.5	0.81
3. 20/60 to 20/100	6/18 to 6/30	6/16.5 to 16/45	0.57
4. 20/200 to 20/400	6/60 to 6/120	6/45 to 6/150	0.52
5. 'Counting fingers' to 'light perception only'	6/180 to 6/360 (Assumed)	≥6/150	0.40

To use the Brown utilities in our model, we first assumed that the Brown et al. VA ranges are continuous, and that the gap between any two VA ranges is split at its midpoint. We then estimated the utility values for our model health states by assuming a weighted average of the relevant Brown utilities. For example:

- Our model health state 'VA: 85 to 71' (i.e. 6/6 to 6/12) straddles two Brown VA ranges: 20/20 to 20/25 (i.e. 6/6 to 6/7.5) and 20/30 to 20/50 (i.e. 6/9 to 6/15).
- We assume that these two Brown ranges are actually joined at the midpoint: 6/8.25.
- The proportion of our health state (6/6 to 6/12) that is captured within Brown VA range 1 (6/6 to 6/8.25) is 37.5%.
- The proportion of our health state (6/6 to 6/12) that is captured within Brown VA range 2 (6/8.25 to 6/15) is 62.5%.
- These proportions are used to weight the Brown VA range 1 and range 2 utilities, providing an estimated health state utility in our model for people whose BSE is in the VA 6/12 to 6/24 state.

The resulting utility weights for each BSE health state are presented in Table 43.

Table 44: Health states utilities used in model scenario analysis

Health state in model – BSE	*Equivalent as Snellen /6*	*Utility weight*
>85 letters	>6/6	0.890 (assumed to be the maximum Brown value)
85-71 letters	6/6 to 6/12	0.840
70-56 letters	6/12 to 6/24	0.660
55-41 letters	6/24 to 6/48	0.564
40-26 letters	6/48 to 6/95	0.520
≤25 letters	≤6/96	0.425

The Brown health state utilities do not contain an explicit age-related factor like the Czoski-Murray regression model. As such, in this scenario analysis, VA-related utilities are weighted by patient age using UK population norms of the EQ-5D (Kind et al. 1999). The age weights are shown in Table 47.

Table 45: Kind et al. (1999) age-related EQ-5D norms

Age	*EQ-5D weight: men*	*EQ-5D weight: women*	*Gender-weighted average utility weight*
≤24 years	0.940	0.940	0.940
25-34 years	0.930	0.930	0.930
35-44 years	0.910	0.910	0.910
45-54 years	0.840	0.850	0.846
55-64 years	0.780	0.810	0.799
65 to 74 years	0.780	0.780	0.780

Age	EQ-5D weight: men	EQ-5D weight: women	Gender-weighted average utility weight
≥75 years	0.750	0.710	0.725

– Adverse events

Utility in the model is affected by the occurrence of serious adverse events, in addition to VA. Patients are subject to a risk of treatment-related events as long as at least one eye is currently being treated. The direct impact of some events on HRQL was obtained from a study by Brown et al (2007), in which a cohort of 233 US patients with AMD completed a time trade-off exercise if they experienced an adverse event, in order to directly estimate the impact of the event on their HRQL. The study reported utility decrements associated with ocular events, which were subsequently used in Health Technology Assessment monograph exploring the effectiveness of OCT as a monitoring tool (Mowatt et al. 2014). The duration over which each decrement should apply was informed through discussion with the guideline committee. The HRQL impact of non-ocular events associated with anti-VEGF treatments were obtained from a Sullivan et al. (2011) for gastrointestinal events and the economic evaluation conducted for NICE GC 181 (lipid modification) for stroke. The guideline committee also advised on the types of AE that are associated with PDT treatment in particular; the decrement for infusion-related back pain was from Sullivan et al. (2011). All utility decrements and durations associated with adverse events presented in Table 46.

The committee also described the potential for patients to experience anxiety in the days preceding a treatment, and the debilitating impact of pain in the days following treatment. It was agreed that applying a 100% utility loss for one day would be an acceptable way to model the impact of an injection on quality of life during the days either side of an injection and the injection day itself. This is equivalent to a QALY loss of 0.003 from a baseline of otherwise perfect health. In the base-case analysis we assume that this is experienced by 50% of patients. The resulting utility decrement per administration is applied to PDT as well as anti-VEGF therapies, given that PDT also requires an injection (of verteporfin). While these inputs are not expected to be key determinants of cost–utility results, this is tested by varying them to extreme values in one-way sensitivity analysis, having been informed by advice from the guideline committee. The proportion of patients that experiences 100% utility loss is varied to 0%, such that no decrement is applied, to 100%, such that all patients experience it.

Table 46: Adverse event utility values used within the model

Serious adverse event	Treatment cause	Utility decrement	Event duration	Equivalent QALY loss
Back pain	PDT	0.090	1 day	0.0002
Cataract	Anti-VEGF	0.142	1 month	0.010
Endophthalmitis	Anti-VEGF	0.300	20%: 1 year 80%: 1.5 months	0.090
Gastrointestinal event	Anti-VEGF	0.044	1 month	0.004
Injection anxiety/pain	All injections	100% utility loss	1 day	e.g. 0.003 [a]
Injection site reaction	PDT	0 – assumed to be captured in the 100% injection-related anxiety/pain utility loss		
Retinal detachment	Anti-VEGF	0.270	3 months	0.068
Retinal tear	Anti-VEGF	0.000	Immediate repair	0.000
Skin photosensitivity	PDT	0 – assumed to be captured in the 100% injection-related anxiety/pain utility loss		
Stroke	Anti-VEGF	31% utility loss	Lifetime	e.g. 0.310 [a]

Serious adverse event	Treatment cause	Utility decrement	Event duration	Equivalent QALY loss
Temporary acute vision loss	PDT	100% utility loss	2 weeks	e.g. 0.038 [a]
Note: a) Illustrative utility loss from 1 year of otherwise perfect health.				

J.5.3.8 Summary

All parameters used in the model are summarised in Table 47, including details of the distributions and parameters used in probabilistic analysis.

Table 47: All parameters in new cost–utility model

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Model settings				
Discount rate, QALYs	3.5%	N/A	N/A	Guidelines Manual 2014
Discount rate, costs	3.5%	N/A	N/A	Guidelines Manual 2014
Baseline population				
Demographics				
Cohort age (years)	79.7	Normal	Mu: 79.700 Delta: 0.070	Tufail et al. (2014)
Cohort sex (% male)	36.4%	Beta	Alpha: 7062 Beta: 4073	Tufail et al. (2014)
Baseline VA: unilateral neovascular AMD				
Affected eye				
>85	1.0%	Dirichlet	Alpha: 2 Beta: 196	Royal Liverpool & Broadgreen University Hospitals Trust
85-71	15.2%	Dirichlet	Alpha: 30 Beta: 168	
70-56	29.8%	Dirichlet	Alpha: 59 Beta: 139	
55-41	29.3%	Dirichlet	Alpha: 48 Beta: 140	
40-26	15.7%	Dirichlet	Alpha: 31 Beta: 167	
≤25	9.1%	Dirichlet	Alpha: 18 Beta: 180	
Fellow eye				
>85	1.3%	Dirichlet	Alpha: 1, 0 Beta: 39, 6	Royal Liverpool & Broadgreen University Hospitals Trust Sheffield Teaching Hospitals NHS Foundation
85-71	31.3%	Dirichlet	Alpha: 5, 3 Beta: 35, 3	
70-56	42.5%	Dirichlet	Alpha: 14, 3 Beta: 26, 3	
55-41	15.0%	Dirichlet	Alpha: 12, 0 Beta: 28, 6	
40-26	7.5%	Dirichlet	Alpha: 6, 0	

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
			Beta: 34, 6	
≤25	2.5%	Dirichlet	Alpha: 2, 0 Beta: 38, 0	
Baseline VA: bilateral neovascular AMD				
Either eye				Royal Liverpool & Broadgreen University Hospitals Trust Sheffield Teaching Hospitals NHS Foundation
>85	5.8%	Dirichlet	Alpha: 12, 2 Beta: 144, 50	
85-71	69.9%	Dirichlet	Alpha: 86, 44 Beta: 70, 8	
70-56	15.7%	Dirichlet	Alpha: 40, 3 Beta: 116, 49	
55-41	4.8%	Dirichlet	Alpha: 9, 2 Beta: 147, 50	
40-26	3.8%	Dirichlet	Alpha: 9, 1 Beta: 147, 51	
≤25	0.0%	Dirichlet	Alpha: 0, 0 Beta: 156, 52	
Natural history				
Proportion of fellow eyes with neovascular AMD at baseline	7.3%	Beta	Alpha: 20, 3 Beta: 198, 52	Royal Liverpool & Broadgreen University Hospitals Trust Sheffield Teaching Hospitals NHS Foundation
Rate of neovascular AMD development in fellow eye at year 3	42.0%	Beta	Alpha: 628.424 Beta: 867.823	Zarranz-Ventura et al. (2014)
First treated eyes with baseline VA >6/12	17.0%	Beta	Alpha: 324 Beta: 1672	Zarranz-Ventura et al. (2014)
Second treated eyes with baseline VA >6/12	47.0%	Beta	Alpha: 214 Beta: 242	Zarranz-Ventura et al. (2014)
Mortality				
Hazard ratio, VA <55 in either eye	1.23	Lognormal	Mu: 0.207 Delta: 0.430	Christ et al. (2008)
Hazard ratio, VA ≤25 in both eyes	1.54	Lognormal	Mu: 0.430 Delta: 0.062	Christ et al. (2008)
Treatment frequency				

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Injection frequency, year 1				
Sham injections	3.23	Normal	N: 160 SE: 0.005	VIM, VIO
Aflibercept				
Monthly, continuous	11.90	N/A	N/A	Schmidt-Erfurth et al (2014)
Every 2 months, continuous	7.00	N/A	N/A	Schmidt-Erfurth et al (2014)
Every 2 months for 1 year, then PRN	7.00	N/A	N/A	Schmidt-Erfurth et al (2014)
Treat-and-extend	8.81	N/A	N/A	Estimated [a]
PRN and extend	6.28	N/A	N/A	Estimated [a]
Bevacizumab				
Monthly, continuous	11.65	Normal	N: 399 SE: 0.081	CATT, IVAN
Every 2 months, continuous	5.82	N/A	N/A	Estimated [a]
Loading phase then every 3 months, continuous	5.88	N/A	N/A	Estimated [a]
As needed (PRN)	7.54	Normal	N: 301 SE: 0.203	Barikian, CATT
Loading phase then PRN	7.74	N/A	N/A	Barikian 2015
Treat-and-extend	8.90	Normal	N: 213 SE: 0.178	LUCAS
PRN and extend	6.56	N/A	N/A	Estimated [a]
PDT	2.90	Uniform	Min: 2.9 Max: 2.9	VIM, VIO
Ranibizumab				
Monthly, continuous	11.37	Normal	N: 1141 SE: 0.055	CATT, EXCITE, HARBOR, IVAN, TREND
Every 2 months, continuous	5.69	N/A	N/A	Estimated [a]
Loading phase then every 3 months, continuous	5.50	N/A	N: 118 SE: 0.097	EXCITE
As needed (PRN)	6.90	Normal	N: 285 SE: 0.178	CATT
Loading phase then PRN	7.10	N/A	N: 803 SE: 0.083	Barikian 2015
Treat-and-extend	8.42	Normal	N: 541 SE: 0.109	LUCAS, TREND
PRN and extend	6.00	Normal	N: 38 SE: 0.342	SALUTE

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Injection frequency, load+PRN vs PRN				
Immediate PRN	6.10	Normal	N: 30 SE: 0.694	Barikian 2015
Loading phase then PRN	6.30	Normal	N: 30 SE: 0.657	Barikian 2015
Difference due to loading	0.20	N/A	N/A	Barikian 2015
Injection frequency, 24 month data where required				
Sham injections	4.88	Normal	N: 597 SE: 0.007	VIM, VIO
Aflibercept				
VIEW monthly then PRN regimen: weeks 0 to 96	16.00	Normal	N: 613 SE: 0.129	Schmidt-Erfurth et al (2014)
VIEW monthly then PRN regimen: weeks 52 to 96	4.10	Normal	N: 613 SE: 0.073	Schmidt-Erfurth et al (2014)
VIEW 2-monthly then PRN regimen: weeks 0 to 96	11.20	Normal	N: 607 SE: 0.118	Schmidt-Erfurth et al (2014)
VIEW 2-monthly then PRN regimen: weeks 52 to 96	4.20	Normal	N: 607 SE: 0.069	Schmidt-Erfurth et al (2014)
Bevacizumab				
Monthly, continuous: 0-2 years total	22.65	Normal	N: 277 SE: 0.158	CATT, IVAN
As needed (PRN): 0-2 years total	14.10	Normal	N: 251 SE: 0.442	CATT
Loading phase then PRN: 0-2 years total	13.00	Normal	N: 145 SE: 0.383	IVAN
PDT: 0-2 years total	4.36	Normal	N: 651 SE: 0.008	ANCHOR, VIM, VIO, VIP
Ranibizumab				
Monthly, continuous: 0-2 years total	22.25	Normal	N: 311 SE: 0.187	CATT, IVAN
As needed (PRN): 0-2 years total	12.60	Normal	N: 264 SE: 0.406	CATT
Loading phase then PRN: 0-2 years total	12.70	Normal	N: 155 SE: 0.357	IVAN
Treat-and-extend	16.49	Normal	N: 212 SE: 0.355	LUCAS, TREX-AMD
Injection frequency, year 2				
Sham injections	1.65	N/A	N/A	Estimated [a]
Aflibercept				
Monthly, continuous	11.38	N/A	N/A	Estimated [a]
Every 2 months, continuous	5.33	N/A	N/A	Estimated [a]

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Every 2 months for 1 year, then PRN	5.04	N/A	N/A	Estimated [a]
Treat-and-extend	7.28	N/A	N/A	Estimated [a]
PRN and extend	5.19	N/A	N/A	Estimated [a]
Bevacizumab				
Monthly, continuous	11.01	N/A	N/A	Estimated [a]
Every 2 months, continuous	5.50	N/A	N/A	Estimated [a]
Loading phase then every 3 months, continuous	3.67	N/A	N/A	Estimated [a]
As needed (PRN)	6.56	N/A	N/A	Estimated [a]
Loading phase then PRN	5.26	N/A	N/A	Estimated [a]
Loading phase then TRX	9.20	Normal	N: 167 SE: 0.271	TREX-AMD
PRN and extend	5.70	N/A	N/A	Estimated [a]
PDT	1.46	N/A	N/A	Estimated [a]
Ranibizumab				
Monthly, continuous	10.88	N/A	N/A	Estimated [a]
Every 2 months, continuous	5.44	N/A	N/A	Estimated [a]
Loading phase then every 3 months, continuous	3.63	N/A	N/A	Estimated [a]
As needed (PRN)	5.70	N/A	N/A	Estimated [a]
Loading phase then PRN	5.60	N/A	N/A	Estimated [a]
Loading phase then TRX	8.07	N/A	N/A	Estimated [a]
PRN and extend	4.96	N/A	N/A	Estimated [a]
Injection frequency, year 3+				
Sham injections	1.07	N/A	N/A	Estimated [a]
Continuous regimens				
Planned injections per year, monthly treatment	12.00	N/A	N/A	Assumption (1 per month)
Planned injections per year, 2-monthly treatment	6.00	N/A	N/A	Assumption (1 per 2 months)
Planned injections per year, quarterly treatment	4.00	N/A	N/A	Assumption 9(1 per 3 months)
Adherence, ranibizumab monthly	21.7 (/24)	Beta	Alpha: 21.7 Beta: 2.3	IVAN (Chakravarthy 2015)
Adherence, bevacizumab monthly	22.0 (/24)	Beta	Alpha: 22.0 Beta: 2.0	IVAN (Chakravarthy 2015)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Adherence to continuous treatment	91.0%	N/A	N/A	Pooled estimate of above 2 rows
Injections per year, monthly treatment	10.92	N/A	N/A	Calculated using data above
Injections per year, 2-monthly treatment	5.46	N/A	N/A	
Injections per year, 3-monthly treatment	3.64	N/A	N/A	
Discontinuous regimens				
CATT: ranibizumab PRN injections (2 yrs)	12.60	Normal	N: 264 SE: 0.406	Martin et al. (2012)
CATT: ranibizumab monthly injections (2 yrs)	22.40	Normal	N: 134 SE: 0.337	
CATT: bevacizumab PRN injections (2 yrs)	14.10	Normal	N: 251 SE: 0.442	
CATT: bevacizumab monthly injections (2 yrs)	23.40	Normal	N: 135 SE: 0.241	
VIEW: ranibizumab PRN injections (yr 2)	4.60	Normal	N: 595 SE: 0.090	Schmidt-Erfurth et al. (2014)
VIEW: aflibercept PRN injections (yr 2)	4.20	Normal	N: 607 SE: 0.069	
TREX-AMD: ranibizumab monthly injections (2 yrs)	25.50	Normal	N: 18 SE: 0.919 (no SD; assumed equal to CATT ranibizumab monthly SD)	Wykoff et al. (2017)
TREX-AMD: ranibizumab TREX injections (2 yrs)	18.60	Normal	N: 23 SE: 1.147 (no SD; assumed equal to LUCAS ranibizumab 2-yr SD)	
LUCAS: ranibizumab TREX injections (yr 2)	8.00	Normal	N: 172 SE: 0.274	Berg et al. (2016)
LUCAS: bevacizumab TREX injections (yr 2)	9.20	Normal	N: 167 SE: 0.271	
SALUTE: ranibizumab PRN injections (1-yr)	6.60	Normal	N: 39 SE: 0.336	Eldem et al. (2015)
SALUTE: ranibizumab PRNX injections (1-yr)	6.00	Normal	N: 38 SE: 0.342	
Number of injections required relative to ranibizumab PRN				
Ranibizumab PRN	1.00	N/A	N/A	Calculated from above network (see Section J.5.3.5 for method)
Ranibizumab TREX	1.30	N/A	N/A	
Ranibizumab PRNX	0.91	N/A	N/A	
Aflibercept PRN	0.91	N/A	N/A	
Aflibercept TREX	1.18	N/A	N/A	

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Aflibercept PRNX	0.83	N/A	N/A	
Bevacizumab PRN	1.12	N/A	N/A	
Bevacizumab TREX	1.49	N/A	N/A	
Bevacizumab PRNX	1.02	N/A	N/A	
Number of injections per year in long-term treatment				
Ranibizumab PRN	3.70	Normal	N: 994 SE: 0.072	Tufail et al. (2014)
Ranibizumab TREX	4.80	N/A	N/A	Calculated using ratios above and ranibizumab PRN value from Tufail et al. (2014); see Section J.5.3.5 for methods
Ranibizumab PRNX	3.36	N/A	N/A	
Aflibercept PRN	3.38	N/A	N/A	
Aflibercept TREX	4.38	N/A	N/A	
Aflibercept PRNX	3.07	N/A	N/A	
Bevacizumab PRN	4.14	N/A	N/A	
Bevacizumab TREX	5.52	N/A	N/A	
Bevacizumab PRNX	3.76	N/A	N/A	
PRN and PRNX monitoring visit frequency				
UK ARMD database data				
Total visits, year 1	9.20	Lognormal	Mu: 2.219 Delta: 0.003	Tufail et al. (2014)
Total visits, year 2	8.20	Lognormal	Mu: 2.104 Delta: 0.004	Tufail et al. (2014)
Total visits, year 3	8.20	Lognormal	Mu: 2.104 Delta: 0.005	Tufail et al. (2014)
SALUTE trial				
Total visits, PRN	12.69	Lognormal	Mu: 2.541 Delta: 0.009	Eldem et al. (2015)
Total visits, PRNX	10.10	Lognormal	Mu: 2.313 Delta: 0.019	Eldem et al. (2015)
Adverse event probabilities				
Anti-VEGF therapies				
Cataracts (% in year)	0.16%	Beta	Alpha: 2 Beta: 608	Solomon et al. (2014)
Endophthalmitis	0.47%	Beta	Alpha: 11 Beta: 1174	Solomon et al. (2014)
GI disorder (bevacizumab)	2.12%	Beta	Alpha: 37 Beta: 845	Solomon et al. (2014)
GI disorder (other)	0.77%	Beta	Alpha: 14 Beta: 899	Solomon et al. (2014)
Retinal detachment	0.08%	Beta	Alpha: 1 Beta: 609	Solomon et al. (2014)
Retinal tear	0.33%	Beta	Alpha: 4 Beta: 606	Solomon et al. (2014)
Stroke	0.70%	Beta	Alpha: 25 Beta: 1770	Solomon et al. (2014)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
PDT				
Back pain	2.59%	Beta	Alpha: 49 Beta: 909	Wormald et al. (2007)
Injection site reaction	6.14%	Beta	Alpha: 85 Beta: 629	Wormald et al. (2007)
Skin photosensitivity	1.20%	Beta	Alpha: 15 Beta: 612	Wormald et al. (2007)
Temporary acute vision loss	0.99%	Beta	Alpha: 14 Beta: 700	Wormald et al. (2007)
Costs (£)				
Treatments				
Aflibercept, list price	816.00	N/A	N/A	BNF
Aflibercept, PAS price	[redacted]	N/A	N/A	N/A
Bevacizumab, aliquoted	49.00	Gamma	Alpha: 3.026 Beta: 16.194	Chakravarthy et al. (2015)
PDT – administration	135.96	Gamma	Alpha: 493.06 Beta: 0.276	NHS reference costs (2014-15)
PDT – verteporfin	850.00	N/A	N/A	BNF
Ranibizumab, list price	551.00	N/A	N/A	BNF
Ranibizumab, PAS price	[redacted]	N/A	N/A	N/A
Administration				
Outpatient attendance, consultant led	88.59	Gamma	Alpha: 2764.35 Beta: 0.032	NHS reference costs (2014-15)
Outpatient attendance, non-consultant led	58.69	Gamma	Alpha: 521.545 Beta: 0.113	NHS reference costs (2014-15)
Day case admission	637.19	Gamma	Alpha: 485.286 Beta: 1.313	NHS reference costs (2014-15)
Proportion of attendances as outpatients – base case	100%	N/A	N/A	Guideline Committee
Proportion of attendances as outpatients – scenario	63.2%	Beta	Alpha: 189953 Beta: 110656	Hosp. Episode Stats (2014-15)
Attendance cost multiplier if treated in both eyes	1.50	Triangular	Min: 1.0 Max: 2.0	Guideline Committee
Imaging				
OCT scan	115.52	Gamma	Alpha: 760.997 Beta: 0.152	NHS reference costs (2014-15)
FFA	153.22	Gamma	Alpha: 1487.60 Beta: 0.103	NHS reference costs (2014-15)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Low vision support				
Unit costs – NHS/PSS				
Depression	2478.95	Uniform	Min: 2433.37 Max: 2433.37	McCrone et al. (2008)
Hip replacement	5777.80	Uniform	Min: 1755.62 Max: 5866.47	Meads et al. (2003)
Low vision aids	214.69	Uniform	Min: 88.83 Max: 214.69	Meads et al. (2003)
Low vision rehabilitation	323.30	Uniform	Min: 196.85 Max: 486.60	Meads et al. (2003)
Home care worker	8361.70	Uniform	Min: 3977.40 Max: 13968.70	Meads et al. (2003)
Registration as sight impaired (one-off cost)	153.40	Uniform	Min: 40.10 Max: 169.73	Meads et al. (2003)
Residential care (less 30% privately funded)	22859.20	Uniform	Min: 11273.03 Max: 33897.38	Meads et al. (2003)
Unit costs – Other resources				
Housing and council tax benefit	2714.40	Uniform	Min: 3799.58 Max: 5650.24	Meads et al. (2003)
Social security	3029.84	Uniform	Min: 0 Max: 4528.38	Meads et al. (2003)
Tax allowances	502.35	Uniform	Min: 228.34 Max: 502.35	Meads et al. (2003)
Uptake in people with BSE VA <55				
Depression	39.0%	Beta	Alpha: 14.860 Beta: 23.243	Meads et al. (2003)
Hip replacement	5.0%	Beta	Alpha: 23.700 Beta: 450.300	Meads et al. (2003)
Low vision aids (33% of people with VA 70-55 , 100% of people with VA <55)	100.0%	N/A	N/A	Guideline Committee
Low vision rehabilitation	11.0%	Beta	Alpha: 22.140	Meads et al. (2003)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
			Beta: 179.133	
Home care worker	6.0%	Beta	Alpha: 23.440 Beta: 367.227	Meads et al. (2003)
Registration as sight impaired	94.5%	Beta	Alpha: 0.430 Beta: 0.025	Meads et al. (2003)
Residential care	30.0%	Beta	Alpha: 17.200 Beta: 40.133	Meads et al. (2003)
Housing and council tax benefit	45.0%	Beta	Alpha: 13.300 Beta: 16.256	Meads et al. (2003)
Social security	63.0%	Beta	Alpha: 8.620 Beta: 5.063	Meads et al. (2003)
Tax allowances	5.0%	Beta	Alpha: 23.700 Beta: 450.300	Meads et al. (2003)
Adverse event treatment				
Anti-VEGF therapies				
Cataract	850.84	Gamma	Alpha: 10389.4 Beta:0.082	NHS reference costs (2014-15)
Endophthalmitis	788.09	N/A	N/A	Calculated
Procedure	713.23	Gamma	Alpha: 504.157 Beta:1.415	NHS reference costs (2014-15)
Amikacin	9.64	Uniform	Min: 9.64 Max: 9.64	BNF
Vancomycin	140.08	Uniform	Min: 140.08 Max: 140.08	BNF
Gastrointestinal disorder	431.28	Gamma	Alpha: 13734.6 Beta: 0.031	NHS reference costs (2014-15)
Retinal detachment	1122.95	Gamma	Alpha: 499.129 Beta: 2.250	NHS reference costs (2014-15)
Retinal tear	713.23	Gamma	Alpha: 504.136 Beta: 1.415	NHS reference costs (2014-15)
Stroke – event	4128.62	Uniform	Min: 2064.31 Max: 8257.25	NICE CG 181
Stroke – management/year	156.39	Uniform	Min: 78.19 Max: 312.77	NICE CG 181
PDT				

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Back pain	0.89	Uniform	Min: 0.89 Max: 0.89	Assumption & NHS Electronic Drug Tariff
Injection site reaction	0.00	N/A	N/A	Assumption
Skin photosensitivity	1.98	Uniform	Min: 1.98 Max: 1.98	Assumption & NHS Electronic Drug Tariff
Temporary acute vision loss	0.00	N/A	N/A	Assumption
HRQL and utilities				
Utility regression model				
Intercept term	0.860	Beta	Alpha: 21.533 Beta: 3.505	Czoski-Murray et al. (2009)
Coefficient for age	0.001	Normal	Mu: 0.001 Delta:0.002	Czoski-Murray et al. (2009)
Coefficient for VA	-0.386	Normal	Mu: 0.368 Delta:0.046	Czoski-Murray et al. (2009)
Scaling factor (WSE)	0.300	N/A	N/A	Czoski-Murray et al. (2009)
Alternative scaling factor (WSE)	0.429	N/A	N/A	Cummins et al, NICE TA 346
Scenario analysis utilities				
Visual acuity				
20/20 to 20/25	0.89	Beta	Alpha: 67.418 Beta: 8.333	Brown et al. (2000)
20/30 to 20/50	0.81	Beta	Alpha: 74.014 Beta: 17.361	Brown et al. (2000)
20/60 to 20/100	0.57	Beta	Alpha: 53.098 Beta: 40.056	Brown et al. (2000)
20/200 to 20/400	0.52	Beta	Alpha: 24.918 Beta: 23.002	Brown et al. (2000)
Counting fingers (20/600) to light perception (20/1200)	0.40	Beta	Alpha: 33.0493 Beta: 49.574	Brown et al. (2000) Exact VA range assumed.
Age-related UK norms				
Men				
Aged <25 years	0.94	Beta	Alpha: 470.313 Beta: 30.020	Kind et al. (1999)
Aged 25-34 years	0.93	Beta	Alpha: 779.507 Beta: 58.673	Kind et al. (1999)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Aged 35-44 years	0.91	Beta	Alpha: 659.278 Beta: 65.203	Kind et al. (1999)
Aged 45-54 years	0.84	Beta	Alpha: 341.410 Beta: 65.030	Kind et al. (1999)
Aged 55-64 years	0.78	Beta	Alpha: 333.840 Beta: 94.160	Kind et al. (1999)
Aged 65 to 74 years	0.78	Beta	Alpha: 388.472 Beta: 109.569	Kind et al. (1999)
Aged 75+	0.75	Beta	Alpha: 192.968 Beta: 64.323	Kind et al. (1999)
Women				
Aged <25 years	0.94	Beta	Alpha: 647.033 Beta: 41.300	Kind et al. (1999)
Aged 25-34 years	0.93	Beta	Alpha: 1137.28 Beta: 85.602	Kind et al. (1999)
Aged 35-44 years	0.91	Beta	Alpha: 1009.37 Beta: 99.828	Kind et al. (1999)
Aged 45-54 years	0.85	Beta	Alpha: 546.147 Beta: 96.379	Kind et al. (1999)
Aged 55-64 years	0.81	Beta	Alpha: 530.282 Beta: 124.387	Kind et al. (1999)
Aged 65 to 74 years	0.78	Beta	Alpha: 556.028 Beta: 156.828	Kind et al. (1999)
Aged 75+	0.71	Beta	Alpha: 412.389 Beta: 168.441	Kind et al. (1999)
Utility effect of injections				
Injection-related utility multiplier	0 (100% loss)	N/A	N/A	Guideline Committee
Duration of effect	1 day	N/A	N/A	Guideline Committee
Proportion of patients	50.0%	N/A	N/A	Guideline Committee
Adverse event HRQL decrements				
Anti-VEGF therapies				

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Cataract	-0.142	N/A	N/A	Brown et al. (2007)
Endophthalmitis	-0.300	N/A	N/A	Brown et al. (2007)
Gastrointestinal disorder	-0.044	Normal	Mu: -0.044 Delta: 0.016	Sullivan et al. (2011)
Retinal detachment	-0.270	N/A	N/A	Brown et al. (2007)
Retinal tear	0	N/A	N/A	Guideline Committee
Stroke (utility multiplier)	0.628	Beta	Alpha: 91.066 Beta: 53.944	NICE CG 181
PDT				
Back pain	-0.087	Normal	Mu: -0.087 Delta: 0.006	Sullivan et al. (2011)
Injection site reaction	0	N/A	N/A	Assumption
Skin photosensitivity	0	N/A	N/A	Assumption
Temporary acute vision loss (utility multiplier)	0 (100% loss)	N/A	N/A	Guideline Committee
Adverse event effect duration (years)				
Anti-VEGF therapies				
Cataract	0.083	N/A	N/A	Guideline Committee
Endophthalmitis	0.300	N/A	N/A	Guideline Committee
Gastrointestinal disorder	0.083	N/A	N/A	Guideline Committee
Retinal detachment	0.250	N/A	N/A	Guideline Committee
Retinal tear	0	N/A	N/A	Guideline Committee
PDT				
Back pain	1 day	N/A	N/A	Guideline Committee
Injection site reaction	0	N/A	N/A	Assumption
Skin photosensitivity	0	N/A	N/A	Assumption
Temporary acute vision loss (utility multiplier)	0.038	N/A	N/A	Guideline Committee
Treatment effects				
Mean difference NMA, year 1				
Mean change from baseline to year 1, monthly ranibizumab	8.243	Multivariate normal		Baseline synthesis
Aflib. vs. rani.	-0.182	Multivariate normal		NMA
Beva. vs. rani.	-0.396	Multivariate normal		NMA
PDT vs. rani.	-20.166	Multivariate normal		NMA

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
Sham vs. rani.	-18.947	Multivariate normal		NMA
PRN	-1.467	Multivariate normal		NMA
Loading phase	0.136	Multivariate normal		NMA
TREX	-1.285	Multivariate normal		NMA
PRNX	4.456	Multivariate normal		NMA
Frequency, aflibercept	-0.840	Multivariate normal		NMA
Frequency, beva./rani.	-1.524	Multivariate normal		NMA
Mean difference NMA, year 2				
Mean change, year 1 to year 2	-0.531	Multivariate normal		NMA
Aflib. vs. rani.	-0.318	Multivariate normal		NMA
Beva. vs. rani.	0.132	Multivariate normal		NMA
PDT vs. rani.	0.207	Multivariate normal		NMA
Sham vs. rani.	-3.628	Multivariate normal		NMA
PRN	-0.426	Multivariate normal		NMA
Loading phase (yr 2 only)	0.519	Multivariate normal		NMA
TREX	-3.068	Multivariate normal		NMA
PRNX	4.456	Multivariate normal		No year 2 evidence. Assumed equal to year 1 (due to similarity of other year 1 and year 2 estimates)
Frequency, aflibercept	-0.840	Multivariate normal		
Frequency, beva./rani.	-1.524	Multivariate normal		
NMA, treatment discontinuation				
Baseline ln(odds) of 1-year discontinuation on ranibizumab monthly	-2.314	Normal	Mu: -2.314 Delta: 0.169	NMA
Aflib. vs. rani.	-0.572	Multivariate normal		NMA
Beva. vs. rani.	0.138	Multivariate normal		NMA
PDT vs. rani.	0.759	Multivariate normal		NMA
Sham vs. rani.	1.437	Multivariate normal		NMA
PRN vs. monthly	0.062	Multivariate normal		NMA
Loading vs. no loading	-0.349	Multivariate normal		NMA
TREX vs. monthly	0.097	Multivariate normal		NMA
PRNX vs. loading+PRN	0.557	Multivariate normal		NMA
Frequency, aflibercept	0.368	Multivariate normal		NMA
Frequency, beva./rani.	0.031	Multivariate normal		NMA
Background categorical change				
Proportion achieving 15+ letter **gain** after 1 year	16.8%	Beta	Alpha: 184 Beta: 911	Buckle et al. (2016)

Parameter	Point estimate	Probabilistic analysis		Source
		Distribution	Parameters	
“” if baseline VA: 70-55	11.0%	N/A	N/A	Buckle et al. (2016)
”” if baseline VA: 54-40	20.6%	N/A	N/A	Buckle et al. (2016)
“” if baseline VA: 39-23	28.8%	N/A	N/A	Buckle et al. (2016)
Odds ratio: VA 70-55	1.000	N/A	N/A	Reference category
Odds ratio: VA 54-40	2.1054	Lognormal	Mu: 0.744 Delta: 0.197	Calculated
Odds ratio: VA 39-23	3.2833	Lognormal	Mu: 1.189 Delta: 0.200	Calculated
Probability: VA 70-55	10.2%	N/A	N/A	Calculated
Probability: VA 54-40	19.2%	N/A	N/A	Calculated
Probability: VA 39-23	27.1%	N/A	N/A	Calculated
Proportion with 15+ letter **loss** after 1 year	9.7%	Beta	Alpha: 126 Beta: 1173	Buckle et al. (2016)
“” if baseline VA: >70	9.2%	N/A	N/A	Buckle et al. (2016)
“” if baseline VA: 70-55	9.6%	N/A	N/A	Buckle et al. (2016)
”” if baseline VA: 54-40	12.1%	N/A	N/A	Buckle et al. (2016)
“” if baseline VA: 39-23	6.7%	N/A	N/A	Buckle et al. (2016)
Odds ratio: VA >70	0.950	Lognormal	Mu: 0.051 Delta: 0.275	Calculated
Odds ratio: VA 70-55	1.000	N/A	N/A	Reference category
Odds ratio: VA 54-40	1.289	Lognormal	Mu: 0.254 Delta: 0.229	Calculated
Odds ratio: VA 39-23	0.675	Lognormal	Mu: 0.393 Delta: 0.304	Calculated
Probability: VA >70	9.3%	N/A	N/A	Calculated
Probability: VA: 70-55	9.7%	N/A	N/A	Calculated
Probability: VA 54-40	12.1%	N/A	N/A	Calculated
Probability: VA 39-23	6.8%	N/A	N/A	Calculated
Long-term effects				
Decline from end of year 2 to end of year 3 (letters)	-2.5	Normal	Mu: -2.5 Delta: 0.374	Tufail et al. (2014)

Notes:

a) Estimated using year 1 data, and/or 2-year data, and/or data for alternative therapies, as described in Table 35.

J.5.4 Model convergence

As a Markov patient simulation model, our model simulates the experience of one AMD patient at a time. The user has to specify the total number of patients to be simulated through the model for each strategy. This introduces 'first-order' uncertainty, or Monte Carlo error, a form of sampling uncertainty caused by differences in the random numbers used in each model run. It is important to identify a suitable number of patients per strategy to be simulated through the model (Davis et al. 2014). Increasing the number of patient simulations per strategy will reduce the effect of Monte Carlo error on the overall mean results. When increasing the number of patients is seen to have negligible impact on model results, we can say that number of patients is the point at which the model 'converges', such that the effect of this first-order uncertainty is minimised.

A practical cost of increasing the number of patients is the heavier computational requirement, taking more time and potentially limiting the number of scenario analyses that can be explored. This constraint becomes even more problematic when undertaking probabilistic sensitivity analysis (PSA), to capture 'second-order' uncertainty in model input parameters. For PSA each individual patient is simulated a specified number of times, with model inputs drawn from their underlying distribution each time. Simulating 50,000 patients and choosing 10,000 PSA runs per patient will require 500,000,000 model runs per strategy.

The NICE Decision Support Unit published a technical support document that provides guidance on optimising the number of patients per strategy (Davis et al. 2014). We adopted the suggested approach of increasing the number of patients per strategy, running the model and comparing the results across model runs. A limitation of our analysis is that our model, with its underlying Markov structure, does not store individual patient level results with which to produce estimates of first-order variance. Instead, we sought to identify the number of patients at which results stopped visibly fluctuating. We compared total costs and QALYs, and incremental outcomes of each strategy compared with 3-monthly bevacizumab, across different numbers of patients simulated, from 1,000 to 500,000.

The results of this exercise are shown in Figure 12. Note, however, that this was undertaken during model development using a near-final – not final – model. As such, only the convergence of results should evaluated, not the absolute results. In all figures, there is large variation in results when 10,000 or fewer patients are simulated. This variation begins to decrease notably when more than 50,000 patients are simulated, shown by the charts flattening. The results suggest that we can be fairly confident that the model converges by 100,000 patients, meaning this should be a big enough sample size to minimise the impact of first-order uncertainty. We therefore established that our deterministic results would come from models runs of at least 100,000 simulated patients.

During the final stages of model development, it became apparent that the incremental QALYs between some strategies were likely to be very small, for example with differences of 0.005 QALYs or fewer (see Section J.5.6.2). Such small QALY differences can easily become lost in the noise of first-order uncertainty, making it difficult to disentangle the 'true' difference in QALYs from the random Monte Carlo error. We therefore conservatively opted to increase our model runs, such that our base-case results are from a 2,000,000 simulated patients. However, simulating 2,000,000 individuals for all strategies in sensitivity analysis – capturing our uncertainty in input parameters – is impractical. We therefore use our base-case results to exclude some strategies that are routinely dominated and/or not cost effective, and then run sensitivity analyses on a smaller subset of strategies with a reduced number of individuals.

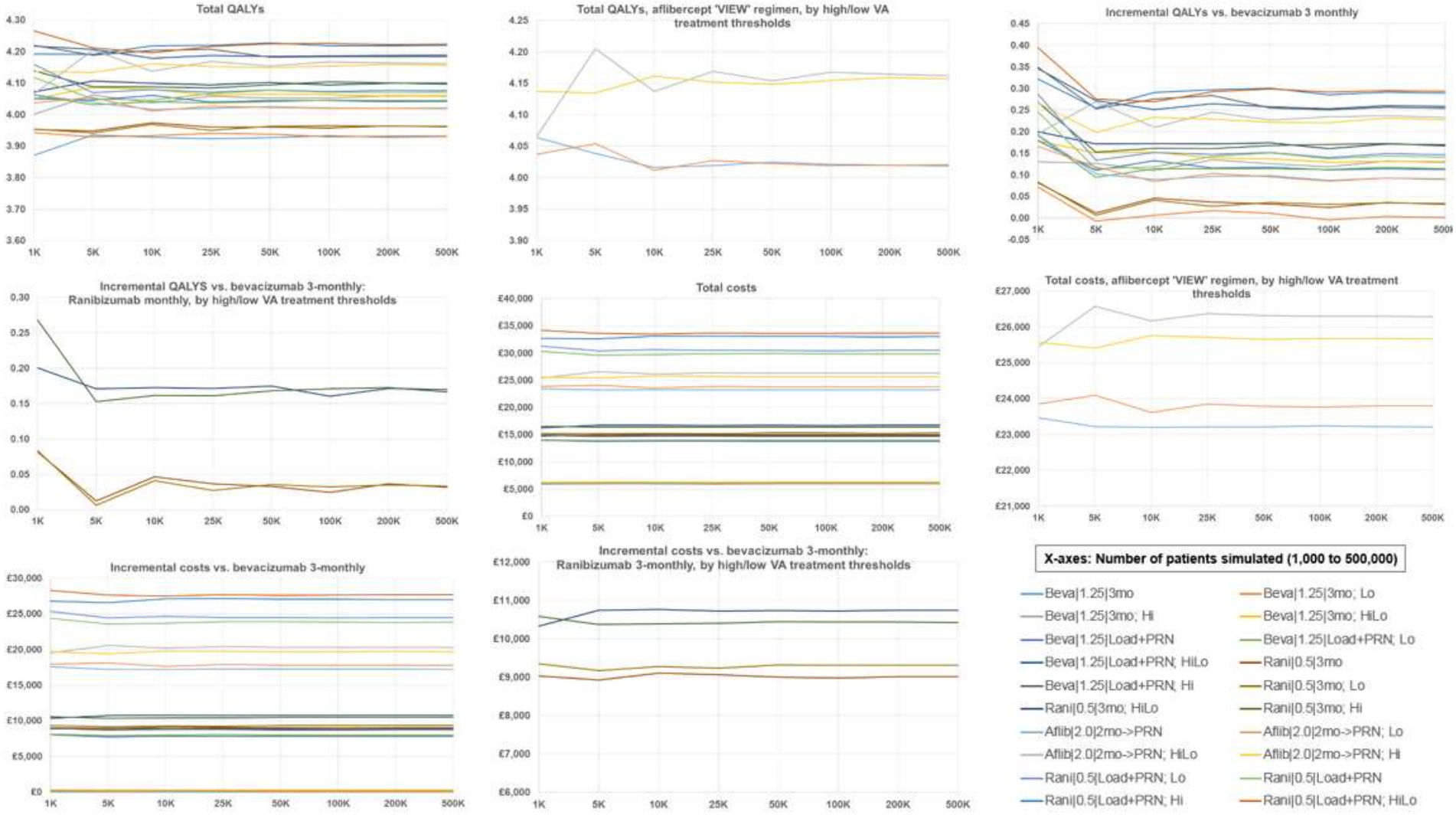


Figure 12: Results of preliminary model convergence testing

J.5.5 Sensitivity analyses

J.5.5.1 Probabilistic sensitivity analyses

We configured the models to perform probabilistic sensitivity analysis (PSA) to quantify uncertainty in the true values of input parameters. Probability distributions were estimated for all input variables (see Table 47) with the exception of:

- direct (drug) costs,
- parameters whose inputs were estimated by guideline committee opinion and lie at and extreme end of a natural distribution, and
- parameters where no distribution information was available (e.g. number of observations, standard error).

Distribution parameters were sourced from the study in which the value was obtained, where possible, or were estimated based on the usual properties of data of that type. For PSA, we ran 20,000 individual patients per strategy through 5,000 probabilistic parameter resamples, meaning each strategy had a total of 100,000,000 individual patient simulations.

J.5.5.2 Scenario analyses

A number of scenario analyses have been conducted using the economic model. They are captured within one-way sensitivity analysis results, effectively treating the scenario as an input parameter that can be varied to an alternative or extreme value.

PRNX regimens

The PRNX treatment regimen is not included in the base-case results, because of its reliance on an individual trial with a small sample size to inform clinical effectiveness and injection frequency (see J.5.2.3). This leads to highly uncertain estimates. While some regimens are included in our base-case despite a lack of clinical data, such as 2-monthly bevacizumab, the individual components of these – agent: bevacizumab; frequency: 2-monthly – are themelves well-informed branches of the network. As such, the estimates for 2-monthly bevacizumab are much more certain, whereas PRNX is only connected to the network by a single, small trial. Furthermore, its limited evidence base means our network meta-analysis predicts it to be superior to routine monthly treatment on average, which is not consistent with the expected dose–response relationship. PRNX is therefore included only as a scenario analysis.

Treatment effect scenarios

A number of scenarios were evaluated in which alternative assumptions are made about the application of treatment effects. In the base-case model, transition probabilities for the first year of treatment are effectively weighted according to the different probabilities of VA change by initial VA (see Section J.5.3.3). This generally means that eyes with better initial VA are less likely to improve, that eyes with worse VA are more likely to improve, and that the opposite is true of VA decline. A first scenario removes this effect, applying the mean VA change treatment effects equally across the board, regardless of baseline VA. A second scenario expands the use of this weighting effect, assuming that initial VA continues to affect the treatment effect after year 1. Finally, a scenario applies the NMA estimates for the relative effect of sham injections to the no treatment arm, rather than repeating the year 1 results as per the base-case analysis.

Cost scenarios

In the base-case model, the unit cost of an ophthalmologist-led outpatient attendances is applied for treatment and/or monitoring appointments (£88.59). In one scenario, the unit cost is reduced to that of a non-consultant led outpatient attendance (£58.69), reflecting a scenario where clinics are led by non-ophthalmologist staff members (e.g. nurses). Another scenario assumes that a proportion of appointments are conducted as day case admissions, informed by Hospital Episode Statistics (2014-15). This increases the unit cost of a treatment and/or monitoring attendance to a weighted average of £290.53. A scenario is also captured in which the lower injection and OCT unit costs derived from the IVAN microcosting analysis are applied, which the guideline committee judged to be too low to be used in the base-case model.

In the base-case model, monitoring by an OCT examination is assumed to occur at each treatment-related appointment (that is, where an injection is given or for monitoring-only appointments on PRN regimens). A scenario analysis has been included in which monitoring by OCT is only required when it has the potential inform treatment decision making. This means that an OCT is only performed once per year in patients on a regimen of continuous treatment (at diagnosis in year 1). No OCT costs are incurred thereafter, because the results of a scan would not alter the continuous treatment (over and above treatment suspension and discontinuation already implicitly captured by within mean number of injections parameters). In this scenario, discontinuous regimens (PRN and TREX) do not require OCTs at every visit during any treatment loading phase, but otherwise their OCT requirement is unchanged from the base-case model.

A scenario analysis is included in which non-NHS/PSS costs associated with low vision, such as housing benefit and council tax benefit, are counted by the model. This therefore takes a wider societal perspective to blindness than the base-case model, where only NHS/PSS costs are counted.

Finally, all analyses were performed using PAS prices for aflibercept and ranibizumab, compared with published list prices in the base-case analysis. These results were presented to the guideline committee, but are not presented in this document to protect PAS confidentiality. However, the findings are briefly discussed at the end of the results section.

Treatment discontinuation scenario

In the base-case model, treatment can continue beyond 2 years. Treatment discontinuation can occur for 1 of 2 reasons. The first of these is if the VA of an eye falls to the ≤25 letters (≤6/96) health state; the second is based on the clinical evidence of discontinuation in clinical trials. We developed a network meta-analysis to synthesis discontinuation data at 1 year, and apply the resulting rates to each year thereafter. A scenario analysis is included to explore the sensitivity of the model to this assumption, by setting all discontinuation rates equal to the rate predicted for monthly ranibizumab treatment (which is the reference treatment of the meta-analysis). In this scenario, any differences in treatment dropouts are caused by VA declining to ≤25 letters (therefore difference in effectiveness).

Long-term model inputs scenarios

In the base-case model, 2-year RCT data are utilised such that the first 2 years of our model are based on ‘known’ estimates of comparative effectiveness. We conducted an analysis that utilitises only 1-year RCT data, therefore extrapolating our year 2 model inputs in addition to year 3 onwards. While we believe utilising the second year RCT evidence provides a more informed and informative analysis, this scenario explores the extent to which our use of year 2 data influences cost–utility results. In this scenario, only relative year 1 treatment effects are used (extrapolated from year 2 onwards); the mean number of treatments and PRN monitoring visits in year 1 are carried forward for longer-term treatment; and ocular adverse

event rates are based only on 1-year data in Solomon et al. (2014) (1-year Cochrane Review data are not reported for PDT). The reference long-term mean change in VA in treated eyes is re-estimated to be -2.4 letters per year, compared with the base-case value of -2.5 letters, reflecting a marginally shallower decline in the ARMD data from year 1 to year 3 compared with year 2 to year 3 (Tufail et al. 2014).

As noted above, the base-case analysis assumes that the annual VA decline in eyes that remain on treatment beyond year 2 is anchored at 2.5 letters, derived from the ARMD database (Tufail et al. 2014). Scenarios are explored whereby the long-term VA of treated eyes are assumed to decline more rapidly (-3.7 letters per year; Rofagha et al. 2013) and less rapidly (-0.7 letters per year; Gillies et al. 2015) in eyes that remain on treatment beyond year 2. In these scenarios, the 'anchor' number of injections per year, for ranibizumab PRN, also varies from 3.7 to 2.0 and 4.9, respectively.

We also explore scenarios in which the model assumes that all treatments are equivalent beyond year 2 (which is the maximum duration of randomised evidence). First, a resource use only scenario sets all injection requirements per year beyond year 2 to the ranibizumab PRN value (3.7 per year), and makes all eyes require additional monitoring visits as per ranibizumab PRN (8.2 outpatient visits, in total, per year). Second, a comprehensive scenario sets all injection and monitoring requirements, relative effects and treatment discontinuation rates equal to ranibizumab PRN. For the releative effects, all differences are 'switched off' beyond year 2 of treatment; in the base-case, the modest relative treatment effects for year 1 to year 2 are applied for all subsequent years on treatment. Instead, all treatments are assumed to experience VA decline associated with ranibizumab PRN from the ARMD databse (Tufail et al. 2014). In all, this scenario therefore effectively makes all treatments equivalent beyond year 2. While we feel that our attempt to model long-term outcomes provide a useful and appropriate base-case analysis, this scenario provides understanding of the degree to which our results are dependent on modelling treatments differently beyond the duration of available randomised data.

Quality of life scenarios

Two scenarios focusing on alternative health state utilities have been explored. The first uses of an alternative scaling factor for estimating the relative impact of VA change in the WSE compared with the BSE. In the base-case model, the scaling factor is 0.30; in the scenario it is 0.4285, as suggested by the ERG for NICE Technology Appraisal 346. The second uses alternative utility values entirely, informed by Brown et al. (2000; see Table 43), instead of the regression model by Czoski-Murray et al. (2009) that is used in the base-case model.

Adverse event scenarios

Two scenarios focusing on AEs have been explored. The first applied a RR to the base-case ocular event rates for PRN regimens, based on the clinical evidence described in Section J.5.3.4. The RR of 0.31 means the rate of all ocular events is reduced across anti-VEGF treatments delivered as PRN regimens (including aflibercept delivered as per the VIEW trial from year 2 onward). The second AE scenario involved us increasing the annual probability of experiencing endophthalmitis while receiving treatment with bevacizumab. This scenario was included to explore how different its ocular AE profile would have to be to affect any decision-making based on its cost–utility outcomes.

Baseline data scenario

A scenario was included that treats our baseline VA data, from Sheffield and Liverpool, as a single combined sample by taking a weighted average of the two datasets. This makes our baseline patient cohort more representative of the larger Liverpool dataset. In the base-case we treat them as 2 unique and equal samples, taking a simple, unweighted average of the two sets of data.

Geographic atrophy

Lastly, a scenario has been developed to estimate cost – utility results if unaffected eyes had the potential to develop geographic atrophy (GA; dry AMD), for which there is no treatment currently available in NHS practice. In the base-case analysis all modelled patients begin with late AMD (wet active) in at least 1 eye. In most patients this will be the only eye affected, with a fellow, unaffected (i.e. non-neovascular) eye that is at risk of developing late AMD (wet active) over time. These baseline model parameters are detailed in Section J.5.3.2. However, there is a possibility that non-neovascular fellow eyes could develop geopgraphic atrophy before they would otherwise have become neovascular.

To estimate the potential effect of unaffected fellow eyes being at risk of GA, the following data and assumptions were used:

- The risk of non-neovascular fellow eyes having GA at baseline is **8.5%**, obtained from analysis of the CATT study by Grunwald et al. (2014).
- Other unaffected eyes are subject to a **6.3%** probability of developing GA each year, derived from an Australian and US study that found 14.0% of 200 fellow eyes developed GA over 2.3 years (Finger et al. 2014).
- Late AMD (wet active) and GA are mutually exclusive, and an eye cannot swtich from having one to the other.
- No treatment is available for eyes that develop GA.
- The decline in VA in eyes with GA is equivalent to 'no treatment' from our late AMD (wet active) treatment NMA (derived from sham injections data). In the model, this is made functional by transitioning eyes with GA into the 'post-treatment' health state (see Figure 8).

J.5.6 Cost–utility model – results

In the first instance, clinical and cost–utility outcomes from the model are presented for all 137 base-case strategies (see Section J.5.2.3). These results are presented first to compare the entire base-case decision space, capturing all of the different features of a potential treatment strategy and, in doing so, highlighting the single optimal multicomponent strategy, providing the highest NHB. This is important given that, theoretically, it is appropriate to capture all strategies that the committee consider to be relevant jointly, as valid alternatives for comparison.

A limitation of this approach is that a large number of results are presented at once, which may make identifying and comparing particular strategies, or individual features of different strategies, difficult to do. We take 2 approaches to simpifly the interpretation of cost–utility results after the initial 137-strategy results:

1. Firstly, results are thereafter presented as fully incremental analyses, rather than NHB, with the vast majority of strategies not shown due to being dominated or extendedly dominated by those shown. This presents much smaller sets of results that are simpler to interpet at a glance, albeit lacking cost and QALY results for the (dominated) majority of strategies.
2. Secondly, we break down the full 137-strategy results to explore their different features individually. This is presented in a series of "Focus on" sections, in which the cost effectiveness of different treatment frequencies, different PRN regimens, and different treatment threshold VA levels are explored in turn. Each section focuses on the results when the feature of interest is allowed to vary, holding everything else constant. For example, where it might be difficult to compare 1-monthly treatment regimens with 2-monthly treatment regimens in the main 137-strategy results, this section will present a cost–utility comparison of 1-monthly and 2-monthly regimens, holding the drug used, VA treatment thresholds and WSE eligibility constant.

Note that both aflibercept and ranibizumab are available to the NHS at discounted prices which remain confidential. Results are predominantly presented from analyses using their publicly available list price; however, all analyses were also performed using the discounted prices, and were presented to the guideline committee as the most relevant to NHS decision-making. Key cost–utility results using the lower prices are presented at the end of the results section (see 0), though care has been taken to protect their confidentiality, with cost results redacted and ICERs presented as ranges instead of precise values.

J.2.6.11 Clinical outcomes from the model

The following key clinical outcomes are presented from the base-case analysis:

- Time spent on treatment, in years, for the average patient
- Number of treatments given (e.g. anti-VEGF injections), by eye, for the average patient
- Visual acuity change over time for the average patient.

Time on treatment and number of injections

Time and volume of treatment for 137 base-case model strategies are presented in Table 48, which is ordered in descending 'years on treatment' for 'eye 1'. In the model, 'eye 1' has late AMD (wet active) in all patients at baseline. In the majority of patients, the fellow eye will not have late AMD (wet active) at a presentation, with a proportion experiencing bilateral neovascularisation (see Section J.5.3.2).

Table 48 shows that eyes treated with aflibercept at monthly intervals receive treatment for the longest duration – 5.85 years, on average. It is also associated with the highest number of injections, for example requiring 60.6 in 'eye 1' and 32.8 in the fellow eye if treated according to current practice VA thresholds (6/12 to 6/96). The average patient treated with ranibizumab can expect to receive fewer injections in total than aflibercept, reflecting the higher discontinuation rate associated with ranibizumab. Ranibizumab is associated with a slightly longer treatment duration and higher number of total injections than bevacizumab. PDT is associated with the shortest treatment duration of all active therapies.

As would be expected, the average patient can expect to receive the most treatment when the most inclusive population-level eligibility criteria exist; treating eyes regardless of whether they are the BSE or WSE and regardless of presenting VA. Strategies in which only BSEs are treated have the shortest treatment time for 'eye 1'. This is to be expected, given that most patients present with unilateral late AMD (wet active) where their fellow eye has better VA than 'eye 1'. A population-level strategy to treat only BSEs would therefore mean many of those presenting eyes would go untreated, unless they went on to become the BSE. The maximum treatment provided among strategies treating only BSEs is 28.5 injections in 'eye 1' and 31.6 in the fellow eye (monthly aflibercept).

Extending the visual acuity threshold beyond the range used in current practice also has the expected impact on time on treatment and the number of injections. Treating as per current practice (6/12 to 6/96) provides the least treatment overall, when comparing strategies that are otherwise identical. Extending eligibility to treat eyes with poor VA (≤6/96) leads to the average patient receiving slightly more treatment. This increase is particularly small in strategies treating the BSE only, given that eyes with VA ≤6/96 letters are likely to be the WSE in most patients, and therefore unaffected by extending treatment eligibility this way.

Extending treatment from current practice to including eyes with VA better than 6/12 leads to a bigger increase in the amount of treatment provided to the average patient. For example, treatment of both BSEs and WSEs with 2-monthly bevacizumab causes 'eye 1' to go from 4.23 years on treatment (23.5 injections) to 4.4 years (24.6 injections). Treatment of the fellow eye also increases, from 2.08 years (11.5 injections) to 2.42 years (13.4 injections).

241 Treatment of eyes with good VA maintains their VA for longer, thereby extending the time
242 until the eye declines to the point at which treatment is stopped.

243 **Table 48: Clinical outcomes – treatment duration and number of treatments**

Strategy Treatment | Regimen | Eyes treated | VA range treated	Eye 1		Fellow eye	
	Years on treatment	No. of injections	Years on treatment	No. of injections
Aflib | 1mo | Treat any eye | at any VA level	5.85	65.2	3.39	37.9
Aflib | 1mo | Treat any eye | including VA >6/12	5.71	63.7	3.41	38.1
Aflib | 1mo | Treat any eye | including VA <6/96	5.56	62.1	2.92	32.7
Aflib | 1mo | Treat any eye | with VA in range: 6/12 to 6/96	5.43	60.6	2.93	32.8
Rani | 1mo | Treat any eye | at any VA level	5.12	56.3	2.71	29.8
Rani | 1mo | Treat any eye | including VA >6/12	4.98	54.8	2.73	30.0
Beva | 1mo | Treat any eye | at any VA level	4.89	54.2	2.52	27.9
Rani | 1mo | Treat any eye | including VA <6/96	4.88	53.7	2.33	25.7
Beva | 1mo | Treat any eye | including VA >6/12	4.76	52.8	2.55	28.2
Rani | 1mo | Treat any eye | with VA in range: 6/12 to 6/96	4.75	52.3	2.36	25.9
Beva | 1mo | Treat any eye | including VA <6/96	4.67	51.8	2.17	24.1
Beva | 1mo | Treat any eye | with VA in range: 6/12 to 6/96	4.55	50.4	2.20	24.4
Beva | TREX | Treat any eye | at any VA level	4.24	29.7	2.24	15.7
Aflib | 2mo | Treat any eye | at any VA level	5.15	29.6	2.89	16.6
Beva | TREX | Treat any eye | including VA >6/12	4.14	29.0	2.27	15.9
Aflib | 2mo | Treat any eye | including VA >6/12	5.03	28.9	2.91	16.7
Aflib | TREX | Treat any eye | at any VA level	4.94	28.6	2.99	17.3
Aflib | 1mo | Treat only BSEs | at any VA level	2.55	28.5	2.83	31.6
Beva | TREX | Treat any eye | including VA <6/96	4.02	28.4	1.91	13.6
Aflib | 2mo | Treat any eye | including VA <6/96	4.89	28.1	2.48	14.3
Aflib | TREX | Treat any eye | including VA >6/12	4.85	27.9	3.01	17.4
Beva | TREX | Treat any eye | with VA in range: 6/12 to 6/96	3.93	27.7	1.93	13.7
Aflib | 1mo | Treat only BSEs | including VA >6/12	2.48	27.6	2.83	31.7
Rani | TREX | Treat any eye | at any VA level	4.41	27.5	2.40	15.0
Aflib | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	4.78	27.4	2.49	14.4
Aflib | TREX | Treat any eye | including VA <6/96	4.67	27.2	2.54	15.0
Rani | TREX | Treat any eye | including VA >6/12	4.31	26.7	2.43	15.1
Aflib | TREX | Treat any eye | with VA in range: 6/12 to 6/96	4.57	26.6	2.55	15.0
Rani | TREX | Treat any eye | including VA <6/96	4.18	26.2	2.05	13.0
Rani | 2mo | Treat any eye | at any VA level	4.74	26.1	2.57	14.2
Rani | TREX | Treat any eye | with VA in range: 6/12 to 6/96	4.09	25.5	2.07	13.1
Rani | 2mo | Treat any eye | including VA >6/12	4.63	25.5	2.60	14.3
Beva | 2mo | Treat any eye | at any VA level	4.55	25.2	2.40	13.3
Beva | Load+PRN | Treat any eye | at any VA level	4.91	24.9	2.58	13.2
Rani | 2mo | Treat any eye | including VA <6/96	4.50	24.8	2.20	12.1
Beva | PRN | Treat any eye | at any VA level	4.66	24.7	2.41	12.8
Beva | 2mo | Treat any eye | including VA >6/12	4.44	24.6	2.42	13.4
Rani | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	4.40	24.2	2.22	12.2
Beva | Load+PRN | Treat any eye | including VA >6/12	4.79	24.2	2.60	13.3

Strategy Treatment | Regimen | Eyes treated | VA range treated	Eye 1		Fellow eye	
	Years on treatment	No. of injections	Years on treatment	No. of injections
Beva | 2mo | Treat any eye | including VA <6/96	4.32	24.0	2.05	11.4
Beva | PRN | Treat any eye | including VA >6/12	4.55	24.0	2.43	12.9
Rani | 1mo | Treat only BSEs | at any VA level	2.18	23.9	2.43	26.8
Rani | Load+PRN | Treat any eye | at any VA level	5.11	23.9	2.76	13.0
Beva | Load+PRN | Treat any eye | including VA <6/96	4.68	23.8	2.22	11.4
Beva | PRN | Treat any eye | including VA <6/96	4.44	23.6	2.07	11.1
Beva | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	4.23	23.5	2.08	11.5
Rani | 1mo | Treat only BSEs | including VA >6/12	2.12	23.3	2.44	26.8
Rani | Load+PRN | Treat any eye | including VA >6/12	4.99	23.2	2.77	13.1
Beva | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	4.57	23.2	2.24	11.5
Beva | PRN | Treat any eye | with VA in range: 6/12 to 6/96	4.34	23.0	2.09	11.2
Beva | 1mo | Treat only BSEs | at any VA level	2.07	22.9	2.32	25.8
Rani | Load+PRN | Treat any eye | including VA <6/96	4.87	22.9	2.37	11.3
Rani | PRN | Treat any eye | at any VA level	4.88	22.9	2.59	12.2
Aflib | 2mo->PRN | Treat any eye | at any VA level	5.26	22.8	2.92	12.8
Beva | 1mo | Treat only BSEs | including VA >6/12	2.02	22.4	2.32	25.8
Rani | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	4.76	22.3	2.39	11.4
Rani | PRN | Treat any eye | including VA >6/12	4.76	22.3	2.61	12.3
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	5.14	22.2	2.94	12.8
Rani | PRN | Treat any eye | including VA <6/96	4.65	21.9	2.23	10.6
Aflib | 2mo->PRN | Treat any eye | including VA <6/96	5.00	21.8	2.51	11.1
Rani | PRN | Treat any eye | with VA in range: 6/12 to 6/96	4.54	21.3	2.25	10.7
Aflib | 2mo->PRN | Treat any eye | with VA in range: 6/12 to 6/96	4.89	21.3	2.53	11.2
Aflib | 1mo | Treat only BSEs | including VA <6/96	1.78	19.9	2.47	27.7
Aflib | 1mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.68	18.8	2.47	27.7
Rani | 3mo | Treat any eye | at any VA level	4.37	17.8	2.43	9.9
Beva | 3mo | Treat any eye | at any VA level	4.20	17.6	2.27	9.5
Rani | 3mo | Treat any eye | including VA >6/12	4.28	17.3	2.45	10.0
Beva | 3mo | Treat any eye | including VA >6/12	4.12	17.1	2.30	9.6
Rani | 3mo | Treat any eye | including VA <6/96	4.13	16.9	2.07	8.4
Rani | 1mo | Treat only BSEs | including VA <6/96	1.53	16.8	2.17	23.9
Beva | 3mo | Treat any eye | including VA <6/96	3.98	16.7	1.93	8.1
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	4.05	16.5	2.08	8.5
Beva | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	3.90	16.3	1.95	8.2
Beva | 1mo | Treat only BSEs | including VA <6/96	1.46	16.2	2.09	23.2
Rani | 1mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.45	16.0	2.18	24.0
Beva | 1mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.39	15.4	2.09	23.2
Aflib | TREX | Treat only BSEs | at any VA level	2.35	13.5	2.66	15.4
Beva | TREX | Treat only BSEs | at any VA level	1.92	13.4	2.19	15.4
Aflib | 2mo | Treat only BSEs | at any VA level	2.28	13.1	2.56	14.7

Strategy Treatment | Regimen | Eyes treated | VA range treated	Eye 1		Fellow eye	
	Years on treatment	No. of injections	Years on treatment	No. of injections
Beva | TREX | Treat only BSEs | including VA >6/12	1.85	12.8	2.19	15.4
Aflib | TREX | Treat only BSEs | including VA >6/12	2.24	12.8	2.65	15.4
Aflib | 2mo | Treat only BSEs | including VA >6/12	2.22	12.7	2.57	14.8
Rani | TREX | Treat only BSEs | at any VA level	2.01	12.5	2.29	14.3
Rani | TREX | Treat only BSEs | including VA >6/12	1.94	11.9	2.29	14.3
Rani | 2mo | Treat only BSEs | at any VA level	2.11	11.6	2.38	13.1
Rani | 2mo | Treat only BSEs | including VA >6/12	2.04	11.2	2.38	13.1
Beva | 2mo | Treat only BSEs | at any VA level	2.01	11.1	2.28	12.6
Beva | 2mo | Treat only BSEs | including VA >6/12	1.95	10.8	2.27	12.6
Beva | Load+PRN | Treat only BSEs | at any VA level	2.11	10.7	2.38	12.2
Beva | PRN | Treat only BSEs | at any VA level	2.01	10.6	2.27	12.1
Beva | Load+PRN | Treat only BSEs | including VA >6/12	2.06	10.3	2.38	12.2
Rani | Load+PRN | Treat only BSEs | at any VA level	2.21	10.3	2.48	11.8
Beva | PRN | Treat only BSEs | including VA >6/12	1.96	10.3	2.27	12.1
Rani | Load+PRN | Treat only BSEs | including VA >6/12	2.15	10.0	2.48	11.8
Aflib | 2mo->PRN | Treat only BSEs | at any VA level	2.30	9.9	2.58	11.3
Aflib | TREX | Treat only BSEs | including VA <6/96	1.66	9.9	2.27	13.5
Rani | PRN | Treat only BSEs | at any VA level	2.11	9.9	2.38	11.3
Beva | TREX | Treat only BSEs | including VA <6/96	1.36	9.7	1.93	13.8
Aflib | 2mo->PRN | Treat only BSEs | including VA >6/12	2.24	9.6	2.58	11.3
Rani | PRN | Treat only BSEs | including VA >6/12	2.06	9.6	2.38	11.3
Aflib | 2mo | Treat only BSEs | including VA <6/96	1.60	9.3	2.25	13.0
Rani | TREX | Treat only BSEs | including VA <6/96	1.43	9.1	2.01	12.8
Beva | TREX | Treat only BSEs | with VA in range: 6/12 to 6/96	1.27	9.0	1.93	13.8
PDT | 3mo | Treat any eye | at any VA level	3.04	9.0	1.60	4.7
Aflib | TREX | Treat only BSEs | with VA in range: 6/12 to 6/96	1.52	9.0	2.26	13.5
PDT | 3mo | Treat any eye | including VA >6/12	3.01	8.9	1.62	4.8
Aflib | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.51	8.7	2.25	13.0
Rani | TREX | Treat only BSEs | with VA in range: 6/12 to 6/96	1.33	8.4	2.01	12.8
PDT | 3mo | Treat any eye | including VA <6/96	2.84	8.3	1.34	3.9
PDT | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	2.80	8.2	1.35	3.9
Rani | 3mo | Treat only BSEs | at any VA level	2.03	8.2	2.31	9.4
Rani | 2mo | Treat only BSEs | including VA <6/96	1.49	8.2	2.10	11.6
Beva | 3mo | Treat only BSEs | at any VA level	1.93	8.0	2.21	9.2
Beva | 2mo | Treat only BSEs | including VA <6/96	1.42	7.9	2.02	11.2
Rani | 3mo | Treat only BSEs | including VA >6/12	1.95	7.9	2.31	9.4
Beva | 3mo | Treat only BSEs | including VA >6/12	1.86	7.7	2.21	9.3
Rani | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.40	7.7	2.10	11.6
Beva | Load+PRN | Treat only BSEs | including VA <6/96	1.49	7.7	2.13	11.0
Beva | PRN | Treat only BSEs | including VA <6/96	1.42	7.6	2.03	11.0

Strategy Treatment | Regimen | Eyes treated | VA range treated	Eye 1		Fellow eye	
	Years on treatment	No. of injections	Years on treatment	No. of injections
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.34	7.4	2.02	11.2
Rani | Load+PRN | Treat only BSEs | including VA <6/96	1.55	7.4	2.21	10.6
Beva | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	1.42	7.3	2.13	11.0
Beva | PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	1.35	7.2	2.03	11.0
Aflib | 2mo->PRN | Treat only BSEs | including VA <6/96	1.62	7.2	2.27	10.2
Rani | PRN | Treat only BSEs | including VA <6/96	1.48	7.1	2.12	10.2
Rani | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	1.48	7.0	2.21	10.6
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	1.53	6.7	2.27	10.2
Rani | PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	1.41	6.7	2.11	10.2
Rani | 3mo | Treat only BSEs | including VA <6/96	1.43	5.9	2.01	8.3
Beva | 3mo | Treat only BSEs | including VA <6/96	1.37	5.8	1.94	8.2
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.33	5.4	2.01	8.3
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.28	5.4	1.94	8.2
PDT | 3mo | Treat only BSEs | at any VA level	1.50	4.5	1.77	5.2
PDT | 3mo | Treat only BSEs | including VA >6/12	1.47	4.4	1.77	5.2
PDT | 3mo | Treat only BSEs | including VA <6/96	1.05	3.1	1.55	4.5
PDT | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	1.00	2.9	1.55	4.5
No treatment (sham)	-	0.0	-	0.0

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Visual acuity over time

The average change in VA over time for 'eye 1' – the eye that always has late AMD (wet active) at the start of the model – is presented in Figure 13, Figure 14 and Figure 15. A reduced number of strategies is presented in each case for ease of comparison.

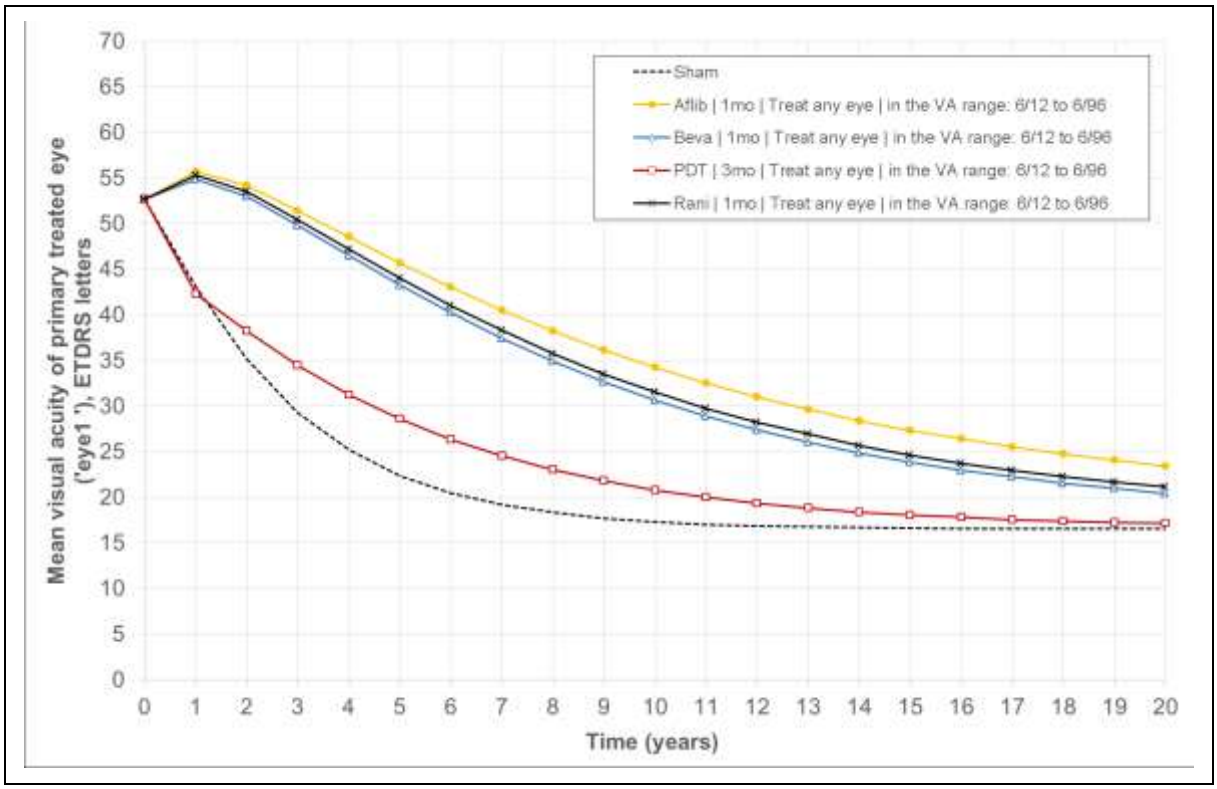
In Figure 13, the strategies that include monthly anti-VEGF injections are shown, as these are the most effective interventions (with the exception of PRNX, based on limited evidence), by virtue of providing the most frequent injections. The sham injections (no treatment) and PDT arms are also shown. In the strategies shown, better- and worse-seeing eyes were treated providing they met VA thresholds used in current practice (6/12 to 6/96). Average VA in 'eye 1' is 52.6 letters at presentation (year 0). In year 1, eyes treated with an anti-VEGF therapy experience a positive change in VA, with mean of 55 to 56 letters. Note that these average outcomes will include patients who discontinued treatment or who had not been treated at all (for example, if their VA was above the upper treatment threshold). From year 3 onward, the VA of the average eye on the anti-VEGF arms has declined to less than its baseline level, and then continues to decline further. This reflects the long-term decline included in the model (see Section J.5.3.3), and the increasing number of patients discontinuing treatment. By year 20, the eyes of patients still alive has plateaued at 20 to 23 letters. Monthly aflibercept performs better than monthly ranibizumab, and both perform slightly better than bevacizumab. Eyes treated with PDT or sham injections fare much worse, with average VA declining in year 1 to 42 letters. By year 5, an untreated eye will have VA of less than 23 letters. While PDT is slightly more effective than sham injections in the long

term, this is a result of our assumption that its long-term efficacy is equivalent to that of treatment with an anti-VEGF therapy (see Section J.5.3.3). Even with this potentially optimistic assumption, eyes on the PDT arm have much worse VA than those on anti-VEGF arms, plateauing with sham injections at around 17 letters after 20 years.

Figure 14 shows the typical VA progression of different dosing regimens. To compare different regimens, the choice of drug and eye eligibility criteria are held constant – ranibizumab, used to treat BSEs or WSEs, providing they meet current practice VA thresholds (6/12 to 6/96). The lines marked with crosses are continuous regimens, and comparison of these shows that eyes do better with more frequent injections. At 5 years, average VA on the monthly, 2-monthly and 3-monthly treatment arms is 44, 40 and 36 letters, respectively. Treatment as needed (PRN) produces a VA profile that is slightly better than 2-monthly treatment, and a marginal additional benefit is associated with the presence of an initial loading phase. The PRNX regimen is shown to have the best long-term VA projection; however, this is inconsistent with the expect dose-response relationship, caused by the overall lack of evidence regarding this treatment protocol. For this reason, cost–utility results including PRNX regimens are a scenario analysis only.

Figure 15 displays the effect on VA of treating only BSEs compared with not making this restriction, and of extending the VA thresholds at which eyes become eligible for treatment. For the purpose of this comparison, the treatment was the same for each strategy – aflibercept delivered every 2 months for 1 year, then as needed. It is clear that restricting treatment to only BSEs (triangle markers) produces worse VA outcomes for ‘eye 1’ than treating any eye (circle markers). Treating only BSEs means the average VA of ‘eye 1’ declines from baseline, with no visible treatment effect. This is because in the majority of patients ‘eye 1’ is the unilaterally affected WSE, and would therefore be ineligible for treatment. Comparing different VA threshold strategies, treating all eyes regardless of VA provides the best VA profile (darkest shaded lines). It leads to average ‘eye 1’ VA of 58 letters at 1 year, compared with 55 letters by current practice (6/12 to 6/96).

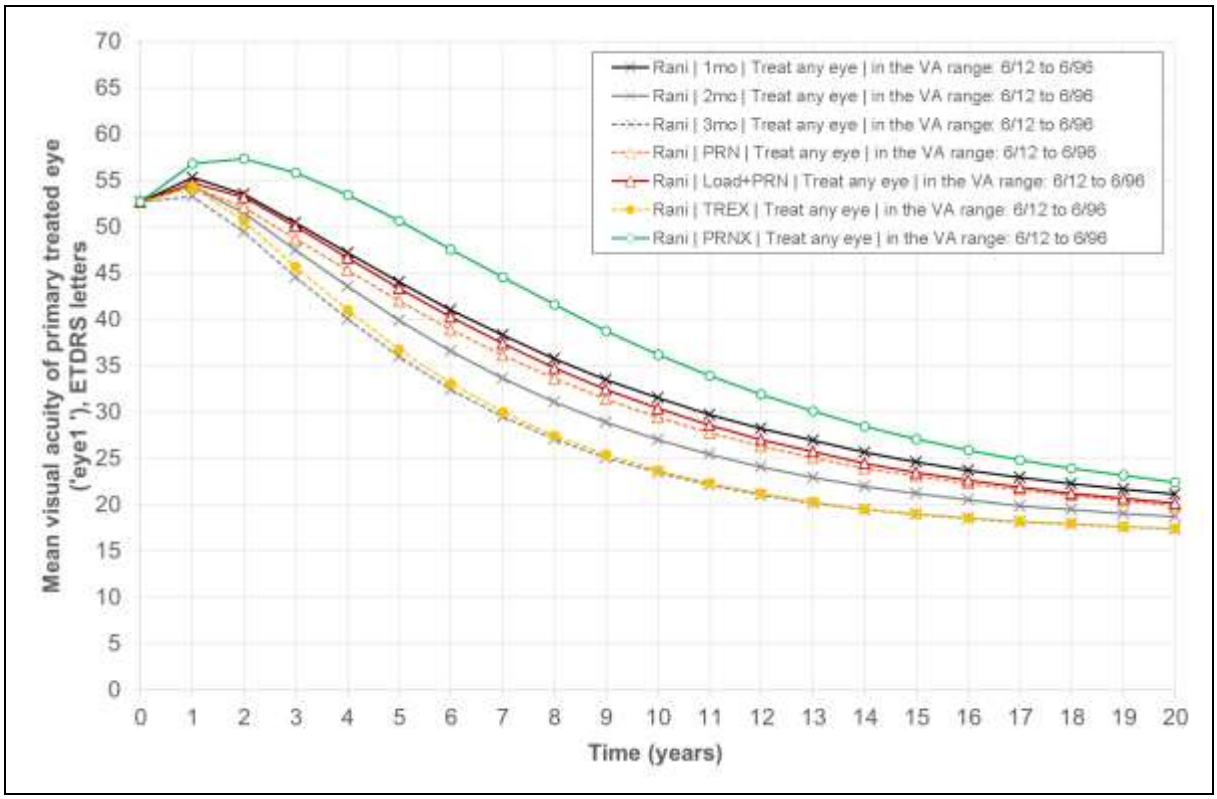
Figure 16 compares long-term VA in the model using the 3 available data sources to inform long-term VA decline with ranibizumab PRN. In the base-case model, the ARMD database (Tufail et al. 2014) provides the reference decline in VA for ranibizumab PRN (-2.5 letters per year), to which all other active treatments are anchored. By comparison, a shown in the figure, the Gillies et al. (2015) data point (-0.7 letters per year) produces a slower long-term decline in average VA, whereas the more pessimistic SEVEN-UP data point (-3.7 letters per year; Rofagha et al. 2013) produces a quicker decline.



300 **Figure 13: Average VA over time, by treatment**

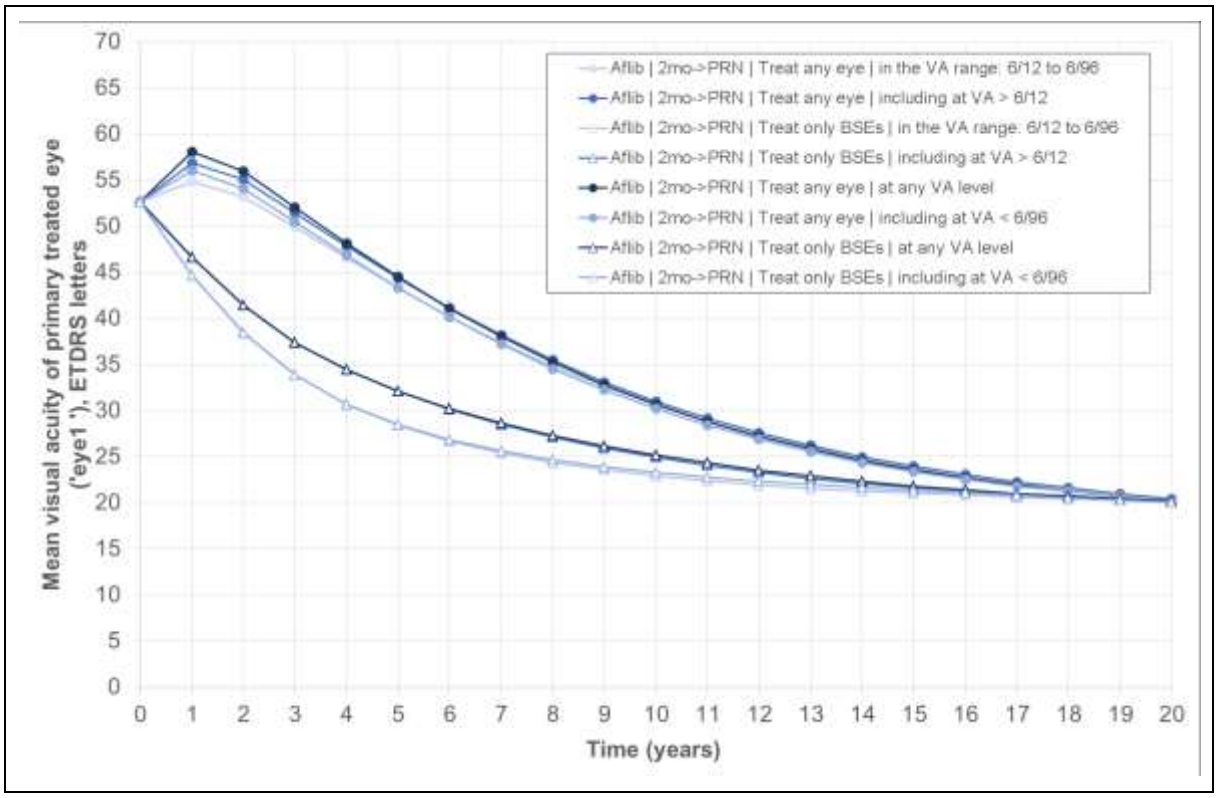
301

302

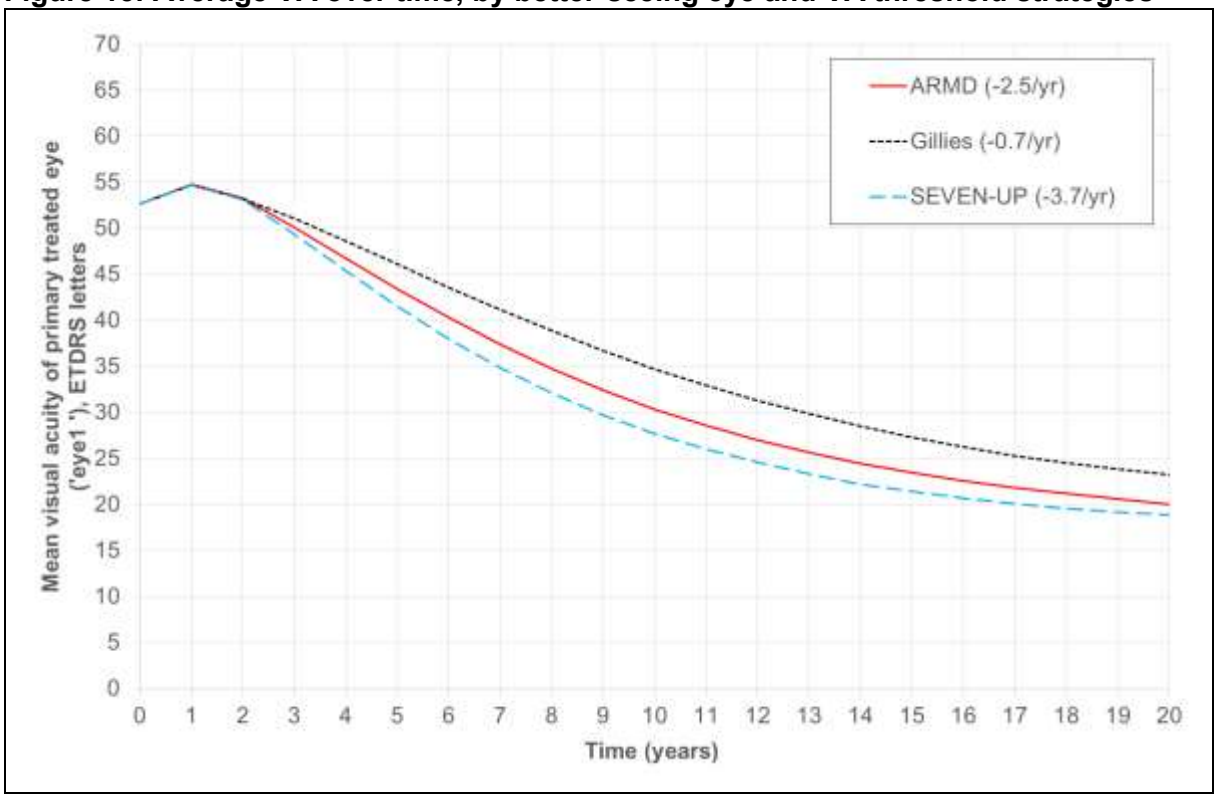


303 **Figure 14: Average VA over time, by treatment frequency**

304



305 **Figure 15: Average VA over time, by better-seeing eye and VA threshold strategies**



306 **Figure 16: Comparison of VA outcomes compared with SEVEN-UP linear decline**

J.5.6.2 Base-case cost–utility results

308 Deterministic NHB results from 2,000,000 simulations are presented in Table 49. These
309 results include all regimens except those using a PRNX protocol, which are explored in

scenario analyses only. The NHB results include strategies BSEs only, any BSEs or WSEs, and all 4 VA-threshold strategies (treat eyes according to current practice [6/12 to 6/96]; extend to treat eyes that present with VA worse than 6/96; extend to treat eyes that present with VA better than 6/12; treat any level of VA).

The NHB of a strategy can be interpreted as the number of QALYs accrued by the health service per patient treated with the strategy of interest. It represents the number of QALYs gained by the patient receiving the strategy, net of the QALYs foregone by diverting resources from elsewhere in the system to provide it. Any two NHB figures can be compared directly, and the strategy with higher NHB is cost effective over the other, at that particular opportunity cost of 1 QALY foregone (e.g. £20,000). It follows that the strategy with the highest NHB is cost effective.

Net health benefit

The base-case NHB results (Table 49), at an opportunity cost of £20,000 per QALY, show the following strategy to be optimal:

- **Bevacizumab;**
- injected **every 2 months;**
- **without** restricting treatment to BSEs only;
- extending eligibility to **include eyes with VA better than 6/12**.

This produces the highest NHB, generating 3.652 QALYs per patient for the health care system as a whole. Treating eyes every 3 months, rather than every 2, produces fewer QALYs to the treated patient. This pattern is shown for all therapies, and reflects the improved clinical outcomes gained from providing more frequent treatment. Bevacizumab delivered every 2 months also produces the largest NHB if the opportunity cost of a QALY forgone is considered to be £30,000. Monthly aflibercept produces the largest benefit to the patient being treated (4.6 QALYs if all eyes are treated) but is also the highest-cost regimen (at £86,286 per patient when evaluated at its list price).

At an opportunity cost of £20,000 per QALY, only 52 of the 137 alternative base-case strategies provide a higher NHB than providing no treatment (sham injections); that is, only 52 are better than doing nothing (Figure 17). The best 48 of these strategies involve treatment with bevacizumab, which represents all bevacizumab strategies. The remaining 4 strategies that are better than providing no treatment involve ranibizumab, restricted to treating only BSEs at 3-month intervals. Here, the additional cost of treating WSEs achieves comparatively small health gains for the patient. All other strategies provide a net health loss of QALYs to the NHS compared with providing no treatment for AMD. Although the AMD patient will experience more QALYs if they are treated, the resources spent to do so would provide more QALYs if used elsewhere in the system. However, both aflibercept and ranibizumab are available to the NHS at confidential, reduced prices. When these are applied, 16 further strategies become cost-effective compared with doing nothing, including 2-monthly ranibizumab, and aflibercept given every 2 months for 1 year then PRN. However, these remain restricted to treating only better-seeing eyes.

Table 49 shows that strategies that do not restrict treatment to BSEs produce the highest NHB only if bevacizumab is the active treatment. It also shows that, unless treatment is restricted to BSEs, comparing 2 strategies that are otherwise identical, treating according to current VA thresholds (6/12 to 6/96) provides higher NHB than extending treatment to people with VA ≤6/96. Similarly, extending treatment only to people with good baseline VA (>6/12) provides higher NHB than extending treatment further to include VA ≤6/96, all else equal.

This implies that extending treatment eligibility to eyes with VA ≤6/96 is *never* superior to the equivalent strategy without doing so, unless treatment is restricted to only BSEs. Extending treatment to eyes with poor VA incurs significant additional costs but comparatively small health gains, because it typically causes treatment in WSEs; a person's WSE has less influence on his or her quality of life than the BSE. For this reason, all strategies that extend treatment to eyes with VA worse than 6/96 have been omitted from results herein, including sensitivity analyses. Fully incremental results including ICERs for all remaining, non-dominated, base-case strategies are presented in Figure 18 and Table 50.

Note that the result described above is not true of strategies that treat only BSEs, where allowing eyes with VA worse than 6/96 will only extend treatment to people whose *better*-seeing eyes have VA of this level. This is a small subgroup of patients who stand to benefit a relatively large amount from treatment.

Table 49: Base-case deterministic cost–utility results – all base-case strategies, NHB (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Absolute net health benefit	
	Costs	QALYs	£20,000	£30,000
Beva | 2mo | Treat any eye | including VA >6/12	£13,688	4.337	3.652	3.880
Beva | 2mo | Treat only BSEs | at any VA level	£11,355	4.215	3.647	3.837
Beva | 2mo | Treat any eye | at any VA level	£13,846	4.337	3.645	3.876
Beva | 2mo | Treat only BSEs | including VA >6/12	£11,437	4.211	3.639	3.830
Beva | 2mo | Treat only BSEs | including VA <6/96	£10,403	4.130	3.610	3.783
Beva | 3mo | Treat any eye | including VA >6/12	£12,524	4.231	3.604	3.813
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,510	4.126	3.601	3.776
Beva | 3mo | Treat only BSEs | at any VA level	£10,843	4.143	3.601	3.781
Beva | 3mo | Treat any eye | at any VA level	£12,623	4.230	3.599	3.809
Beva | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£13,516	4.274	3.598	3.823
Beva | 3mo | Treat only BSEs | including VA >6/12	£10,949	4.141	3.593	3.776
Beva | Load+PRN | Treat only BSEs | at any VA level	£13,912	4.285	3.589	3.821
Beva | 2mo | Treat any eye | including VA <6/96	£13,682	4.268	3.584	3.812
Beva | Load+PRN | Treat only BSEs | including VA >6/12	£13,958	4.282	3.584	3.817
Beva | Load+PRN | Treat any eye | including VA >6/12	£17,395	4.445	3.575	3.865
Beva | Load+PRN | Treat any eye | at any VA level	£17,601	4.443	3.563	3.857
Beva | Load+PRN | Treat only BSEs | including VA <6/96	£12,454	4.186	3.563	3.771
Beva | 3mo | Treat only BSEs | including VA <6/96	£10,189	4.071	3.562	3.732
Beva | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£12,500	4.182	3.557	3.765
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,313	4.069	3.554	3.726
Beva | PRN | Treat only BSEs | at any VA level	£14,020	4.253	3.552	3.785
Beva | PRN | Treat only BSEs | including VA >6/12	£14,041	4.250	3.548	3.782
Beva | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£12,491	4.172	3.547	3.755
Beva | 3mo | Treat any eye | including VA <6/96	£12,610	4.171	3.540	3.751
Beva | PRN | Treat any eye | including VA >6/12	£17,298	4.396	3.531	3.820
Beva | PRN | Treat only BSEs | including VA <6/96	£12,613	4.160	3.530	3.740
Beva | PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£12,662	4.155	3.522	3.733
Beva | PRN | Treat any eye | at any VA level	£17,519	4.392	3.516	3.808
Beva | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£17,142	4.369	3.512	3.798
Beva | 1mo | Treat only BSEs | including VA <6/96	£13,688	4.184	3.499	3.728
Beva | 1mo | Treat only BSEs | at any VA level	£15,588	4.278	3.499	3.758

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Absolute net health benefit	
	Costs	QALYs	£20,000	£30,000
Beva | TREX | Treat only BSEs | at any VA level	£13,085	4.151	3.497	3.715
Beva | Load+PRN | Treat any eye | including VA <6/96	£17,404	4.366	3.495	3.786
Beva | 1mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£13,718	4.180	3.495	3.723
Beva | 1mo | Treat only BSEs | including VA >6/12	£15,621	4.274	3.493	3.753
Beva | TREX | Treat only BSEs | including VA >6/12	£13,148	4.147	3.490	3.709
Beva | TREX | Treat only BSEs | including VA <6/96	£11,953	4.079	3.481	3.681
Beva | TREX | Treat only BSEs | with VA in range: 6/12 to 6/96	£12,074	4.077	3.474	3.675
Beva | PRN | Treat any eye | with VA in range: 6/12 to 6/96	£17,105	4.325	3.470	3.755
Beva | PRN | Treat any eye | including VA <6/96	£17,322	4.321	3.454	3.743
Beva | TREX | Treat any eye | including VA >6/12	£15,804	4.244	3.453	3.717
Beva | TREX | Treat any eye | at any VA level	£15,959	4.239	3.442	3.707
Beva | 1mo | Treat any eye | including VA >6/12	£20,252	4.440	3.427	3.765
Beva | 1mo | Treat any eye | at any VA level	£20,520	4.439	3.413	3.755
Beva | TREX | Treat any eye | with VA in range: 6/12 to 6/96	£15,595	4.188	3.408	3.668
Beva | TREX | Treat any eye | including VA <6/96	£15,773	4.184	3.395	3.658
Beva | 1mo | Treat any eye | with VA in range: 6/12 to 6/96	£19,765	4.366	3.377	3.707
Beva | 1mo | Treat any eye | including VA <6/96	£20,011	4.366	3.365	3.699
Rani | 3mo | Treat only BSEs | including VA <6/96	£15,752	4.082	3.294	3.557
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£15,698	4.078	3.293	3.555
Rani | 3mo | Treat only BSEs | at any VA level	£17,830	4.158	3.266	3.563
Rani | 3mo | Treat only BSEs | including VA >6/12	£17,808	4.154	3.264	3.561
No treatment (effects: sham injections)	£11,936	3.842	3.245	3.444
Rani | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£18,182	4.141	3.232	3.535
Rani | 2mo | Treat only BSEs | including VA <6/96	£18,244	4.143	3.231	3.535
Rani | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£19,575	4.196	3.218	3.544
Rani | Load+PRN | Treat only BSEs | including VA <6/96	£19,682	4.200	3.216	3.544
Rani | PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£19,410	4.172	3.201	3.525
Rani | PRN | Treat only BSEs | including VA <6/96	£19,523	4.177	3.201	3.526
Rani | 2mo | Treat only BSEs | at any VA level	£21,323	4.232	3.166	3.522
Rani | Load+PRN | Treat only BSEs | at any VA level	£22,832	4.306	3.164	3.545
Rani | 2mo | Treat only BSEs | including VA >6/12	£21,281	4.227	3.163	3.518
Rani | Load+PRN | Treat only BSEs | including VA >6/12	£22,752	4.299	3.161	3.541
Rani | PRN | Treat only BSEs | including VA >6/12	£22,454	4.271	3.148	3.522
Rani | PRN | Treat only BSEs | at any VA level	£22,503	4.273	3.148	3.523
PDT | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£16,240	3.921	3.109	3.379
PDT | 3mo | Treat only BSEs | including VA <6/96	£16,371	3.921	3.103	3.376
PDT | 3mo | Treat only BSEs | including VA >6/12	£17,715	3.978	3.093	3.388
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£22,182	4.201	3.092	3.461
Aflib | 2mo->PRN | Treat only BSEs | including VA <6/96	£22,315	4.205	3.089	3.461
PDT | 3mo | Treat only BSEs | at any VA level	£17,796	3.978	3.088	3.385
Rani | 3mo | Treat any eye | including VA >6/12	£23,332	4.253	3.086	3.475
Rani | TREX | Treat only BSEs | with VA in range: 6/12 to 6/96	£20,178	4.090	3.082	3.418
Rani | TREX | Treat only BSEs | including VA <6/96	£20,382	4.094	3.075	3.415

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Absolute net health benefit	
	Costs	QALYs	£20,000	£30,000
Rani | 3mo | Treat any eye | at any VA level	£23,541	4.252	3.075	3.467
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£22,449	4.192	3.070	3.444
Rani | 3mo | Treat any eye | including VA <6/96	£22,634	4.190	3.058	3.435
Aflib | 2mo->PRN | Treat only BSEs | including VA >6/12	£26,141	4.307	3.000	3.435
PDT | 3mo | Treat any eye | including VA >6/12	£20,019	4.000	2.999	3.333
Rani | TREX | Treat only BSEs | including VA >6/12	£23,281	4.163	2.999	3.387
PDT | 3mo | Treat any eye | at any VA level	£20,056	4.000	2.997	3.331
Rani | TREX | Treat only BSEs | at any VA level	£23,383	4.166	2.997	3.387
Aflib | 2mo->PRN | Treat only BSEs | at any VA level	£26,250	4.309	2.997	3.434
Aflib | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£23,659	4.178	2.995	3.389
Aflib | 2mo | Treat only BSEs | including VA <6/96	£23,826	4.181	2.990	3.387
PDT | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£19,616	3.955	2.974	3.301
PDT | 3mo | Treat any eye | including VA <6/96	£19,640	3.953	2.971	3.299
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,023	4.476	2.874	3.408
Rani | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£28,463	4.297	2.874	3.349
Rani | PRN | Treat any eye | including VA >6/12	£31,146	4.430	2.873	3.392
Rani | 2mo | Treat any eye | including VA >6/12	£29,938	4.368	2.871	3.370
Aflib | 2mo | Treat only BSEs | including VA >6/12	£28,315	4.277	2.862	3.334
Aflib | 2mo | Treat only BSEs | at any VA level	£28,406	4.281	2.861	3.334
Rani | 2mo | Treat any eye | including VA <6/96	£28,762	4.294	2.856	3.336
Aflib | TREX | Treat only BSEs | with VA in range: 6/12 to 6/96	£25,141	4.112	2.855	3.274
Rani | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£30,851	4.397	2.854	3.369
Rani | Load+PRN | Treat any eye | at any VA level	£32,434	4.476	2.854	3.395
Rani | PRN | Treat any eye | at any VA level	£31,506	4.429	2.854	3.379
Rani | PRN | Treat any eye | with VA in range: 6/12 to 6/96	£30,031	4.355	2.853	3.354
Rani | 2mo | Treat any eye | at any VA level	£30,223	4.364	2.852	3.356
Aflib | TREX | Treat only BSEs | including VA <6/96	£25,561	4.117	2.839	3.265
Rani | Load+PRN | Treat any eye | including VA <6/96	£31,225	4.395	2.834	3.354
Rani | PRN | Treat any eye | including VA <6/96	£30,414	4.353	2.832	3.339
Aflib | TREX | Treat only BSEs | including VA >6/12	£29,746	4.195	2.708	3.204
Rani | 1mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£29,846	4.197	2.705	3.202
Rani | 1mo | Treat only BSEs | including VA <6/96	£30,060	4.202	2.699	3.200
Aflib | TREX | Treat only BSEs | at any VA level	£30,098	4.202	2.697	3.199
Rani | TREX | Treat any eye | with VA in range: 6/12 to 6/96	£30,623	4.209	2.678	3.189
Rani | TREX | Treat any eye | including VA >6/12	£31,935	4.268	2.671	3.203
Rani | TREX | Treat any eye | including VA <6/96	£30,948	4.205	2.658	3.173
Rani | TREX | Treat any eye | at any VA level	£32,281	4.264	2.649	3.187
Aflib | 2mo->PRN | Treat any eye | with VA in range: 6/12 to 6/96	£36,263	4.408	2.595	3.199
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	£37,979	4.488	2.589	3.222
Aflib | 2mo->PRN | Treat any eye | including VA <6/96	£36,718	4.406	2.571	3.183
Aflib | 2mo->PRN | Treat any eye | at any VA level	£38,428	4.487	2.566	3.206
Rani | 1mo | Treat only BSEs | including VA >6/12	£36,122	4.294	2.488	3.090
Rani | 1mo | Treat only BSEs | at any VA level	£36,311	4.299	2.483	3.089
Aflib | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£39,602	4.365	2.384	3.044
Aflib | 2mo | Treat any eye | including VA <6/96	£40,078	4.363	2.360	3.027

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Absolute net health benefit	
	Costs	QALYs	£20,000	£30,000
Aflib | 2mo | Treat any eye | including VA >6/12	£41,984	4.442	2.342	3.042
Aflib | 2mo | Treat any eye | at any VA level	£42,451	4.444	2.321	3.029
Aflib | TREX | Treat any eye | with VA in range: 6/12 to 6/96	£40,398	4.255	2.235	2.908
Aflib | TREX | Treat any eye | including VA <6/96	£40,802	4.252	2.212	2.892
Aflib | TREX | Treat any eye | including VA >6/12	£42,579	4.320	2.191	2.901
Aflib | TREX | Treat any eye | at any VA level	£42,976	4.318	2.169	2.886
Aflib | 1mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£42,594	4.236	2.107	2.816
Aflib | 1mo | Treat only BSEs | including VA <6/96	£43,112	4.239	2.084	2.802
Rani | 1mo | Treat any eye | with VA in range: 6/12 to 6/96	£52,003	4.400	1.800	2.666
Rani | 1mo | Treat any eye | including VA <6/96	£52,687	4.397	1.762	2.640
Rani | 1mo | Treat any eye | including VA >6/12	£55,129	4.474	1.718	2.637
Aflib | 1mo | Treat only BSEs | including VA >6/12	£53,084	4.353	1.699	2.584
Aflib | 1mo | Treat only BSEs | at any VA level	£53,463	4.357	1.683	2.574
Rani | 1mo | Treat any eye | at any VA level	£55,875	4.475	1.681	2.612
Aflib | 1mo | Treat any eye | with VA in range: 6/12 to 6/96	£79,464	4.479	0.506	1.830
Aflib | 1mo | Treat any eye | including VA <6/96	£80,525	4.479	0.453	1.795
Aflib | 1mo | Treat any eye | including VA >6/12	£85,243	4.569	0.307	1.727
Aflib | 1mo | Treat any eye | at any VA level	£86,286	4.569	0.255	1.693

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Note: aflibercept and ranibizumab are available to the NHS at confidential prices that reflect a discount on their list prices.

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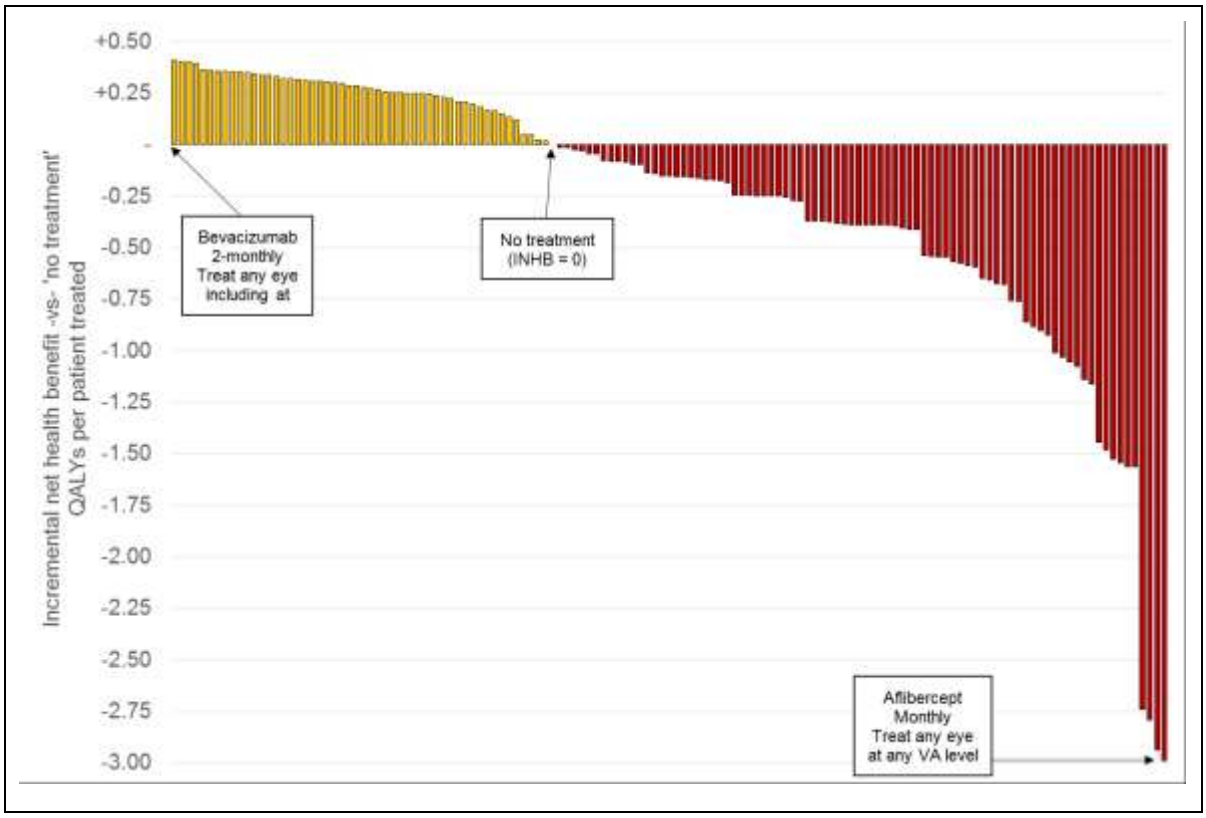


Figure 17: Incremental NHB of 137 base-case active treatment strategies compared with doing nothing (at list prices)

Incremental analysis

Incremental base-case results are presented having been cut in 3 different ways:

1. including all anti-VEGF treatments, PDT and 'no treatment'
2. excluding bevacizumab, as it is not licensed for the treatment of AMD
3. excluding all regimens that are not listed on product labels, therefore including only regimens that are commonly used in current NHS practice.

<u>All treatments included</u>

Figure 18 shows the cost–utility plane of results when no treatments are excluded, with a point depicting the expected total QALYs and costs from 2,000,000 simulations of each strategy. The majority of strategies are dominated (they provide fewer QALYs and incur higher costs than an alternative option) or extendedly dominated strategies (would never logically be chosen as there is always a clinically better, cost effective alternative). Such strategies can be removed from the decision space. The remaining strategies form the 'cost–utility frontier', depicited by the red line. No strategy on the frontier is dominated by any other, therefore only these strategies should be appropriate for decision making based on cost-effectiveness. Whether they are considered to be cost effective or not depends on the opportunity cost of 1 QALY foregone (e.g. £20,000).

The ICER between any two strategies on the cost–utility frontier is depicted by the gradient of the frontier between them. A steeper gradient represents a higher ICER. The frontier becomes increasingly steep, meaning increasingly higher extra costs are required to obtain the extra QALYs on offer. The cost effective strategy is the one that produces the biggest health benefit (QALYs) and has an ICER that does not exceed the opportunity cost of

utilising the resources elsewhere in the health care system. This is calculated in Table 50, in a fully incremental analysis of the strategies along the cost–utility frontier.

The strategy of providing no treatment is dominated and therefore does not appear in the results table. The lowest-cost non-dominated strategy, which is the origin of the cost-effectiveness plane, is treating only BSEs with bevacizumab every 3 months. This is estimated to cost £1,623 less than providing no treatment, because treatment prevents sufficient low-vision resource use (e.g. community and residential care) to more-than-offset the cost of treatment itself.

Providing 2-monthly treatment has an ICER of £3,458 per QALY gained. Extending treatment to BSEs with VA better than 6/12 is associated with an ICER of £10,955 with 2-monthly injections. Removing the 'BSE only' restriction with 2-monthly bevacizumab, and including eyes with VA >6/12, produces an ICER of £17,895, which is the highest ICER that remains under £20,000. Treating according to a loading phase followed by PRN generates 0.108 extra QALYs at an extra cost of £3,707, with an ICER of £34,405. The only other antiangiogenic treatment strategies that feature among the non-dominated options, involving treatment with aflibercept or ranibizumab for all eyes with no upper VA threshold, are the most effective strategies, producing the most QALYs for the person being treated. However, their comparatively large incremental costs produce ICERs in excess of £470,000 per QALY gained.

The interpretation of these results is, therefore, ultimately the same as the NHB results; treatment with 2-monthly bevacizumab, including eyes with VA better than 6/12, is cost effective at both £20,000 and £30,000 per QALY thresholds.

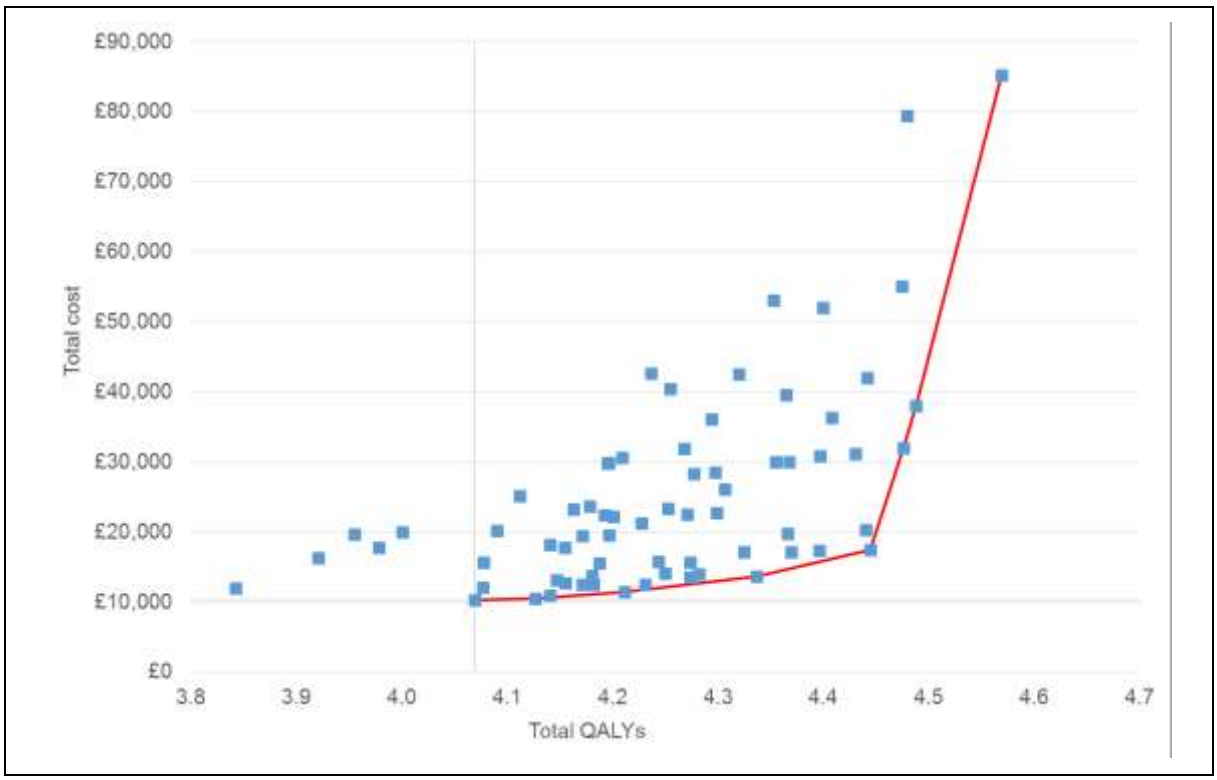


Figure 18: Cost-effectiveness plane – all treatments included – list prices

Table 50: Base-case deterministic cost–utility results – all treatments included – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes to treat | VA range to treat*	*Total*		*Incremental*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*

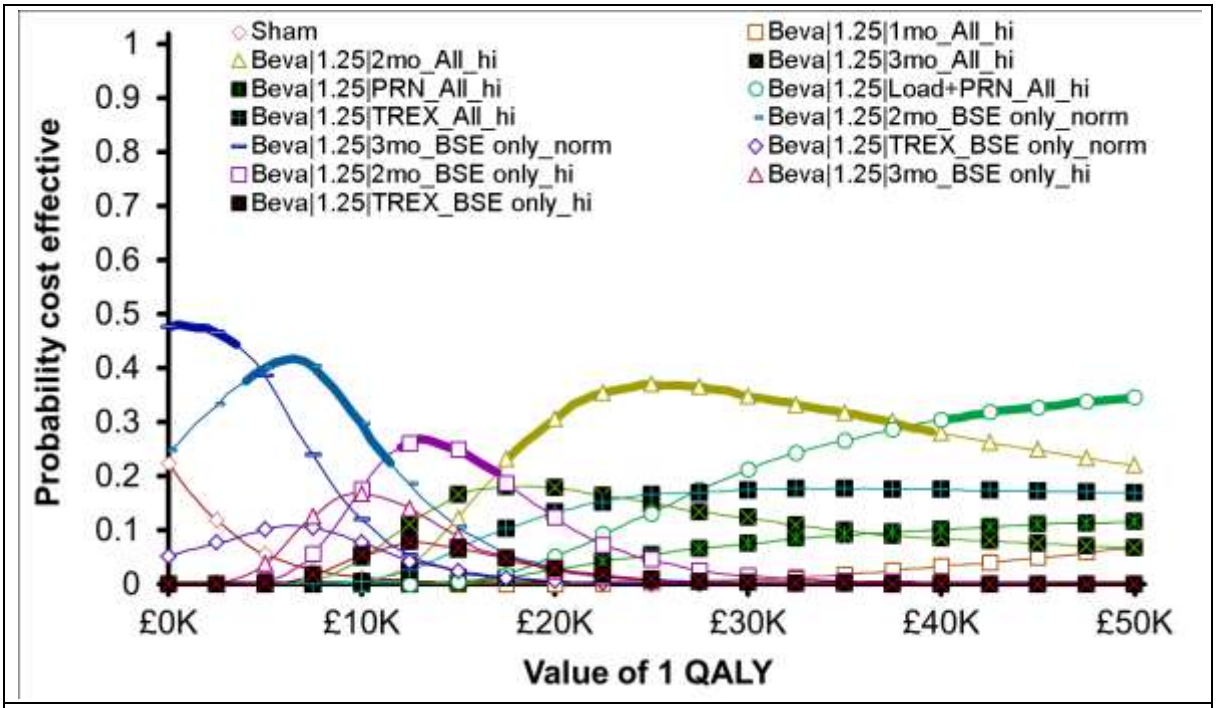
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,313	4.069			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,510	4.126	£197	0.057	£3,458
Beva | 2mo | Treat only BSEs | including VA >6/12	£11,437	4.211	£927	0.085	£10,955
Beva | 2mo | Treat any eye | including VA >6/12	£13,688	4.337	£2,251	0.126	£17,895
Beva | Load+PRN | Treat any eye | including VA >6/12	£17,395	4.445	£3,707	0.108	£34,405
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,023	4.476	£14,627	0.031	£470,559
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	£37,979	4.488	£5,956	0.012	£483,462
Aflib | 1mo | Treat any eye | including VA >6/12	£85,243	4.569	£47,264	0.081	£584,215

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Probabilistic sensitivity analysis (PSA) results are presented as cost-effectiveness acceptability curves (CEACs). These show the proportion of probabilistic model simulations in which each strategy produced the highest NHB, at increasing QALY valuations. This can be interpreted as the probability that a strategy is optimal, for a given value of 1 QALY (e.g. £20-30,000). Focusing on the strategies with the highest probability of being optimal across the range of QALY values shows the cost-effectiveness acceptability frontier.

In the base-case PSA, the CEAC shows that the optimal strategy from the deterministic results – 2-monthly bevacizumab, with treatment of WSEs permitted, and including eyes with VA >6/12 – has the highest probability of being cost-effective, when 1 QALY is valued at £17,000 or higher (Figure 19). At QALY values of £20,000 and £30,000, its likelihood of being the optimal strategy out of the 69 options is 30.6% and 34.8% respectively. However, bevacizumab delivered by some regimen is almost certain to be cost-effective.

If additional QALYs held no value – such that cost effectiveness was determined entirely by cost impact – then 3-monthly bevacizumab used to treat only BSEs would have the highest probability of being optimal (47.6%), higher than providing ‘no treatment’ (22.4%). This is because it is typically the lowest cost strategy, costing less than sham injections by offsetting treatment costs through averting resource use associated with low vision. As the value of 1 QALY increases, 2-monthly treatment of BSEs and then extending treatment to eyes with VA >6/12 become the most likely to be optimal, until the value of 1 QALY reaches £17,000.



CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are nowt shown in the key for diagram simplicity.

Bold line indicates cost-effectiveness acceptability frontier.

Figure 19: Cost-effectiveness acceptability curve – all treatments included – list prices

Bevacizumab excluded

Five of the 8 strategies on the base-case cost–utility frontier include treatment with bevacizumab. As such, the frontier changes significantly when strategies that include bevacizumab are omitted. Here, providing no treatment is no longer dominated; it represents the lowest cost strategy and marks the origin of the cost-effectiveness plane (Figure 20). The frontier becomes steeper at a faster rate than in Figure 18, signalling that incremental QALY gains along the frontier are accrued at higher additional costs, which is to be expected if the previously cost effective strategies have been removed from the analysis. Previously, around 4.3 QALYs could be achieved for a cost of £13,688 per patient; here, £22,752 is required to achieve a similar number of QALYs.

The value of this analysis is that bevacizumab is not licensed for the treatment of AMD, therefore removing it from the decision space might provide useful information. Only 1 strategy has an ICER of £20,000 or less; ranibizumab injections every 3 months, for BSEs only, without extending the current VA thresholds. This strategy provides the fewest ranibizumab injections in total of all base-case ranibizumab strategies. Doing so gains 0.236 QALYs compared with doing nothing, per patient, at an additional cost of £3,761, resulting in an ICER of £15,967 per QALY gained. The next non-dominated strategy is the same strategy, but extending treatment eligibility to include BSEs with VA better than 6/12; its ICER is £27,521 per QALY gained.

The lowest ICER when removing the restriction of treating BSEs only is £52,478 per QALY (ranibizumab PRN). This shows that allowing WSEs to be treated with anything other than bevacizumab is not a cost-effective course of action. Similarly, treating eyes more frequently than once every 3 months is not cost-effective unless bevacizumab is used.

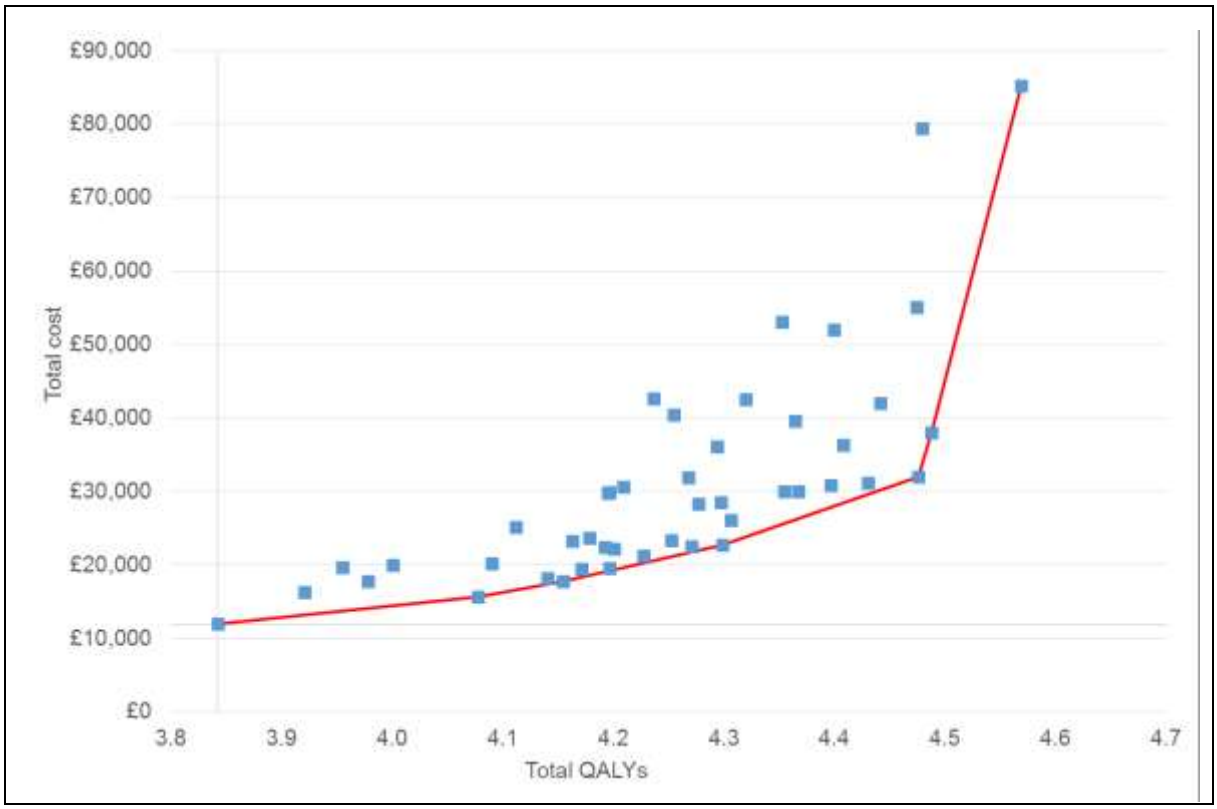


Figure 20: Cost-effectiveness plane – excluding bevacizumab – list prices

Table 51: Base-case deterministic cost–utility results – excluding bevacizumab – fully incremental analysis, non-dominated strategies shown (at list prices)

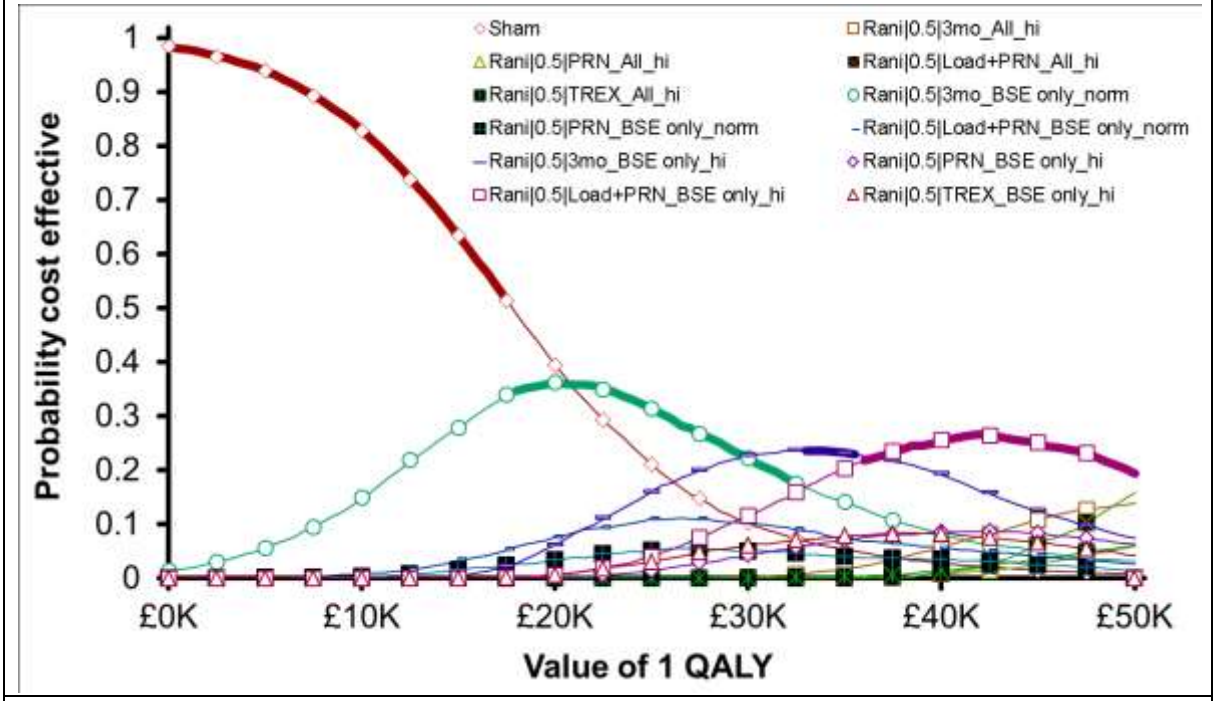
Strategy *Treatment | Regimen | Eyes to treat | VA range to treat*	*Total*		*Incremental*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
No treatment	£11,936	3.842			
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£15,698	4.078	£3,761	0.236	£15,967
Rani | 3mo | Treat only BSEs | including VA >6/12	£17,808	4.154	£2,110	0.077	£27,521
Rani | Load+PRN | Treat only BSEs | including VA >6/12	£22,752	4.299	£4,945	0.144	£34,226
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,023	4.476	£9,270	0.177	£52,478
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	£37,979	4.488	£5,956	0.012	£483,462
Aflib | 1mo | Treat any eye | including VA >6/12	£85,243	4.569	£47,264	0.081	£584,215

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

PSA when excluding bevacizumab treatment from the set of possible strategies produces the CEAC shown in Figure 21, with aflibercept and ranibizumab evaluated at their list prices. If cost effectiveness was determined entirely by cost impact, then providing no treatment would have a 98.5% probability of being the cost effective strategy. This result holds until the value of 1 QALY reaches £21,000, beyond which ranibizumab used to treat only BSEs at 3-month intervals becomes more likely to be optimal (associated with a £15,967 per QALY deterministic ICER). At a QALY value of £20,000, it is 36.2% likely to optimal in a decision space without bevacizumab; the equivalent probability for 'no treatment' is 39.5%. At a QALY value of £30,000, this ranibizumab strategy extended to treat eye with VA better than 6/12

478 has a 22.6% probability of being cost effective, compared with 22.3% for this strategy without
479 extending treatment eligibility. Permitting ranibizumab for the treatment of WSEs as well as
480 BSEs does not have the highest likelihood of being optimal at any QALY value up to
481 £50,000.

482



CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.
Bold line indicates cost-effectiveness acceptability frontier.

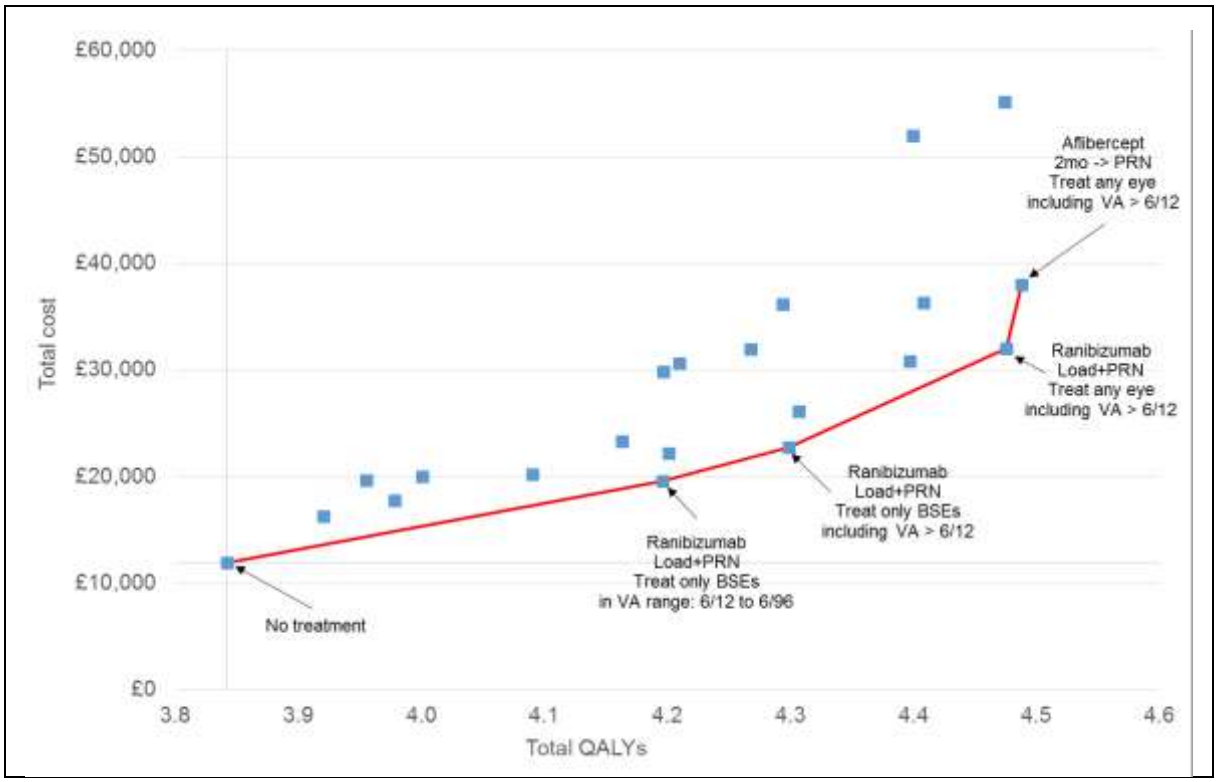
483 **Figure 21: Cost-effectiveness acceptability curve – excluding bevacizumab – list**
484 **prices**

485 Product label regimens only

486 When the pool of base-case strategies is limited further, by removing any that are not listed
487 on product labels, the number of strategies is significantly lower, depicted by a number of
488 points on the cost-effectiveness plane Figure 22. The lowest-cost strategy is providing no
489 treatment, which is the origin of the cost–utility frontier. The frontier progresses at an even
490 steeper rate than in Figure 20. This is because some strategies that previously featured on
491 the cost–utility frontier – namely those featuring 3-monthly ranibizumab – have been
492 removed, being off-label.

493 No active treatment strategy produces an ICER below £20,000 per QALY when treatments
494 are evaluated at their list prices, such that providing no treatment is the cost-effective option.
495 One strategy produces an ICER below £30,000 per QALY when treatments are evaluated at
496 their list prices – ranibizumab, with a loading phase followed by PRN, for only BSEs
497 according to current VA treatment thresholds. Extending this regimen to eyes with VA better
498 than 6/12 has an ICER of £30,965. The lowest ICER removing the BSEs only restriction
499 £52,478, also associated with ranibizumab PRN. Aflibercept has an ICER in excess of
500 £480,000 per QALY gained. Even when compared with only product label regimens, PDT is
501 not a cost effective use of resources.

502



503 **Figure 22: Cost-effectiveness plane – product label regimens – list prices**

504 **Table 52: Base-case deterministic cost–utility results – product label regimens – fully**
505 **incremental analysis, non-dominated strategies shown (at list prices)**

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
No treatment	£11,936	3.842			
Rani | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£19,575	4.196	£7,639	0.354	£21,572
Rani | Load+PRN | Treat only BSEs | including VA >6/12	£22,752	4.299	£3,177	0.103	£30,965
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,023	4.476	£9,270	0.177	£52,478
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	£37,979	4.488	£5,956	0.012	£483,462

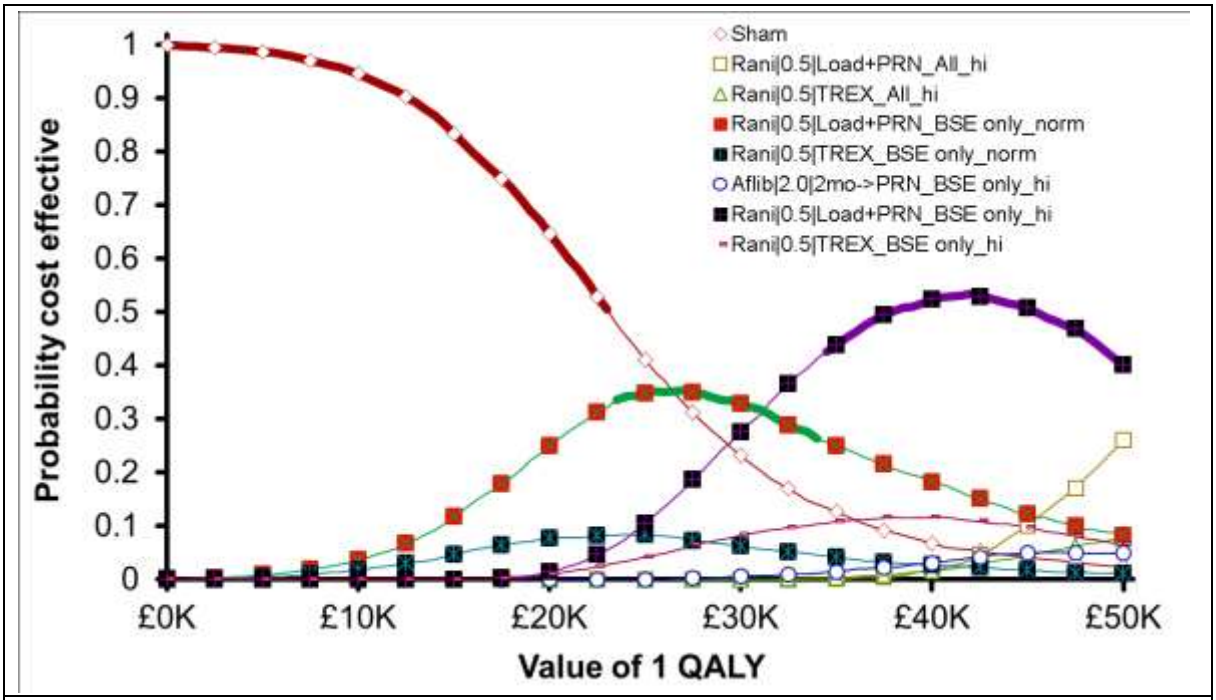
Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

506 List-price PSA results suggest that providing no treatment has the highest probability of
507 producing the highest NHB at all QALY valuations up to £26,500 (Figure 23), at which point
508 ranibizumab given to BSEs according to a loading phase then PRN regimen is more likely to
509 be cost effective. At a value of £20,000 per QALY, the likelihood of 'no treatment' being
510 optimal is 64.7%.

511 Alternative sets of probabilistic results were obtained, the first omitting the no treatment and
512 PDT strategies. This is to evaluate the CEAC in a decision space where providing no
513 treatment to people with late AMD (wet active) is not considered to be an appropriate
514 strategy, and omitting the clearly cost-ineffective PDT option. Here, ranibiuzmab PRN used
515 to treat only BSEs, according to current VA thresholds, has a 79.6% probability of being
516 optimal at £20,000 per QALY, and maintains the highest likelihood up to a QALY valuations
517 of £32,500 (Figure 24). Extending this treatment to eyes with VA better than 6/12 then has

the highlest likelihood at all values up to the maximum shown of £50,000. Therefore, at list prices, no active treatment strategy in this analysis was cost-effective if it allowed for the treatment of WSEs as well as BSEs.

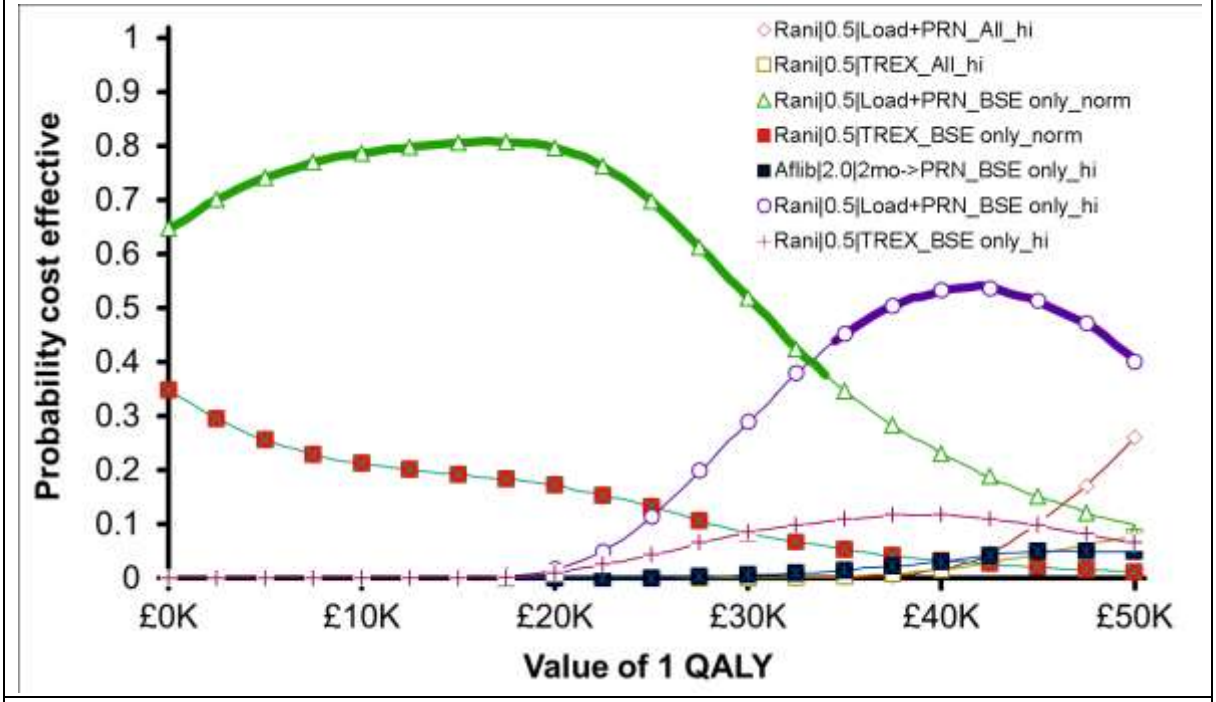
The set of base-case strategies was restricted once further, excluding strategies that limit treatment to only BSEs. This is because the treatment of WSEs is currently permitted and commonly occurs in practice. By including only regimens on product labels, omitting PDT, assuming that providing no treatment is not an option, and making WSEs eligible for treatment, this analysis becomes the most reflective of current practice. The resulting CEAC (Figure 25) shows that ranibizumab delivered PRN is likely to be the optimal of the commonly-used strategies, when evaluated at their list prices. At a value of £20,000 per QALY, it produced the highest NHB in 59.8% of iterations when including eyes with VA baove 6/12, and in 24.1% of iterations using current practice VA thresholds. At a value of £30,000 per QALY, the former probability increases to 75.3%. Aflibercept at its list price is unlikely to be cost-effective across the range shown (<5%), while monthly ranibizumab has a 0% probability of being cost-effective across this range. Importantly, these results are evaluated at the list prices of the two interventions. An equivalent CEAC was produced at their confidential PAS prices, which is described briefly at the end of Section J.5.6.4.



CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.

Bold line indicates cost-effectiveness acceptability frontier.

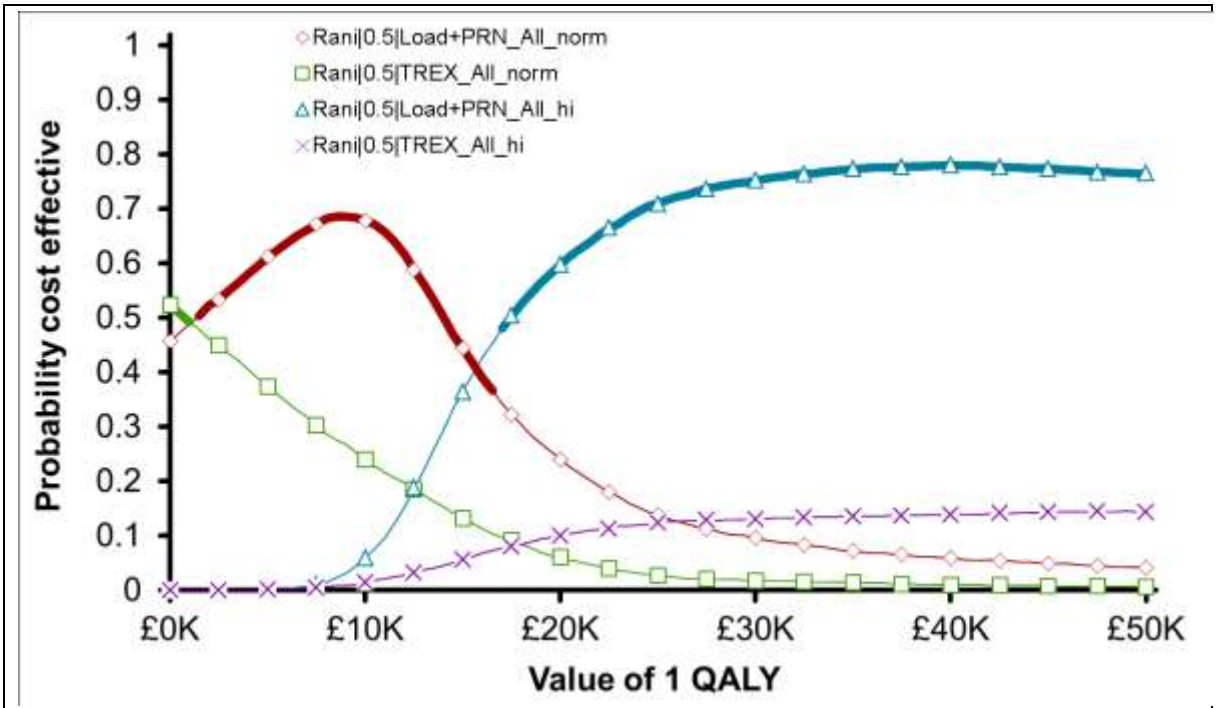
Figure 23: Cost-effectiveness acceptability curve – product label regimens – list prices



CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.

Bold line indicates cost-effectiveness acceptability frontier.

Figure 24: Cost-effectiveness acceptability curve – product label regimens, excluding 'no treatment' and PDT strategies – list prices



CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.

Bold line indicates cost-effectiveness acceptability frontier.

Figure 25: Cost-effectiveness acceptability curve – product label regimens, excluding 'no treatment', PDT and better-seeing eye only strategies – list prices

Focus on: treatment frequency

The results above – that is, the comprehensive NHB results in Table 49, and subsequent cost–utility frontiers – suggest that bevacizumab delivered every 2 months is a cost effective strategy. However, it is important to recognise that the cost effectiveness of providing treatment at 2-month intervals relies on bevacizumab being the active treatment provided, which is not licensed for intraocular use for late AMD (wet active). Table 53 shows this by comparing 2-monthly and 3-monthly regimens head-to-head. Treating eyes with bevacizumab every 2 months is associated with an ICER of £10-11,000 per QALY gained compared with treating every 3 months, varying slightly depending on the population-level VA eligibility criteria used. The equivalent ICERs for ranibizumab, evaluated at its list price, are around £57,000 per QALY gained. The increased treatment frequency produces a bigger QALY gain with ranibizumab, but this gain is accompanied by a much larger relative increase in costs.

Table 53: Head-to-head cost–utility results of different treatment frequencies (at ranibizumab list price)

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Bevacizumab, with VA in range: 6/12 to 6/96					
Beva | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£12,491	4.172	-	-	-
Beva | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£13,516	4.274	£1,025	0.102	£10,049
Ranibizumab, with VA in range: 6/12 to 6/96					
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£22,449	4.192	-	-	-
Rani | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£28,463	4.297	£6,014	0.105	£57,074
Bevacizumab, extend to treat VA >6/12					
Beva | 3mo | Treat any eye | including at VA > 6/12	£12,524	4.231	-	-	-
Beva | 2mo | Treat any eye | including at VA > 6/12	£13,688	4.337	£1,165	0.106	£10,978
Ranibizumab, extend to treat VA >6/12					
Rani | 3mo | Treat any eye | including at VA > 6/12	£23,332	4.253	-	-	-
Rani | 2mo | Treat any eye | including at VA > 6/12	£29,938	4.368	£6,606	0.115	£57,405

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Increasing treatment frequency to every month is not a cost-effective strategy, even with bevacizumab, as reflected in Table 50. It is, therefore, logical that monthly injections of other anti-angiogenic therapies are not cost-effective compared with 2-monthly injections. For example, the head-to-head ICER of 1-monthly ranibizumab injections exceeds £230,000 per QALY gained compared with 2-monthly ranibizumab injections.

Focus on: PRN regimens

Bevacizumab and ranibizumab strategies include 2 PRN regimens: one with an initial 3-month loading dose phase and one with 'immediate PRN' (i.e. no loading phase). The cost-

effectiveness of having a loading phase depends on which treatment is provided. Table 54 shows that, in both cases, having a loading phase is more effective than not having one, producing around 0.04 additional QALYs per patient. If bevacizumab is given, the additional treatment cost of a loading phase almost entirely offset by its effectiveness at reducing low-vision resource use, with a net cost of £37, and ICER of £831 per QALY gained. For ranibizumab, at its list price, the additional treatment cost of a loading phase is higher, and does not get offset to the same extentby reduced low-vision resource use. However, the ICER of having a loading phase remains under £20,000, at £19,529 per QALY, as is lower still when its confidential discounted NHS price is applied.

Table 54: Head-to-head cost–utility results of loading phase then PRN and immediate PRN (at ranibizumab list price)

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Bevacizumab					
Beva | PRN | Treat any eye | with VA in range: 6/12 to 6/96	£17,105	4.325	-	-	-
Beva | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£17,142	4.369	£37	0.044	£831
Ranibizumab					
Rani | PRN | Treat any eye | with VA in range: 6/12 to 6/96	£30,031	4.355	-	-	-
Rani | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£30,851	4.397	£820	0.042	£19,529

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 55 presents head-to-head cost–utility results of 2-monthly and 3-monthly regimens versus PRN regimens. For ranibizumab and bevacizumab, PRN regimens are associated with additional costs per patient compared with continuous 2- and 3-monthly regimens which, with comparatively small difference in QALYs, produce high ICERs. This is largely attributable the requirement for additional monitoring burden of PRN regimens, whereas patients on a continuous regimen will only be monitored at their injection appointments (not the months in between). For aflibercept, however, 2-monthly injections for 1-year followed by PRN injections costs less than ongoing continuous 2-monthly treatment. This is because long-term PRN treatment with aflibercept requires 2.2 fewer injections per year than ongoing 2-monthly treatment which, at a cost saving of the aflibercept list price per injection, outweighs the extra cost of PRN-related monitoring visits.

Table 55: Head-to-head cost–utility results of PRN and routine treatment (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Aflibercept, 2-mo vs. 2-mo+PRN					
Aflib | 2mo->PRN | Treat any eye | with VA in range: 6/12 to 6/96	£36,263	4.408	-	-	-
Aflib | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£39,602	4.365	£3,339	-0.043	Dominated
Bevacizumab, 3-mo vs. load+PRN					
Beva | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£12,491	4.172	-	-	-

Beva | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£17,142	4.369	£4,651	0.198	£23,543
Bevacizumab, 2-mo vs. load+PRN					
Beva | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£13,516	4.274	-	-	-
Beva | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£17,142	4.369	£3,626	0.096	£37,952
Ranibizumab, 3-mo vs. load+PRN					
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£22,449	4.192	-	-	-
Rani | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£30,851	4.397	£8,402	0.205	£41,009

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Focus on: extending treatment eligibility to eyes with VA better than 6/12

The possibility of extending treatment eligibility criteria to include eyes with VA better than 6/12 was included as a component of our comprehensive treatment strategies. Our base-case results suggest that extending treatment eligibility this way is part of the optimal strategy, which involves treatment with unlicensed bevacizumab. Table 56 shows head-to-head cost–utility results comparing: (1) extending treatment to eyes with VA better than 6/12 with (2) not doing so under various different strategies.

If the active anti-VEGF being offered is bevacizumab, then allowing eyes with VA better than 6/12 to be treated is associated with ICERs far below £20,000 per QALY gained, such that the health gains from extending treatment eligibility to eyes with VA >6/12 are unequivocally good value for money if treating with bevacizumab.

If the treatment of choice is aflibercept or ranibizumab, the decision to extend eligibility to VA >6/12 is less clear when evaluated at their list prices. The ICERs are £14,614 and £21,041 per QALY gained for 3-monthy and 2-monthly ranibizumab, respectively. The ICER is £14,913 per QALY gained for the label regimen of a loading phase then PRN. If aflibercept is delivered every 2 months, the ICER for extending treatment is £30,904 per QALY gained, and £21,468 if the patient moves onto PRN after 1 year. However, when aflibercept and ranibizumab are evaluated at their confidential discounted NHS prices, the ICER for extending treatment to eyes with VA above 6/12 is under £20,000 in all of the strategies shown below.

Table 56: Head-to-head cost–utility results of extending treatment eligibility to eyes with VA >6/12 compared with not extending treatment eligibility (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Aflibercept, 2-monthly					
Aflib | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£39,602	4.365	-	-	-

Aflib | 2mo | Treat any eye | including at VA > 6/12	£41,984	4.442	£2,382	0.077	£30,904
Aflibercept, 2-monthly then PRN					
Aflib | 2mo->PRN | Treat any eye | with VA in range: 6/12 to 6/96	£36,263	4.408	-	-	-
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	£37,979	4.488	£1,716	0.080	£21,468
Bevacizumab, 3-monthly					
Beva | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£12,491	4.172	-	-	-
Beva | 3mo | Treat any eye | including at VA > 6/12	£12,524	4.231	£33	0.059	£562
Bevacizumab, 2-monthly					
Beva | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£13,516	4.274	-	-	-
Beva | 2mo | Treat any eye | including at VA > 6/12	£13,688	4.337	£173	0.063	£2,735
Ranibizumab, 3-monthly					
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£22,449	4.192	-	-	-
Rani | 3mo | Treat any eye | including at VA > 6/12	£23,332	4.253	£883	0.060	£14,614
Ranibizumab, 2-monthly					
Rani | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£28,463	4.297	-	-	-
Rani | 2mo | Treat any eye | including at VA > 6/12	£29,938	4.368	£1,475	0.070	£21,041
Ranibizumab, loading then PRN					
Rani | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	£30,851	4.397	-	-	-
Rani | Load+PRN | Treat any eye | including at VA > 6/12	£32,023	4.476	£1,172	0.079	£14,913

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

The cost-effectiveness case for extending treatment to eyes with VA better than 6/12 is weaker if only BSEs are eligible for treatment. This is because a ceiling effect exists whereby eyes with better VA have less potential to improve, such that the benefits from doing so are small relative to the additional treatment costs. Here, the ICER of extending treatment using 2-monthly ranibizumab is £35,935 per QALY gained, using its list price. With aflibercept given as per the VIEW trial it is £37,384. However if bevacizumab is used, the ICER of extending treatment remains under £20,000 per QALY with 3-monthly injections (£8,932) and 2-monthly injections (£10,955). Its lower price per dose means the modest QALY gains from extending treatment (0.07 & 0.08 QALYs) are relatively large compared with the additional costs (£636 & £927).

Focus on: extending treatment eligibility to eyes with VA worse than 6/96

The modelled strategies also included the possibility of extending treatment eligibility criteria to include eyes with VA of 6/96 or worse. Our base-case results suggest that extending treatment eligibility this way is never optimal compared with not doing so. Table 57 shows that this is true, as long as treatment is not restricted to just BSEs, with 4 head-to-head comparisons. Even if the treatment used is bevacizumab on a 3-monthly basis, the additional treatment cost to the average patient does not represent value for money because it is accompanied a very small loss of QALYs. This is because, firstly, the eye with VA ≤6/96 is likely to be a person's WSE, which limits the extent to which improving its VA can affect quality of life (predominantly determined by the BSE). Secondly, even with a modest to good improvement in VA, an eye starting at ≤6/96 is likely to remain at a relatively low absolute level. Thirdly, with little scope for quality of life gains due to improved VA, the negative factors associated with treatment – injection anxiety, pain and adverse events – offset any QALY gains. It represents overtreatment; the unnecessary treatment of WSEs.

Table 57: Head-to-head cost–utility results of extending treatment eligibility to eyes with VA ≤6/96 compared with not extending treatment eligibility (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Aflibercept, 2-monthly then PRN					
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£36,263	4.408	-	-	-
Aflib | 2mo->PRN | Treat only BSEs | Extend for VA <6/96	£36,718	4.406	£454	-0.002	Dominated
Bevacizumab, 3-monthly					
Beva | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£12,491	4.172	-	-	-
Beva | 3mo | Treat any eye | Extend for VA <6/96	£12,610	4.171	£120	-0.001	Dominated
Bevacizumab, 2-monthly					
Beva | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	£13,516	4.274	-	-	-
Beva | 2mo | Treat any eye | Extend for VA <6/96	£13,682	4.268	£166	-0.005	Dominated
Ranibizumab, 3-monthly					
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	£22,449	4.192	-	-	-
Rani | 3mo | Treat any eye | Extend for VA <6/96	£22,634	4.190	£185	-0.002	Dominated

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

This result does not hold true if a strategy is chosen in which only BSEs are eligible for treatment (Table 58). If this restriction applies, then allowing eyes with VA ≤6/96 to be treated will only affect people whose *better*-seeing eyes have VA ≤6/96. This means WSEs with VA ≤6/96 will not be unnecessarily treated, which does occur when there is no BSE only

restriction. A person will experience greater benefit from treating an eye with low vision if that eye is their BSE. Here, the additional treatment cost to the average patient is small given that it is such a small patient subgroup who will have VA ≤6/96 in their BSE, relative to the QALYs gained by those patients. As such, the ICER of extending treatment is less than £20,000 per QALY gained for the bevacizumab regimens shown, and is less than £30,000 for most other regimens evaluated at list prices.

Table 58: Head-to-head cost–utility results of extending treatment eligibility to eyes with VA ≤6/96 compared with not extending treatment eligibility – BSEs only (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Aflibercept, 2-monthly then PRN					
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£22,182	4.201	-	-	-
Aflib | 2mo->PRN | Treat only BSEs | Extend for VA ≤6/96	£22,315	4.205	£133	0.004	£33,669
Bevacizumab, 3-monthly					
Beva | 3mo | Treat only BSEs | Extend for VA <6/96	£10,189	4.071	-	-	-
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,313	4.069	£124	-0.002	Dominated
Bevacizumab, 2-monthly					
Beva | 2mo | Treat only BSEs | Extend for VA <6/96	£10,403	4.130	-	-	-
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,510	4.126	£107	-0.003	Dominated
Ranibizumab, 3-monthly					
Rani | 3mo | Treat only BSEs | including VA <6/96	£15,698	4.078	-	-	-
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£15,752	4.082	£54	0.004	£12,817
Ranibizumab, 2-monthly					
Rani | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£18,182	4.141	-	-	-
Rani | 2mo | Treat only BSEs | including VA <6/96	£18,244	4.143	£62	0.003	£23,407
Ranibizumab, loading then PRN					
Rani | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	£19,575	4.196	-	-	-
Rani | Load+PRN | Treat only BSEs | Extend for VA <6/96	£19,682	4.200	£107	0.004	£27,028

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

J.6.5.23 One-way sensitivity analysis

One-way sensitivity analysis was conducted to evaluate the sensitivity of cost–utility results to variation of individual input parameters between sensible upper and lower bounds. These are presented for head-to-head strategy comparisons in tornado diagrams, showing the difference in incremental net monetary benefit (INMB) caused by variation in each parameter, evaluated at a value of £20,000 per 1 QALY. Parameters are presented in descending order of INMB sensitivity. INMB is shown rather than differences in ICERs to avoid negative ICERs distorting the diagrams.

Figure 26 shows the sensitivity of results comparing 2-monthly bevacizumab with 3-monthly bevacizumab, regardless of fellow eye status and including eyes with VA >6/12. This analysis was performed to explore what circumstances might make providing treatment as frequently as once every 2 months suboptimal relative to just once every 3 months. In the

base-case analysis, 2-monthly treatment produces a positive INMB here; a net gain to the health care system as a whole. Five parameters have the potential to reverse this result, notably: the NMA effectiveness parameter for an additional month of bevacizumab frequency; if bevacizumab cost £300 per dose; and if treatment was conducted in a day case admission for 37% of patients. However, for many parameters, variation in the opposite direction further strengthened the cost-effectiveness case for 2-monthly treatment.

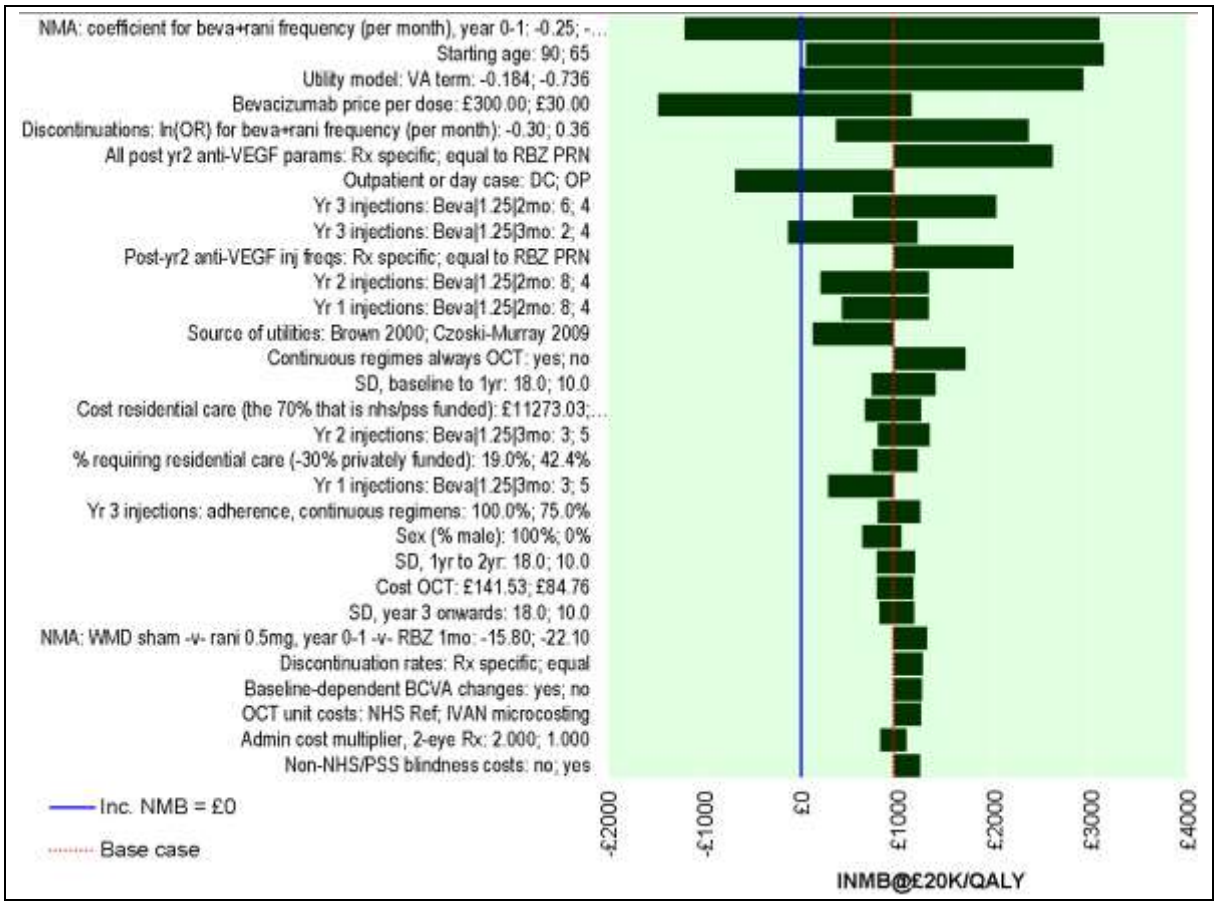


Figure 26: Tornado diagram – 2-monthly bevacizumab vs. 3-monthly bevacizumab – any eye, including VA >6/12 – 30 most influential parameters

Figure 27 and Figure 28 present one-way sensitivity analysis results comparing extending treatment to eyes with VA >6/12 with not doing so. The first shows aflibercept given on a 2-monthly basis for 1 year, followed by PRN; the second shows ranibizumab given PRN following a 3-month loading phase. These are 2 of the commonly used regimens, both listed on product labels. Both figures compared strategies that are not restricted to treating only BSEs. Both drugs are evaluated at their list prices here, but are available to the NHS at confidential prices.

For the aflibercept regimen, at its list price, extending treatment is shown to be sub-optimal relative to current practice VA thresholds, producing less net benefit (the ICER is £21,468 per QALY gained. A number of model parameters have the potential to change this outcome, which reflects how close the ICER is the the £20,000 threshold. Variation in a coefficient of the Czoski-Murray utility regression is influential, as is the number of injections required in long-term treatment. The latter affects results in the expected way, whereby requiring fewer injections makes the more inclusive treatment strategy – extending treatment to eyes with VA >6/12 – more attractive. The age of patients also features among the most important parameters when it comes to this decision; results imply that extending ranibizumab treatment may be preferable to not doing so in younger patients (age 65 shown). However, it

is an increasingly sub-optimal in older patients (age 90 shown). For ranibizumab the ICER was £14,913 per QALY gained, reflect in a positive (cost-effective) NMB. However, the same parameters still have the capacity to change whether treating eyes with VA better than 6/12 is cost-effective or not, crossing the zero incremental net benefit line. Results of extending treatment this way when the drugs are evaluated at their list prices are described in Section J.5.6.5.

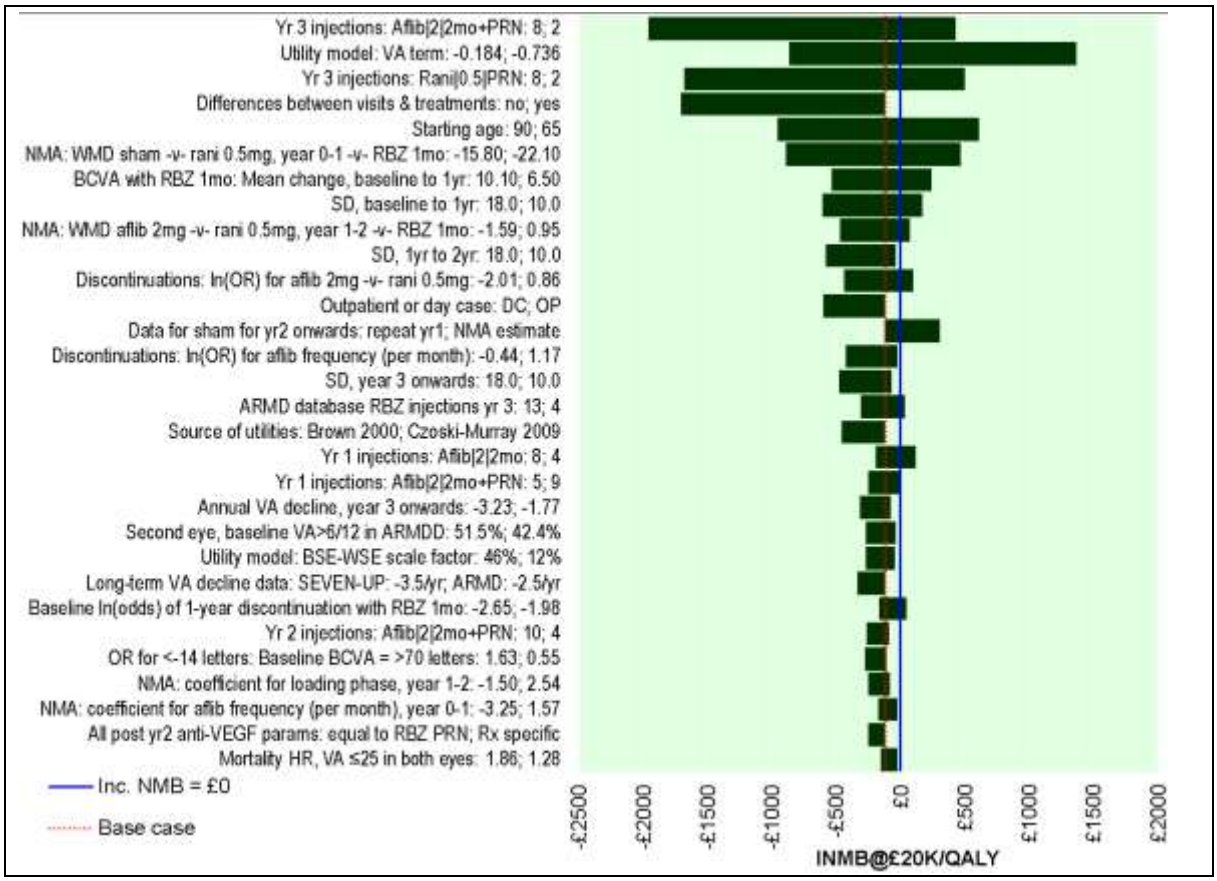


Figure 27: Tornado diagram – extending treatment to VA >6/12 vs. current practice VA thresholds – aflibercept (VIEW regimen), any eye – 30 most influential parameters (at list price)

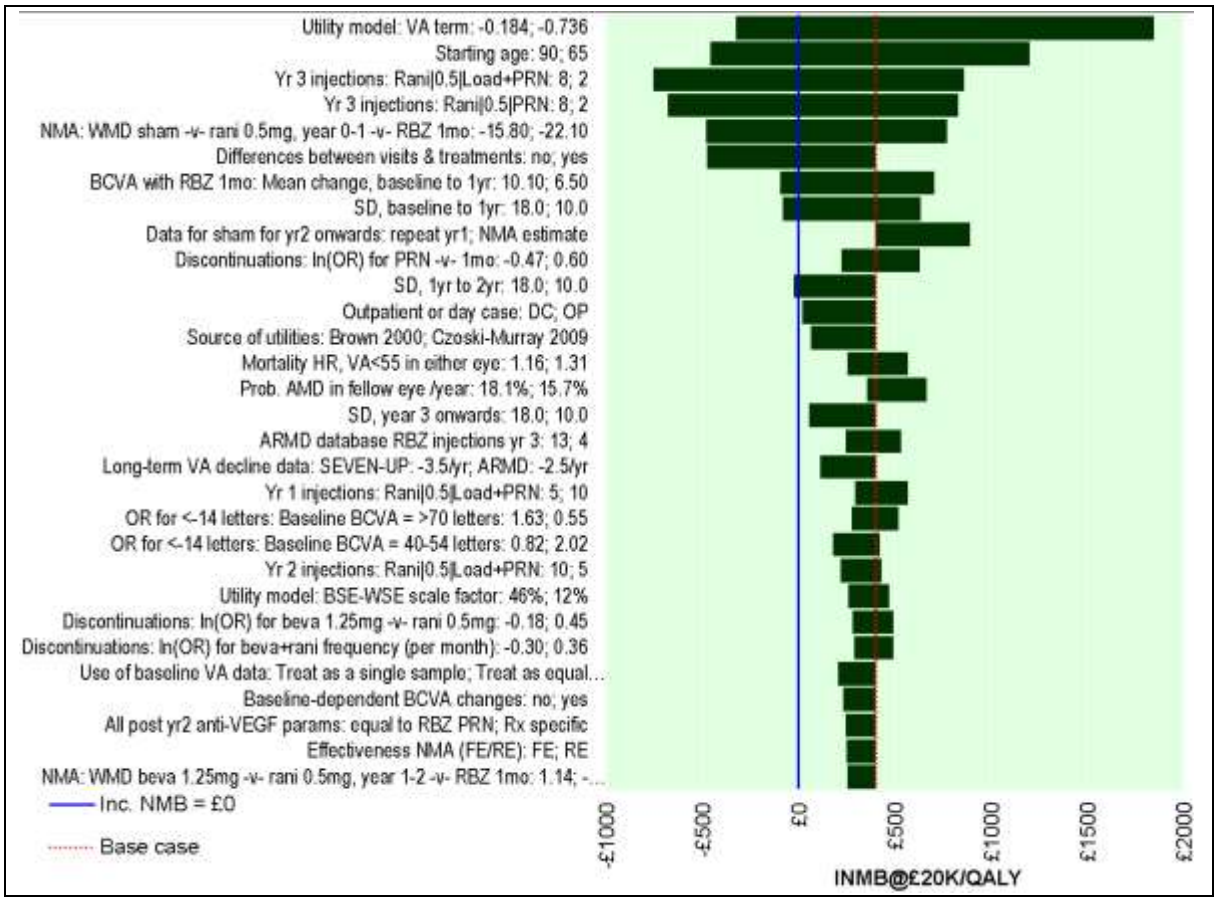
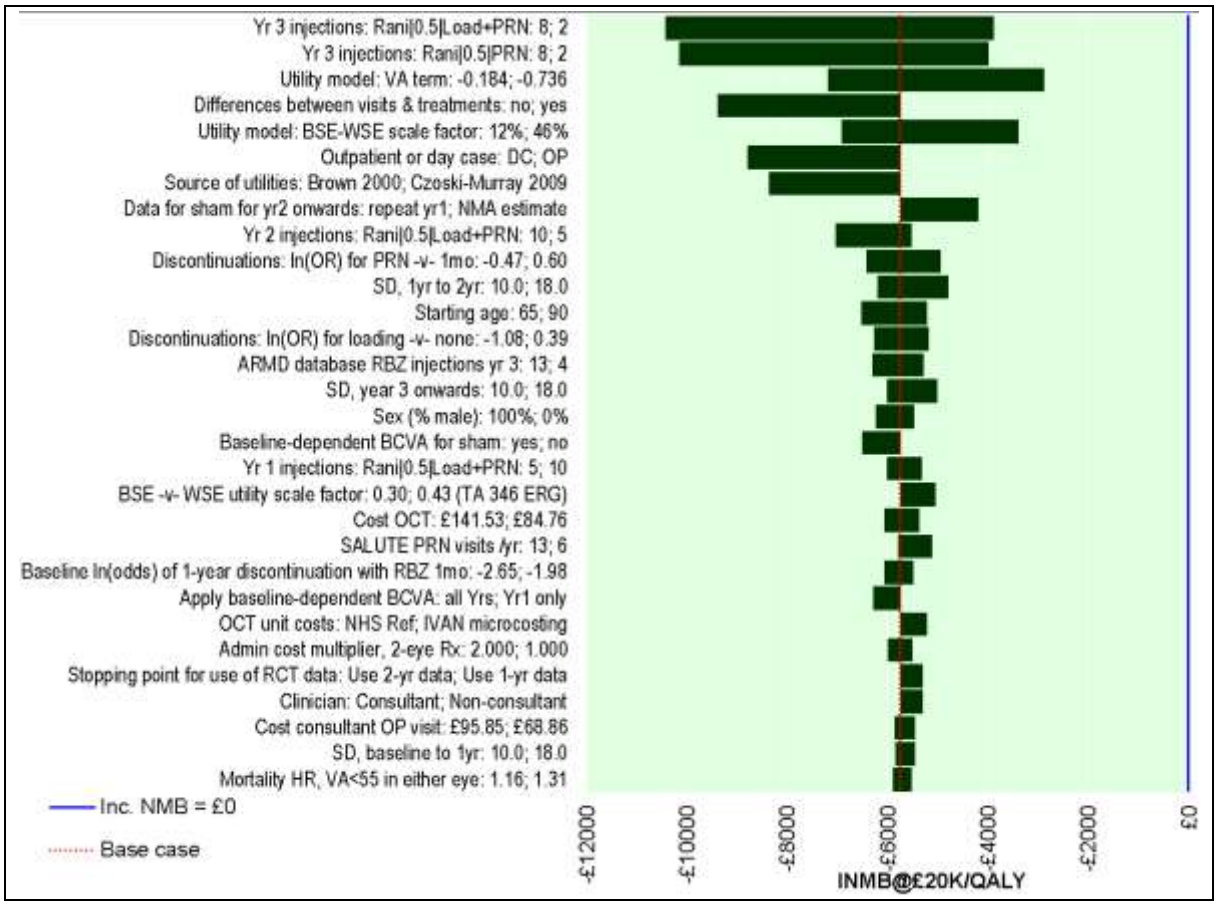


Figure 28: Tornado diagram – extending treatment to VA >6/12 vs. current practice VA thresholds – ranibizumab loading+PRN, any eye – 30 most influential parameters (at list price)

Figure 29 shows the one-way sensitivity analysis results comparing a strategy that treats only BSEs with one that permits the treatment of any eye, as long as it meets a treatment eligibility threshold VA (here, above 6/96, including above 6/12). Both strategies involve treatment with PRN ranibizumab at its list price. The tornado diagram shows that permitting this treatment in WSEs is associated with lower NMB than restricting treatment to BSEs only. There is some notable variation in the INMB value caused by sensitivity to some parameters or scenarios, however, none is sufficient to make lifting the restriction cost effective.



712 **Figure 29: Tornado diagram – permitting treatment of worse-seeing eyes vs. treating**
713 **better-seeing eyes only – ranibizumab loading phase then PRN, including**
714 **VA >6/12 – 30 most influential parameters (at list price)**

715 Figure 30 shows that the base-case result comparing aflibercept delivered as per the VIEW
716 trial – 2-monthly for 1 year, then PRN – with ranibizumab as a loading phase then PRN is
717 generally robust to one-way sensitivity analysis. The only parameter that univariately
718 changes the base-case result (favouring ranibizumab) is variation in the number of
719 ranibizumab injections per year for long-term treatment. If ranibizumab PRN required 8
720 injections per year from year 3 onwards (instead of its base-case value of 3.7), then
721 aflibercept would be associated with a positive net benefit per patient treated; though this
722 more than doubling of the injection frequency would, in reality, probably have a positive
723 treatment effect, which is not captured in a one-way sensitivity analysis. Importantly, these
724 results are evaluated at the list prices of the two interventions. An equivalent analysis was
725 conducted at their confidential NHS prices, which found there to be much less to choose
726 between the 2 strategies than at their list prices (see Section J.5.6.5).

727

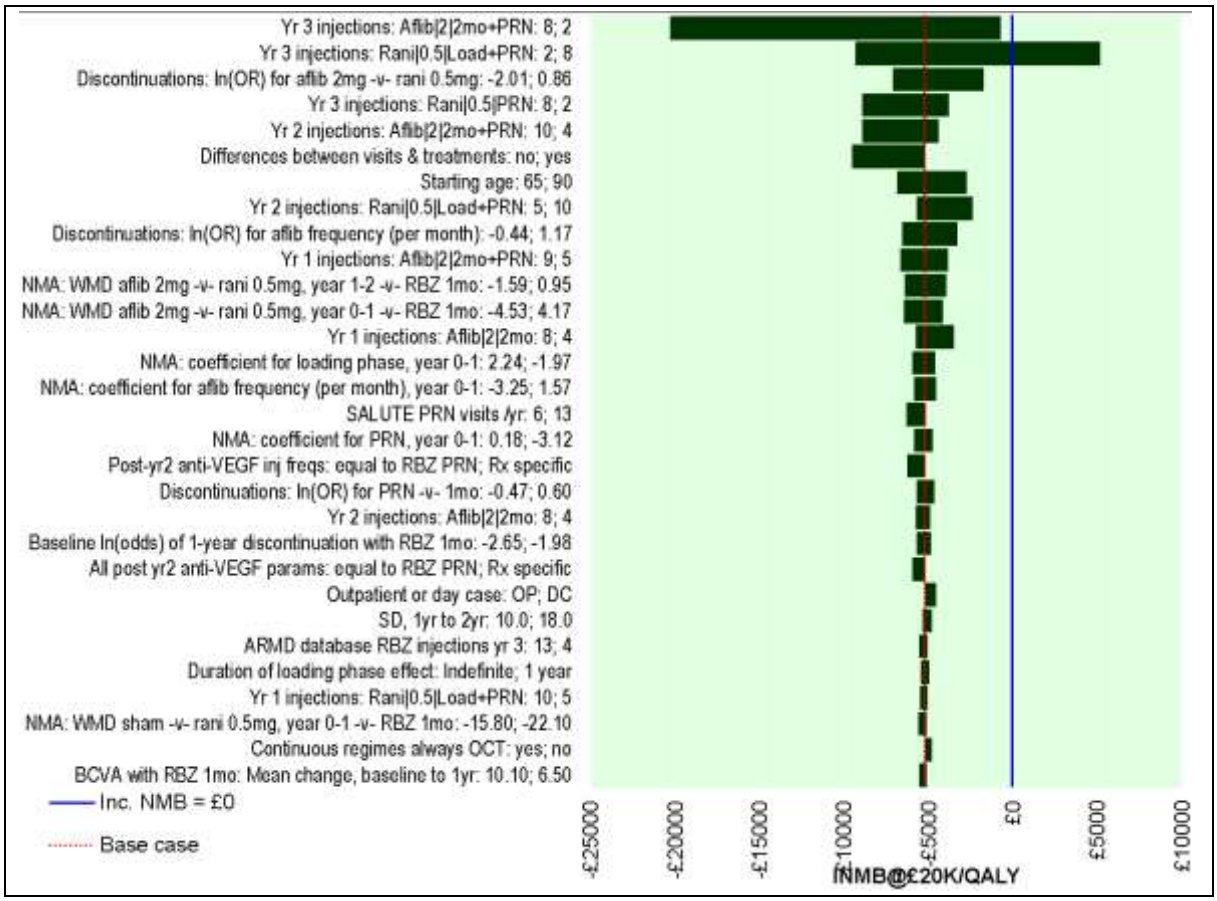
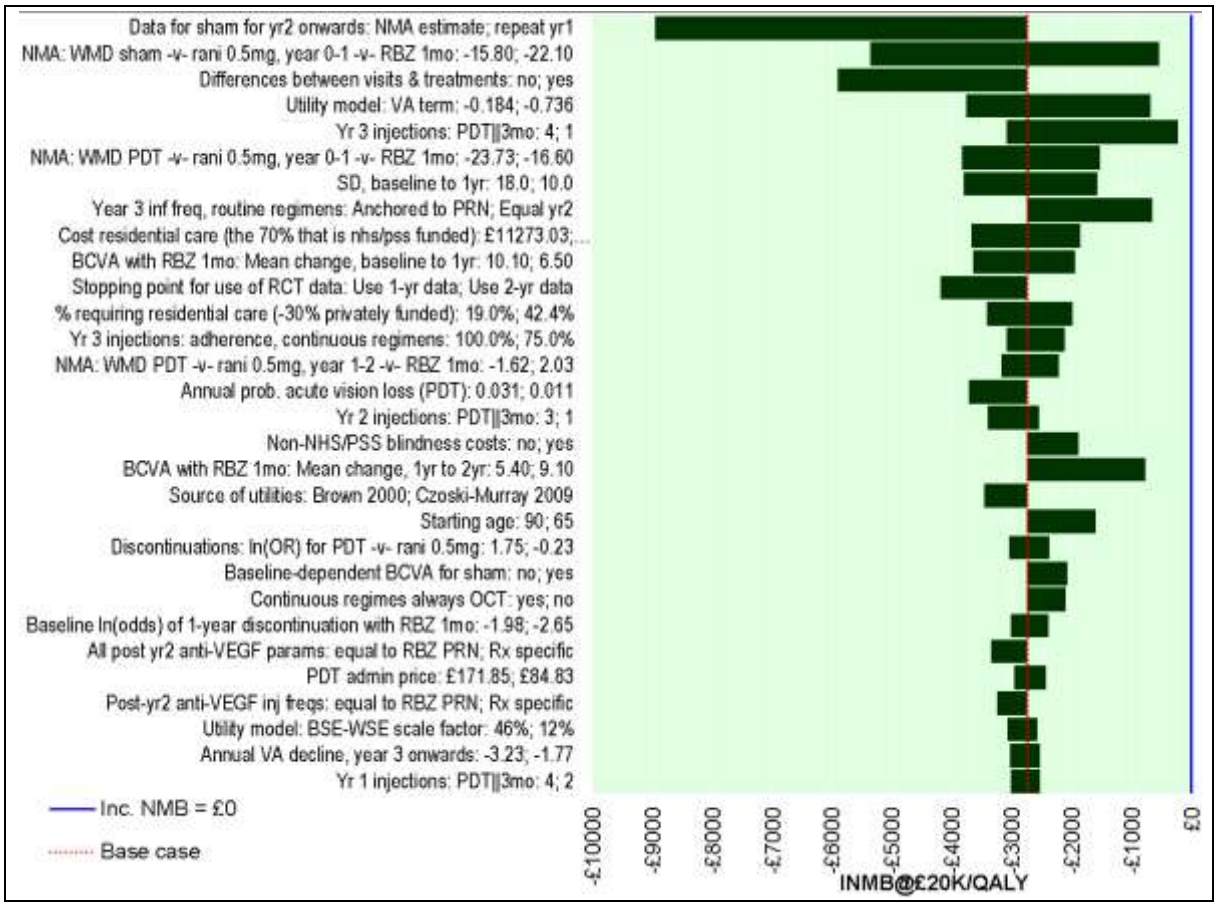


Figure 30: Tornado diagram – 2-monthly aflibercept followed by PRN vs. ranibizumab loading phase followed by PRN – any eye, current practice VA thresholds – 30 most influential parameters (at list prices)

Figure 31 presents the one-way sensitivity analysis results comparing the PDT regimen that produced the highest NHB – treating only BSEs according to current practice VA thresholds – with providing no treatment at all. This shows the base-case finding, that the best and least intensive PDT option is suboptimal compared with doing nothing, is not reversed by any parameter when allowed to vary within its plausible range. Using PDT would produce a net loss of health to the NHS.



738 **Figure 31: Tornado diagram – PDT in better-seeing eyes, current practice VA**
739 **thresholds vs. no treatment – 30 most influential parameters**

J.5.4 Scenario analyses

741 **PRNX regimens**

742 The relative effectiveness and treatment frequency evidence used to inform the PRNX
743 treatment protocol in the NMA is limited, relying connected to the network by an individual,
744 small trial. This led to our analysis achieving only a highly uncertain prediction of PRNX
745 effectiveness, with a point estimate that appears conspicuously effective (even more so than
746 regular monthly injections). For these reasons, we have included PRNX in a scenario
747 analysis only.

748 As PRNX regimens are not explicitly included on product labels, its scenario analysis
749 includes all potential treatment regimens used in the model (Table 59). As in our base-case
750 analysis, we have excluded strategies that extend treatment eligibility to eyes with VA ≤6/96.
751 The first non-dominated strategies are identical to the base-case model. However,
752 bevacizumab delivered every 2 months, to both better and WSEs, and including those with
753 VA >6/12, does not feature on the cost–utility frontier in this analysis. Instead, bevacizumab
754 given to the same patients using the PRNX regimen becomes the cost effective strategy at a
755 maximum acceptable ICER of £20,000 per QALY gained (ICER: £14,560). This reflects its
756 high level of effectiveness predicted by the NMA. Aflibercept PRNX has an ICER of £79,054
757 per QALY gained, at its list price, compared with bevacizumab.

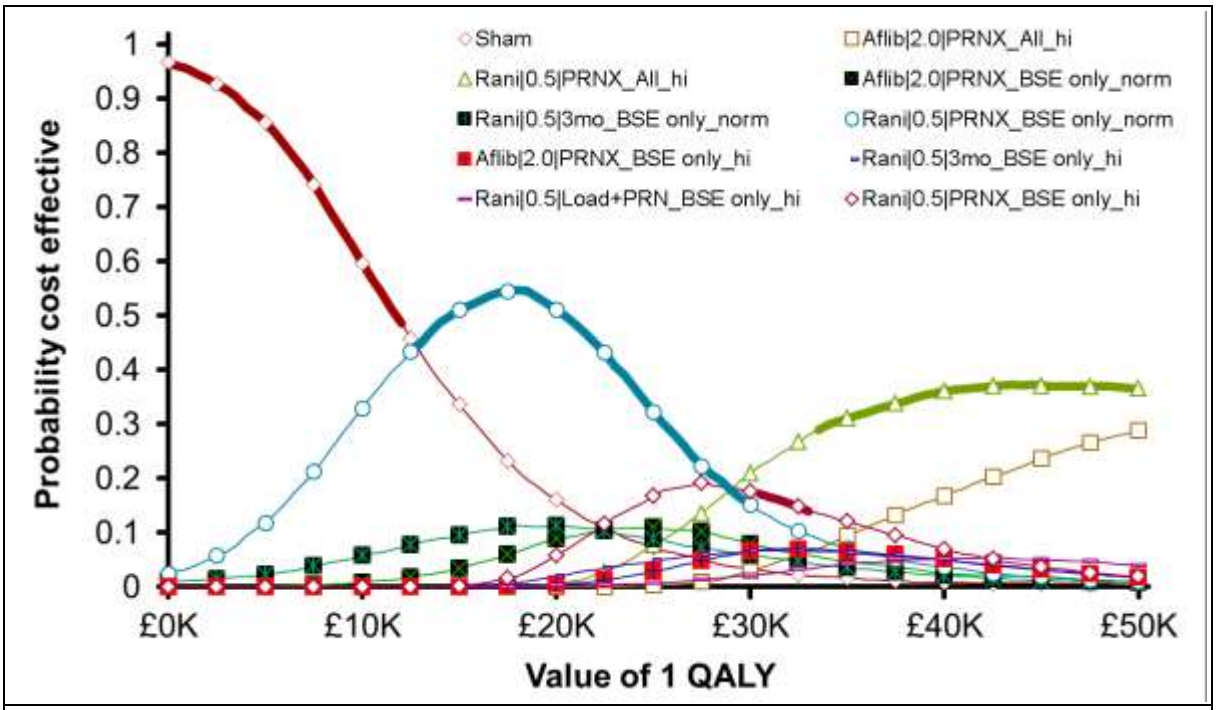
758 **Table 59: Deterministic base-case results including PRNX regimens – fully incremental**
759 **analysis, non-dominated strategies shown (at list prices)**

	Absolute	*Fully incremental analysis*

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Costs*	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,313	4.069			
Beva | PRNX| Treat only BSEs | with VA in range: 6/12 to 6/96	£10,904	4.264	£591	0.194	£3,043
Beva | PRNX| Treat any eye | including VA >6/12	£15,127	4.554	£4,224	0.290	£14,560
Aflib | PRNX| Treat any eye | including VA >6/12	£36,439	4.823	£21,311	0.270	£79,054

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); PRNX, treat as needed and extend assessment interval; QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

If bevacizumab is removed from this analysis, reflecting that it is not licensed for intraocular use for late AMD (wet active), the resulting CEAC from PSA (Figure 32) shows that ranibizumab PRNX becomes the most likely strategy to be optimal beyond a QALY value of £12,500, in BSEs only. At a QALY value of £20,000, its probability is 51.0%. Beyond a value of £29,000 per QALY, PRNX treatment in better or worse seeing eyes and including eyes with VA >6/12 becomes most likely to be optimal. However these results are highly uncertain, owing to the limited evidence base for PRNX regimens. At a QALY value of £50,000, ranibizumab PRNX (36.6%) and aflibercept PRNX (28.9%) are very close on the CEAC. Again, this analysis included aflibercept and ranibizumab at their list prices.



CEAC key displays all strategies that have a ≥5% probability of being cost-effective at any point along the 'value of 1 QALY' range shown. Other strategies are not shown in the key for diagram simplicity.
Bold line indicates cost-effectiveness acceptability frontier.

Figure 32: Cost-effectiveness acceptability curve – PRNX included, bevacizumab excluded – list prices

Limiting the relative effectiveness of PRNX regimens to that of monthly regimens – which is still likely to present a highly optimistic view of the PRNX treatment protocol – produces the

cost–utility results in Table 60. This causes no notable impact on the results shown above, with bevacizumab remaining optimal, with a bevacizumab PRNX ICER of under £20,000 per QALY gained. If bevacizumab is removed from this analysis, PRNX regimens continue to feature on the cost–utility frontier with an ICERs below £20,000 per QALY for ranibizumab given only to better-seeing eyes (Table 61).

Table 60: Scenario analysis results including PRNX regimens, with effectiveness equal to monthly treatment – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£10,277	4.070			
Beva | 2mo | BSE only | with VA in the range: 6/12 to 6/96	£10,536	4.125	£259	0.054	£4,752
Beva | 2mo | Treat only BSEs | including with VA > 6/12	£11,426	4.207	£890	0.082	£10,832
Beva | 2mo | Treat any eye | including with VA > 6/12	£13,729	4.346	£2,303	0.139	£16,626
Beva | PRNX | Treat any eye | including with VA > 6/12	£16,050	4.464	£2,320	0.118	£19,634
Aflib | PRNX | Treat any eye | including with VA > 6/12	£38,248	4.594	£22,199	0.130	£170,973

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); PRNX, treat as needed and extend assessment interval; QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 61: Scenario analysis results including PRNX regimens, with effectiveness equal to monthly treatment, excluding bevacizumab – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
No treatment	£11,878	3.839			
Rani | PRNX | Treat only BSEs | with VA in the range: 6/12 to 6/96	£17,784	4.217	£5,907	0.379	£15,592
Rani | PRNX | Treat only BSEs | including with VA > 6/12	£20,565	4.314	£2,781	0.096	£28,825
Rani | PRNX | Treat any eye | including with VA > 6/12	£28,833	4.506	£8,268	0.192	£42,982
Aflib | PRNX | Treat any eye | including with VA > 6/12	£38,248	4.594	£9,415	0.087	£107,788

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); PRNX, treat as needed and extend assessment interval; QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Treatment effect scenarios

In the base-case analysis, first year treatment effects are weighted to account for the observed ceiling and floor effects on VA change in eyes with good and poor baseline VA, respectively. Removing this adjustment, instead applying treatment effects equally across all levels of baseline VA, has negligible impact on base-case model results (Table 62). Extending the adjustment beyond the first year of treatment has the effect of raising most ICERs along the frontier; however, 2-monthly bevacizumab remains the most effective treatment with an ICER under £20,000 per QALY gained (Table 63).

Neither of these scenarios have a major impact on the base-case model results where bevacizumab is excluded from the analysis.

Table 62: Scenario analysis results – treatment effects not weighted by baseline VA – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Fully incremental analysis		
	Costs	QALYs	Costs	QALYs	ICER
Beva | 3mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£10,227	4.095			
Beva | 2mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£10,414	4.157	£187	0.062	£3,014
Beva | 2mo | Treat only BSEs | including with VA > 6/12	£11,344	4.241	£930	0.084	£11,024
Beva | 2mo | Treat any eye | including with VA > 6/12	£13,565	4.379	£2,221	0.137	£16,167
Beva | Load+PRN | Treat any eye | including with VA > 6/12	£17,262	4.471	£3,697	0.092	£40,035
Aflib | 2mo->PRN | Treat any eye | including with VA > 6/12	£37,735	4.524	£20,473	0.053	£389,677
Aflib | 1mo | Treat any eye | including with VA > 6/12	£84,797	4.600	£47,062	0.076	£615,259

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 63: Scenario analysis results – treatment effect baseline VA weights applied beyond year 1 – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Fully incremental analysis		
	Costs	QALYs	Costs	QALYs	ICER
Beva | 3mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£10,186	4.061			
Beva | 2mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£10,431	4.111	£245	0.049	£4,963
Beva | 2mo | Treat only BSEs | including with VA > 6/12	£11,432	4.196	£1,001	0.085	£11,767
Beva | 2mo | Treat any eye | including with VA > 6/12	£13,745	4.319	£2,313	0.123	£18,751
Beva | Load+PRN | Treat any eye | including with VA > 6/12	£17,464	4.408	£3,720	0.089	£41,750
Aflib | 2mo->PRN | Treat any eye | including with VA > 6/12	£38,220	4.450	£20,756	0.042	£497,658
Aflib | 1mo | Treat any eye | including with VA > 6/12	£86,166	4.524	£47,946	0.074	£647,809

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Resource use and cost scenarios

Assuming that all treatment and monitoring appointments occur at non-consultant led outpatient clinics, rather than ophthalmologist-led clinics, improves the cost-effectiveness of all active treatments relative to providing no treatment, by reducing the cost of treatment. The base-case fully incremental results are little-changed, however, with the same 2-monthly bevacizumab strategy providing the most QALYs with an ICER under £20,000 (Table 64).

This is also the case if non-NHS/PSS costs associated with blindness are included in the total cost calculations (Table 65).

Table 64: Scenario analysis results – non-consultant led appointments – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£9,990	4.069			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,068	4.126	£79	0.057	£1,380
Beva | 2mo | Treat only BSEs | including at VA > 6/12	£10,885	4.211	£816	0.085	£9,646
Beva | 2mo | Treat any eye | including at VA > 6/12	£12,876	4.337	£1,991	0.126	£15,827
Beva | Load+PRN | Treat any eye | including at VA > 6/12	£15,936	4.445	£3,060	0.108	£28,400
Rani | Load+PRN | Treat any eye | including at VA > 6/12	£30,512	4.476	£14,576	0.031	£468,894
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	£36,556	4.488	£6,044	0.012	£490,596
Aflib | 1mo | Treat any eye | including at VA > 6/12	£83,114	4.569	£46,559	0.081	£575,495

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 65: Scenario analysis results – including non-NHS/PSS costs of blindness – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£12,614	4.126			
Beva | 2mo | Treat only BSEs | including at VA > 6/12	£13,552	4.211	£938	0.085	£11,086
Beva | 2mo | Treat any eye | including at VA > 6/12	£15,882	4.337	£2,330	0.126	£18,521
Beva | Load+PRN | Treat any eye | including at VA > 6/12	£19,347	4.445	£3,465	0.108	£32,160
Rani | Load+PRN | Treat any eye | including at VA > 6/12	£33,863	4.476	£14,516	0.031	£466,958
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	£39,741	4.488	£5,878	0.012	£477,152
Aflib | 1mo | Treat any eye | including at VA > 6/12	£86,658	4.569	£46,916	0.081	£579,916

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

If the cost of treatment and monitoring is increased – by assuming that 37% are conducted as day case admissions (Hospital Episode Statistics, 2014-15) – then the optimal base-case strategy of 2-monthly bevacizumab has an ICER in excess of £30,000. This reflects the cost-effectiveness case of all active treatments being weakened by higher treatment costs (providing no treatment becomes the lowest-cost strategy and is no longer dominated). Three-month treatment intervals for BSE only are associated with an ICER of £16,127 when the upper VA threshold is removed.

This scenario also has a notable effect on the base-case results when bevacizumab strategies are excluded (Table 67). It means no active treatment strategy has an ICER of £20,000 or less. Three-monthly ranibizumab used to treat BSEs only – which has a base-case list-price ICER of £15,967 per QALY gained – has an ICER of £25,287 in this scenario. This reflects the increased costs associated with all treatments, due to the higher average cost of treatment and monitoring visits.

Table 66: Scenario analysis results – 37% day case admissions – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
No treatment	£11,936	3.842			
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£12,496	4.069	£559	0.227	£2,462
Beva | 3mo | Treat only BSEs | including at VA > 6/12	£13,645	4.141	£1,149	0.071	£16,127
Beva | 2mo | Treat only BSEs | including at VA > 6/12	£15,166	4.211	£1,522	0.070	£21,642
Beva | 2mo | Treat any eye | including at VA > 6/12	£19,175	4.337	£4,009	0.126	£31,864
Beva | Load+PRN | Treat any eye | including at VA > 6/12	£27,252	4.445	£8,077	0.108	£74,956
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	£47,591	4.488	£20,339	0.043	£468,598
Aflib | 1mo | Treat any eye | including at VA > 6/12	£99,620	4.569	£52,028	0.081	£643,103

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 67: Scenario analysis results – Table 66 analysis, excluding bevacizumab (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
No treatment	£11,936	3.842			
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£17,893	4.078	£5,957	0.236	£25,287
Rani | 3mo | Treat only BSEs | including at VA > 6/12	£20,547	4.154	£2,653	0.077	£34,607
Rani | 2mo | Treat only BSEs | including at VA > 6/12	£25,143	4.227	£4,597	0.073	£63,297
Rani | Load+PRN | Treat only BSEs | including at VA > 6/12	£29,918	4.299	£4,775	0.072	£66,454
Rani | Load+PRN | Treat any eye | including at VA > 6/12	£42,229	4.476	£12,310	0.177	£69,686
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	£47,591	4.488	£5,363	0.012	£435,282
Aflib | 1mo | Treat any eye | including at VA > 6/12	£99,620	4.569	£52,028	0.081	£643,103

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

In another cost scenario, base-case (list-price) results are not notably affected by using lower unit costs of treatment administration and OCTs, which were estimated by a microcosting

exercise for the IVAN study (Chakravarthy et al., 2015). Here, all treatments represent slightly better value for money relative to providing no treatment, compared with the base-case model, but the optimal strategy remains the same (Table 68).

Table 68: Scenario analysis results – administration and OCT unit costs informed by IVAN study micro-costing analysis – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£9,851	4.069			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£9,881	4.126	£29	0.057	£516
Beva | 2mo | Treat only BSEs | including at VA > 6/12	£10,659	4.211	£779	0.085	£9,202
Beva | 2mo | Treat any eye | including at VA > 6/12	£12,669	4.337	£2,010	0.126	£15,975
Beva | Load+PRN | Treat any eye | including at VA > 6/12	£15,414	4.445	£2,745	0.108	£25,476
Rani | Load+PRN | Treat any eye | including at VA > 6/12	£29,961	4.476	£14,547	0.031	£467,973
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	£36,042	4.488	£6,080	0.012	£493,534
Aflib | 1mo | Treat any eye | including at VA > 6/12	£82,620	4.569	£46,578	0.081	£575,732

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

A further resource use scenario assumes that an OCT examination occurs only when it has the potential inform whether another injection is required or not. This reduces the OCT requirement to once per year for patients on continuous treatment regimens. In this scenario, continuous regimens represent better value for money than before, with a lower ICER for the base-case optimal 2-monthly bevacizumab strategy (£13,733 per QALY gained). However, providing fewer OCT examinations is not sufficiently cost-saving to reduce the ICER of monthly treatment below £20,000. Furthermore, this scenario might miss negative health outcomes associated with less frequent monitoring, for example if monitoring improves the rate at which AEs are identified and treated; however the model has not been developed to capture any such potential effects.

Excluding strategies that contain bevacizumab, this scenario sees the list-price ICER of extending 3-monthly ranibizumab in BSEs to eyes with VA >6/12 fall to £24,7838 per QALY (from £27,521).

Table 69: Scenario analysis results – OCT only required to inform treatment decisions – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£9,145	4.126			
Beva | 2mo | Treat only BSEs | including at VA > 6/12	£9,752	4.211	£606	0.085	£7,163
Beva | 2mo | Treat any eye | including at VA > 6/12	£11,479	4.337	£1,728	0.126	£13,733
Beva | 1mo | Treat any eye | including at VA > 6/12	£15,164	4.440	£3,685	0.103	£35,737

Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	£37,580	4.488	£22,416	0.048	£466,482
Aflib | 1mo | Treat any eye | including at VA > 6/12	£78,925	4.569	£41,345	0.081	£511,055

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

A final resource use scenario assumes that there is no difference in the number of injections required per year for different anti-VEGF therapies delivered by ostensibly equivalent regimens. In Section J.5.3.5, we detailed the sources of evidence used to inform how many injections are required for each intervention, which suggest that, as an example, monthly ranibizumab and monthly bevacizumab require a slightly different average number of injections per year, despite both being monthly regimens. While this is clinically plausible, the scenario analysis was performed to explore the sensitivity of model results to these injection differentials between alternative therapies. Table 70 shows that our base-case model results are not sensitive to differences in the number of injections between therapies. This is also true when bevacizumab strategies are omitted from the analysis, with the same non-dominated strategies and similar ICERs to the base-case model.

Table 70: Scenario analysis results – equal number of injections for equivalent regimens – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,314	4.069			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,505	4.126	£190	0.057	£3,338
Beva | 2mo | Treat only BSEs | including at VA > 6/12	£11,431	4.211	£926	0.085	£10,942
Beva | 2mo | Treat any eye | including at VA > 6/12	£13,679	4.337	£2,248	0.126	£17,867
Beva | Load+PRN | Treat any eye | including at VA > 6/12	£18,159	4.438	£4,480	0.101	£44,354
Aflib | 1mo | Treat any eye | including at VA > 6/12	£84,403	4.569	£66,244	0.132	£503,068

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Treatment discontinuation scenario

If annual treatment discontinuation rates are equal for all strategies, except for dropouts due to differences in effectiveness (VA declining to ≤25 letters), the cost–utility results are those shown in Table 71. The optimal base-case strategy with 2-monthly bevacizumab remains the most effective strategy with an ICER under £20,000 per QALY. Base-case results with bevacizumab excluded from the analysis are also not meaningfully affected by this scenario analysis. This implies that the model is not particularly sensitive to the treatment discontinuation rates used.

Table 71: Scenario analysis results – equal discontinuation rates – fully incremental analysis, non-dominated strategies shown (at list prices)

	Absolute	*Fully incremental analysis*

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Costs*	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | BSE only | with VA in the range: 6/12 to 6/96	£10,222	4.086			
Beva | 2mo | BSE only | with VA in the range: 6/12 to 6/96	£10,349	4.141	£126	0.055	£2,315
Beva | 2mo | BSE only | including with VA > 6/12	£11,331	4.229	£983	0.088	£11,106
Beva | 2mo | Treat any eye | including with VA > 6/12	£13,733	4.383	£2,401	0.153	£15,660
Beva | Load+PRN | Treat any eye | including with VA > 6/12	£17,456	4.456	£3,724	0.074	£50,592
Beva | 1mo | Treat any eye | including with VA > 6/12	£20,605	4.474	£3,149	0.018	£177,886
Rani | 1mo | Treat any eye | including with VA > 6/12	£55,240	4.479	£34,635	0.005	£7,318,544

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Long-term input scenarios

A set of scenario analyses are included exploring the sensitivity of base-case results to assumptions made regarding long term outcomes. The first of these involves assuming that 2-year RCT data do not exist, such that we have to extrapolate treatment effects, number of injections required, ocular adverse events and long-term VA change from available 1-year data. This scenario explores the extent to which our use of year 2 data influences cost–utility results. While the ordering of strategies changes in places, and total QALYs increase across the board as 2-year RCT results are generally less positive the 1-year results, costs results remain similar to the base-case model and the optimal strategy remains the same (Table 72). This suggests that our use of the available 2-year evidence, maximising our use of RCT data and thereby providing a more complete and informative model, does not dramatically alter cost–utility findings compared with using a simpler set of model inputs using only 1-year evidence.

Table 72: Scenario analysis results – 1-year RCT data only – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£10,116	4.090			
Beva | 2mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£10,270	4.152	£153	0.062	£2,486
Beva | 2mo | Treat only BSEs | including VA > 6/12	£11,149	4.244	£879	0.092	£9,578
Beva | 2mo | Treat any eye | including VA > 6/12	£13,437	4.375	£2,288	0.131	£17,403
Beva | 1mo | Treat any eye | including VA > 6/12	£20,009	4.466	£6,573	0.091	£72,365
Aflib | 1mo | Treat any eye | including VA > 6/12	£85,936	4.662	£65,927	0.197	£335,309

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

The second long-term data scenario explored the effect of changing the reference rate of long-term VA decline in treated eyes. First, it was reduced by using data extracted from

Gillies et al. (2015). This study estimated ranibizumab PRN treatment to be associated with a loss of 0.65 letters per year, on average, following 2 years of treatment. This is a notably slower decline than our base case model input of 2.5 letters per year, derived from the ARMD database (Tufail et al. 2014). This scenario also increases the number of injections in the long-term, to 4.9 per year with ranibizumab PRN. Assuming VA declines at the slower rate causes no change in the cost–utility frontier compared with the base-case results. All treatments become associated with larger QALY gains, because it takes longer for VA to decline following the initial 2-year treatment effects (Table 73). For this reason, strategies that treat BSEs only are slightly less likely to be cost-effective. The ICER of the base-case strategy that provides the highest QALY return at an incremental cost of less than £20,000 is slightly lower (£15,827 here compared with £17,895). If we make a more pessimistic assumption about long-term VA decline, by using the ranibizumab PRN figure of 3.7 letters per year from the SEVEN-UP study (Rofagha et al. 2013), the base-case optimal strategy continues to be optimal, but is much closer to £20,000 per QALY (Table 74). QALYs are reduced in all strategies as VA declines more rapidly, which makes long-term treatment less useful. This scenario also reduces the number of injections in the long-term, to 2.0 injections per year with ranibizumab PRN, but the associated cost reduction is tempered by an increase in low-vision resource use.

Table 73: Scenario analysis results – slower long-term VA decline (Gillies et al. 2015) – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	*Total*		*Incremental*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat BSEs only | with VA in range: 6/12 to 6/96	£9,858	4.108			
Beva | 2mo | Treat BSEs only | with VA in range: 6/12 to 6/96	£10,096	4.157	£238	0.050	£4,786
Beva | 2mo | Treat BSEs only | Extend to treat >6/12	£11,041	4.272	£944	0.114	£8,271
Beva | 2mo | Treat any eye | Extend to treat >6/12	£13,410	4.421	£2,369	0.150	£15,827
Beva | Load+PRN | Treat any eye | Extend to treat >6/12	£17,204	4.520	£3,794	0.099	£38,360
Aflib | 2mo->PRN | Treat any eye | Extend to treat >6/12	£38,330	4.586	£21,126	0.066	£321,357
Aflib | 1mo | Treat any eye | Extend to treat >6/12	£87,629	4.683	£49,299	0.097	£508,162

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 74: Scenario analysis results – more rapid long-term VA decline (Rofagha et al. 2013) – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	*Total*		*Incremental*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat BSEs only | with VA in range: 6/12 to 6/96	£10,586	4.051			
Beva | 2mo | Treat BSEs only | with VA in range: 6/12 to 6/96	£10,770	4.103	£185	0.052	£3,526
Beva | 2mo | Treat BSEs only | Extend to treat >6/12	£11,736	4.179	£966	0.076	£12,649
Beva | 2mo | Treat any eye | Extend to treat >6/12	£13,907	4.294	£2,171	0.114	£19,012
Beva | Load+PRN | Treat any eye | Extend to treat >6/12	£17,615	4.393	£3,707	0.099	£37,340

Aflib | 1mo | Treat any eye | Extend to treat >6/12	£83,372	4.494	£65,757	0.101	£652,402

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

A number of long-term input scenario analyses were performed to explore the assumption that all treatments are equivalent beyond 2 years – the maximum duration of randomised clinical evidence – in terms of resource use, effectiveness or both. The first of these is focused on resource use; it assumes that all treatments require the same number of injections and monitoring appointments as ranibizumab PRN beyond 2 years of treatment. This regimen was selected because it is the treatment upon which our long-term 'reference' VA decline evidence, the ARMD database, was based (Tufail et al. 2014). In this scenario relative treatment effects from the second year of treatment are still maintained for all subsequent years on treatment, as per the base-case model. Results show that by assuming injections and monitoring are equivalent to ranibizumab PRN beyond year 2, the cost-effectiveness of 2-monthly bevacizumab is reduced (Table 75). This is because although the number of injections required per year falls from 5.5 to 3.7, those cost savings are more than offset by the increased monitoring costs associated with a PRN regimen. Only strategies treating only BSEs have ICERs under £20,000, though this now includes monthly bevacizumab. This is because monthly treatment experiences the opposite effect to 2-monthly described above; its total number of clinic visits is reduced, leading to a lower ICER than before. Extending this regimen to worse-seeing eyes has an ICER only marginally higher than £20,000. This is because the better relative effectiveness of monthly treatment is maintained in in the long-term.

In the most comprehensive long-term inputs scenario – combining equal injections, monitoring, effectiveness, and discontinuation rates – the optimal base-case strategy of 2-monthly bevacizumab, including with VA >6/12, has an ICER of £16,750 per QALY gained and remains the optimal decision (Table 76). Delivering monthly bevacizumab injections has an ICER of £22,466 per QALY.

This comprehensive equalisation of long-term model inputs has a notable impact on model results when bevacizumab is excluded from the analysis: 2-monthly ranibizumab for BSEs becomes the most cost-effective strategy (Table 77). In the base-case results, the lowest-intensity (3-monthly) ranibizumab was optimal when bevacizumab was excluded. Here, like the base-ase result, no strategy that treats both better and worse-seeing eyes has a cost-effective ICER.

Table 75: Scenario analysis results – all injection requirements equal to ranibizumab PRN after year 2 – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£11,183	4.128			
Beva | 2mo | Treat only BSEs | including with VA > 6/12	£12,332	4.213	£1,149	0.085	£13,469
Beva | 1mo | Treat only BSEs | including with VA > 6/12	£13,685	4.284	£1,353	0.071	£19,079
Beva | 1mo | Treat any eye | including with VA > 6/12	£17,087	4.454	£3,402	0.170	£20,019
Aflib | 1mo | Treat any eye | including with VA > 6/12	£52,898	4.588	£35,811	0.134	£267,267

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as

needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 76: Scenario analysis results – all injection requirements, treatment effects and discontinuation rates equal to ranibizumab PRN after year 2 – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Fully incremental analysis		
	Costs	QALYs	Costs	QALYs	ICER
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,570	4.136			
Beva | 2mo | Treat only BSEs | including with VA > 6/12	£11,530	4.222	£960	0.087	£11,074
Beva | 1mo | Treat only BSEs | including with VA > 6/12	£13,842	4.360	£2,312	0.138	£16,750
Beva | 1mo | Treat any eye | including with VA > 6/12	£16,117	4.462	£2,275	0.101	£22,466
Aflib | 1mo | Treat any eye | including with VA > 6/12	£48,837	4.501	£32,721	0.039	£839,138

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Table 77: Scenario analysis results – Table 76 analysis, excluding bevacizumab (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Fully incremental analysis		
	Costs	QALYs	Costs	QALYs	ICER
No treatment	£11,895	3.838			
Rani | 2mo | Treat only BSEs | with VA in the range: 6/12 to 6/96	£16,880	4.144	£4,985	0.306	£16,310
Rani | 2mo | Treat only BSEs | including with VA > 6/12	£19,421	4.234	£2,541	0.090	£28,232
Rani | Load+PRN | Treat only BSEs | including with VA > 6/12	£22,768	4.303	£3,347	0.070	£48,094
Rani | Load+PRN | Treat any eye | including with VA > 6/12	£32,043	4.471	£9,275	0.167	£55,381
Rani | 1mo | Treat any eye | including with VA > 6/12	£35,550	4.478	£3,507	0.007	£474,821
Aflib | 1mo | Treat any eye | including with VA > 6/12	£48,837	4.501	£13,287	0.023	£587,417

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Adverse event scenarios

When the rate of ocular AEs for PRN regimens is reduced compared with routine regimens, using a RR of 0.31, results remain very similar to the base-case model (Table 78). This is also true of the base-case results when bevacizumab strategies are excluded from the analysis.

Table 78: Scenario analysis results – fewer ocular AEs for PRN regimens – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Fully incremental analysis		
	Costs	QALYs	Costs	QALYs	ICER

Beva | 3mo | BSE only | Current practice VA range	£8,302	3.668			
Beva | 2mo | BSE only | Current practice VA range	£8,565	3.712	£262	0.045	£5,883
Beva | 2mo | BSE only | Extend to treat >6/12	£9,497	3.787	£932	0.075	£12,381
Beva | 2mo | Any eye | Extend to treat >6/12	£11,670	3.913	£2,173	0.125	£17,332
Beva | Load+PRN | Any eye | Extend to treat >6/12	£16,952	4.001	£5,282	0.088	£59,734
Rani | Load+PRN | Any eye | Extend to treat >6/12	£34,483	4.032	£17,531	0.031	£567,587
Aflib | 1mo | Any eye | Extend to treat >6/12	£76,271	4.104	£41,788	0.071	£585,105

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Increasing the probability of experiencing endophthalmitis associated with treatment with bevacizumab does not have a meaningful impact on results, unless that probability is increased to a level far in excess of the clinical data. For the results in Table 79, the annual probability of endophthalmitis was set to 20% per year for patients receiving bevacizumab (compared with <1% for other anti-VEGF therapies). At this implausible risk of endophthalmitis risk, the ICER for 2-monthly bevacizumab, delivered to better or WSEs and including eye with VA >6/12, only just surpasses £20,000 per QALY. We can therefore be confident that the base-case model results are not sensitive to a potentially different ocular AE profile associated with bevacizumab.

Table 79: Scenario analysis results – 20% annual probability of endophthalmitis due to bevacizumab – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£11,095	3.956			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£11,323	4.013	£228	0.057	£4,012
Beva | 2mo | Treat only BSEs | including with VA >6/12	£12,444	4.098	£1,121	0.085	£13,248
Beva | 2mo | Treat any eye | including with VA >6/12	£15,009	4.224	£2,564	0.126	£20,382
Beva | Load+PRN | Treat any eye | including with VA >6/12	£18,797	4.332	£3,788	0.108	£35,155
Rani | Load+PRN | Treat any eye | including with VA >6/12	£32,023	4.476	£13,226	0.144	£91,788
Aflib | 2mo->PRN | Treat any eye | including with VA >6/12	£37,979	4.488	£5,956	0.012	£483,462
Aflib | 1mo | Treat any eye | including with VA >6/12	£85,243	4.569	£47,264	0.081	£584,215

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Our model assumes that 50% of patients experience a 100% utility loss for 1 day, on the day of treatment, to reflect potential pre-injection anxiety and injection-related pain. This was based on advice from the guideline committee. The proportion of patients affected was varied from 0% (such that there is no decrement at all) to 100% (such that all patients on

977 treatment experience the 1-day discomfort effect). This variation did not feature on any of the
978 OSA diagrams presented above, and is not something to which model conclusions are
979 sensitive.

980 **Quality of life scenarios**

981 Using the alternative scaling factor for estimating the relative impact of VA change in the
982 WSE compared with the BSE (0.4285 instead of 0.3), as suggested by the Evidence Review
983 Group in NICE TA 346, has minimal impact on base-case cost–utility results (Table 80),
984 including when bevacizumab strategies are removed from the analysis.

985 Using utility weights reported by Brown et al. (2000) to estimate health state utilities for our
986 model VA health states (see Table 43), and assuming that quality of life is not affected by the
987 VA of WSEs, has a substantial impact (Table 81). Here, the QALY gains associated with
988 treating eyes regardless of whether they are better or worse-seeing, compared with BSEs
989 only, are much reduced. It is therefore much less likely that removing the BSE only restriction
990 will be cost-effective; the optimal base-case strategy has an ICER of £60,415 per QALY
991 gained in this scenario. Only strategies that treat just BSEs have ICERs below £20,000.
992 When bevacizumab strategies are removed from this scenario, the ICER for 3-monthly
993 ranibizumab for BSEs according to current practice VA thresholds is £30,297 per QALY
994 gained compared with doing nothing.

995 **Table 80: Scenario analysis results – TA 346 ERG utility scaling factor for worse-**
996 **seeing eye – fully incremental analysis, non-dominated strategies shown**
997 **(at list prices)**

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | BSE only | Current practice VA range	£8,302	3.548			
Beva | 2mo | BSE only | Current practice VA range	£8,565	3.590	£262	0.042	£6,296
Beva | 2mo | BSE only | Extend to treat >6/12	£9,497	3.665	£932	0.075	£12,370
Beva | 2mo | Any eye | Extend to treat >6/12	£11,670	3.815	£2,173	0.150	£14,508
Beva | Load+PRN | Any eye | Extend to treat >6/12	£17,015	3.903	£5,345	0.088	£60,833
Rani | Load+PRN | Any eye | Extend to treat >6/12	£34,531	3.934	£17,516	0.031	£563,166
Aflib | 1mo | Any eye | Extend to treat >6/12	£76,271	4.007	£41,740	0.074	£567,606

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

998 **Table 81: Scenario analysis results – utilities depend on better-seeing eye, Brown et**
999 **al. (2000) values – fully incremental analysis, non-dominated strategies**
1000 **shown (at list prices)**

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | BSE only | Current practice VA range	£8,302	3.410			
Beva | 2mo | BSE only | Current practice VA range	£8,565	3.444	£262	0.034	£7,783
Beva | 2mo | BSE only | Extend to treat >6/12	£9,497	3.501	£932	0.057	£16,277
Beva | 2mo | Any eye | Extend to treat >6/12	£11,670	3.537	£2,173	0.036	£60,415
Beva | Load+PRN | Any eye | Extend to treat >6/12	£17,015	3.592	£5,345	0.055	£96,829
Rani | Load+PRN | Any eye | Extend to treat >6/12	£34,531	3.612	£17,516	0.019	£903,684

Aflib | 1mo | Any eye | Extend to treat >6/12	£76,271	3.654	£41,740	0.042	£986,711

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Baseline data scenario

Reanalysing our baseline VA data in a way that treats the Liverpool and Sheffield data as a single combined sample, rather than as 2 unique and equal samples, has no notable impact on the base-case cost–utility results (Table 82). There is also no notable impact on base-case results when the unlicensed bevacizumab regimens are excluded from the analysis.

Table 82: Scenario analysis results – baseline VA data treated as 1 sample – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Fully incremental analysis		
	Costs	QALYs	Costs	QALYs	ICER
Beva | 3mo | Treat only BSEs | Current practice VA range	£10,641	4.032			
Beva | 2mo | Treat only BSEs | Current practice VA range	£10,812	4.093	£171	0.060	£2,829
Beva | 2mo | Treat only BSEs | including with VA > 6/12	£11,701	4.172	£889	0.079	£11,261
Beva | 2mo | Treat any eye | including with VA > 6/12	£13,905	4.305	£2,203	0.133	£16,581
Beva | Load+PRN | Treat any eye | including with VA > 6/12	£17,573	4.408	£3,668	0.103	£35,656
Rani | Load+PRN | Treat any eye | including with VA > 6/12	£32,171	4.435	£14,599	0.027	£536,835
Aflib | 1mo | Treat any eye | including with VA > 6/12	£85,207	4.525	£53,035	0.090	£588,473

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Geographic atrophy scenario

Key results do not change when the fellow eyes that do no have late AMD (wet active) at baseline are able to develop untreatable GA. The base-case optimal remains the most cost-effective option (Table 83). The main effect on results is apparent in the total QALY and cost values. Total QALYs are lower for all strategies, as a proportion of eyes develop GA, become untreatable and experience significant vision loss. For the lower-cost and/or less-intensive treatment strategies, total costs increase due to more people incurring costs associated with low-vision sooner. For higher-cost strategies, total costs actually fall slightly, because the increase in low-vision costs and more than offset by the treatment costs avoided when an eye develops untreatable GA. Incremental results do not change dramatically, however, such that base-case conclusions remain the same. This is also the case when comparing aflibercept 2-monthly then PRN with ranibizumab PRN, and when considering the cost-effectiveness of extending treatment to eyes with VA above 6/12.

Table 83: Scenario analysis results – fellow eyes can develop geographic atrophy – fully incremental analysis, non-dominated strategies shown (at list prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	Total		Incremental		
	Costs	QALYs	Costs	QALYs	ICER

Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£12,412	3.902			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£12,565	3.967	£154	0.065	£2,346
Beva | 2mo | Treat only BSEs | including VA >6/12	£13,265	4.047	£700	0.079	£8,810
Beva | 2mo | Treat any eye | including VA >6/12	£15,241	4.186	£1,975	0.139	£14,229
Beva | Load+PRN | Treat any eye | including VA >6/12	£18,720	4.293	£3,479	0.107	£32,504
Rani | Load+PRN | Treat any eye | including VA >6/12	£32,869	4.332	£14,149	0.039	£361,270
Aflib | 1mo | Treat any eye | including VA >6/12	£83,751	4.411	£50,882	0.080	£639,877

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

J.6.5 Patient access scheme results

All results from the new model presented above have used the published list prices of aflibercept and ranibizumab. However, both these medicines are made available to the NHS at a confidentially discounted price agreed in a Patient Access Scheme (PAS). Therefore, all analyses were also evaluated using their PAS prices, with the results presented to the guideline committee. However, the confidentiality of the PAS prices may be compromised if empirical results are presented with the economic model itself. Results are therefore presented descriptively in this section.

All treatments included

The base-case result was unchanged; 2-monthly bevacizumab remains cost effective compared with both aflibercept and ranibizumab even at theirlower PAS prices (Table 84). Ranibizumab PRN is no longer on the cost–utility frontier, and the aflibercept regimens that are on the frontier continue to have ICERs far in excess of what is typically considered to be a reasonable use of NHS resources.

Table 84: Base-case deterministic cost–utility results – all treatments included – fully incremental analysis, non-dominated strategies shown (at PAS prices)

Strategy Treatment | Regimen | Eyes to treat | VA range to treat	*Total*		*Incremental*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Beva | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,313	4.069			
Beva | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	£10,510	4.126	£197	0.057	£3,458
Beva | 2mo | Treat only BSEs | including VA >6/12	£11,437	4.211	£927	0.085	£10,955
Beva | 2mo | Treat any eye | including VA >6/12	£13,688	4.337	£2,251	0.126	£17,895
Beva | Load+PRN | Treat any eye | including VA >6/12	£17,395	4.445	£3,707	0.108	£34,405
Aflib | 2mo->PRN | Treat any eye | including VA >6/12	[redacted]	4.488	[redacted]	0.043	>£30,000
Aflib | 1mo | Treat any eye | including VA >6/12	[redacted]	4.569	[redacted]	0.081	>£30,000

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio;

Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

The main conclusions remain the same in all analyses containing bevacizumab; therefore, the PAS results described hereafter focus on those in which bevacizumab was omitted from the decision space.

Excluding bevacizumab

When bevacizumab is removed from the decision space, low-intensity ranibizumab used to treat only BSEs remains potentially cost effective (Table 85). However, extending treatment eligibility to permit treatment in WSEs remained associated with ICERs in excess of £20,000 per QALY gained.

Table 85: Base-case deterministic cost–utility results – excluding bevacizumab – fully incremental analysis, non-dominated strategies shown (at PAS prices)

Strategy *Treatment | Regimen | Eyes to treat | VA range to treat*	*Total*		*Incremental*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
No treatment	£11,936	3.842			
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	[redacted]	4.078	[redacted]	0.236	<£20,000
Rani | 3mo | Treat only BSEs | including VA >6/12	[redacted]	4.154	[redacted]	0.077	£20-30,000
Aflib | 2mo->PRN | Treat only BSEs | including VA >6/12	[redacted]	4.307	[redacted]	0.152	>£30,000
Rani | Load+PRN | Treat any eye | including VA >6/12	[redacted]	4.476	[redacted]	0.169	>£30,000
Aflib | 2mo->PRN || Treat any eye | including VA >6/12	[redacted]	4.488	[redacted]	0.012	>£30,000
Aflib | 1mo | Treat any eye | including VA >6/12	[redacted]	4.569	[redacted]	0.081	>£30,000

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Product label regimens only

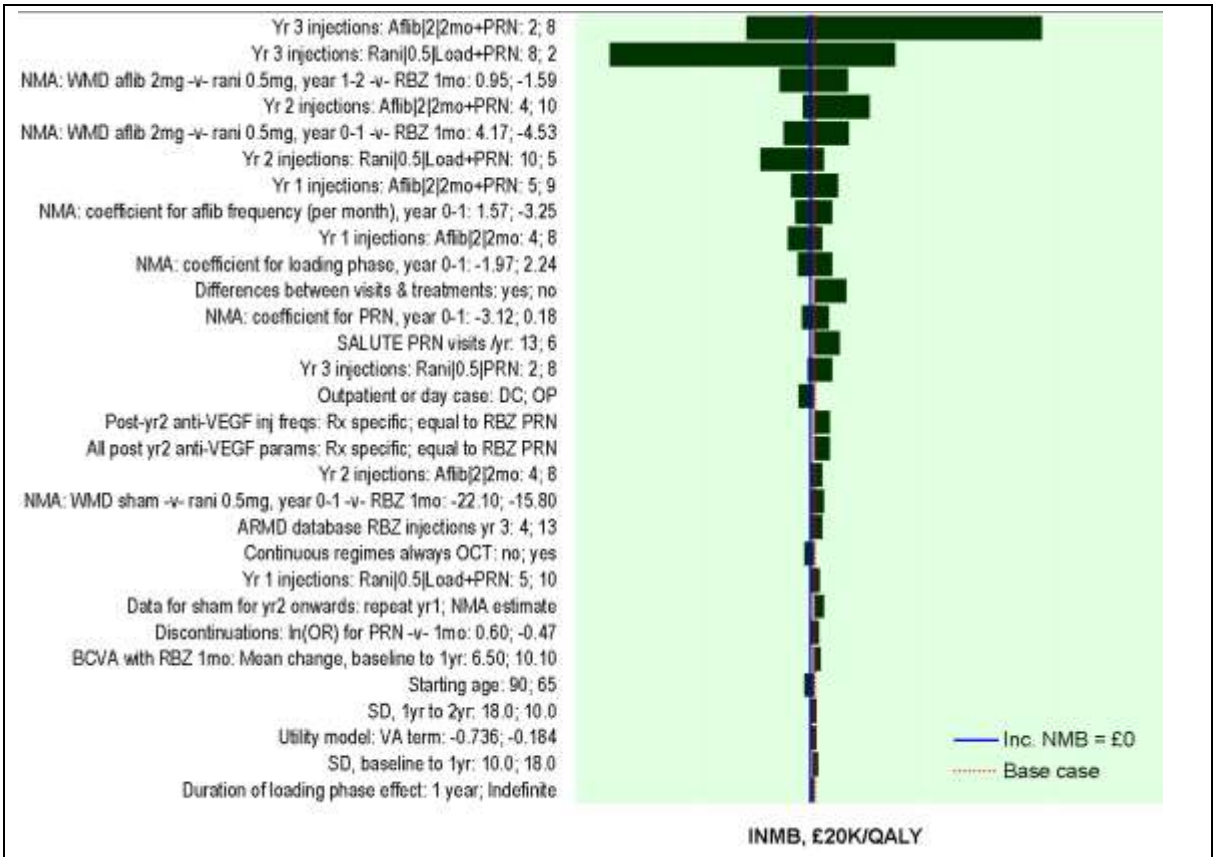
In this scenario at list prices, no interventions had an ICER below £20,000. However, when evaluated at the discounted prices, aflibercept given by the VIEW study protocol, but only to BSEs, achieves an ICER below £20,000 (Table 86). Perhaps more importantly, the PAS price analyses show there to be very little to choose between aflibercept and ranibizumab when the decision space was limited to their commonly-used product label regimens (in particular, 2-monthly for 1 year then PRN, and loading then PRN, respectively). When providing no treatment is omitted, comparing these aflibercept and ranibizumab PRN regimens at the current practice VA range and extending to VA >6/12 strategies (i.e. 4 strategies in total), the PSA suggests that there is large uncertainty regarding which regimen is the most likely to be optimal at QALY values of £20,000 (all <50%), such that no option was unequivocally cost-effective over the others.

This similarity was reinforced by one-way sensitivity analyses using PAS prices (Figure 33). Again comparing their commonly used PRN regimens, many parameters were found to have the potential to change the cost-effectiveness decision between aflibercept and ranibizumab. This does not reflect a lack of robustness in the base-case model; rather, it shows that there is very little to choose between these 2 strategies when evaluated at their true NHS prices. Ranibizumab being cost effective over aflibercept was found to be a more robust finding when evaluated at their higher, list prices (Figure 30).

Table 86: Base-case deterministic cost–utility results – product label regimens – fully incremental analysis, non-dominated strategies shown (at PAS prices)

Strategy Treatment | Regimen | Eyes treated | VA range treated	Absolute		Fully incremental analysis		
	Costs	QALYs	Costs	QALYs	ICER
No treatment	£11,936	3.842			
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	[redacted]	4.201	[redacted]	0.359	<£20,000
Aflib | 2mo->PRN | Treat only BSEs | including VA >6/12	[redacted]	4.307	[redacted]	0.106	£20-30,000
Rani | Load+PRN | Treat any eye | including VA >6/12	[redacted]	4.476	[redacted]	0.169	>£30,000
Aflib | 2mo->PRN || Treat any eye | including VA >6/12	[redacted]	4.488	[redacted]	0.012	>£30,000

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.



Scale deliberately omitted to preserve confidentiality of PAS prices

Figure 33: Tornado diagram – ranibizumab 3-month loading phase then PRN vs. aflibercept 2-monthly for 1 year then PRN – BSEs and WSEs treated if VA is between 6/12 and 6/96 – 30 most influential parameters (at PAS prices)

Focus on: treatment frequency

The base-case, list-price conclusions regarding treatment frequency are unchanged when the PAS prices are used. If both BSEs and WSEs are eligible for treatment then 2-monthly ranibizumab injections are not cost-effective compared with 3-monthly injections. This is the

case regardless of whether treatment eligibility is extended to include eyes with VA better than 6/12.

Focus on: PRN regimens

All base-case, list-price conclusions regarding the cost-effectiveness of PRN regimens remain unchanged when the PAS prices are used. Low-frequency continuous ranibizumab remains cost effective compared with PRN ranibizumab. For aflibercept, moving onto a PRN regimen after 1 year remains cost-effective (dominant) compared with remaining on regular 2-monthly injections. The ICER of a 3-month loading phase compared with going straight onto PRN ranibizumab remains under £20,000 per QALY gained.

Focus on: extending treatment eligibility to eyes with VA better than 6/12

Extending treatment to eyes with VA better than 6/12 is the area in which the confidential aflibercept and ranibizumab discounts has the most influence on cost-effectiveness outcomes (Table 87). At list prices, extending treatment was associated with an ICER below £20,000 with bevacizumab, and with ranibizumab 3-monthly or PRN. At its PAS price, 2-monthly ranibizumab also achieves an ICER under £20,000 per QALY gained. Additionally, when the lower price is used for aflibercept, its ICER falls below £20,000 when given every 2-months, regardless of whether or not this switches to PRN after 1 year. However, for strategies that restrict treatment to only BSEs, the base-case results are unchanged, with ICERs above £20,000 for extending treatment compared with not doing so.

Table 87: Head-to-head cost–utility results of extending treatment eligibility to eyes with VA >6/12 compared with not extending treatment eligibility (at PAS prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Aflibercept, 2-monthly					
Aflib | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.365	-	-	-
Aflib | 2mo | Treat any eye | including at VA > 6/12	[redacted]	4.442	[redacted]	0.077	<£20,000
Aflibercept, 2-monthly then PRN					
Aflib | 2mo->PRN | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.408	-	-	-
Aflib | 2mo->PRN | Treat any eye | including at VA > 6/12	[redacted]	4.488	[redacted]	0.080	<£20,000
Ranibizumab, 3-monthly					
Rani | 3mo | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.192	-	-	-
Rani | 3mo | Treat any eye | including at VA > 6/12	[redacted]	4.253	[redacted]	0.060	<£20,000
Ranibizumab, 2-monthly					
Rani | 2mo | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.297	-	-	-
Rani | 2mo | Treat any eye | including at VA > 6/12	[redacted]	4.368	[redacted]	0.070	<£20,000
Ranibizumab, loading then PRN					
Rani | Load+PRN | Treat any eye | with VA in range: 6/12 to 6/96	[redacted]	4.397	-	-	-
Rani | Load+PRN | Treat any eye | including at VA > 6/12	[redacted]	4.476	[redacted]	0.079	<£20,000

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio;

Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

Focus on: extending treatment eligibility to eyes with VA worse than 6/96

The base-case, list-price conclusion was that extending treatment to eyes with VA worse than 6/96 is not cost-effective, compared with not doing so. This is also the case when the confidential, lower prices are used. However, when treatment is restricted to only BSEs, extending treatment with aflibercept or ranibizumab is associated with an ICER below £20,000 per QALY gained (Table 88). In particular, extending treatment this way with aflibercept given by the VIEW regimen, and 2 or 3-monthly ranibizumab, becomes highly cost-effective. Equivalent ICERs exceeded £20,000 at their list prices. Extending treatment this way is, therefore, likely to be cost-effective compared with not doing so, as long as only BSEs are treated.

Table 88: Head-to-head cost–utility results of extending treatment eligibility to eyes with VA ≤6/96 compared with not extending treatment eligibility – BSEs only (at PAS prices)

Strategy *Treatment | Regimen | Eyes treated | VA range treated*	*Absolute*		*Fully incremental analysis*		
	Costs	*QALYs*	*Costs*	*QALYs*	*ICER*
Aflibercept, 2-monthly then PRN					
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	[redacted]	4.201	-	-	-
Aflib | 2mo->PRN | Treat only BSEs | Extend for VA ≤6/96	[redacted]	4.205	[redacted]	0.004	<£20,000
Ranibizumab, 3-monthly					
Rani | 3mo | Treat only BSEs | including VA <6/96	[redacted]	4.078	-	-	-
Rani | 3mo | Treat only BSEs | with VA in range: 6/12 to 6/96	[redacted]	4.082	[redacted]	0.004	<£20,000
Ranibizumab, 2-monthly					
Rani | 2mo | Treat only BSEs | with VA in range: 6/12 to 6/96	[redacted]	4.141	-	-	-
Rani | 2mo | Treat only BSEs | including VA <6/96	[redacted]	4.143	[redacted]	0.003	<£20,000
Ranibizumab, loading then PRN					
Rani | Load+PRN | Treat only BSEs | with VA in range: 6/12 to 6/96	[redacted]	4.196	-	-	-
Rani | Load+PRN | Treat only BSEs | Extend for VA <6/96	[redacted]	4.200	[redacted]	0.004	<£20,000

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

J.5.47 Discussion

J.5.51 Principal findings

Cost–utility results from the new model suggest that 52 out of 137 comprehensive strategies are superior to providing no treatment for AMD, at an opportunity cost of £20,000 per 1 QALY. Of these 52 strategies, 48 involve bevacizumab as the active therapy. The following strategy is optimal, when 1 QALY is valued at £20,000 or £30,000:

- Bevacizumab;
- given continuously, at 2-month intervals;
- used to treat all affected eyes, regardless of whether they are the better or worse-seeing eye;

- and extending treatment eligibility to include eyes with VA better than 6/12.

However, bevacizumab is not licensed for intraocular use for late AMD (wet active).

With strategies that permit both BSEs and WSEs to receive treatment, it is not cost effective to extend treatment eligibility to eyes with VA worse than 6/96. Doing so would lead to the treatment of a significant number of WSEs, which does not produce substantive health gains because quality of life is much more closely linked to VA in BSEs. Extending treatment to eyes with VA better than 6/12 is optimal compared with not doing so, including with aflibercept and ranibizumab when evaluated at their confidential prices.

If ranibizumab or aflibercept are used, our analysis suggests that they should be used only to treat BSEs, with the longest possible treatment intervals. Permitting the treatment of WSEs with these treatments does not provide sufficient QALY gains relative to the additional costs of doing so, largely attributable to the cost of the active therapy, which holds true when evaluated at their discounted prices. Furthermore, if only BSEs are to be considered for treatment, then eligibility should not be extended to include eyes with VA better than 6/12. However, it may be cost effective to treat eyes with VA worse than 6/96, as this would only apply to people whose BSEs have VA of this level. Treatment of such eyes would provide sufficient benefit to the patient to represent value for money. Our results also suggest that PDT is highly unlikely to be cost effective, even relative to providing no treatment.

Our results indicate that, when evaluated at their list prices, ranibizumab is likely to be cost effective compared with aflibercept if both are given according to their typical PRN regimens. In this analysis, if BSE-only strategies are omitted, then it is 83.9% likely that a strategy which includes the ranibizumab regimen has an ICER below £20,000 compared with the aflibercept regimen (2-monthly injections for 1 year, then PRN). In practice, both aflibercept and ranibizumab are subject to confidential PAS agreements, meaning the price paid by the NHS is lower than the list price. Cost–utility analyses using PAS prices showed very little difference in the cost effectiveness of the 2 strategies.

J.5.2 Strengths of the analysis

We have sought to develop a flexible model that can support a number of review questions simultaneously, and have used the expert guidance of the Guideline Committee at all stages. The model has a number of particular strengths, which distinguish it from previous cost–utility models in AMD.

Firstly, the new model is explicitly a two-eye model. Most previous models have been single-eye models, in which the fellow eye plays a peripheral role and, typically, has no possibility of developing AMD itself. Single-eye models can therefore only hope to tell half of the story of a condition that can, and often does, affect both eyes. In our model, both eyes of every patient are simulated independently. The fellow eye can enter the model with neovascular AMD or, if not, can develop it over time. Treatment of the fellow eye can occur, either alongside or after the first eye, and its visual acuity is modelled over time. This has important implications for the individual's quality of life, which is more closely linked to visual acuity in the BSE than the WSE.

The model has a lifetime horizon, and uses available long-term follow-up data to estimate treatment effects beyond the two years of randomised trial evidence typically available. This again makes the model a more realistic characterisation of AMD than many previous analyses, which had short-term time horizons or made simplistic, blanket assumptions about long-term effects.

We have used the most recently available data, included in a synthesis of RCTs used to model relative treatment effects and discontinuation. This has allowed us to estimate the relative effect of different components of a potential treatment – the drug used, the dosing frequency, and whether an intensive initial loading phase is given. The model can use the

outputs of this NMA to simulate the effects, and then health economic outcomes, associated with a wide range of treatment regimens, including some that have no clinical evidence (e.g. 2-monthly ranibizumab), meaning it is not restricted to modelling interventions that have been evaluated in trials. These treatment effects are applied to a baseline patient cohort distributed between VA health states using current data from 2 hospitals in England. Our baseline population is therefore likely to be more representative of UK clinical practice than if we were relying on baseline data from clinical trials.

The outputs of our NMA are used to estimate transition probabilities between 15-letter VA health states. However, we have diverted from an assumption that is common of previous cost–utility models – that the probability of moving up (or down) by one 15-letter state is the same as the probability of gaining (or losing) 15 letters. We have shown that this simplifying assumption is incorrect. If an eye in particular 15-letter VA-range state is expected to be situated at the midpoint of that range, then its probability of moving up to the next state is in fact equal to the probability of gaining between 7.5 and 22.5 letters. The probability of moving up by 2 health states is equal to the probability of gaining more than 22.5 letters. These assumptions are used in our calculation of transition probabilities.

Lastly, our modelling includes a large number of strategies. Each strategy is composed of 4 parts: 2 patient-level decisions regarding the drug and dosing frequency, and two population-level decisions regarding whether treatment should be restricted to BSEs only and what levels of VA should (and should not) be treated. There are 20 drug and regimen combinations, two potential BSE decisions, four potential VA treatment threshold decisions, and 1 sham arm, equating to 161 unique strategies in total. Previous cost–utility models have focused on only a few components of these strategies, typically comparing different drugs and/or different dosing regimens. Very few have considered the cost effectiveness of treating eyes with different levels of VA and, to our knowledge, none have compared treating only BSEs with treating any eye. Comparing treating any eye with 'no treatment' runs counter to the principles of incremental cost-effectiveness analysis, by missing the potential intermediate step of treating just 1 eye. Consequently, we assert that all of these components are important aspects of any treatment decision, and that all possible combinations of them should all be compared in a fully incremental analysis. To our knowledge, this model is the first that is comprehensive and flexible enough to do so.

J.2.3 Weaknesses of the analysis

The economic model contains a number of potential limitations, over and above the usual modelling caveat that no model can perfectly represent or predict of reality. These limitations, described below, should be considered during interpretation of its results. All potential limitations were presented to, or discussed with, the guideline committee during the guideline development process, to ensure that none fundamentally undermined the model results.

Network meta-analysis and transition probabilities

The methodology used for our NMA has allowed us to estimate relative treatment effects for each component of a potential intervention. This in turn allows us to simulate interventions for which there is currently no clinical evidence (for example, ranibizumab given every 2 months). Doing so makes the implicit assumption that the various relative effects are independent of one another; for example, the impact attributable to 'TREX' is the same when aflibercept, ranibizumab or bevacizumab are used. This will be a potential simplification if treatment effects are in fact interdependent – say, if the effect attributable to 'treat-and-extend dosing' varies depending on whether the drug being given this way is aflibercept, ranibizumab or bevacizumab. However, we found that synthesis models that assumed effect modifiers are shared between agents fitted the empirical data at least as well – and frequently better – than models that treated every combination of agent and regimen separately (see appendix G). This made it credible to extend inference to include the simulation of some interventions that have not been evaluated in trials. The benefit of being

able to do this was deemed to outweigh the potential simplification, particularly as the guideline committee was satisfied that relative effects can be assumed to be independent of one another.

A potential limitation of our use of mean VA differences to inform the distribution of patients between categorical VA health states is that it is necessary to place those mean changes on an underlying distribution. We do not have evidence of, or data to estimate, the true distribution, and have therefore made the simplification that mean VA changes are normally distributed, as other researchers have before. In the absence of alternative evidence, this allows us to move from mean changes to transition probabilities between our categorical health states. Another assumption made as part of that process is that all eyes are, on average, located at the midpoint of their 15-letter VA health state. This means that the probability of moving up by one state is the probability of gaining between 7.5 and 22.5 letters, on average. This is a simplification of reality; if we know that the overall distribution of presenting eyes is non-uniform, then we can be reasonably certain that the distribution of patients *within* any particular 15-letter range is skewed towards the mean of the overall distribution. However, estimating different transition probabilities for all possible distributions of patients within a health state is an impractical task that would require far more data than are available to us.

Long-term treatment effects

The model is a lifetime model, with treatment permitted to continue for longer than 2 years. However, like previous cost–utility models that have estimated long-term effects, some simplifying assumptions have been necessary to do so. The first is that our treatment relative treatment effects estimated for the second year of treatment are assumed to persist for all future years of treatment. These effects are much smaller than those for the first year of treatment; clinical evidence shows that the majority of VA change occurs in year 1, and it would be incorrect to apply this large effect for all future years.

Secondly, these long-term relative effects must be applied to some reference level of long-term VA change. We have used observational UK data on eyes treated with ranibizumab PRN, the ARMD database (Tufail et al. 2014), to inform this parameter. The study found that patients treated with ranibizumab PRN lost, on average, 2.5 letters in their third year of treatment, and received 3.7 injections. In our model, this is the reference VA change, after year 2, to which all relative treatment effects are anchored. However, the Guideline Committee were satisfied that this is a reasonable method for estimating long term treatment outcomes. A complication of this approach was that the ARMD study does not provide a suitable standard deviation for this third-year VA change. Our method require a standard deviation to map a mean change onto an estimated transition probabilities between VA health states. The CATT trial, of ranibizumab PRN, does provides a suitable standard deviation; therefore this is used as a reasonable approximate value. However, we cannot verify how close it is to the unpublished 'true' standard deviation of the ARMD data.

Finally, like anti-VEGF treatments, the long-term effectiveness of PDT is also anchored to the ARMD dataset's ranibizumab PRN data. It is unclear whether this biases in favour of PDT or against PDT. It may be optimistic given 2 year superiority of anti-VEGFs (see J.5.3.3); it may be pessimistic given the VA plateau observed after year 2 in TAP trial 5-year follow up (Kaiser et al. 2009). However, we are confident that PDT is highly unlikely to be cost effective at any threshold opportunity cost per QALY, meaning this assumption is unlikely to affect decision making. An alternative approach is take from long-term transition probabilities on the sham injections arm; they are fixed at their 'year 1 to year 2' values, in order to produces a stable projected natural history of VA decline.

Fellow eyes

As a two-eye model, it was necessary to estimate what happens to VA in potentially non-neovascular fellow eyes. We obtained UK data regarding the baseline VA of fellow eyes in people who presented with unilateral neovascular AMD. However, we were not able to identify any data informing how VA changes over time in those eyes. We therefore assume the VA of these eyes remains constant, such that they remain in the same VA health state. A previous cost–utility analysis, by Butt et al. (2015), made the same assumption. This will not be true of all patients; some may experience substantial vision loss in their unaffected eye, for example due to other ocular pathologies or trauma. The Guideline Committee advised that the proportion of patients who experience extensive vision loss in their unaffected eye is very low, therefore our assumption is likely to be a reasonable simplification. A fellow eye will be subject to VA change, and therefore transitions between VA health states, if it is neovascular at baseline or becomes neovascular over time.

Explicitly modelling 2 eyes allowed us to explore the effect of a population-level strategy whereby only BSEs are eligible for treatment. An artefact of this is that it is mathematically possible for the BSE and WSE to switch during a patient simulation, meaning the eye eligible for treatment changes, and this happens in a small number of patient simulations. Here, an eye may be treated, then have a break from treatment (due to becoming the WSE), then later resume treatment again. We do not have evidence of the impact of pauses in treatment like this; the second round treatment effect might be higher, lower, or remain the same as the first round. In the absence of evidence we assume that BSE-only strategies will identify the BSE at presentation, and will go on to treat only that eye, even if it goes on to become the WSE. This represents a simplification; a more complete way of modelling BSE-only strategies would be to allow the eye being treated to change if BSE and WSE switch around. However, this would require additional data that are not currently available to us. In any case, it is highly unlikely that a treated eye will become worse than the untreated eye. In practice, in rare cases where the VA of a WSE would be deteriorating at a slower rate than the treated BSE, it is likely that the WSE possesses different or additional pathology than the treated eye, such that it would not be treated in the same way anyway. The scenario is made mathematically possible only by modelling both eyes independently, but will occur in only a very small proportion of patient simulations, such that we are confident it will not materially affect our base-case results which are the average of 2,000,000 patient simulations per strategy.

Resource use

In terms of modelling inputs to inform resource use, the most important model input – aside from the price of treatments – is the number of injections required. This dictates the number of hospital appointments required, the number of vials needed, and the number of OCT examinations performed. However, the number of injections is not a widely reported intermediate clinical outcome, meaning some injection frequencies have necessarily been estimated, based on the data that are available (see Section J.5.3.5). This is particularly true of those drug and regimen combinations that do not presently exist, which are simulated by the model. These have been reviewed, discussed and accepted by the Guideline Committee, with the Committee's advice used to refine the parameters where required.

The Guideline Committee also advised that appointments to treat bilateral neovascular AMD will require more resource than appointments to treat just 1 eye. However, committee members explained that doubling the appointment cost would be an overestimate, as many tasks can be performed relatively quickly together; an attendance cost multiplier of 1.5 was suggested, and is used in the model. This is likely to overestimate the cost of injection appointments, as the mean NHS reference cost for an outpatient attendance will capture some attendances that were used to treat two eyes. However, the NHS reference unit cost is likely to be sufficiently broad in scope that the differential effect of treating 2 eyes for

neovascular AMD, compared with just 1 eye, is unlikely to have dramatically distorted its mean value.

Adverse events

The model uses adverse event rates for ranibizumab and bevacizumab (pooled), and assumes aflibercept to have equal event rates. Aflibercept is recognised as having an equivalent safety profile. This simplification, acknowledged by the Guideline Committee, allows us to use the large amount of safety evidence for ranibizumab and bevacizumab to inform adverse event rates.

The model includes no background incidence of adverse events; all events that occur only to patients receiving treatment. This is a plausible assumption for ocular adverse events and those associated with PDT, given that these are likely to be directly related to the treatment given. It is less plausible for non-ocular events, namely gastrointestinal disorders and stroke. People may experience these events without treatment, and as such, the model would ideally apply a background incidence rate to patients who are not being treated. However, we are confident that these are minor assumptions to have made. Adverse events do not play an important role in determining model outcomes, as shown by adverse event parameters featuring little in the tornado diagrams in Section J.5.6.3.

J.5.7.4 Comparison with other CUAs

In terms of headline messages, our modelling results are consistent with those published previously: cost–utility analyses that included a bevacizumab treatment arm found it to be the cost-effective intervention, and our model comes to the same conclusion. Our model is also consistent with the common finding among previous analyses that PDT is not cost effective. However, at face value, our results differ from previous analyses in a few of notable ways.

Firstly, earlier cost–utility analyses comparing a PRN regimen with a continuous treatment regimen have typically found the PRN strategy to be cost effective (Dakin et al. 2014; Elshout et al. 2014; Stein et al. 2014; Panchmatia et al. 2016). Our model partially concurs with this result: previous cost–utility analyses have largely compared PRN treatment with just 1 continuous regimen (monthly treatment) and, when our model looks at this comparison specifically, its results are consistent with the literature (see Table 89). However, our model also compared PRN treatments with other continuous regimens – 2 or 3-monthly – and it typically finds thes to be cost effective compared with their discontinuous counterparts. This is easily explained: the effectiveness estimates from our NMA suggest that PRN effectiveness is fairly similar to continuous 2-monthly treatment, and the number of injections per year is also similar. However, PRN regimens require additional appointments for monitoring, because an OCT examination is used to determine whether treatment is required. Such appointments do not occur with continuous regimens, where OCTs occur only at scheduled treatment visits. It is therefore logical that 2- or 3-monthly treatment regimens are likely to be optimal compared with PRN regimens.

Secondly, previous models – such as those used in NICE TAs – have determined that aflibercept and ranibizumab – given to BSEs and WSEs using their common regimens – are cost-effective interventions. In the case of TA 294, this is understandable, as aflibercept was compared with ranibizumab, finding little to choose between the 2 – a conclusion with which we concur (once the PAS discounts available for each agent are applied). A summary of the differences and similarities between our model and previous analyses that compared aflibercept with ranibizumab is presented in Table 90. In the earlier TA 155, ranibizumab was compared with PDT and sham injections; in our modelling results, it is not cost effective compared with these alternatives. This is because our analysis is far removed from the modelling work undertaken for TA 155. Since TA 155, more RCT (and observational) evidence has become available; in the present model, RCT data are synthesised to inform treatment effect inputs, and we used mean VA changes, from which the distribution of eyes

by VA is estimated. A NMA has also been calculated to provide treatment discontinuation inputs. Our model is a lifetime analysis, with long-term outcomes explicitly captured using the available long-term evidence. Furthermore, our model is explicitly a 2-eye model, in which both eyes can develop neovascular AMD independent, and be treated separately. The VA of each eye can change over time and influence the individual's quality of life, differentially depending on whether the eye is the better- or worse-seeing of the two. Our model also moves away from the assumption made in previous models – often implicitly, sometimes explicitly – including the assessment group model for TA 155, that the probability of a 15-letter change in VA equates to the probability of moving by one 15-letter VA health state. This simplification is mathematically incorrect and, to our knowledge, ours is the first model with a Markov structure to correct it.

Furthermore, our model results necessarily differ from previous studies because of the number of strategies included. This is the first model to treat comprehensive, population-level treatment decisions – the drug, dosing frequency, whether to treat the BSE only, and whether to extend the VA treatment threshold range – as all components of one strategy; one that should be compared with all other possible combinations of those components. Previous models have typically compared a small number of alternatives, such as ranibizumab with aflibercept, or ranibizumab with no treatment. In our model, these head-to-head comparisons produce ICERs that are not dissimilar to previous analyses(Table 89, Table 90 and Table 91). However, for the reasons expressed above, we argue that many such comparisons are inappropriate, if well established principles of incremental cost-effectiveness analysis are adopted.

In terms of differences between the new model and previous CUAs in their cost and QALY results, these can typically be explained by alternative clinical inputs, time horizons, or assumptions about long-term treatment effects (see Table 89 and Table 90). For example, a recent 2-eye, lifetime, patient-level simulation model comparing PRN aflibercept and ranibizumab reported around 5.1 total QALYs, in analyses where quality of life affected by BCVA in both eyes (Claxton et al. 2016). This result suggests these PRN treatments produce around 0.7 more QALYs than is predicted by our model. One key reason for this difference is likely to be the published study's assumption of stable BCVA in treated eyes from month 24 to month 60. During this period in the present model the VA of treated eyes declines, anchored at a decline of 2.5 letters per year (informed by the ARMD database [Tufail et al., 2013). A second determinant of the difference in total QALYs will be the different baseline patient ages used in the 2 models; ours simulates patients aged 79 years, informed by observed UK data (Tufail et al. 2014), compared with a mean age of patients simulated in the published model of 76 years, informed by the EXCITE trial (Schmidt-Erfurth et al. 2011). With mortality informed by national life tables in both models, the younger starting age in the published model effectively means its lifetime horizon is longer than the new model's lifetime horizon, and more QALYs are invariably accrued.

Conclusions

Our model is the only CUA to date in late AMD (wet active) that compares a comprehensive set of potential interventions defined by various different features of a treatment strategy. Interpretation of its results varies considerably depending on which strategies are included within the analysis. Bevacizumab is not licensed for intraocular use for late AMD (wet active), but if it is included in the decision space, it is very likely to be the most cost-effective active treatment. Bevacizumab is the agent in 48 out of 52 strategies that provide a better balance of costs and benefits than providing no active treatment at all, when aflibercept and ranibizumab are evaluated at their list prices. Given at 2-month intervals, and extending treatment eligibility beyond current practice to include eyes with VA better than 6/12, it is 34.8% likely to be optimal at a cost-per-QALY value of £30,000. Bevacizumab delivered by some regimen is almost certain to be cost-effective. If bevacizumab is excluded from the analysis, then the most cost-effective active treatment strategy – ranibizumab at 3-month intervals – involves the treatment of BSEs only, without treating eyes with VA better than

6/12. No active treatment strategy produces an ICER below £20,000 per QALY gained when they are restricted further to include only regimens that are commonly used in current practice, though low-intensity, BSE-only strategies do so when PAS prices are applied. If providing no treatment is not considered to be an appropriate potential strategy, then ranibizumab given as needed is more cost-effective than aflibercept (given every 2 months for 1 year, then as needed), when they are evaluated at their list prices. When the PAS prices of both drugs are used, there is very little to choose between those 2 options (empirical results not presented to protect the confidentiality of PAS agreements).

Table 89: Comparison of new model (at list prices) with previous cost–utility analyses comparing continuous ranibizumab with PRN ranibizumab

	Current analysis (at list prices)	Dakin 2014	Elshout 2014	Panchmatia 2016	Stein 2014	Vottonen & Kankaanpää 2016	Yanagi 2016
Continuous regimen, rani.	1-monthly	1-monthly	1-monthly	1-monthly	1-monthly	1-monthly	1-monthly
PRN regimen, rani.	load →PRN	load →PRN	PRN	load →PRN	PRN	load →PRN	PRN
Cost ranibizumab	£551	£742.17	773.24 €	8,910 kr	$2,389	1,336.40 € *	rani: ¥176,235
Analysis type	2-eye Markov microsimulation	trial-based CUA (RCT: IVAN)	2-eye patient simulation	1-eye Markov model	1-eye Markov model	2-eye Markov model	1-eye Markov model
Source for treatment effect	network meta-analysis (MD in VA, RCTs)	RCT: IVAN	RCTs: CATT, MARINA	RCT: VIEW; Swedish Macular Registry	RCT: CATT	RCTs: CATT, VIEW	RCT: VIEW; unpublished indirect comp.
Extrapolation of benefit beyond year 2	second-year relative effects carried forward	N/A	treatment: -0.05 letters per month; no treatment: -0.5	none	stable VA maintained	stable VA maintained	stable VA maintained
Max treatment duration	no maximum	2 years	no maximum	2 years	not clear	8 years	5 years
Source of HRQL	Czoski-Murray (2009)	IVAN study EQ-5D data (unpublished)	Unpublished HUI-3 cross-section	Czoski-Murray (2009)	Brown (2003)	Brown (2000)	TTO study, Japan (Yanagi 2011)
Discount rate	3.5%	3.5%	C: 4.0%, Q: 1.5%	3.0%	3.0%	3.0%	2.0%
Time horizon	lifetime	2 years	5 years	lifetime	20 years	8 years	12 years
Absolute costs:							
Continuous treatment	£52,003	£18,590	74,837 €	686,598 kr	$257,496	147,322 €	¥2.954m
PRN treatment	£30,851	£11,500	45,491 €	573,570 kr	$163,694	95,505 €	¥2.216m
Absolute QALYs:							
Continuous treatment	4.400	1.608	2.15	4.59	6.68	6.880	6.87
PRN treatment	4.397	1.582	2.16	4.41	6.64	6.873	6.88
Incremental Cont. -v- PRN:							
Costs	£21,152	£7,090	29,346 €	113,028 kr	$93,802	51,817 €	¥737,376
QALYs	0.003	0.026	-0.01	0.18	0.04	0.007	-0.01
ICER	£7.87 m	£270.217	dominated	627,933 kr	$2.345m	740,243 €	dominated
Probabilistic sensitivity analysis	0% prob. that ICER is <£30,000/QALY	>99.9% prob. that PRN ICER is <£20,000/QALY	not reported	not reported	not reported	not reported	not reported

*Note: * includes cost of intravitreal injection.*

1438 **Table 90: Comparison of new model (at list prices) with previous cost–utility analyses comparing aflibercept with ranibizumab**

	Current analysis (at list prices)	Claxton 2016	Elshout 2014	Ghosh 2016	Panchmatia 2016	Vottonen & Kankaanpää 2016	Yanagi 2016	NICE TA 294
Aflibercept regimen	2-mo (1y) ➔PRN	2-mo (1y) ➔PRN	2-monthly	2-mo (1y) ➔PRN	2-mo (1y) ➔PRN	2-monthly	2-mo (1y) ➔PRN	2-mo (1y) ➔PRN
Ranibizumab regimen	load ➔PRN	load ➔PRN	PRN	treat-and-extend	load ➔PRN	load ➔PRN	PRN	PRN
Cost aflibercept	£816	£816.00	906.88 €	£816.00	8,902 kr	692.95 € *	¥159,289	£816.00
Cost ranibizumab	£551	£742.17	773.24 €	£551.00	8,910 kr	1,336.40 € *	¥176,235	£742.17
Analysis type	2-eye Markov microsimulation	2-eye patient simulation	2-eye patient simulation	2-eye patient simulation	1-eye Markov model	2-eye Markov model	1-eye Markov model	1-eye Markov model (BSE)
Source for treatment effect	network meta-analysis (MD in VA, RCTs)	RCT: IVAN; unpublished meta-analysis	RCTs: VIEW, CATT	network meta-analysis (RCTs)	RCT: VIEW; Swedish Macular Registry	RCTs: CATT, VIEW	RCT: VIEW; unpublished indirect comp.	RCT: VIEW-2; indirect comparison
Extrapolation of benefit beyond year 2	second-year relative effects carried forward	stable VA maintained	treatment: -0.05 letters per month; no treatment: -0.5	none	none	stable VA maintained	stable VA maintained	stable VA maintained (years 3 to 5)
Max treatment duration	no maximum	5 years	no maximum	2 years	2 years	8 years	5 years	5 years
Source of HRQL	Czoski-Murray (2009)	Czoski-Murray (2009)	Unpublished HUI-3 cross-section	Czoski-Murray (2009)	Czoski-Murray (2009)	Brown (2000)	TTO study, Japan (Yanagi 2011)	VIEW-2 study EQ-5D data (AiC)
Discount rate	3.5%	3.5%	C: 4.0%, Q: 1.5%	3.5%	3.0%	3.0%	2.0%	3.5%
Time horizon	lifetime	lifetime	5 years	lifetime	lifetime	8 years	12 years	lifetime
Absolute costs:								
Aflibercept	£36,263	£39,700	36,030 €	£48,887	578,360 kr	39,921 €	¥1.867m	£19,075
Ranibizumab	£30,851	£31,351	45,491 €	£29,282	573,570 kr	95,505 €	¥2.216m	£20,714
Absolute QALYs:								
Aflibercept	4.408	5.044	2.15	3.63	4.58	6.888	6.90	6.692
Ranibizumab	4.397	5.085	2.16	4.69	4.41	6.873	6.88	6.719
Incremental Aflib -v- Rani:								
Costs	£5,413	£8,349	-9,461 €	£19,604	4,790 kr	-55,584 €	- ¥387,774	-£1,639
QALYs	0.011	-0.043	-0.01	-1.058	0.17	0.015	0.02	-0.027
ICER	£492,078	dominated	946,100 €	dominated	26,787 kr	dominant	dominant	£61,653
Probabilistic sensitivity analysis	99.7% prob. that rani. ICER is <£30,000/QALY	>95% prob. that rani. ICER is below any threshold value of 1 QALY	not reported	100% prob. that rani. ICER is <£20,000/QALY	100% prob. that aflib. ICER is <500,000kr/QALY	not reported	>80% prob. that aflib. ICER is <¥5m/QALY	ERG: not reported; manufacturer: 100% prob. that aflib. ICER <£20,000

*Note: * includes cost of intravitreal injection.*

Table 91: Head-to-head cost–utility results of aflibercept (VIEW regimen) and monthly ranibizumab compared with no treatment (list price and PAS price results shown)

Strategy Treatment | Regimen | Eyes treated | VA range	Absolute		Fully incremental analysis			Previous published results (intervention ICER vs. no active treatment)
	Costs	QALYs	Costs	QALYs	ICER	
Aflibercept, better-seeing eyes only						
No treatment	£11,936	3.842				No data
Aflib | 2mo->PRN | Treat only BSEs | with VA in range: 6/12 to 6/96 At list price At PAS price	£22,182 [redacted]	4.201	£10,246 [redacted]	0.359	£28,572 <£20,000	
Aflibercept, not restricted to better-seeing eyes						
No treatment	£11,936	3.842				Yanagi et al. (2016): £1,242,414
Aflib | 2mo->PRN | Treat any eye | with VA in range: 6/12 to 6/96 At list price At PAS price	£36,263 [redacted]	4.408	£24,327 [redacted]	0.566	£42,998 £20-30,000	
Ranibizumab, better-seeing eyes only						
No treatment	£11,936	3.842				TA155: £9,900 - £19,904 (committee most plausible ICERs)
Rani | 1mo | Treat only BSEs | with VA in range: 6/12 to 6/96 At list price At PAS price	£29,846 [redacted]	4.197	£17,910 [redacted]	0.355	£50,503 >£30,000	
No treatment	£11,936	3.842				No data
Rani | Load+PRN | Treat only BSEs | with VA: 6/12 to 6/96 At list price At PAS price	£19,575 [redacted]	4.196	£7,639 [redacted]	0.354	<£20,000 >£30,000	
Ranibizumab, not restricted to better-seeing eyes						
No treatment	£11,936	3.842				TA155: £14,800 - £29,900 (committee most plausible ICERs) Colquitt et al. (2008): £11,412 - £25,098 Elshout et al. (2014): £343,721 Fletcher et al. (2008): $992,103 Wu et al. (2016): £36,089 - £102,828 Yanagi et al. (2016): ~£2.500,000
Rani | 1mo | Treat any eye | with VA in range: 6/12 to 6/96 At list price At PAS price	£52,003 [redacted]	4.400	£40,067 [redacted]	0.557	£71,874 >£30,000	
No treatment	£11,936	3.842				Yanagi et al. (2016): ~£1,900,000
Rani | Load+PRN | Treat only BSEs | with VA: 6/12 to 6/96 At list price At PAS price	£30,851 [redacted]	4.397	£18,914 [redacted]	0.555	£34,094 £20-30,000	

Key: 1mo/2mo/3mo, 1/2/3-month treatment intervals; 2mo->PRN, 2-month treatment intervals followed by treatment as needed; Aflib, aflibercept; Beva, bevacizumab; BSE, better-seeing eyes; ICER, incremental cost-effectiveness ratio; Load+PRN, loading phase followed by treatment as needed; PDT, photodynamic therapy; PRN, pro re nata (treatment as needed); QALYs, quality-adjusted life years; Rani, ranibizumab; TREX, tread-and-extend; VA, best-corrected visual acuity; WSE, worse-seeing eyes.

J.6 Evidence tables, published cost–utility analyses

J.6.1 Vitamin supplementation

Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Costs ($)	QALYs	ICER		
Rein et al., 2007 Population: People with AMD, cohort age 50 years. Interventions: vitamin therapy vs no vitamin therapy, adjunct to conventional care. Setting: US secondary care	Effects: Data from AREDS trial used to inform disease progression and visual impairment. Costs: Data from AREDS trial used to inform cost of treatment and nursing home use. US$2004. Utilities: QALYs obtained from AREDS trial data (time trade-off method used).	A Markov model based on 5 physiological AMD states. Health states are not defined by VA. Lifetime horizon (3% discount rate). Vitamin therapy estimated to cause a 25% risk reduction of disease progression, sustained for treatment duration.	Conventional treatment	848.96	0.26049	-	'Our model demonstrates that vitamin therapy compares favourably with other medical therapies to prevent visual impairment from AMD and to improve health more generally.'	One-way sensitivity analysis showed the base case ICER to be relatively sensitive to the cost of vitamin supplementation and the discount rate. Probabilistic sensitivity analysis was not presented.
			Vitamin therapy	937.38	0.22501	21,887		
Partially applicable [a,b,c]								
Very serious limitations [d,e,f]								

[a] Setting is US.
[b] Discount rate of 3% on costs and health outcomes.
[c] Health states defined by physiology, might not capture direct effects on people with AMD.
[d] Treatment continuation and treatment effects appear to have been held constant for the lifetime duration of the model.
[e] It is unclear whether the 25% progression risk reduction should have been applied to progression through every health state.

[f] No cost-effectiveness acceptability analysis is presented.

1462 Zeaxanthin supplementation

Study, population, country and quality	Data sources	Other comments	Strategy	Incremental Results			Conclusions	Uncertainty
				Cost ($)	Effect (QALYs)	ICER		
Olk et al., 2015 Population: People with classic, minimally classic and/or occult subfoveal CNV; VA ≥20/400. Interventions: Zeaxanthin vs. No zeaxanthin, in combination with PDT + bevacizumab + dexamethasone ("triple therapy") Setting: US secondary care **Partially applicable** [a,b] **Very serious limitations** [c,d,e,f,g]	Effects: Categorical VA gain data obtained from interventional comparative study (non-randomised). 424 participants (543 eyes). Costs: Costs include treatments, administration, tests and evaluation, from a US payer perspective (2015 US$). Utilities: Utility weights from Brown et al (2003), 1 day disutility due to injections, and PDT QALY loss (Brown et al. 2007).	A cost–utility model was developed with a 9-year time horizon (discount rate 3%). The precise model structure is unclear. Benefits observed during the study follow-up were assumed to persist for 9-year model duration. Model is presented as 3 sub-models: first eye with disease being treated; second eye with disease being treated; bilateral disease being treated.	First-eye treated model				'…triple combination therapy for neovascular AMD appears to be very cost-effective. The addition of oral Zx is more cost-effective yet.'	Probabilistic sensitivity analysis was not presented. The base case result sensitive to alternative treatment effect and treatment duration assumptions
			Zeaxanthin	859	0.115	7,740		
			Second-eye treated model					
			Zeaxanthin	859	0.253	3,395		
			Combined-eye model					
			Zeaxanthin	859	0.162	5,302		

[a] Setting is US.
[b] Discount rate of 3% on costs and health outcomes.
[c] Model structure is unclear.
[d] Costs associated with profound low vision are not captured. Only treatment-related costs are captured (identical regardless of number of eyes treated).
[e] Treatment effect is assumed to persist for the model duration.
[f] No cost-effectiveness acceptability analysis presented.
[g] Conflict of interest in favour of zeaxanthin.

1463 **Diagnosis, referral and monitoring**

Study, population, country and quality	Data sources	Other comments	Strategy D=diagnosis M=monitoring	Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Mowatt et al., 2014 Population: Men with suspected AMD, aged 65. Interventions: Nine diagnosis and treatment strategies, defined by test(s) and staff required. Setting: UK secondary care	Effects: Diagnostic accuracy of OCT from a systematic review; FFA assumed 100% accurate; ophthalmologist, nurse and technician assessment accuracies from expert opinion. Costs: Direct NHS/PSS costs related to diagnosis and monitoring, treatment with ranibizumab (list price), and profound vision loss (2011-12 £). Utilities: Utility weights from Colquitt et al (2004), based on Brown et al (2000).	A Markov model with 5 VA health states underlying disease status and treatment status health states, and a death state. Prevalence of neovascular AMD (70%) from expert opinion and systematic review. VA change over time in treated and untreated eyes informed by MARINA, CATT and IVAN trials. A lifetime horizon was used, with a 3.5% discount rate.	D: FFA M: Nurse/tech.	39,769	10.473	-	'A strategy that based its diagnostic decision on the results of FFA only, combined with VA and OCT interpreted together by a nurse or technician as a first monitoring step, had … a 46.5% probability of being cost-effective at a £30,000 threshold, [and] dominated all others apart from one (diagnosis with FFA, ophthalmologist-led monitoring).' 'Strategies that used OCT test results alone were unlikely to be a cost-effective use of resources.'	FFA+Nurse/technician had a 57.4% probability of an ICER ≤£20,000. The authors estimate the baseline demographics of a female cohort. The base case results were not sensitive to this. Results were sensitive to treatment unit cost. Unit cost of £50 made FFA+OCT the lowest cost option, as errors caused by OCT false positives become less costly.
			D: Ophthal. M: Nurse/tech.	39,790	10.472	Dominated		
			D: OCT M: Nurse/tech.	41,607	10.465	47,768		
			D: FFA M: Ophthal.	44,649	10.575	Dominated		
			D: Ophthal. M: Ophthal.	44,669	10.574	Dominated		
			D: OCT M: Ophthal.	47,131	10.567	Dominated		
			D: FFA M: OCT	62,759	10.449	Dominated		
			D: Ophthal. M: OCT	62,778	10.449	Dominated		
			D: OCT M: OCT	67,421	10.442	Dominated		
Directly applicable								
Potentially serious limitations [a,b,c]								

[a] The diagnostic and monitoring accuracy data used to drive model results are dependent on expert opinion, rather than a high quality source of evidence.
[b] All treatment is with ranibizumab at the list price. This reflects the clinical evidence used, but sensitivity analysis shows results to be highly sensitive to treatment costs, therefore a treatment strategy more reflective of routine practice might alter conclusions.
[c] It is a single-eye model, which omits costs and health outcomes of bilateral neovascular AMD. It may also miss differences in the relative effectiveness of alternative monitoring strategies if monitoring is associated with improved diagnosis of AMD in the second eye.

J Anti-angiogenic therapies and frequency of administration

J.1 Anti-VEGF studies

Study, population, country and quality	Data sources	Other comments	Lesion Strategy	Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Colquitt et al., 2008 Population: People with AMD. Interventions: ranibizumab, PDT, pegaptanib sodium [1] and BSC. Setting: UK secondary care	Effects: Transition probabilities derived from ANCHOR (PC lesions), MARINA (MC lesions/OC) and PIER (0.3 mg vs 0.5 mg). Costs: Direct costs (NHS & PSS) derived from UK clinical experts and national unit cost sources. Treatment assumed monthly. AEs and blindness (Meads et al. 2003) also costed. Utilities: Utility values from Brown et al. (2003).	A Markov model was developed with 5 VA health states plus death. The cohort starting age was 75 years. A short time horizon (1-2 years) is used to reflect the trial evidence. A 10-year time horizon was also used (3.5% discount rate). Long-term progression matched BSC.	PC (ANCHOR)	1 year			'Bevacizumab confers considerably greater value than ranibizumab for the treatment of neovascular macular degeneration.'	Probabilistic sensitivity analysis showed ranibizumab to be 72% likely to be cost effective compared with PDT in PC patients at the threshold value of £20,000/QALY and 97% at £30,000/QALY (15% and 81% respectively for MC/OC). Deterministic sensitivity analysis showed ranibizumab to be less cost effective in older patients. The ICER was also sensitive to the cost of injection.
			PDT	4,182	0.77	-		
			Ranibizumab	12,427	0.81	202,450		
			PC (ANCHOR)	10 years				
			PDT	21,498	3.81	-		
			Ranibizumab	26,888	4.15	15,638		
			PC (ANCHOR)	1-year				
			BSC	933	0.74	-		
			Ranibizumab	12,427	0.81	160,181		
			PC (ANCHOR)	10 years				
			BSC	20,431	3.59	-		
			Ranibizumab	36,888	4.15	11,412		
			MC/OC (MARINA)	2 years				
			BSC	1,541	1.40	-		
Directly applicable			Ranibizumab	23,902	1.54	152,464		
			MC/OC (MARINA)	10 years				
			BSC	13,787	4.10	-		
Potentially serious limitations [a,b]			Ranibizumab	31,096	4.79	25,098		

1. Note: pegaptanib results not presented here, as this chapter focuses on anti-VEGF therapies.
[e] Fully incremental analysis not presented.
[b] Single-eye model.

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Study, population, country and quality	Data sources	Other comments	Utility model used Strategy	Bae-case results Cost (£)	Effect (QALYs)	ICER	Conclusions	Uncertainty
Claxton et al., 2016 Population: People with neovascular AMD. Interventions: aflibercept PRN, ranibizumab PRN. Setting: UK secondary care **Directly applicable** **Potentially serious limitations** [a,b,c]	Effects: Ranibizumab mean BCVA change at 2 years from IVAN trial. Aflibercept relative effect from VIEW study via an unpublished NMA. Eyes modelled independently. Costs: Direct costs (NHS & PSS) derived from UK sources, 2014£. Include injections, outpatient administration, monitoring by OCT and blindness (Meads et al. 2003). Utilities: Utility regression models from Czoski-Murray et al. (2009).	A two-eye, lifetime, patient-level simulation model was developed. 3.5% discount rate. The cohort starting age was 76 years. 18.5% of patients were bilaterally affected at baseline. Unaffected eyes could become affected. BCVA change independent of change in previous months. Remains stable if treated between year 2 and 5. Natural history applied after discontinuation.	BSE only				‘The total costs and life-years gained were very similar in both treatment arms, with the small decrease for aflibercept reflecting the higher mortality rate in patients with lower BCVA.’ ‘Simulation modelling is a suitable alternative for modelling in ophthalmology. The advantages … may mean that the results of this analysis are more accurately estimated than in previously developed models.’	Probabilistic sensitivity analysis results were consistent with the base-case results. Incremental costs and QALYs were statistically significant at the 5% level. Ranibizumab is more than 95% likely to be cost effective at any QALY valuation. One-way sensitivity analysis was not presented.
			Ranibizumab	31,361	5.772	-		
			Aflibercept	39,745	5.728	Dominated		
			WSE only					
			Ranibizumab	31,362	4.406	-		
			Aflibercept	39,736	4.364	Dominated		
			Both eyes, no interaction					
			Ranibizumab	31,351	5.165	-		
			Aflibercept	39,700	5.122	Dominated		
			Both eyes, with interaction					
			Ranibizumab	31,386	5.085	-		
			Aflibercept	39,746	5.044	Dominated		
			Both eyes, with blindness term					
			Ranibizumab	31,366	5.009	-		
			Aflibercept	39,713	4.968	Dominated		

[e] Baseline data were informed by one RCT.
[b] Clinical effectiveness data informed by 1 trial for ranibizumab, and an unpublished network meta analysis for aflibercept. Discontinuation rates informed by naïve comparison of 2 trials.
[c] Conflict of interest in favour of ranibizumab.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	NMB (at £20K/QALY)		
Dakin et al., 2014 Population: People with untreated neovascular AMD. Interventions: ranibizumab monthly and PRN, bevacizumab monthly and PRN Setting: UK secondary care	Effects: Efficacy data obtained directly from the IVAN trial. Costs: Costs of injections, monitoring were obtained from a trial micro-costing survey. Staff and facility costs were included. Drug costs were from BNF (2011) and the trial provider. Expected AE costs included. Utilities: Utility weights were obtained from the IVAN (EQ-5D), and captured any decrements due to SAEs.	The analysis was a within-trial CUA, undertaken alongside the IVAN study. The authors assumed the near-equivalence of continuous ranibizumab and bevacizumab, and so took a cost-minimisation approach to this comparison.	Study Arm	Total (95% CI)			'Ranibizumab is not cost effective compared with bevacizumab, being substantially more costly and producing little or no QALY gain. Discontinuous bevacizumab is likely to be the most cost effective of the four treatment strategies evaluated.'	At a threshold of £20,000 per QALY, the authors estimated a 63% probability that discontinuous bevacizumab is cost-effective, and a 37% probability that continuous bevacizumab is cost-effective. Bevacizumab was cost-effective compared with ranibizumab in all one-way sensitivity analyses presented.
			Bevacizumab PRN	£3,002 (2601, £3403)	1.584 (1.538, 1.630)	£28,683 (£27,707, £29,658)		
			Bevacizumab monthly	£3,601 (£3259, £3,943)	1.604 (1.563 – 1.845)	£28,480 (£27,548, £29,412)		
			Ranibizumab PRN	£11,500 (£10,798, £12,202)	1.582 (1.530 – 1.634)	£20,142 (£18,963 – £21,321)		
			Ranibizumab monthly	£18,590 (£18,258, £18,922)	1.608 (1.565 – 1.651)	£13,576 (£12,769-£14,383)		
			Ranibizumab vs. Bevacizumab	Incremental (95% CI)				
			Continuous	£14,989 (£14,522, £15,546)	0.004 (-0.046, 0.054)	-£14,904 (-£15,995, -£13,813)		
			Discontinuous	£8,498 (£7,700, £9,295)	- 0.002 (-0.064, 0.060)	-£8,541 (-£9,939, -£7,144)		
			Continuous vs.. discontinuous	Incremental (95% CI)				
Directly applicable			Ranibizumab	£7,090 (£6,337, £7,844)	0.026 (-0.032, 0.085)	-£6,566 (-£7,861, -£5,271)		
Potentially serious limitations [a,b,c]			Bevacizumab	£599 (£91, £107)	0.020 (-0.032, 0.071)	-£203 (-£1,372, £967)		

[a] Two-year time horizon.
[b] Based on one RCT only.
[c] PRN regimen is atypical of practice (characterised by blocks of 3 injections over 3 months).

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Study	Effect (QALYs)	Cost (€)		
Elshout et al., 2014 Population: People with neovascular AMD. Interventions: aflibercept, ranibizumab and bevacizumab. Setting: Netherlands secondary care	Effects: Efficacy data were derived from RCTs (CATT, MARINA, VIEW, ABC). Costs: Resource use data were obtained from interviews with AMD patients and clinical experts. Unit costs were standard local values. Ocular AEs were costed. Utilities: Utility values were from an unpublished cross-sectional study of 184 AMD patients (HUI-3 questionnaire), which was used to estimate a linear relationship between utility and VA loss.	The CUA was based on a patient-level two-eye model. The authors took a societal perspective. Costs were discounted at 4% per year, benefits at 1.5% per year.		2 year analysis [5 year analysis]			'The authors concluded that there was little difference in the QALY gains across treatment options, but substantial differences in costs. Whilst injection frequency of aflibercept would need to fall to an interval of between 15-38 weeks in order for its costs to approximate PRN bevacizumab.	One-way sensitivity analyses suggested that the model is highly sensitive to the time horizon and whether only the BSE is treated. PSA suggested that bevacizumab PRN is likely to be the most cost effective strategy, whether informed by ABC or CATT.
			Aflibercept 2-monthly	VIEW 1 & 2	1.02 [2.05]	17,963 [36,030]		
			Bevacizumab PRN	ABC	1.01 [2.16]	8,427 [19,367]		
			Bevacizumab PRN	CATT	1.02 [2.17]	12,664 [26,746]		
			Bevacizumab monthly	CATT	1.01 [2.15]	13,021 [30,520]		
			Ranibizumab PRN	CATT	1.01 [2.16]	19,919 [45,491]		
			Ranibizumab monthly	MARINA	1.01 [2.15]	31,706 [74,837]		
			No treatment (usual care)	Literature review	0.96 [1.96]	3,298 [9,530]		
Partially applicable [a,b,c]								
Potentially serious limitations [d,e,f,g]								

[a] Setting is the Netherlands.
[b] QALYs were estimated using HUI-3 (not EQ-5D), and the linear model fit is not discussed.
[c] Discount rates of 4% on costs and 1.5% on health outcomes.
[d] Inputs are largely based on patient and clinical opinion, including an unpublished cross-sectional study.
[e] Linear model fit to estimate utility values is not discussed.
[f] A fully incremental analysis was not presented. ICERs were presented for each strategy compared only with no treatment.
[g] Rationale for method of extrapolation of treatment effect beyond year 2 (-0.05 letters per month for all treatments) is unclear.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results ICER vs. BSC	Conclusions	Uncertainty
Fletcher et al., 2008 Population: People with wet AMD. Interventions: ranibizumab, PDT, pegaptanib, BSC. Setting: US secondary care **Partially applicable** [a] **Very serious limitations** [b,c,d,e,f,g]	Effects: Two-year categorical VA change obtained from MARINA, PIER, TAP and VISION trials. Costs: Direct costs include investigations and treatments (from Current Procedural Terminology) and blindness (Meads et al., 2003). Administration costs excluded, assumed equivalent. Utilities: Related to BSE VA through Sharma et al. (2000) regression model. AE disutilities included for ranibizumab and PDT.	A decision tree analysis with a 2-year time horizon. Outcomes in year 2 not discounted. Results reported for different starting VA levels and treatment eyes. Same effectiveness evidence used in each scenario. Only results presented are ICERs.	PDT	$986,913	'… despite having the highest unit cost, [ranibizumab] is the most cost-effective treatment in most cases.' [1]	ICERs for alternative starting VA and treatment eyes are not presented. The authors report that no treatments are cost-effective when the treated eye has substantially worse VA (-18 letters) than the fellow eye. No analysis of parameter uncertainty was reported.
			Ranibizumab - MARINA	$992,103		
			Ranibizumab - PIER	$626,938		
			Bevacizumab simulation • $50 cost • Equal effect • ATE event utility decrement for 2% of patients	$104,748		

1. The authors cite a cost-effectiveness threshold value of $50,000 per QALY gained. However, their narrative conclusions appear to compare average cost per QALY ratios to this threshold, rather than ICERs (which are significantly higher than $50,000).
[a] Setting is the US. [b] Neither total nor incremental cost or QALY results are reported; only ICERs and average cost per QALY ratios.
[c] A fully incremental analysis was NR. Reporting only ICERs does not allow a fully incremental analysis to be estimated.
[d] The time horizon is 2 years only.
[e] Various data sources are used, with different baseline populations.
[f] The same effectiveness data appear to have been applied for different starting levels of VA.
[g] Analysis of parameter uncertainty, such as probabilistic sensitivity analysis, was NR.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Ghosh et al., 2016. Population: People with AMD. Interventions: ranibizumab T&E and aflibercept. Setting: UK secondary care.	Effects: Relative effects derived from a NMA of RCTs in order to link aflibercept with ranibizumab T&E. Costs: NHS/PSS costs used. Injection frequency from NICE TA294 and the LUCAS trial. Resource use (e.g. monitoring) costed using national sources. Meads et al. (2003) blindness costs used. Utilities: Czoski-Murray (2009) regression model.	An individual patient model was developed, based on mean monthly VA change. A lifetime horizon was used (discount rate 3.5% per year). Natural history progression is assumed after treatment (max 2 years). Cohort starting age is 75.5 years.	Ranibizumab T&E Aflibercept	29,282 48,887	4.69 3.63	- Dominated	'…ranibizumab T&E is likely to be a more effective and less costly treatment option compared with the currently licensed regime of aflibercept within the UK setting.'	Probabilistic sensitivity analysis showed ranibizumab T&E to be cost effective compared with aflibercept in all model simulations. The base case result was not sensitive to the deterministic scenario analyses presented.
Directly applicable								
Potentially serious limitations [a,b]								

[a] Ranibizumab is associated with a QALY gain of 1.06 compared with aflibercept, which appears incongruous with the observed clinical evidence.
[b] Conflict of interest in favour of ranibizumab.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost (US$)	Cost vs. sham	ICER		
Hurley et al., 2008 Population: People with newly diagnosed AMD. Interventions: ranibizumab compared with no treatment. Setting: Australian secondary care **Partially applicable** [a,b] **Very serious limitations** [c,d,e,f,g]	Effects: Efficacy data were derived from MARINA (years 0-4), followed by progression as per geographic atrophy (Sunness et al, 1999). Costs: Two costs of rani. used: US$1,950 and US$50. Fixed administration cost. Other costs based on Medicare resource use. Caregiver costs included. US$2004 Utilities: Utility values were from Brown et al. (2000).	A Markov model, based on starting VA and VA change. A 10-year time horizon was used (discounting at 3% per year). A 'sustained effect' scenario assumed no VA decline beyond year 4. A 'non-sustained effect' scenario assumed sham efficacy for years 3 and 4.	Base case				'Under all plausible assumptions, ranibizumab was cost-saving from a societal perspective. From a health care funder's perspective, ranibizumab was cost-effective over a 10-year time horizon when it cost $1000 per dos or less (about half the current wholesale price).'	Excluding caregiver costs results in ICERs of $91,900 (list price) and $5,600 (lower price).
			Ranibizumab: list price	205,800	-32,500	Dominant		
			Ranibizumab: $50 price	147,100	-91,100	Dominant		
			Sustained effect					
			Ranibizumab: list price	144,400	-93,800	Dominant		
			Ranibizumab: $50 price	125,500	-112,700	Dominant		
			Non-sustained effect					
			Ranibizumab: list price	209,800	-28,500	Dominant		
			Ranibizumab: $50 price	164,800	-73,500	Dominant		

[a] Setting is Australia.
[b] Discount rate of 3% on costs and health outcomes.
[c] 2-year effectiveness data from MARINA applied for 4 years in base case scenario.
[d] No cost-effectiveness acceptability analysis or parameter uncertainty analysis is presented..
[e] Disaggregated QALYs not presented.
[f] Societal perspective taken (i.e. including caregiver costs), and results are highly sensitive to their exclusion.
[g] Single-eye model.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results				Conclusions	Uncertainty
				Cost (SEK)	Effect (QALYs)	ICER vs. next-lowest cost	Approx. £ ICER		
Panchmatia et al., 2016 Population: Adult patients with subfoveal choroidal neovascularisation associated with wet AMD. Interventions: aflibercept, ranibizumab. Setting: Swedish secondary care	Effects: VIEW trials for aflibercept and ranibizumab monthly for 1 year then PRN. Registry data for ranibizumab in practice: 3-month loading then PRN. Costs: Treatments for max 2 years. Direct costs, including blindness and endophthalmitis, from national sources. Carer time to attend hospital included. 2012 SEK. Utilities: Czoski-Murray (2009) regression model from TTO analysis.	A Markov model based on 5 VA range health states. Lifetime horizon (3% discount rate). Injection frequency from effectiveness sources. Baseline data from VIEW trials, mean age 77 years. Discontinuation included reflecting non-adherence. Vision loss then equal to natural history.	Ranibizumab 3-month loading then PRN	573,570	4.41	-	-	'Aflibercept is … a cost-effective alternative to the ranibizumab PRN clinical practice regimen in Sweden, based on an assumed cost-effectiveness threshold of 500,000 SEK/QALY gained.'	Aflibercept was cost effective compared with rani. in 100% of PSA iterations. Scenario analysis using the CATT trial to simulation rani. given per that trial suggested that aflib. dominates that regimen. Results were sensitive to aflib. efficacy estimates and the number of injections given in rani. PRN.
			Aflibercept	578,360	4.58	26,787	2,392		
			Ranibizumab monthly for 1 year then PRN	686,598	4.59	20.4m	1.83m		
Partially applicable [a,b]									
Potentially serious limitations [c,d]									

[a] Setting is Sweden.
[b] Discount rate of 3% on costs and health outcomes.
[c] The effectiveness data for ranibizumab PRN (observational registry data; Swedish Macular Registry) are non-randomised and are compared directly with the VIEW effectiveness data for aflibercept. The registry did not report the same granularity of letter gains/losses, therefore the probability of achieving a 30+ letter gain with ranibizumab PRN was assumed to be 0%, compared to 5.5% for ranibizumab in VIEW. Furthermore, the registry suggests ranibizumab in practice is notably less effective than in trials; however, the only aflibercept effectiveness data used are from trial settings. Given the relatively small difference in costs between rani. PRN and aflibercept, the plausibility of the relative effectiveness estimates has the potential to alter the interpretation of results.
[d] Conflict of interest in favour of aflibercept.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost ($)	Effect (QALYs)	ICER		
Patel et al., 2012 Population: People with AMD. Interventions: ranibizumab and bevacizumab. Setting: US secondary care	Effects: Transition probabilities derived from ANCHOR and MARINA for rani., and from observational data for bevacizumab. Long term transitions are based on assumptions. Costs: All patients assumed to receive continuous monthly treatment. Resource use and direct costs, including monitoring and drugs, were from Medicaid. Utilities: Utility values were reportedly from Brown et al. (2000) and were condensed to fit the chosen model structure.	A Markov model was developed based on whether VA was improving, stable or deteriorating. The cohort starting age was 75 years. A 20-year time horizon was used.	Bevacizumab	30,349	21.60	-	'Bevacizumab confers considerably greater value than ranibizumab for the treatment of neovascular macular degeneration.'	Probabilistic sensitivity analysis showed bevacizumab to be 95% likely to be cost effective at the threshold value of $50,000/QALY. The base case results were sensitive to drug costs of the study medications.
			Ranibizumab	220,649	18.12	Dominated		
Partially applicable [a,b,c]								
Very serious limitations [d,e,f,g,h]								

[a] Setting is US.
[b] Discount rates of 3% on costs and 0% on health outcomes.
[c] Direct effects and resource use of adverse events and severe vision loss not included.
[d] It is not clear how the Brown (2000) utility weights were mapped onto the health states described by directional change in vision.
[e] Bevacizumab is associated with 21.60 total QALYs despite the time horizon being shorter than this (20 years).
[f] It is not clear how transition probabilities were derived. They suggest bevacizumab is ten times more likely to caused improved vision than ranibizumab, which does not appear to be accurate compared with the body of clinical evidence.
[g] Long-term transition probabilities are based on assumptions, for example an ongoing 90% probability of remaining in the 'improving VA' state.
[h] Single-eye model.

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Study, population, country and quality	Data sources	Other comments	Results	Conclusions	Uncertainty
Raftery et al., 2007 Population: People with newly diagnosed AMD. Interventions: ranibizumab and PRN, bevacizumab. Setting: UK secondary care **Directly applicable** **Very serious limitations** [a,b]	Effects: Efficacy data were obtained from the licensing trials. Costs: Treatment frequency and duration (1 or 2 years) were based on the licensing trials and AMD subtype. The cost of near blindness was included (Meads et al., 2003). National unit cost sources used. Utilities: Utility values were from Brown (2000). No utility decrement for AEs applied.	The authors adapted a Markov model previously developed to explore the cost-effectiveness of PDT. Patients enter the model aged 75. The model has a 10-year horizon (3.5% discount rate). After treatment, untreated disease progression applies.	The authors presented cost-utility ratios of ranibizumab vs bevacizumab at varying levels of efficacy and price ratios (10, 25 and 39) for the two subgroups (PC and MC/OC lesions). These results suggested that the relative efficacy of bevacizumab compared to ranibizumab would need to be 0.4 in for a cost-utility ratio of £31,092. For ranibizumab to achieve a cost-utility ratio below £20,000, relative efficacies of 0.65 and 0.85 would be needed where ranibizumab is 25x and 10x the price, respectively, of bevacizumab.	'Ranibizumab is not cost effective compared to bevacizumab at current prices unless it is at least 2.5 times more efficacious. However, in observational studies bevacizumab appears to have similar efficacy.'	Deterministic sensitivity analysis showed that doubling the serious ocular events in the bevacizumab group did not change the model result for either cohort.

[a] The authors do not present disaggregated cost and QALY results, and therefore do not present a fully incremental analysis.
[b] Probabilistic sensitivity analysis was not performed.
[c] Single-eye model.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost ($)	Effect (QALYs)	ICER		
Stein et al., 2014 Population: People with newly diagnosed AMD. Interventions: ranibizumab monthly and PRN, bevacizumab monthly and PRN. Setting: US secondary care	Effects: Efficacy data were derived from the CATT trial. Costs: Direct costs of managing AMD were obtained from Medicaid (2011), including visits, OCT, FA, and treating side effects and blindness. Drug costs were also included. All costs were in $2012 US. Utilities: Utility values were from Brown et al. (2003) based on VA in BSE. A literature review identified utility decrements for AEs.	A Markov model, based on VA health states, took a lifetime perspective (starting age: 80). No change in VA occurs after 2 years.	Bevacizumab PRN	65,267	6.60	-	'Bevacizumab confers considerably greater value than ranibizumab for the treatment of neovascular macular degeneration.'	Deterministic sensitivity analysis showed bevacizumab to remain cost effective unless only extreme parameter inputs were used. Bevacizumab would need to have a 2.5x higher risk of SAEs than observed in CATT to ranibizumab to have an ICER <$100,000.
			Bevacizumab monthly	79,771	6.66	242,357		
			Ranibizumab PRN	163,694	6.64	Dominated		
			Ranibizumab monthly	257,496	6.68	10,708,377		
Partially applicable [a,b]								
Potentially serious limitations [c,d,e]								

[a] Setting is US.
[b] Discount rate of 3% on costs and health outcomes.
[c] VA is not assumed to change beyond two years, which is likely to exaggerate long-term QALYs.
[d] Efficacy data sourced from one trial only.
[e] Single-eye model.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost (EUR)	Effect (QALYs)	ICER vs. next non-dominated alternative[2]		
Vottonen & Kankaanpää, 2016 Population: People with wet AMD. Interventions: aflibercept, ranibizumab, bevacizumab. Setting: Finnish secondary care	Effects: Two-year effectiveness data obtained from CATT and VIEW trials (transition probabilities NR). Extrapolated by assuming stability [1]. Costs: Patients treated for the duration of the model (unless VA falls below 0.05). Injection frequencies per protocol (continuous regimens) or from CATT (PRN regimens). Direct costs: diagnosis, drugs, administration, blindness, AEs. Costs obtained from 1 hospital. 2013 euros. Utilities: From Brown et al. (2000).	A Markov model based on 5 BSE VA range health states. 8-year horizon, estimate to reflect long term treatment duration. Costs discounted at 3% per year. Health outcomes not discounted. Two-eye treatment model with 9.5% annual incidence of AMD in fellow-eye. Monitoring appointments are assumed to be required when useful for informing treatment decisions.	Bevacizumab monthly	9,219	6.870	-	'Bevacizumab is cost-efficient when compared with aflibercept, which in turn is cost-efficient compared with ranibizumab.'	Base case results are probabilistic, but neither a measure of uncertainty nor cost-effectiveness acceptability analysis are reported. Results were not sensitive to any of 4 one-way sensitivity analyses presented (0% discount rate, costs of blindness and AEs ±20%, 10-year horizon).
			Bevacizumab PRN	16,784	6.862	Dominated		
			Aflibercept	39,921	6.888	1,705,667		
			Rani. monthly	95,505	6.873	Dominated		
			Rani. PRN	147,322	6.880	Dominated		
Partially applicable [a,b]								
Potentially serious limitations [a,b,c]								

1. It is unclear whether this implies visual acuity is stable until the end of the analysis or whether the transition probabilities are assumed to be stable and carried forward.
2. ICERs were reported for all strategies compared with aflibercept. NICE have estimated the fully incremental ICERs presented, which are subject to rounding error.
[a] Setting is Finland.
[b] Discount rates of 3% on costs and 0% on health outcomes.
[a] Cost-effectiveness acceptability results are NR.
[b] Costs were obtained from a single hospital.
[c] The method used to extrapolate treatment effectiveness is unclear.

Study, population, country and quality	Data sources	Other comments	Lesion Strategy	Results				Conclusions	Uncertainty
				Cost (US$)	Effect (QALYs)	ICER vs usual care	Statement		
Wu et al., 2016 Population: People with newly diagnosed wet AMD. Interventions: ranibizumab, bevacizumab, PDT and usual care. Setting: Chinese secondary care **Partially applicable** [a,b] **Potentially serious limitations** [c,d]	Effects: ANCHOR and MARINA (rani.); TAP, VIP (PDT); MARINA, TAP and VIP (usual care). CATT trial used to estimate relative risk of bevacizumab vs ranibizumab. Costs: Direct costs of treatment, follow-up, SAEs, blindness and non-medical items. Injection frequency from RCTs. Outpatient administration. US$2012. Utilities: Utility weights from Brown et al (2000).	A Markov model based on 5 VA range health states. Lifetime horizon (3% discount rate). Usual care transitions in year 2 assumed to apply after year 2 for all patients. Baseline data from 2 Chinese PDT studies. Starting age is 73.6 years.	Predominantly classic disease					'Bevacizumab is highly cost-effective compared with ranibizumab and verteporfin with PDT because of the more favourable ICER in the Chinese health care setting.'	Probabilistic sensitivity analysis showed bevacizumab to be cost-effective in 95.4%, 77.6%, and 95.2% of PC, MC and OC cases, respectively Deterministic sensitivity analysis suggested that treatment is more cost effective in younger patients and in patients with initial VA ≤20/40.
			Usual care (no treatment)	8,619	3.97	-	-		
			Bevacizumab	9,233	4.46	1,258	Cost-effective		
			PDT	18,293	4.19	44,333	Dominated		
			Ranibizumab	29,468	4.55	36,089	Not cost-effective		
			Minimially classic disease						
			Usual care	8,664	4.10	-	-		
			Bevacizumab	9,243	4.26	3,803	Cost-effective		
			PDT	18,289	4.19	112,992	Dominated		
			Ranibizumab	29,480	4.31	102,828	Not cost-effective		
			Occult disease						
			Usual care	8,595	3.90	-	-		
			Bevacizumab	18,240	4.21	2,066	Cost-effective		
			PDT	29,465	4.01	91,424	Dominated		
			Ranibizumab	9,228	4.26	58,790	Not cost-effective		

[a] Setting is China.
[b] Discount rate of 3% on costs and health outcomes.
[c] ICERs were reported for each active treatment compared with usual care only; though a fully incremental analysis can be estimated.
[d] Single-eye model.

Study, population, country and quality	Data sources	Other comments	Lesion Strategy	Results [1]			Conclusions	Uncertainty
				Cost (¥) [2]	Effect (QALYs)	ICER		
Yanagi et al., 2016 Population: People with wet AMD as per VIEW. Interventions: aflibercept, ranibizumab (monthly, PRN), pegaptanib, PDT, BSC. Setting: Japanese secondary care **Partially applicable** [a,b,c] **Potentially serious limitations** [d,e,f,g,h]	Effects: 24-month probabilities of gaining or losing 15 letters from VIEW (aflib. and rani. monthly). Indirect comparison for other relative effects. Costs: Drug, monitoring and AE costs included. Blindness costs are societal (associated with extent of family care required). ¥2016. Utilities: Health state utilities derived from Japanese TTO study.	A Markov model based on 5 VA range health states. Lifetime horizon (12 years) – no mortality applied. 2% annual discount rate. VA remains stable in years 3 to 5 (on treatment). Natural history after discontinuation and/or year 6.	BSC	38,316	6.09	-	'[Aflibercept] was more effective in terms of QALYs and less costly compared with other widely available treatments for wAMD in Japan.'	Sensitivity analyses included societal costs and were presented as head-to-head comparisons of aflibercept vs each other comparator. Suggest that the base-case result is robust, and that aflibercept is at least 80% likely to be cost-effective in each head-to-head comparison.
			PDT	1,228,615	6.41	Extendedly dominated		
			Aflibercept	1,837,398	6.90	1,242,414		
			Ranibizumab PRN	2,216,172	6.88	Dominated		
			Pegaptanib	2,224,693	6.53	Dominated		
			Ranibizumab monthly	2,953,548	6.87	Dominated		

1. ICERs were reported for all strategies compared with aflibercept. NICE have estimated the fully incremental ICERs presented, which are subject to rounding error.
2. Excluding societal costs (time associated with family care due to blindness).
[a] Setting is Japan.
[b] Discount rate of 2% on costs and health outcomes.
[c] QALYs derived using utilities from TTO study.
[d] ICERs were reported for each active treatment compared with usual care only; though a fully incremental analysis can be estimated.
[e] Single-eye model.
[f] Efficacy data obtained from 1 trial and an unpublished indirect comparison (methods NR). Results suggest visual acuity decline is substantially more likely to occur when being treated with PDT or pegaptanib than with no treatment.
[g] Sensitivity analyses presented with societal costs as head-to-head comparisons only.
[h] Conflict of interest in favour of aflibercept.

J1622 **NICE Technology Appraisal for anti-VEGF**

Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Bayer, 2013 (submitted for NICE TA 294) Cummins et al., 2013 (ERG report for NICE TA 294). Population: Adults with wet AMD. Interventions: ranibizumab PRN and aflibercept (two-monthly). Setting: UK secondary care	Effects: Two-year relative risk of maintaining or improving vision from VIEW 2 and a systematic literature review. Costs: NHS/PSS costs. Injection frequency from SPCs. Outpatient administration (50/50 one/two stop). Meads et al. (2003) blindness costs used. Drug costs included with and without confidential PAS. Utilities: EQ-5D by VA in both eyes from VIEW. Academic in confidence.	A two-eye Markov model was developed, based on gains/losses in VA. A lifetime horizon was used (discount rate 3.5% per year). Eyes have stable VA in years 3-5. From year 6 all treatment ceases and gradual VA loss occurs per BSC. Second eye treatment only permitted in years 3-5. ERG interprets two-year evidence as RR from baseline to year 2 (does not favour aflibercept). Manufacturer interprets this as from year 1 to year 2 (favours aflibercept).	Bayer				ERG: 'Aflibercept appears to be a cost-effective option … compared with ranibizumab.'	Bayer probabilistic sensitivity analysis resulted in no model iterations in which ranibizumab was cost-effective compared with aflibercept, for any threshold value. Bayer's base case result was not sensitive to the deterministic scenario analyses presented. The ERG's model is highly sensitive to whether the BSE or WSE is treated, and to varying the non-significant RRs to their upper and lower CI limits.
			Aflibercept	25,009 [1]	7.767	-		
			Ranibizumab	28,615 [1]	7.758	Dominated		
			Cummins et al.	WSE model				
			Aflibercept	19,075 [1]	8.014	-		
			Ranibizumab	20,714 [1]	8.018	£399,140		
			Cummins et al.	BSE model				
			Aflibercept	19,075 [1]	6.692	-		
			Ranibizumab	20,714 [1]	6.719	£61,653		
Directly applicable								
Potentially serious limitations [a,b,c,d,e]								

1. Analyses without patient access schemes.
[a] Results appear to be highly sensitive to point estimates of relative risk of improvement, and to whether a WSE or BSE model is adopted.
[b] Results appear to be highly sensitive to interpretation of the two-year efficacy data; namely whether it represents the relative risk of improvement from year 0 to year 2 or from year 1 to year 2.
[c] Second eye treatment only permitted in years 3-5.
[d] Conflict of interest in favour of aflibercept.
[e] ERG analysis based on a single-eye model.

J1633 **PDT studies**

Study, population, country and quality	Data sources	Other comments	Strategy	Incremental Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Grieve et al., 2009 Population: People with wet AMD Interventions: Verteporfin PDT, BSC. Setting: UK secondary care.	Effects: Effectiveness inputs obtained from the TAP RCT. Costs: NHS/PSS perspective, including treatment frequency, social services, day services, residential care, sheltered housing and antidepressant use, using UK VPDT cohort study data. BSC costed by expert opinion. 2007 £. Utilities: QALYs were derived from the use of SF-6D in UK VPDT.	A 2-year model was developed. Mortality was not modelled.	BSC	-	-	-	'The costs of providing VPDT for patients included in the UK VPDT Cohort Study were relatively high compared with the projected QALY gain.'	Probabilistic sensitivity analysis indicated that PDT has a 0% probability of being cost-effective compared with BSC at all threshold maximum ICERs under £100,000/QALY. Deterministic sensitivity analysis showed the ICER was somewhat sensitive to using the TAP trial to inform treatment frequency.
			PDT	3,514	0.02071	170,000		
Directly applicable								
Potentially serious limitations [a,b,c,d]								

[a] Effectiveness data from a single RCT.
[b] Two-year time horizon only.
[c] Resource use associated with BSC informed by expert opinion.
[d] SF-6D used to elicit utility values, rather than EQ-5D.

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Study, population, country and quality	Data sources	Other comments	Strategy	Incremental Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Hopley et al., 2004 Population: People with predominantly classic CNV. Interventions: Verteporfin PDT, placebo. Setting: Australian secondary care. **Partially applicable** [a,b] **Very serious limitations** [a,b,c,d,e,f]	Effects: Effectiveness inputs obtained from 3-year follow up of TAP RCT. Costs: Costs included treatment, administration and follow-up. Costs were obtained from the Australian Medicare Benefits Schedule (2003), and were converted (PPP) to 2003£. Utilities: Derived from Brown et al. (2000).	A 7-year horizon was used (cohort age 75 years). Outcomes were discounted at a rate of 6% per year. Beyond the observed 3-year data, patients were assumed to continue receiving PDT and to experience a fixed ongoing treatment effect relative to placebo. Two scenarios presented: initial VA 6/12 and initial VA 6/60. Untreated eye assumed to be WSE.	Baseline VA: 6/12				‘PDT is at least moderately cost effective … in people with reasonable visual acuity.’ ‘PDT … is relatively cost ineffective in those with poor initial visual acuity.’	Probabilistic sensitivity analysis was not presented. One-way sensitivity analysis, varying input parameters up and down by a fixed proportion, varied the ICER from £25,285 to £37,928 in scenario 1 (high VA), and from £54,183 to £75,856 in scenario 2 (low VA).
			Placebo	-	-	-		
			PDT	12,478	0.395	31,607		
			Baseline VA: 6/60					
			Placebo	-	-	-		
			PDT	12,478	0.197	63,124		

[a] Setting is Australia.
[b] Discount rate of 6% on costs and health outcomes.
[a] No probabilistic sensitivity analysis was presented.
[b] Extrapolation beyond observed data assume ongoing treatment (discontinuation not discussed) and a maintained treatment effect.
[c] It is unclear how well the Brown et al. (2000) utility values can be mapped onto an ‘improvement / no change / worsening’ response.
[d] Effectiveness data were from a single RCT.
[e] Total cost and QALY results NR.
[f] Single-eye model.

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Study, population, country and quality	Data sources	Other comments	Strategy	Incremental Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Meads et al., 2003 Population: Adults with wet AMD Interventions: Verteporfin PDT, placebo. Setting: UK secondary care.	Effects: Effectiveness inputs obtained from the TAP and VIP RCTs. Costs: NHS/PSS perspective. Costs derived from a systematic review of published PDT costing studies. Cost of blindness derived from an Australian study. Utilities: Derived from Brown et al. (2000).	A 2-year decision tree model was developed. Outcomes discounted at a rate of 3% per year. Two base case results presented, differing by whether blindness occurred in year 1 (costed for 2 years) or year 2 (costed for 1 year).	Blindness occurs in year 1				'…we believe that on balance the true cost–utility of verteporfin PDT relative to BSC lies above accepted thresholds denoting efficient use of healthcare resources.'	Probabilistic sensitivity analysis was not presented. One-way sensitivity analysis showed that the model was most sensitive to effectiveness inputs. A 'best case' scenario for PDT gave an ICER of £47,000/QALY.
			Placebo	-	-	-		
			PDT	4,695	0.0311	151,179		
			Blindness occurs in year 2					
			Placebo	-	-	-		
			PDT	5,658	0.0311	182,188		
Directly applicable								
Potentially serious limitations [a,b,c,d]								

[a] No probabilistic sensitivity analysis was presented.
[b] 2-year time horizon only.
[c] It is unclear how well the Brown et al. (2000) utility values can be mapped onto a simple decision tree 'improvement / no change / worsening' structure.
[d] Single-eye model.

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Study, population, country and quality	Data sources	Other comments	Strategy	Incremental Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Meads & Moore, 2001 Population: Adults with wet AMD Interventions: Verteporfin PDT, placebo. Setting: UK secondary care.	Effects: Effectiveness inputs obtained from TAP RCT. Costs: Costs of treatment, including monitoring in two-stop treatments, and the cost of verteporfin. Cost of blindness derived from an Australian study. Standard UK unit cost sources used. Utilities: Obtained from Brown et al. (2000) and linked to VA in TAP.	A 1-year horizon was used, consistent with the available TAP data. The model is a simple decision tree, with the proportion of patients experiencing better, worse or unchanged vision experiencing the associated utility for 1 year.	Placebo	-	-	-	'The incremental cost per QALY … is estimated at £137,138.' 'The cost utility estimate is sensitive to various parameters. More accurate information is required in order to reduce uncertainty.'	Probabilistic sensitivity analysis was not presented. One-way sensitivity analysis showed the result to be more sensitive to changes in effectiveness and utility inputs than changes in costs. The model is not sensitive to the cost of blindness.
			PDT	3,516	NR *	137,138		
			* estimated: 0.026					
Directly applicable								
Potentially serious limitations [a,b,c,d,e]								

[a] No probabilistic sensitivity analysis was presented.
[b] 1-year time horizon only, potentially understating long-term benefits of treatment.
[c] It is unclear how well the Brown et al. (2000) utility values can be mapped onto a simple decision tree 'improvement / no change / worsening' structure.
[d] Effectiveness data were from a single RCT.
[e] Total QALY results NR.

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Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Smith et al., 2004 Population: People with predominantly classic AMD. Interventions: Verteporfin PDT, placebo. Setting: UK secondary care. **Directly applicable** **Potentially serious limitations** [a,b,c,d,e]	Effects: Effectiveness inputs were obtained from the TAP RCT patient level data. Costs: Treatment costs, from published national sources, including the drug and procedure. The government perspective included costs associated with blindness. A scenario analysis included cost offsets from income transfers. AE costs not included. Utilities: Utility weights were derived from Brown et al. (2000). AE utility decrements included.	2-year and 5-year Markov model results were presented. The model has 15 VA health states plus death. Cost outcomes were discounted at 6% per year; health outcomes at 2%. Survival curves were fitted to the observed trial data to model time to worsening VA. These were extrapolated to 5 years. Treatment ceased after year 3.	Two-year model. Starting VA 20/40 [Starting VA 20/100]				'Early treatment with PDT leads to increased efficiency.' 'A broad perspective that incorporates other NHS treatment costs and social care costs suggests that … PDT may yield reasonable value for money.'	Probabilistic sensitivity analysis suggested that patient starting treatment at 20/40 had an ICER of £30,000 or less in 80% of government perspective scenarios (30% treatment only). These figures were 5% and 45% respectively in patients who start treatment at 20/100. Treatment was less cost-effective if income transfers for blind people are included, and if post-treatment follow up was by angiogram.
			Treatment costs only					
			Placebo	0 [0]	1.136 [0.980]			
			Verteporfin	6,173 [6,173]	1.205 [0.995]	89,464 [411,553]		
			Government perspective					
			Placebo	1,275 [4,590]	1.136 [0.980]			
			Verteporfin	6,490 [8,878]	1.205 [0.995]	75,580 [285,867]		
			Five-year model. Starting VA 20/40 [Starting VA 20/100]					
			Treatment costs only					
			Placebo	0 [0]	2.205 [1.999]			
			Verteporfin	6,475 [6,475]	2.375 [2.093]	38,088 [68,882]		
			Government perspective					
			Placebo	10,200 [15,700]	2.205 [1.999]			
			Verteporfin	11,700 [18,500}	2.375 [2.093]	8,823 [29,787]		

[a] The base case cost perspective is narrow and may omit significant important costs, such as adverse events.
[b] Uncertainty around the choice of survival curve is not explored sufficiently, given that the curves are extrapolated beyond the observed data.
[c] Treatment frequency is assumed to be independent of initial visual acuity.
[d] Conflict of interest in favour of verteporfin.
[e] Single-eye model.

Treatment in people presenting with visual acuity better than 6/12 or people presenting with visual acuity worse than 6/96

Study, population, country and quality	Data sources	Other comments	Strategy	Results			Conclusions	Uncertainty
				Cost (£)	Effect (QALYs)	ICER		
Butt et al., 2015 Population: People with AMD. Interventions: ranibizumab PRN in people with VA >6/12 vs. people with ≤6/12. Setting: UK secondary care	Effects: VA over time in treated patients obtained from national observational dataset (UK AMD database). Costs: Direct NHS/PSS costs related to treatment with ranibizumab are included, consistent with NICE TA 294 costing template (2012 £). Utilities: Utility weights from Brown et al (2000).	A Markov model with 5 VA health states and death. A 2-year horizon was used, with no discounting. Once people reach 6/12 on the delayed treatment arm, they are distributed between all other VA states based on untreated fellow-eye data.	Delayed treatment	7,460.21	1.35	-	'…early ranibizumab intervention is associated with an acceptable incremental cost that is well within the NHS acceptable range to pay for health gain. Thus, the maintenance of better VA in patients who are treated early is not only beneficial clinically but also likely cost-effective.'	Probabilistic sensitivity analysis showed early treatment had an ICER of £20,000/QALY or less in over 90% of 10,000 simulations. The base case result was not sensitive to variation in cost, utility, time horizon or starting age inputs.
			Early treatment	8,469.79	1.59	4,251.60		
Directly applicable								
Potentially serious limitations [a,b,c,d,e,f]								

[a] Only treatment-related costs are included. The widely used costs associated with profound vision loss may have been appropriate for this analysis.
[b] All treatment is with ranibizumab at the list price. This reflects the clinical evidence used but results may differ if alternative treatments are used in practice.
[c] Two-year time horizon is insufficient to capture all relevant outcomes, particularly if early treatment is expected to have a prolonged positive impact on VA, or if treatment is delivered for longer than two years.
[d] Study is based on observational data, and may therefore be subject to selection bias (immediate treatment might reflect different types of centre or patient).
[e] Clinical input parameters lack face validity:

- There are large differences in long-term (>3 months) transition probabilities between patients who are established on treatment on the immediate and delayed treatment arms. Details regarding how transition probabilities were informed are not reported.

- The distribution of eyes between VA health states once they reach the time-to-6/12 is informed by the distribution of eyes diagnosed and treated at presentation in the source data. This distribution is unlikely to be appropriate for eyes that are known to have neovascular AMD but are yet to reach the treatment threshold level of VA (6/12). These eyes would have been subject to closer monitoring and would therefore, in all likelihood, have a better expected VA than eyes diagnosed at presentation.

[f] Single eye model.

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Study, population, country and quality	Data sources	Other comments	VA level of interest AMD subtype	Variation in cost-effectiveness of active treatment vs. usual care in this VA group compared with other levels of baseline VA (ICERs presented graphically)	Conclusions	Uncertainty
Wu et al., 2016 Population: People with newly diagnosed wet AMD. Interventions: ranibizumab, bevacizumab, PDT and usual care. Setting: Chinese secondary care	Effects: ANCHOR and MARINA (rani.); TAP, VIP (PDT); MARINA, TAP and VIP (usual care). CATT trial used to estimate relative risk of beva. vs rani. Costs: Direct costs of treatment, follow-up, SAEs, blindness and non-medical items. Injection frequency from RCTs. Outpatient administration. US$2012. Utilities: Utility weights from Brown et al (2000).	A Markov model based on 5 VA range health states. Lifetime horizon (3% discount rate). Usual care transitions in year 2 assumed to apply after year 2 for all patients. Baseline data from 2 Chinese PDT studies. Starting age is 73.6 years.	Baseline VA >20/40		'One-way sensitivity analyses also showed that the ICERs of active treatment were more favourable in patients with VA ≤20/40 to >20/80 for all three types of lesions.'	Sensitivity analysis was not presented for analyses stratified by baseline VA.
			Predominantly classic	No systematic variation in ICERs.		
			Minimally classic	No systematic variation in ICERs.		
			Occult/no classic	No systematic variation in ICERs.		
			Baseline VA ≤20/400			
			Predominantly classic	No systematic variation in ICERs.		
			Minimally classic	No systematic variation in ICERs.		
			Occult/no classic	ICERs appear systematically higher in this VA group than in patients with better initial VA.		
Partially applicable [a,b]						
Very serious limitations [c,d,e]						

[a] Setting is China.
[b] Discount rate of 3% on costs and health outcomes.
[c] Sensitivity analysis was not presented for the cost–utility results stratified by presenting VA.
[d] ICERs for the analysis stratified by presenting VA were reported only graphically.

[e] ICERs were reported for each active treatment compared with usual care only; no fully incremental analysis.

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