NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Ranibizumab (Lucentis) for the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathological myopia (PM)

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Submitted by Novartis Pharmaceuticals Ltd

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List of abbreviations

AE	adverse event
AMD	age-related macular degeneration
ARVO	The Association for Research in Vision and Ophthalmology
BCVA	best-corrected visual acuity
BSE	better-seeing eye
CFT	central foveal thickness
CHMP	Committee for Medicinal Products for Human Use
CMH	Cochran–Mantel–Haenszel
CNV	choroidal neovascularisation
CRT	central retinal thickness
CSR	clinical study report
DMO	diabetic macular oedema
EQ-5D	5-dimension EuroQol questionnaire
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
FA	fluorescein angiography
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
LYG	life-years gained
MacTSQ	Macular Disease Treatment Satisfaction Questionnaire
NEI VFQ-25	25-item National Eye Institute Visual Functioning Questionnaire
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
OCT	optical coherence tomography
PM	pathological myopia
PRN	as needed
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trials
RVO	retinal vein occlusion
SD	standard deviation
SMC	Scottish Medicines Consortium
UK	United Kingdom
VA	visual acuity
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

VIP	Verteporfin in Photodynamic Therapy
vPDT	verteporfin photodynamic therapy
W-BQ12	Well-Being Questionnaire
WPAI-GH	Work Productivity and Activity Impairment Questionnaire: General Health
WSE	worse-seeing eye
WTP	willingness-to-pay

Instructions for manufacturers and sponsors

This is the specification for submission of evidence to the National Institute for Health and Clinical Excellence (NICE) as part of the single technology appraisal (STA) process. It shows manufacturers and sponsors what information NICE requires and the format in which it should be presented. NICE acknowledges that for medical devices manufacturers particular sections might not be as relevant as they are for pharmaceuticals manufacturers. When possible the specification will refer to requirements for medical devices, but if it hasn't done so, manufacturers or sponsors of medical devices should respond to the best of their ability in the context of the question being addressed.

Use of the specification and completion of appendices 1 to 13 (sections 10.1 to 10.13) are mandatory (when applicable), and the format should be followed whenever possible. Reasons for not following this format must be clearly stated. Sections that are not considered relevant should be marked 'N/A' and a reason given for this response. The specification should be completed with reference to the NICE document 'Guide to the methods of technology appraisal' (www.nice.org.uk), particularly with regard to the 'reference case'. Users should see NICE's 'Guide to the single technology appraisal (STA) process' (www.nice.org.uk) for further details on some of the procedural topics referred to only briefly here.

If a submission is based on preliminary regulatory recommendations, the manufacturer or sponsor must advise NICE immediately of any variation between the preliminary and final approval.

A submission should be as brief and informative as possible. It is expected that the main body of the submission will not usually exceed **100 pages excluding the pages covered by the template**. The submission should be sent to NICE electronically in Word or a compatible format, and not as a PDF file.

The submission must be a stand-alone document. Additional appendices may only be used for supplementary explanatory information that exceeds the level of detail requested, but that is considered to be relevant to the submission. Appendices are not normally presented to the Appraisal Committee. Any additional appendices should be clearly referenced in the body of the submission and should not be used for core information that has been requested in the specification. For example, it is not acceptable to attach a key study as an appendix and to complete the clinical-effectiveness section with 'see appendix X'. Clinical trial reports and protocols should not be submitted, but must be made available on request.

Trials should be identified by the first author or trial ID, rather than by relying on numerical referencing alone (for example, 'Trial 123/Jones et al.[126]' rather than 'One trial[126]').

For information on submitting cost-effectiveness analysis models, disclosure of information and equality and diversity, users should see ‘Related procedures for evidence submission’, section 11.

If a patient access scheme is to be included in the submission, please refer to the patient access scheme submission template available on request. Please submit both documents and ensure consistency between them.

Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based when possible and clearly reference the relevant section of the submission. The summary should cover the following items.

- The UK approved name, brand name, marketing status and principal mechanism of action of the proposed technology.
- The formulation(s), strength(s), pack size(s), maximum quantity(ies), anticipated frequency of any repeat courses of treatment and acquisition cost.
- The indication(s) and any restriction(s).
- The recommended course of treatment.
- The main comparator(s).
- Whether the key clinical evidence in the submission comes from head-to-head randomised controlled trials (RCTs), from an indirect and/or mixed treatment comparison, or from non-randomised studies.
- The main results of the RCTs and any relevant non-RCT evidence.
- In relation to the economic evaluation, details of:
  - the type of economic evaluation and justification for the approach used
  - the pivotal assumptions underlying the model/analysis
  - the mean costs, outcomes and incremental cost-effectiveness ratios (ICERs) from the evaluation.
- Tabulation of the base-case results as follows:

Table 1 Base-case cost-effectiveness results

	Intervention	**Comparator 1**	**Comparator 2**	**Etc.**
Technology acquisition cost				
Other costs				
Total costs				
Difference in total costs	N/A	Intervention minus comparator 1	Intervention minus comparator 2	
LYG				
LYG difference	N/A	Intervention minus comparator 1	Intervention minus comparator 2	
QALYs				
QALY difference	N/A	Intervention minus comparator 1	Intervention minus comparator 2	
ICER	N/A			
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio				

- When appropriate, please present the results for the intervention and comparator(s) incrementally to indicate when options are dominated or when there is extended dominance. For example:

Table 2 Incremental cost-effectiveness results

Technology (and comparators)	Total cost	Total QALY	Incremental cost	Incremental QALY	ICERs versus baseline (A)	Incremental analysis
A	100	3	0	0	N/A	N/A
B	200	6	100	3	33.33333	33.33333
C	300	4	200	1	200	Dominated
D	400	8	300	5	60	Extended dominance
E	500	11	400	8	50	60
QALY, quality-adjusted life year; ICERs, incremental cost-effectiveness ratios						

- Subgroup analyses considered and clinical- and cost-effectiveness results.

This submission considers ranibizumab (Lucentis®) for the treatment of visual impairment due to choroidal neovascularisation (CNV) secondary to pathological myopia (PM). Ranibizumab is approved in the European Union (EU) for the treatment of neovascular (wet) age-related macular degeneration (AMD) and for the treatment of visual impairment due to diabetic macular oedema (DMO) or macular oedema secondary to retinal vein occlusion (RVO).[1] An EU regulatory submission for ranibizumab for the treatment of visual impairment due to CNV secondary to PM was made on the [redacted] to the Committee for Medicinal Products for Human Use (CHMP; European Medicines Agency). A positive opinion was received on the 30th May 2013 and marketing authorisation is anticipated between July and September 2013.

Ranibizumab is formulated as a 10 mg/mL solution for intravitreal injection with an acquisition cost of £742.17 per 0.23 mL vial. Treatment is initiated with a single injection. If monitoring reveals signs of activity, further treatment is recommended. Monitoring for disease activity may include clinical examination, optical coherence tomography (OCT) or fluorescein angiography (FA). Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year the frequency of monitoring should be determined by the treating physician.[1]

CNV secondary to PM

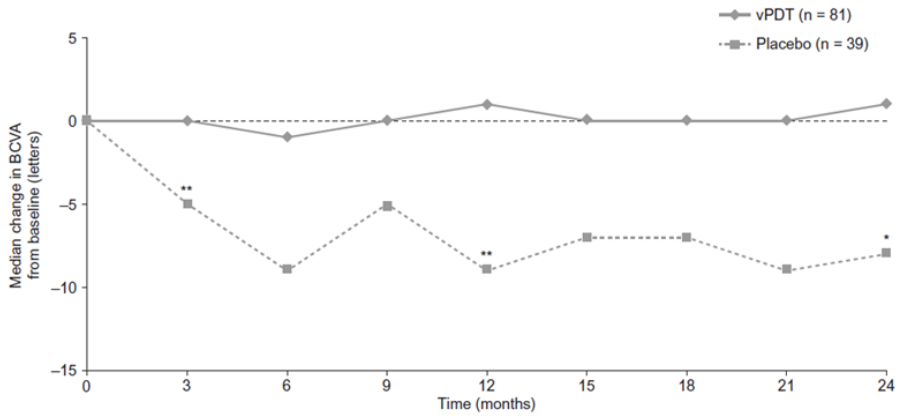
PM is a leading cause of visual impairment and blindness worldwide.[2-9] It is a progressive condition characterised by excessive elongation of the eye and degenerative changes in the posterior segment of the eye. Changes in the retina and choroid associated with PM can lead to the development of fundus lesions such as CNV.[10] CNV is characterised by newly formed abnormal vessels that may penetrate Bruch's membrane and extend into the subretinal space.[11] These vessels can rupture, causing blood and fluid to accumulate within the retinal layers, leading to deterioration of vision. The precise pathogenesis of CNV

associated with PM is unclear, but evidence suggests the expression and secretion of angiogenic factors including vascular endothelial growth factor (VEGF) contributes to the development of CNV secondary to PM and is supported by the observation that eyes with active CNV secondary to PM have higher levels of VEGF in the aqueous humour compared with controls.[12]

If patients with CNV secondary to PM do not receive treatment, their vision will deteriorate over time and they are at risk of going blind. Eleven studies have reported on the visual outcome in untreated patients with CNV secondary to PM; all reported deterioration in vision over time.[13-24] Eight studies reported best corrected visual acuity (BCVA) at baseline and at study end, and all but two of these reported either an increase of at least 20% in the proportion of individuals who were legally blind (BCVA ≤ 20/200), or a statistically significant decrease in mean BCVA, over a mean follow-up ranging from 3 months to 11 years.[13,15-17,19,21-23] The two studies that did not report deterioration in BCVA had a high proportion of legally blind patients at baseline (45% and 60%).[13,15] Seven studies reported the rates of legal blindness (BCVA ≤ 20/200) at follow-up; 53 to 96% of patients were legally blind after a mean follow-up ranging from 1 to 11 years.[13,16,17,21-23]

There is an urgent need for effective treatments for CNV secondary to PM. Verteporfin photodynamic therapy (vPDT), the only therapy currently licensed for CNV secondary to PM, generally stabilises, but does not improve, visual acuity, as demonstrated in the Verteporfin in Photodynamic Therapy (VIP) study, a large, multicentre, double-blind, placebo-controlled trial that randomised 120 eyes with subfoveal CNV secondary to PM to receive placebo or vPDT.[25,26] The median change in BCVA from baseline at 12 months achieved with vPDT was 1 letter (compared with a loss of 9 letters in the placebo group [$p < 0.01$], Figure 1). However, at 24 months, the proportion of patients with stable BCVA (defined as losing no more than 8 letters from baseline) did not differ significantly between treatment groups ($p = 0.11$). Furthermore, a recent study has reported that almost half (46.1%) of patients experienced at least one recurrence during long-term follow-up following vPDT.[27] Additionally, vPDT is associated with various safety concerns including visual disturbances,[25,26,28,29] injection-site reactions,[25,26] choroidal vessel occlusion[30] and haemorrhagic complications.[29]

Figure 1 Change in median BCVA over time during treatment with vPDT or placebo in the VIP study[a]



VIP trial, Blinder et al 2003[25]
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; VIP, verteporfin in photodynamic therapy
[a]The change in median BCVA letter score was a secondary endpoint. The primary endpoint was the proportion of eyes with fewer than 8 letters of BCVA loss at 12 months.
*p < 0.05; **p < 0.01 versus placebo.
Statistical analyses are presented for all time points reported in the original publications.

Clinical efficacy and safety of ranibizumab

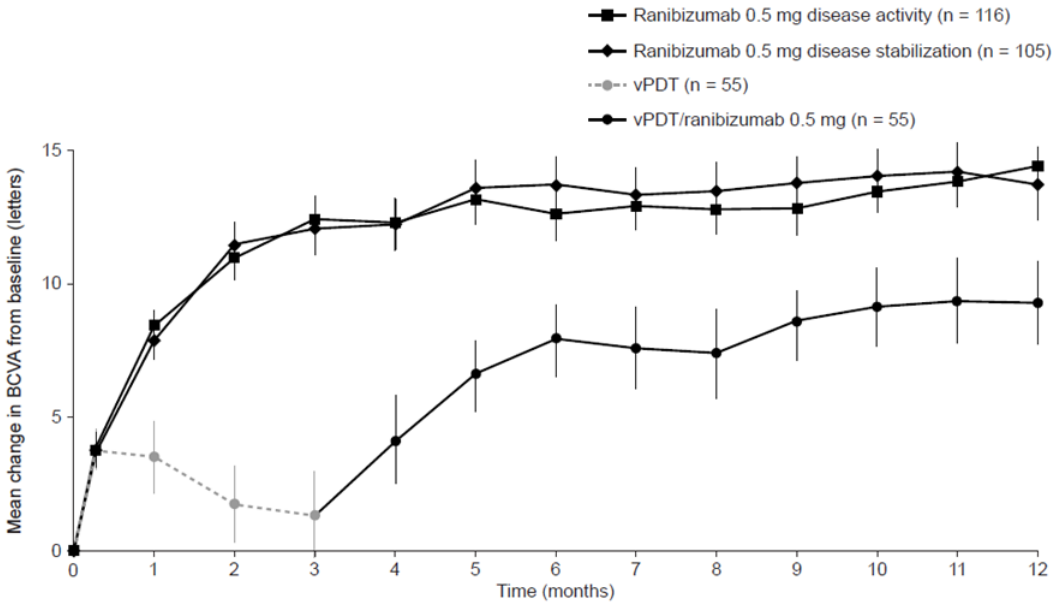
Ranibizumab is a recombinant, humanised, monoclonal antibody fragment developed specifically for intravitreal administration, which binds to the receptor binding site of active forms of VEGF-A.[31] VEGF-A has been shown to cause neovascularisation and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to the pathophysiology of CNV secondary to PM. This is supported by the observation that eyes with active CNV secondary to PM have higher levels of VEGF in the aqueous humour than control eyes.[12] The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage and new blood vessel formation.

The efficacy and safety of ranibizumab for the treatment of CNV secondary to PM has been demonstrated in a phase III, randomised, double-blind, multicentre study evaluating the efficacy and safety of two different dosing regimens of 0.5 mg ranibizumab versus vPDT in patients with visual impairment due to CNV secondary to PM.[32-34] In this study, 277 patients with active CNV secondary to PM and BCVA of at least 24 and at most 78 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart were randomised 2:2:1 to receive ranibizumab, (two groups: ranibizumab disease activity group; ranibizumab stabilisation group) or vPDT. All patients received initial treatment on day 1 and received retreatment according to predefined criteria. In the ranibizumab disease activity group, patients received ranibizumab 0.5 mg on day 1. From month 1 onwards, dosing was stopped if no disease activity was seen (i.e. vision impairment, attributable to intra- or subretinal fluid or active leakage secondary to PM as assessed by OCT and/or FA). Treatment was resumed when the disease activity criterion was fulfilled and continued until no disease

activity was seen. In the ranibizumab stabilisation group, patients received ranibizumab 0.5 mg on day 1 and month 1. For the following months, treatment was stopped if the stabilisation criterion for BCVA was fulfilled (i.e. no change in BCVA as compared to the two preceding monthly visits). Treatment was resumed with monthly injections when there was a loss of BCVA due to disease activity and was continued until stable BCVA was reached again for three consecutive monthly assessments. In the vPDT group, patients received vPDT on day 1. For months 3 to 11, based on the physician's discretion, patients with disease activity could receive ranibizumab 0.5 mg, vPDT or ranibizumab 0.5 mg plus vPDT. Treatment was stopped if no disease activity was seen. Treatment was resumed when the disease activity criterion was fulfilled (defined as for the ranibizumab group) and continued until no disease activity was seen. The primary outcome was the mean average change in BCVA from baseline to month 3 measured using an ETDRS chart, and secondary outcomes included: mean average change from baseline in BCVA at 3, 6 and 12 months; proportion of patients with at least 10 letters or at least 15 letters gained from baseline at months 3, 6 and 12; change from baseline in central retinal thickness (CRT) over time; and the number of ranibizumab re-treatments from baseline to month 2, month 5 and month 11.

The results for the Novartis phase III trial demonstrated that ranibizumab, administered according to disease activity or disease stabilisation criteria, significantly improved BCVA compared with vPDT, the only licensed treatment for CNV secondary to PM (Table 3). The study met its primary endpoint demonstrating a superior mean average change in BCVA from baseline to month 3 for both ranibizumab groups compared with vPDT. The mean (± standard deviation [SD]) average gains in BCVA for this period were 10.6 ± 7.3 letters in the ranibizumab disease activity group and 10.5 ± 8.2 letters in the ranibizumab disease stabilisation group compared with 2.2 ± 9.5 letters in the vPDT group, ($p < 0.00001$ for both comparisons). Thus patients achieved clinically meaningful gains in BCVA with ranibizumab whereas vPDT achieved only stabilisation of BCVA. The majority of gains in BCVA over baseline were achieved rapidly in the first 3 months; further small improvements in the ranibizumab groups were observed at months 6 and 12 (Figure 5). There was no significant difference between the ranibizumab groups in gain in BCVA over 6 months in a non-inferiority comparison ($p < 0.00001$), and gains at 12 months were similar for both ranibizumab groups. The benefits of ranibizumab compared to vPDT were evident regardless of age, sex, race, baseline visual acuity or CNV location. The proportions of patients gaining at least 10 letters or at least 15 letters from baseline at 3 months were also statistically significantly greater for both ranibizumab groups compared with vPDT ($p < 0.005$ for all four comparisons). Both ranibizumab groups also achieved greater reductions in CRT at 3 months compared with the vPDT group.

Figure 2 **Mean (± SE) change in BCVA over time during treatment with ranibizumab or vPDT/ranibizumab**



Bandello et al., 2013[33]
BCVA, best-corrected visual acuity; SE, standard error; vPDT, verteporfin photodynamic therapy.
From month 3 to 11, the investigators had the option to treat the disease activity of patients randomised to vPDT with 0.5 mg ranibizumab, vPDT, or a combination of 0.5 mg ranibizumab and vPDT.

Gains in BCVA were accompanied by improvements in vision-related functioning, as assessed using the 25-item National Eye Institute Visual Functioning Questionnaire (NEI VFQ-25).[35,36] The NEI VFQ-25 is a validated tool that uses 25 questions to elicit information on general health, quality of vision and vision-related quality of life.[37] Higher scores represent better functioning on a 0 to 100 scale for the composite and each subscale. At month 3, the improvement in mean composite score from baseline was significantly greater in both ranibizumab groups (4.3 points in the disease activity group and 5.3 points in the stabilisation group) compared with vPDT (0.3 points, $p < 0.05$) and the improvement from baseline for these two groups was maintained at 6 and 12 months. A 4- to 6-point improvement in the mean composite NEI VFQ-25 scores is considered to represent a clinically meaningful change, corresponding to at least a 15-letter change in BCVA;[38] hence the improvements achieved with ranibizumab can be considered to be clinically meaningful. Statistically significant ($p < 0.05$) improvements from baseline compared with vPDT were also reported for both ranibizumab groups at 3 months for general vision, near activities, mental health and dependency.

Improvements in BCVA and visual functioning were achieved with fewer ranibizumab injections when therapy was given according to the disease activity criteria rather than the disease stabilisation criteria (mean ± SD number of ranibizumab injections received over the 12 months: disease activity, 3.5 ± 2.92; disease stabilisation, 4.6 ± 2.59). Furthermore, 72% of patients in the disease activity group required 4 injections or less over the 12-month period compared with 59% in the disease stabilisation group. Retreatment according to disease activity criteria is the anticipated posology for ranibizumab in this indication.

Additional evidence for the efficacy of ranibizumab in this indication is provided by the phase II REPAIR study performed in the UK,[39,40] five prospective case series evaluating at least 25 patients for 6 months or longer,[41-45] and two randomised controlled trials that compared ranibizumab and bevacizumab and report the results for follow-up of 27 patients for 18 months[46] and 16 patients for 6 months.[47] The REPAIR study reported a mean improvement in BCVA from baseline at 12 months of 13.6 letters; the prospective case series reported gains of 8−19.1 letters over mean durations of 8 to 16 months;[41-45] and the two randomised controlled trials reported gains in BCVA of 17.3 letters at 6 months[47] and 9 letters at 18 months.[46]

Results from the phase III study indicate that ranibizumab is generally well tolerated and is associated with few treatment-related adverse events (AEs). Most AEs were mild or moderate in severity for both ranibizumab groups, with only two severe ocular events being reported over the 12-month study period, neither of which was suspected to be related to the study drug or ocular injection. Conjunctival haemorrhage was the most frequently reported treatment-related ocular AE in both ranibizumab groups, and the only AE reported in more than 5% of patients in either group over the 12-month follow-up period. Only two ocular serious AEs were reported (corneal erosion in a patient in the disease stabilisation group and retinoschisis in a patient in the disease activity group). Few non-ocular AEs were reported and most were not considered to be related to study medication. These safety results are further supported by the REPAIR study and are in agreement with the established safety profile of ranibizumab in other approved indications, namely wet AMD, DMO and RVO;[1] no new safety signals were identified.

In summary, ranibizumab will be the first licensed therapy to achieve clinically relevant BCVA improvements in patients with visual impairment due to CNV secondary to PM, a patient group for whom there are currently limited treatment options. In the absence of appropriate treatment, patients experience deterioration of vision and are at risk of becoming blind.[13-24] Ranibizumab therefore fulfils an important unmet medical need by providing effective treatment for this important cause of blindness.

Table 3 Summary of efficacy results from the Novartis phase III trial

	Months 0−3			Months 0−6		Months 0−12	
	Ranibizumab disease activity, n = 116	**Ranibizumab disease stabilisation, n = 105**	**vPDT, n = 55**	**Ranibizumab disease activity, n = 116**	**Ranibizumab disease stabilisation, n = 105**	**Ranibizumab disease activity, n = 116**	**Ranibizumab disease stabilisation, n = 105**
Primary endpoint: Mean average change in BCVA (letters) from baseline, mean (SD)	10.6 (7.26)***	10.5 (8.16)***	2.2 (9.47)	11.7 (8.24)	11.9 (8.81)	12.5 (8.83)	12.8 (9.48)
Change in BCVA (letters) from baseline, mean (SD)	12.5 (8.81)	12.1 (10.18)	1.4 (12.21)	12.7 (11.01)	13.7 (10.16)	14.4 (10.20)	13.8 (11.42)
Gain of ≥ 10 letters, n (%)	76 (65.5)***	65 (61.9)***	15 (27.3)	75 (64.7)	75 (71.4)	80 (69.0)	73 (69.5)
Gain of ≥ 15 letters, n (%)	50 (43.1)**	40 (38.1)**	8 (14.5)	52 (44.8)	49 (46.7)	60 (51.7)	56 (53.3)
Change from baseline in CRT (µm), mean (SD)	-77.6 (102.25)	-61.0 (67.46)	-12.0 (65.84)	-74.8 (97.05)	-66.1 (73.63)	-71.3 (100.91)	-66.6 (82.63)
No. of injections, mean (SD)	1.8 (0.8)	2.5 (0.6)	0 (0.0)	2.5 (1.6)	3.5 (1.5)	3.5 (2.9)	4.6 (2.6)
Change from baseline in NEI VFQ-25 composite score, mean (SD)	4.3 (10.09)*	5.3 (13.96)*	0.3 (12.63)	5.1 (14.38)	6.3 (13.98)	5.1 (15.83)	6.6 (15.66)

Bandello et al., 2013;[34] Novartis phase III study 12 month CSR[32]
BCVA, best corrected visual acuity; CRT, central retinal thickness; NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; SD, standard deviation; vPDT, verteporfin photodynamic therapy
*p < 0.05, **p < 0.005; ***p < 0.0001 vs vPDT

Economic evaluation

The economic evaluation considered the cost-utility of ranibizumab in comparison with vPDT in patients with visual impairment due to CNV secondary to PM.

A state transition Markov model comprising nine mutually exclusive health states, eight of which are defined by ranges of BCVA and one an absorbing state, 'death', was developed. Patients enter the model at a BCVA level as defined by the baseline distribution of BCVA levels in the Novartis phase III trial. Using 3-monthly cycles, the model predicts changes in health status (i.e. BCVA), health-related quality of life (HRQoL), resource use and associated costs. Costs and clinical outcomes are extrapolated to a lifetime time horizon. The outcomes for the economic evaluation are thus the total costs per patient and total health outcomes given in quality-adjusted life-years (QALYs). A similar Markov approach as used here has been employed in other economic assessments of interventions (including ranibizumab) used to treat conditions associated with deterioration in BCVA.[1,27,34-36,48-54] This is therefore considered an appropriate approach to modelling the impact of changes in BCVA on costs and HRQoL over time.

Clinical parameters for the effects of treatment on BCVA were taken from the Novartis phase III study and the VIP study. Transition probabilities for ranibizumab in year 1 were derived from patient level data for the disease activity group (the proposed licenced posology) of the Novartis phase III study, while for vPDT, data from the Novartis phase III study were used for baseline to month 3 (cycle 1) and data from the VIP trial were used for months 4 to 12 (cycles 2−4), because in the Novartis phase III study, patients in the vPDT group could receive ranibizumab from month 3 onwards. (Over the 12-month period, 72% of patients in the vPDT group received ranibizumab as part of their treatment.) In the base case, transition probabilities for beyond year 1 were based on data from a natural history study in a Caucasian population,[22] which reports a decline in BCVA over time in the absence of treatment and was used for both treatment groups. A scenario analysis explored using pooled data from multiple natural history studies for transition probabilities for beyond year 1. The probability of all-cause mortality from life tables was included in the model and an increased risk of mortality according to BCVA was also applied.[55]

Utilities according to BCVA were applied to each health state in the model. For the better-seeing eye (BSE) utilities were taken from Czoski-Murray *et al*. (2009)[56] a study performed in the UK general population[56] in which the BCVA health states were simulated in subjects by wearing special contact lenses that created the effects of AMD. Utility values for the worse-seeing eye (WSE) were calculated from the values for the BSE by assuming the maximum gain for the WSE was 0.1 in the base case (based on previous NICE recommendations during the appraisal of ranibizumab for RVO[53]). In order to accomplish this, the utility for the

WSE at the highest health state was anchored to the utility for the same health state in patients who were treated in their BSE. A weighted approach based on the number of patients whose BCVA represents the BSE and WSE was used to determine utilities and this proportion was derived from the Novartis phase III study (i.e. BSE for 20.8% of patients at baseline in the base case).

A number of AEs were included in the model based on their incidence in the Novartis phase III study (for ranibizumab) or the VIP study (for vPDT). Disutilities were taken from published sources or were assumptions and were applied to each patient experiencing an AE as a one-off event weighted by the expected duration of impact on HRQoL.

Total costs for each treatment were determined from the unit costs for treatment (i.e. ranibizumab and vPDT), administration and a monitoring visit, multiplied by the number of treatment and monitoring visits required. As summarised in Table 4, the administration cost for ranibizumab was assumed to consist of the cost of OCT and the injection visit, and that for vPDT was assumed to consist of OCT plus an ophthalmologist consultation visit. The cost of a monitoring visit was assumed to correspond to the cost of OCT plus an ophthalmologist consultation visit. For ranibizumab, the mean number of injections for year 1 was taken from the number of injections in the disease activity arm of the Novartis phase III trial, and it was assumed that these patients would receive one injection in the second year. For vPDT, the number of injections for years 1 and 2 was based on the treatment schedule in the VIP trial. For ranibizumab, patients were monitored 8.5 times in year 1 and were assumed to be monitored four times during year 2. For vPDT, patients were monitored quarterly for year 1 and 2 as per UK label. Based on recommendations from a UK advisory board, it was assumed that patients would be discharged from services after a maximum of 2 years and thus would no longer be treated or monitored after this time, unless they experience a recurrence, which was assumed to occur in 6% of patients per year. Annual costs of blindness were applied when the BSE was declared blind (i.e. BCVA ≤ 35 letters).

Table 4 Unit costs associated with the treatment

Items	Ranibizumab	vPDT
Treatment costs	£742.17	£850.00
Administration costs	£168.53[a]	£174.89[b]
Monitoring visit costs	£174.89[b]	£174.89[b]
[a]Cost of optical coherence tomography (£51.27) + injection visit (£117.26)[57]; [b]Cost of optical coherence tomography (£51.27) + ophthalmologist (£123.62)[57] vPDT, verteporfin photodynamic therapy		

The results of the cost-utility analysis are shown in Table 5. Ranibizumab is dominant compared with vPDT with a cost saving of £2751 and an incremental QALY gain of 0.43 over the patient's lifetime. Results of a deterministic sensitivity analysis are shown in Figure 3. In

general, the ‘direction’ of the results follows the prior expectations. The results are sensitive to the unit costs of each treatment, the frequency of treatment, the cost of an administration visit for both treatments, the utility curve for the WSE and starting age. Probabilistic sensitivity analyses demonstrated there is a 100% probability that ranibizumab is cost-effective compared with vPDT at willingness-to-pay (WTP) thresholds of £20,000 and £30,000 per QALY.

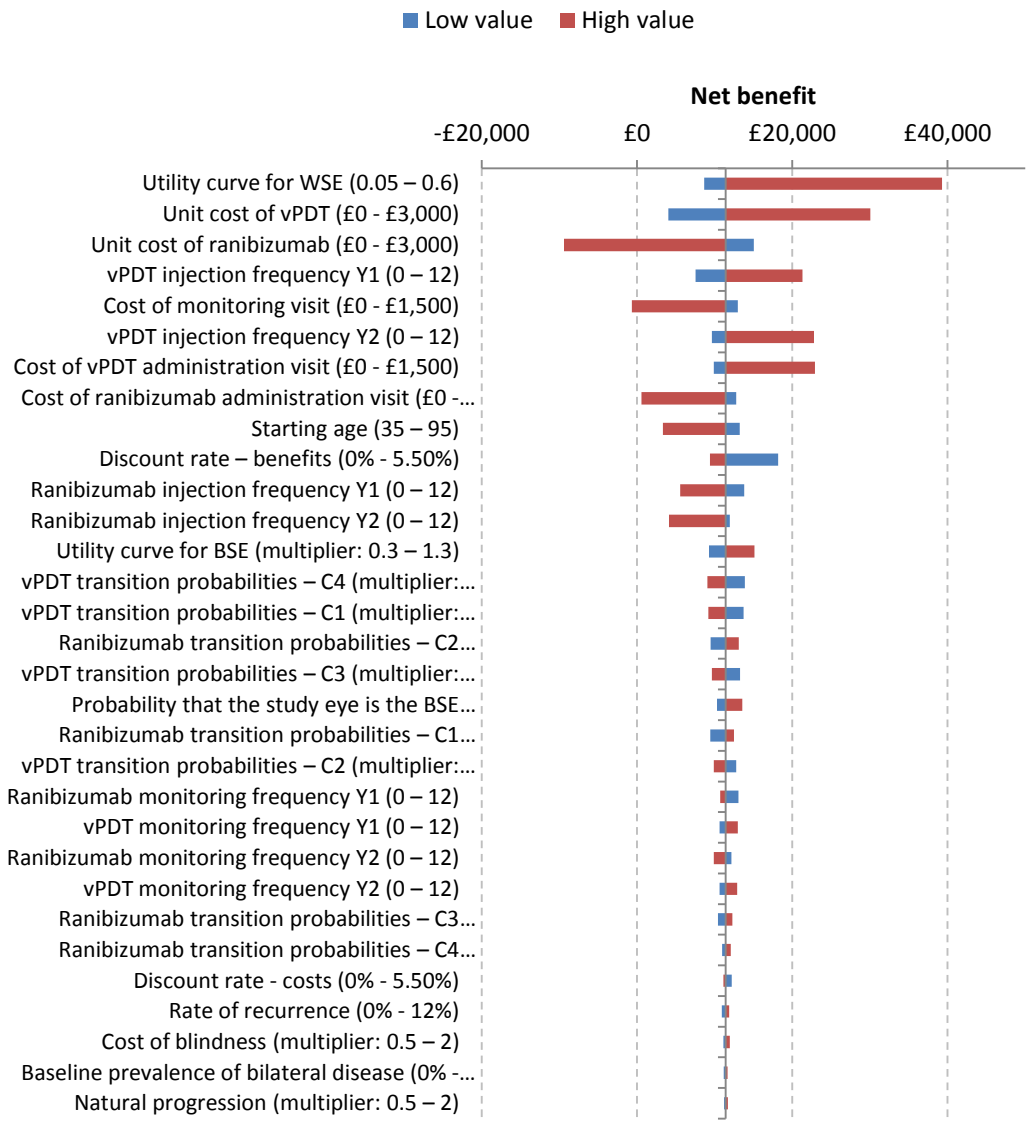
The unit cost for ranibizumab and vPDT and the treatment frequency for both Year 1 and Year 2 are both key drivers of the model. The majority of costs in the model occur in the treatment period (the first two years of the model) and so the unit costs and treatment frequency have a large impact on total costs. Recurrence costs also account for a large proportion of the total costs as these are applied over the model time horizon, so an increase in unit costs and treatment frequency impacts on these as well.

QALYs in the model are driven by the VA-utility relationship for the BSE and the maximum utility gain in the WSE, and also by the probability that the study eye is the BSE. The latter has less of an impact on cost-effectiveness, while the maximum utility gain in the WSE has one of the biggest impacts on the model. There is much uncertainty in this parameter as there is little published evidence in utility relating to BCVA in the WSE. In the base case it is assumed to have a maximum QALY gain of 0.1, resulting in the WSE curve having a greater utility value than the BSE curve. For values of 0.5 and above, the WSE actually has worse utility values than the BSE resulting in a counterintuitive scenario.

Table 5 Base-case cost-effectiveness of ranibizumab relative to vPDT (using deterministic values)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	£9694	16.80	13.18	–£2751	0.11	0.43	Dominant
vPDT	£12,445	16.70	12.75				
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years							

Figure 3 Deterministic sensitivity analysis – tornado diagram of net benefit



Budget impact

Introduction of ranibizumab to England and Wales is expected to produce total healthcare savings for the management of CNV secondary to PM of £227,354 over 5 years. This largely reflects reduced costs for drug acquisition and administration compared with vPDT.

Conclusions

Ranibizumab directly addresses the urgent need for an effective treatment for visual impairment due to CNV secondary to PM, a leading cause of blindness. Ranibizumab has been shown to significantly improve BCVA compared with vPDT, the only treatment currently licensed for this condition. Results of the Novartis phase III study, additional data from the UK phase II REPAIR study and several prospective case series demonstrate that ranibizumab provides clinically meaningful improvements in BCVA and HRQoL that are sustained with as needed treatment according to disease activity. In addition, economic modelling has demonstrated that ranibizumab is dominant compared to the only licensed treatment for this condition, vPDT, under extensive sensitivity analyses. Ranibizumab thus represents a clinically important improvement in the management of CNV secondary to PM and an efficient use of NHS resources compared with vPDT, providing a cost saving of £2751 and a QALY gain of 0.43 over the patient's lifetime. Introduction of ranibizumab in England and Wales is expected to produce cost savings of £227,354 over 5 years based on the small number of patients with this condition.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report [EPAR]), and a (draft) technical manual for devices should be provided (see section 10.1, appendix 1).

1 Description of technology under assessment

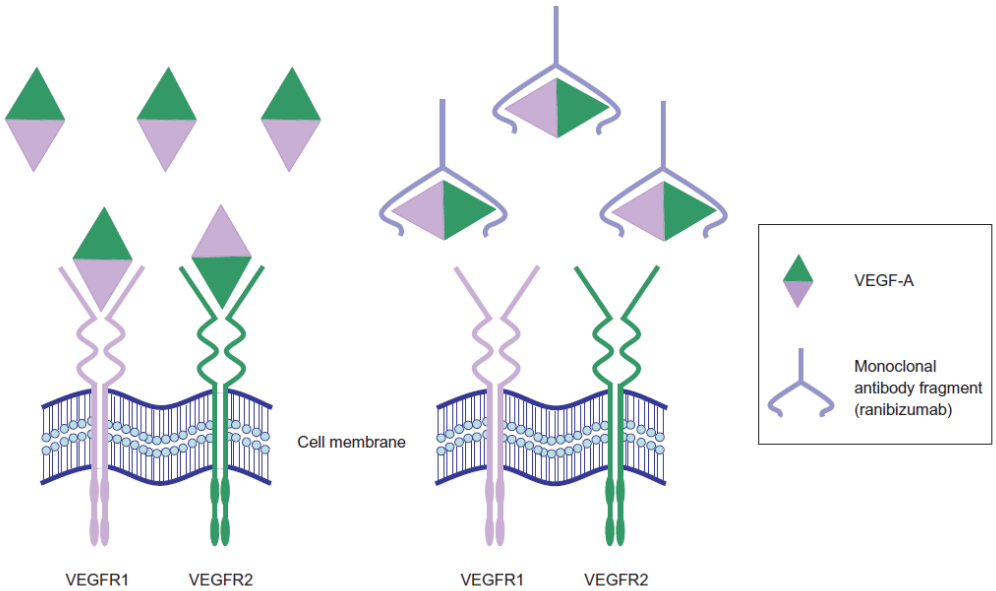
1.1 Give the brand name, approved name and, when appropriate, therapeutic class. For devices, provide details of any different versions of the same device.

Brand name: Lucentis
Approved name: ranibizumab
Therapeutic class: Ophthalmologicals; antineovascularisation agent
Anatomical Therapeutic Chemical (ATC) code: S01LA04

1.2 What is the principal mechanism of action of the technology?

Ranibizumab is a recombinant, humanised, monoclonal antibody fragment (Fab) developed specifically for intravitreal administration, which binds to the receptor binding site of active forms of vascular endothelial growth factor A (VEGF-A) (Figure 4).[31] VEGF-A has been shown to cause neovascularisation and leakage in models of ocular angiogenesis and vascular occlusion, and is thought to contribute to the pathophysiology of choroidal neovascularisation (CNV) secondary to pathological myopia (PM). This is supported by the observation that eyes with active CNV secondary to PM have higher levels of VEGF in the aqueous humour than control eyes.[12] The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage and new blood vessel formation.

Figure 4 **Ranibizumab binds to VEGF-A and prevents it from binding to its receptors.**



1.3 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, give the date on which authorisation was received. If not, state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

Ranibizumab does not have a UK marketing authorisation for visual impairment due to CNV secondary to PM. A European Union (EU) regulatory submission was made on [redacted] to the Committee for Medicinal Products for Human Use (CHMP; European Medicines Agency). A positive opinion was received on 30th May 2013 and marketing authorisation is anticipated between July–September 2013.

Ranibizumab is approved in the EU for the treatment of neovascular (wet) age-related macular degeneration (AMD) and for the treatment of visual impairment due to diabetic macular oedema (DMO) or macular oedema secondary to retinal vein occlusion (RVO).[1]

1.4 Describe the main issues discussed by the regulatory organisation (preferably by referring to the [draft] assessment report [for example, the EPAR]). If appropriate, state any special conditions attached to the marketing authorisation (for example, exceptional circumstances/conditions to the marketing authorisation).

A positive opinion for ranibizumab for the treatment of visual impairment due to CNV secondary to PM, the indication that is the focus of this submission, was granted on 30 May 2013.

1.5 What are the (anticipated) indication(s) in the UK? For devices, provide the (anticipated) CE marking, including the indication for use.

The anticipated indication relating to this submission is the treatment of visual impairment due to CNV secondary to PM in adults.

1.6 Please provide details of all completed and ongoing studies from which additional evidence is likely to be available in the next 12 months for the indication being appraised.

Two studies have investigated ranibizumab for the treatment of visual impairment due to CNV secondary to PM and are described in greater detail in section B of this submission.

In brief, a phase III, 12-month, randomised, controlled trial (NCT01217944; http://www.clinicaltrials.gov/ct2/show/study/NCT01217944) evaluated the efficacy and safety of two different dosing regimens of 0.5 mg ranibizumab versus verteporfin photodynamic therapy (vPDT) in patients with visual impairment due to CNV secondary to PM. From month 3 onwards, treatment with ranibizumab (instead or as well as vPDT) was an option for patients in the vPDT group.[33] The primary endpoint was the mean change in best corrected visual acuity (BCVA), measured in letters, from month 1 to month 3 and compared with baseline. Analyses were planned for 6- and 12-month follow-up, and both are included in this submission. No further analyses are planned.

The phase II, 12-month REPAIR study (NCT01037348; http://www.clinicaltrials.gov/ct2/show/NCT01037348) evaluated the efficacy and safety of 0.5 mg ranibizumab administered according to an individualised as-needed (PRN) dosing schedule in patients with CNV secondary to PM. The study was performed in 12 centres in the UK. The primary endpoint was the mean change from baseline in BCVA at 12 months and an interim analysis at 6 months was also undertaken.[39,40,58] The 6 and 12 month analyses are included in this submission.

1.7 If the technology has not been launched, please supply the anticipated date of availability in the UK.

The UK launch for ranibizumab for the treatment of CNV secondary to PM is anticipated in September 2013.

1.8 Does the technology have regulatory approval outside the UK? If so, please provide details.

Ranibizumab does not have regulatory approval for the treatment of CNV secondary to PM outside the UK; a CHMP positive opinion for a pan European regulatory approval was received on the 30th May 2013. Ranibizumab has regulatory approval for the treatment of wet age-related macular degeneration (AMD), visual impairment due to diabetic macular oedema (DMO) and macular oedema secondary to retinal vein occlusion (RVO) in the European Union (EU) and in the USA.[1,31]

1.9 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

Novartis made a submission to the Scottish Medicines Consortium (SMC) for ranibizumab in the indication described in this submission in June 2013.

Ranibizumab was approved by NICE for treatment of visual impairment due to DMO in patients with a central retinal thickness ≥ 400 µm in February 2013,[59] and by SMC for treatment of visual impairment due to DMO in patients with BCVA ≤ 75 letters in December 2012.[60] Ranibizumab was also recently approved for treatment of visual impairment caused by macular oedema secondary to RVO in May 2013 by NICE,[61] and by SMC (branch RVO [SMC 732/11, May 2013][62] or central RVO, [SMC 732/11, November 2011][63]).

1.10 For pharmaceuticals, please complete the table below. If the unit cost of the pharmaceutical is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Table 6 Unit costs of technology being appraised

Pharmaceutical formulation	10 mg/ml solution for intravitreal injection
Acquisition cost (excluding VAT)	£742.17 per 0.23 ml vial
Method of administration	Intravitreal injection
Doses	0.5 mg given as a single intravitreal injection (injection volume 0.05 ml)
Dosing frequency	Treatment is initiated with a single injection. If monitoring reveals signs of activity, further treatment is recommended. Monitoring for disease activity may include clinical examination, OCT or FA. Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year the frequency of monitoring should be determined by the treating physician.[1]
Average length of a course of treatment	Treatment duration depends on patient response. In the Novartis phase III study, 59% of patients retreated according to disease activity required two or fewer injections over the first 6 months.
Average cost of a course of treatment	The cost of a course of treatment depends on patient response.
Anticipated average interval between courses of treatments	The treatment interval should not be shorter than 1 month.
Anticipated number of repeat courses of treatments	Further injections are required when monitoring reveals disease activity, e.g. reduced visual acuity and/or signs of lesion activity (clinical examination, OCT or FA).
Dose adjustments	Not applicable
FA, fluorescein angiography; OCT, optical coherence tomography; VAT, value added tax	

1.11 For devices, please provide the list price and average selling price. If the unit cost of the device is not yet known, provide details of the anticipated unit cost, including the range of possible unit costs.

Not applicable.

1.12 Are there additional tests or investigations needed for selection, or particular administration requirements for this technology?

It is anticipated that no additional tests or investigations will be needed for selection of patients suitable to receive ranibizumab treatment.

The Royal College of Ophthalmologists (RCO) guidelines for intravitreal injection procedures recommend administration by an experienced ophthalmologist in a dedicated clean room, sterilisation of peri-operative equipment, and a specified mode of administration and post-injection management.[64] These guidelines apply to intravitreal injection of all products, including ranibizumab.

1.13 Is there a need for monitoring of patients over and above usual clinical practice for this technology?

Treatment is initiated with a single injection. If monitoring reveals signs of activity, further treatment is recommended. Monitoring for disease activity may include clinical examination, optical coherence tomography (OCT) or fluorescein angiography (FA). Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician.

1.14 What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

Broad-spectrum antimicrobial eye drops should be given before and after each injection. In addition, the periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia should be applied immediately prior to the injection.[1]

2 Context

In this background section the manufacturer or sponsor should contextualise the evidence relating to the decision problem.

2.1 Please provide a brief overview of the disease or condition for which the technology is being used. Include details of the underlying course of the disease.

Pathology

PM is a leading cause of visual impairment and blindness worldwide.[2-9] It is a progressive condition characterised by excessive elongation of the eye and degenerative changes in the posterior segment of the eye. There is no single definition for PM but it is generally defined in terms of refractive error or axial length elongation and the presence of degenerative changes. In a recent review,[65] PM was defined as having one or more of the following: a refractive error ≥ –6 dioptres, axial length ≥ 26.5 mm and the presence of fundus changes consistent with PM, such as lacquer cracks (linear breaks in Bruch's membrane) and chorioretinal atrophy (discrete areas of macular degeneration).

In highly myopic eyes, stretching and thinning of the retina and choroid following axial elongation and distension of the posterior pole can lead to development of fundus lesions[10] such as: tessellated fundus (choroidal vessels are visible through the retina), patchy or diffuse chorioretinal atrophy, lacquer cracks, CNV (newly formed abnormal blood vessels growing under retinal pigment epithelium [RPE] or retina) and Fuchs' spot (fibrous pigmented scar). Of these lesions, CNV is most commonly associated with vision loss.[66]

CNV is characterised by newly formed abnormal vessels that may penetrate Bruch's membrane and extend into the subretinal space.[11] These vessels can rupture, causing blood and fluid to accumulate within the retinal layers, leading to deterioration of vision. CNV secondary to PM is typically located in close proximity to the fovea.[65] CNV can ultimately produce a fibrous pigmented scar, known as Fuchs' spot or Forster–Fuchs' retinal spot, which can cause central vision loss.[67] The precise pathogenesis of CNV associated with PM is unclear, but evidence suggests it could result from mechanical tissue strain caused by axial elongation, leading to choroidal ischaemia, RPE atrophy and growth factor release.[67] This is then thought to cause further RPE atrophy, development of lacquer cracks and CNV. This theory is supported by findings that lacquer cracks or patchy chorioretinal atrophy are the two most common predisposing fundus changes in the development of CNV secondary to PM,[10,66] and that the prevalence of lacquer cracks is observed to be higher in individuals with CNV

secondary to PM than in individuals with PM alone.[10,13,18,20-22,66] According to the mechanical theory, the RPE cell layer up-regulates the expression and secretion of angiogenic factors including VEGF, which stimulates the development of CNV secondary to PM. Eyes with active CNV secondary to PM have shown higher levels of VEGF in the aqueous humour compared to controls.[12]

Prognosis

Many studies indicate that, over time, further atrophy may develop in eyes with CNV and this can contribute to poor visual acuity. Yoshida et al. (2003)[22] reported that in 96% of eyes with PM secondary to CNV, chorioretinal atrophy developed around the regressed CNV within 5 years of CNV onset. Atrophic tissue is thought to gradually spread from Fuch's spot with time,[20,67] potentially involving the whole posterior pole and preventing the eye from achieving a fixation point in the macula.[67]

Eleven studies have reported on the visual outcome in untreated patients with CNV secondary to PM; all reported deterioration in vision over time.[13-24] For example, the study with the longest follow-up, reported by Yoshida et al. (2003),[23] reviewed the medical records of 25 patients with CNV secondary to PM over a mean follow-up period of 11 years after CNV onset. At the initial examination, 29.4% of eyes were legally blind (i.e. BCVA < 20/200) and by 5 and 10 years 88.9% and 96.3% of eyes, respectively, were legally blind. Similarly, Secretan et al. (1997)[20] reported on the change in BCVA in 50 untreated eyes with CNV secondary to PM seen at a single French centre and followed for at least 5 years. After 5 years, 62% had a 15-letter deterioration in BCVA. At 8 years of follow-up, 58% of the 41 included eyes had deterioration in vision, and this increased to 76% of the 13 eyes followed up at 10 years. In total, eight studies reported BCVA at baseline and at study end, and all but two of these reported either an increase of at least 20% in the proportion of individuals who were legally blind (BCVA ≤ 20/200), or a statistically significant decrease in mean BCVA, over a mean follow-up ranging from 3 months to 11 years.[13,15-17,19,21-23] The two studies that did not report deterioration in BCVA had a high proportion of legally blind patients at baseline (45% and 60%).[13,15] Seven studies reported the rates of legal blindness (BCVA ≤ 20/200) at follow-up; 53 to 96% of patients were legally blind after a mean follow-up ranging from 1 to 11 years.[13,16,17,21-23]

Older age, subfoveal location and larger lesion size are associated with worse prognoses in patients with CNV secondary to PM, according to five studies that have investigated factors associated with prognosis.[14,16,17,19,22] In four of these studies, younger age was associated with a better outcome.[16,17,19,22] Yoshida et al. (2002)[22] found that BCVA deteriorated significantly only in those aged over 40 years (mean follow-up, 7 years). Three studies reported that subfoveal CNV location (as opposed to extrafoveal or juxtafoveal location) [14,16,17]

is an independent risk factor for poor visual prognosis, as is larger lesion size.[16,17,19] Initial BCVA,[17,19] duration of persisting haemorrhage and axial length in patients aged over 40 years,[19] and the development of chorioretinal atrophy[17] have also been found to be associated with poor visual outcomes.

2.2 Please provide the number of patients covered by this particular therapeutic indication in the marketing authorisation and also including all therapeutic indications for the technology, or for which the technology is otherwise indicated, in England and Wales and provide the source of the data.

Visual impairment due to CNV secondary to PM

This submission concerns ranibizumab for the treatment of visual impairment due to CNV secondary to PM. Due to the rapid and irreversible nature of the CNV secondary to PM, once a patient progresses to severe visual loss, the number of patients covered by the marketing authorisation is driven by the incidence of CNV in patients with PM. Only patients with visual impairment will be eligible for treatment. The number of patients covered by this indication was calculated based on the following available evidence.

There are only limited data regarding the prevalence of PM in general populations. The Blue Mountains Eye Study, performed in Australia, is the only study in a Caucasian population and reported a prevalence of PM in adults aged ≥ 49 years of 1.2% (individuals).[24] A single study performed in Tokyo has reported the incidence of CNV in patients with PM.[66] In this follow-up of 218 patients with PM over an 11 year period, 10.2% of patients developed CNV (0.98% per year) and 34.7% developed bilateral CNV (5.5% per year).

The UK population of people aged 40 years or older is estimated at over 30.6 million.[68] Based on the assumptions described below, the numbers of patients eligible for treatment is estimated to increase from 2045 in 2014 to 2119 in 2018, as shown in Table 7. The assumptions behind these calculations are: the prevalence of PM in this population is 1.20%;[24] the annual incidence of CNV is 0.98% in patients with PM;[66] 81% of patients are eligible for pharmacotherapy;[16] the average diagnosis rate increases from 83% in 2014 to 86% in 2018 (see Table 7); 80% of eligible patients are treated and 5.5% have bilateral disease.[66]

Table 7 Average diagnosis rate and the number of patients with CNV secondary to PM estimated to be eligible for treatment with ranibizumab over a 5 year time horizon

Year	2014	2015	2016	2017	2018
Average diagnosis rate	83%	84%	85%	86%	86%
Patients starting treatment	2045	2070	2094	2119	2119

Other indications

Ranibizumab is also approved for the treatment of neovascular (wet) AMD, visual impairment due to DMO and visual impairment due to macular oedema secondary to RVO (branch RVO or central RVO).[1] Estimates for the number of patients for each of these indications are given below:

- According to the NICE costing template for ranibizumab and pegaptanib for the treatment of AMD (NICE technology appraisal guidance TA 155), an estimated 21,520 adults have wet AMD in England, Wales and Northern Ireland.
- According to the NICE costing statement for ranibizumab for the treatment of DMO (NICE technology appraisal guidance TA 274), an estimated 11,700 adults in England, Wales and Northern Ireland may need treatment for DMO. This value may be an underestimate as it is based on the number of people diagnosed with diabetes.
- The annual incident population of patients with visual impairment due to macular oedema secondary to RVO is estimated to be 17,340 patients: 11,640 with branch RVO and 5,700 with central RVO.[69]

2.3 Please provide information about the life expectancy of people with the disease in England and Wales and provide the source of the data.

CNV secondary to PM does not have a direct effect on life expectancy but is associated with blindness. Loss of vision is associated with increased mortality.[55]

2.4 Please give details of any relevant NICE guidance or protocols for the condition for which the technology is being used. Specify whether any specific subgroups were addressed.

There is no NICE guidance or protocols regarding treatment of visual impairment due to CNV secondary to PM.

2.5 Please present the clinical pathway of care that depicts the context of the proposed use of the technology. Explain how the new technology may change the existing pathway. If a relevant NICE clinical guideline has been published, the response to this question should be consistent with the guideline and any differences should be explained.

There are currently no guidelines or treatment algorithms for CNV secondary to PM. Treatment practice varies between centres in the UK and there is no preferred treatment. vPDT is the only licensed treatment for this indication but has not been shown to provide clinical benefit beyond one year.[25,26] Clinical input at the scoping meeting indicated that some areas of the UK are without consistent and regular access to funding in this indication.

2.6 Please describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

There are currently no standard treatments for management of visual impairment due to CNV secondary to PM.

2.7 Please identify the main comparator(s) and justify their selection.

vPDT is the only comparator considered in this submission. vPDT is the only licensed treatment for CNV secondary to PM.

In contrast to the final NICE scope for this appraisal, bevacizumab has not been considered as a comparator to ranibizumab in this single technology appraisal. The use of unlicensed bevacizumab is not considered as established practice across the NHS, according to clinical experts at NICE scoping meetings for technology appraisals in this indication. Furthermore, given the absence of approval for bevacizumab, it cannot be considered best practice.

The use of intravitreal bevacizumab represents the use of a product that does not have regulatory approval for any ocular indications, is not presented in a licensed formulation for administration in the eye and does not have approval for compounding into smaller doses for ocular use. Potential systemic and ocular safety signals for bevacizumab mean that it is inappropriate to include this intervention in an appraisal before safety and quality have been assessed by the regulatory authorities.[70-72] The implications of these safety signals are a need for a large pharmacovigilance programme, as identified by stakeholders during the exploratory work by NICE regarding the feasibility of an appraisal of bevacizumab for eye conditions.[73] There are also liability consequences of unlicensed use. The uncertain costs of these activities cannot be incorporated adequately into an economic analysis using the existing NICE guidance for technology appraisal. Finally, General Medical Council (GMC) guidance is clear that use of an unlincensed medicine might be reasonable when there is no licensed alternative available; however the situation will be entirely different the moment the new medicine receives its marketing authorisation and is available to the NHS. GMC prescribing advice would then support use of the licensed medicine and the use of the unlicensed medicine only in exceptional circumstances where that would serve an individual patient's need. Therefore inclusion of unlicensed bevacizumab as a comparator to ranibizumab in this submission is considered inappropriate and implausible.

Furthermore, there is a lack of reliable and robust efficacy and safety data for bevacizumab in the treatment of CNV secondary to PM as there are only two small head to head trials comparing ranibizumab and bevacizumab,[46,47] which have considerable methodological weaknesses. Gharbiya 2010[47] is unclear with respect to how randomisation and allocation concealment were performed. It is also unclear whether patients were similar at baseline in terms of prognostic factors and whether the treating investigator(s) and outcomes assessors were blinded to treatment. Finally, it is not reported if an intention-to-treat approach was used for the analyses. The lack of rigour associated with this study was further ratified by the critical appraisal within the bevacizumab in eye conditions NICE DSU report by Poku et al 2013.[54] The second trial, by Iacono 2012,[46] is an explorative study and was not designed to produce comparative results. Multiple testing was not accounted for even though there are three defined primary variables and further comparisons between and within groups. The analyses are reported as intent-to-treat but elsewhere the manuscript stated that the analyses excluded "patients who did not complete all visits." Therefore the analyses are inconsistent with the standard intent-to-treat approach. Finally, there are inconsistencies in the reporting of the results as well as limited safety data presented.

To conclude, vPDT is the main comparator of ranibizumab for the treatment of vision impairment due to CNV secondary to PM.

2.8 Please list therapies that may be prescribed to manage adverse reactions associated with the technology being appraised.

The majority of adverse events associated with ranibizumab are mild and transient in nature and therefore require no prescribed therapies. Broad spectrum antibiotic eye drops are recommended before and after intravitreal injection to minimise risk of endophthalmitis.[1]

2.9 Please identify the main resource use to the NHS associated with the technology being appraised. Describe the location of care, staff usage, administration costs, monitoring and tests. Provide details of data sources used to inform resource estimates and values.

The main resource use associated with ranibizumab is hospital outpatient visits, which include the staffing requirements for monitoring of disease activity. Treatment is initiated with a single injection. If monitoring reveals signs of activity, further treatment is recommended. Monitoring for disease activity may include clinical examination, OCT or FA. Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician. It is anticipated that care will most frequently be provided in ophthalmology units under the supervision of consultant ophthalmologists. Non-consultant grade ophthalmologists, specialist and other grade nurses, optometrists, orthoptists and technicians may also be involved in delivering care to patients receiving ranibizumab. In addition to staff time, administration costs may include those associated with maintaining a clean room and sterile equipment, anaesthesia and anti-microbial eye drops. It is expected that the majority of patients will receive intravitreal injections during an outpatient ophthalmologist appointment.

The location of care, staff delivering treatment and frequency of monitoring and tests are likely to vary between ophthalmology units depending on local practice. Table 8 illustrates resource use estimates and their data sources. All resource use estimates have been validated by NHS ophthalmologists that currently treat patients with visual impairment due to CNV secondary to PM.

Table 8 Anticipated resource use associated with ranibizumab treatment

	Resource use	Data sources
Monitoring of disease activity	Hospital outpatient visits [consultant ophthalmologist or non-consultant grade ophthalmologist]	Draft SPC; verified by expert clinical opinion
	BCVA assessment will be undertaken as standard during the appointment [no additional resource as conducted during outpatient appointment]	
	OCT [OCT session with optometrist]	
Injection visit	Hospital outpatient visit, in a clean room [consultant ophthalmologist or non-consultant grade ophthalmologist}	Draft SPC; verified by expert clinical opinion
	BCVA assessment will be undertaken as standard during the appointment [no additional resource as conducted during outpatient appointment]	
	OCT [OCT session with optometrist]	
Additional resource use for treatment administration	Anti-microbial drops and topical anaesthesia	Draft SPC
BCVA, best corrected visual acuity; OCT, optical coherence tomography; SPC, summary of product characteristics		

2.10 Does the technology require additional infrastructure to be put in place?

No additional infrastructure is required. Ranibizumab has been routinely used in the NHS since 2008 for the treatment of wet AMD. Appropriate facilities for the administration of intravitreal injections are therefore already well established.

3 Equality

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. For further information, please see the NICE website (www.nice.org.uk/aboutnice/howwework/NICEEqualityScheme.jsp).

3.1 Identification of equality issues

3.1.1 Please let us know if you think that this appraisal:

- could exclude from full consideration any people protected by the equality legislation who fall within the patient population for which [the treatment(s)] is/are/will be licensed;
- could lead to recommendations that have a different impact on people protected by the equality legislation than on the wider population, e.g. by making it more difficult in practice for a specific group to access the technology
- could lead to recommendations that have any adverse impact on people with a particular disability or disabilities

Please provide us with any evidence that would enable the Committee to identify and consider such impacts.

There are no equality issues or equality legislation pertinent to the technology.

3.1.2 How has the analysis addressed these issues?

Not applicable

4 Innovation

4.1.1 Discuss whether and how you consider the technology to be innovative in its potential to make a significant and substantial impact on health-related benefits, and whether and how the technology is a 'step-change' in the management of the condition.

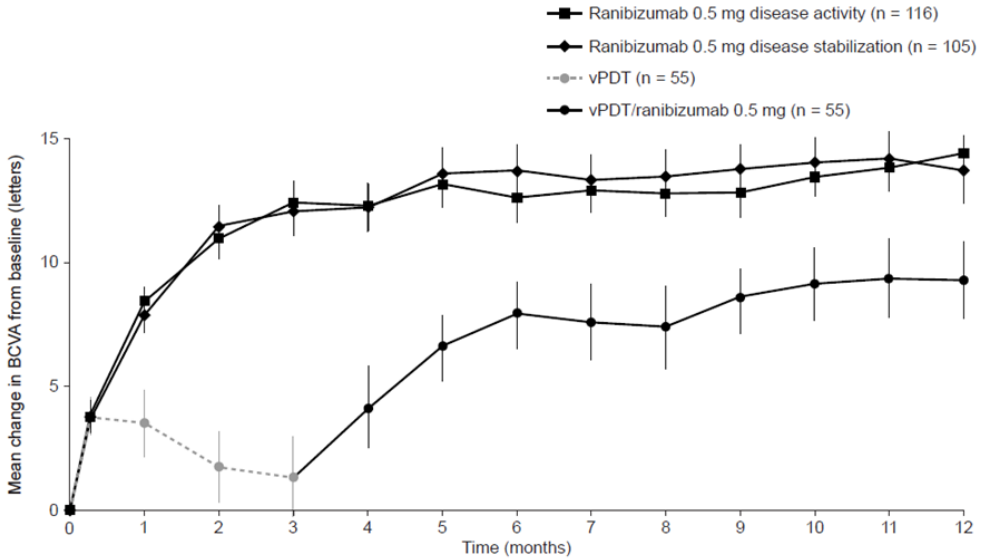
Ranibizumab has the potential to make a clinically significant impact on the treatment of patients with visual impairment due to CNV secondary to PM, a patient group with a mean age of around 55 years[33] who are likely to be working and have family responsibilities, and for whom there are currently limited treatment options

Ranibizumab will be the first licensed therapy to specifically target the pathogenesis of CNV secondary to PM. VEGF is a potent stimulator of angiogenesis, the process that leads to the development of CNV, and increased expression of VEGF has been temporally and spatially correlated with the development of CNV;[65] eyes with active CNV have demonstrated higher levels of VEGF in the aqueous humour compared to controls.[12] Ranibizumab inhibits the binding of VEGF-A to VEGFR1 and VEGFR2, thereby inhibiting the angiogenic effects of VEGF that contribute to the development of CNV.[31] Thus ranibizumab directly targets the development of CNV. This is in contrast to vPDT, the only other licensed therapy for CNV secondary to PM, which is a photoreactive dye that, when activated by non-thermal red light, produces highly reactive short-lived oxygen radicals that cause local damage to neovascular endothelium, resulting in occlusion of blood vessels.[74]

Ranibizumab will be the first licensed therapy to achieve clinically significant **improvements** in BCVA in patients with visual impairment due to CNV secondary to PM. In a phase III, randomised, double-blind, multicentre study evaluating the efficacy and safety of two different dosing regimens of 0.5 mg ranibizumab versus vPDT in patients with visual impairment due to CNV secondary to PM, both ranibizumab treatment arms demonstrated statistically greater mean average changes in BCVA from baseline to month 3 compared with vPDT and the gain in BCVA achieved with ranibizumab was sustained at 12 months (see section 6.5).[33,34] The mean (± SD) average gain in BCVA from baseline to month 3 was 10.6 ± 7.3 letters in the ranibizumab disease activity group and 10.5 ± 8.2 letters in the ranibizumab disease stabilisation group compared to 2.2 ± 9.5 letters in the vPDT group, a difference that was highly statistically significant ($p < 0.00001$ for both comparisons).[32-34] At month 3, patients receiving ranibizumab had achieved a gain of approximately 12 letters from baseline,[33,34] a difference that is considered to be clinically relevant.[75-78] At 12 months, the mean average gain in BCVA from baseline was 12.5 ± 8.83 letters in the ranibizumab disease activity group

and 12.8 ± 9.48 letters in the stabilisation group. Gains in BCVA over baseline were observed in both ranibizumab groups from month 1 onwards (Figure 5).

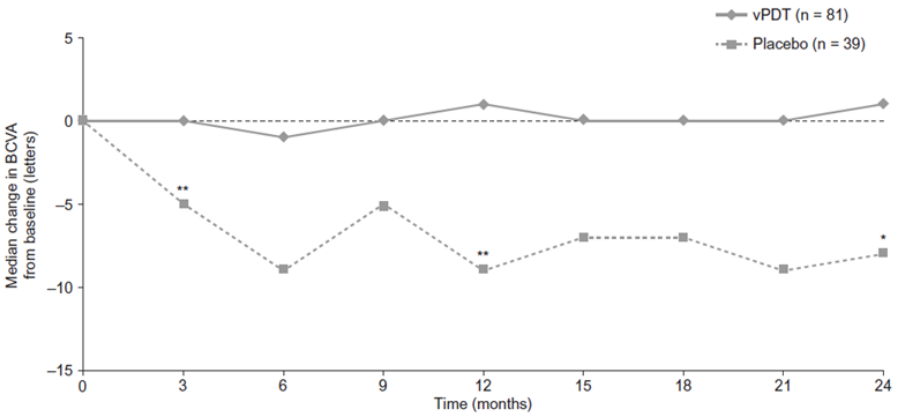
Figure 5 Mean (± SE) change in BCVA over time during treatment with ranibizumab or vPDT/ranibizumab



Bandello et al., 2013[33]
BCVA, best-corrected visual acuity; SE, standard error; vPDT, verteporfin photodynamic therapy.
From month 3 to 11, the investigators had the option to treat the disease activity of patients randomised to vPDT with 0.5 mg ranibizumab, vPDT, or a combination of 0.5 mg ranibizumab and vPDT.

In contrast, vPDT generally stabilises, but does not improve, visual acuity. Thus in the ranibizumab phase III study, at 3 months vPDT was associated with a gain of only 1.4 letters from baseline.[34] This is in agreement with data from the Verteporfin in Photodynamic Therapy (VIP) study, a large, multicentre, double-blind, placebo-controlled trial that randomised 120 eyes with subfoveal CNV secondary to PM to receive placebo or vPDT.[25,26] Patients gained a median of 0 letters from baseline at 3 months and 1 letter from baseline at both 12 and 24 months (Figure 6). A gain of at least 15 letters was achieved by 2%, 6% and 12% of patients at 3, 12 and 24 months, respectively.[25,26] By 24 months, the difference between groups in the number of patients with stable BCVA was no longer significant (64% in the vPDT group versus 49% in the placebo group, p = 0.11). Furthermore, a recent study has reported that almost half (46.1%) of patients experienced at least one recurrence during a 4-year follow-up following vPDT.[27] Additionally, vPDT is associated with various safety concerns including visual disturbances,[25,26,28,29] injection site reactions,[25,26] choroidal vessel occlusion[30] and haemorrhagic complications.[29]

Figure 6 Change in median BCVA over time during treatment with vPDT or placebo in the VIP study[a]



VIP trial, Blinder et al 2003[25]
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; VIP, verteporfin in photodynamic therapy
[a]The change in median BCVA letter score was a secondary endpoint. The primary endpoint was the proportion of eyes with fewer than 8 letters of BCVA loss at 12 months.
*p < 0.05; **p < 0.01 versus placebo.
Statistical analyses are presented for all time points reported in the original publications.

If patients with CNV secondary to PM do not receive treatment, their vision will deteriorate over time. Yoshida et al. (2003)[23] reviewed the medical records of 25 patients with CNV secondary to PM over a mean follow-up period of 11 years after CNV onset. At the initial examination, 29.4% of eyes were legally blind (i.e. BCVA < 20/200) and by 5 and 10 years 88.9% and 96.3% of eyes, respectively, were legally blind. Hayashi et al. (2005)[17] reviewed the medical records of 57 eyes with CNV secondary to PM followed for 5 years after CNV onset. After 5 years, 37 eyes (64.9%) were legally blind, and 91.9% of these patients developed chorioretinal atrophy. Secretan et al. (1997)[20] reported on the change in BCVA in 50 untreated eyes with CNV secondary to PM seen at a single French centre and followed for at least 5 years. After 5 years, 62% had a 15-letter deterioration in BCVA. At 8 years of follow-up, 58% of the 41 included eyes had deterioration in vision, and this increased to 76% of the 13 eyes followed up at 10 years.

Ranibizumab also has a positive effect on patients' health related quality of life (HRQoL). In the Novartis phase III trial HRQoL was assessed at baseline, 3, 6 and 12 months using the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) questionnaire. At 3 months, patients treated with ranibizumab achieved significantly greater mean gains in composite score and for general vision, near activities (disease stabilisation group only), mental health and dependency subscales compared to the vPDT group ($p < 0.05$ for comparisons versus vPDT), and gains in NEI VFQ-25 scores in the two ranibizumab groups were sustained at 12 months (see section 6.5.3).[35,36]

Ranibizumab thus targets the underlying pathogenesis leading to development of CNV and provides clinically relevant improvements in visual acuity and HRQoL. In addition, ranibizumab is generally well tolerated. Ranibizumab therefore constitutes a step change in the management of visual impairment due to CNV secondary to PM.

4.1.2 Discuss whether and how you consider that the use of the technology can result in any potential significant and substantial health-related benefits that are unlikely to be included in the quality-adjusted life year (QALY) calculation.

CNV secondary to PM leads to progressive loss of vision which has a significant impact on HRQoL. This is captured in the economic assessment as the model predicts the deterioration in vision; utilities based on BCVA translate the loss of visual acuity into a deterioration in HRQoL. However the utilities employed do not take into account the additional effects of visual impairment on HRQoL such as the risk of depression and of injurious falls (e.g. leading to fractures). Furthermore, utilities based only on BCVA may not fully capture the impact of vision loss.[79] Impaired contrast sensitivity and loss of visual field are also important factors in determining visual function. For patients with monocular vision loss, these factors may be especially important as aspects of visual functioning such as depth perception and reading speed may impact on utility, but are not captured when utility is mapped solely to visual acuity. In addition, the impact on informal caregivers and loss of productivity in patients of working age is not considered. These represent significant health-related benefits associated with ranibizumab that are not captured in the economic assessment.

4.1.3 Please identify the data you have used to make these judgements, to enable the Appraisal Committee to take account of these benefits.

Various studies have identified that loss of vision is associated with an increased risk of injurious falls and depression. A recent review of the cost of blindness in the UK identified 13 studies reporting odds ratios for falls and hip fractures due to sight loss ranging from 1.43 for multiple falls (associated with a loss of visual acuity of ≥ 10 letters) to 8.4 for hip fracture (associated with a BCVA of ≤ 6/18).[80] On average across all studies, the odds ratio for accidental falls was 1.59, and the odds ratio for hip fracture was 1.83 for individuals with mild or moderate visual impairment and 3.95 for those considered blind. This review also reported on the association between visual impairment and depression and concluded that the relative risk of depression is approximately 3.5 fold higher in individuals with visual impairment compared to elderly individuals without sight loss.

5 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the evidence submission will address.

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	People with visual impairment due to CNV secondary to PM	People with visual impairment due to CNV secondary to PM	
Intervention	Ranibizumab	Ranibizumab	
Comparator(s)	vPDT and bevacizumab	vPDT	Bevacizumab has not been considered as a comparator to ranibizumab for this appraisal because the use of unlicensed bevacizumab is not considered as established practice across the NHS, according to clinical experts at NICE scoping meetings for technology appraisals in this indication. Furthermore, given the absence of approval for bevacizumab, it cannot be considered best practice and and there is a lack of reliable and robust efficacy and safety data for bevacizumab in the treatment of CNV secondary to PM.
Outcomes	The outcome measures to be considered include:	The outcome measures considered are:	The effects on BCVA are only considered for

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	• BCVA (the affected eye) • BCVA (both eyes) • Contrast sensitivity • Adverse effects of treatment • HRQoL	• BCVA (the study eye) • Adverse effects of treatment • HRQoL	the affected eye because there is insufficient information regarding the effects of vPDT on both eyes. Effects on contrast sensitivity are not considered because the impact of visual impairment on HRQoL in this condition is considered to relate to effects on BCVA and data on effects of treatment on contrast sensitivity were not assessed in the studies of ranibizumab and vPDT in this indication
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal	Cost effectiveness has been expressed in terms of incremental cost per quality-adjusted life year. A lifetime horizon has been chosen to capture all relevant outcomes and costs over the lifetime of patients with CNV secondary to PM. Costs have been	

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
	Social Services perspective.	considered from an NHS and Personal Social Services perspective.	
Subgroups to be considered	None to be considered	No subgroups have been considered	
Special considerations, including issues related to equity or equality	None to be considered	No special considerations have been considered	
BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; HRQoL, health related quality of life; NHS, National Health Service; PM, pathological myopia; vPDT, verteporfin photodynamic therapy			

Section B – Clinical and cost effectiveness

When estimating clinical and cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal' – www.nice.org.uk). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.

Element of health technology assessment	**Reference case**	**Section in 'Guide to the methods of technology appraisal'**
Defining the decision problem	The scope developed by NICE	5.2.5 and 5.2.6
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	5.2.5 and 5.2.6
Perspective costs	NHS and PSS	5.2.7 to 5.2.10
Perspective benefits	All health effects on individuals	5.2.7 to 5.2.10
Type of economic evaluation	Cost-effectiveness analysis	5.2.11 and 5.2.12
Synthesis of evidence on outcomes	Based on a systematic review	5.3
Measure of health effects	QALYs	5.4
Source of data for measurement of HRQL	Reported directly by patients and carers	5.4
Source of preference data for valuation of changes in HRQL	Representative sample of the public	5.4
Discount rate	An annual rate of 3.5% on both costs and health effects	5.6
Equity weighting	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	5.12
HRQL, health-related quality of life; NHS, National Health Service; PSS, personal social services; QALY, quality-adjusted life year		

6 Clinical evidence

Manufacturers and sponsors are requested to present clinical evidence for their technology in the following sections. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3 and 5.3.1 to 5.3.8.

6.1 Identification of studies

6.1.1 Describe the strategies used to retrieve relevant clinical data, both from the published literature and from unpublished data that may be held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.2, appendix 2.

A systematic literature review was performed to identify all studies evaluating the clinical effectiveness and safety of treatments for CNV secondary to PM. The databases and resources that were searched are shown in Table 9. Information on ongoing or recently completed trials, unpublished research and grey literature were also searched; these are summarised along with the full search strategy in Section 10.2, Appendix 2. All searches were conducted in November 2012.

Table 9 Databases and resources searched

Resource	Interface/URL
MEDLINE and MEDLINE In-Process	OvidSP
EMBASE	OvidSP
Cumulative Index to Nursing and Allied Health Literature (CINAHL)	EBSCOhost
Science Citation Index (SCI)	Web of Science
Latin American and Caribbean Health Sciences (LILACS)	http://regional.bvsalud.org/php/index.php
Cochrane Database of Systematic Reviews (CDSR)	Cochrane Library/Wiley Interscience
Cochrane Central Register of Controlled Trials (CENTRAL)	Cochrane Library/Wiley Interscience
DARE Database of Abstracts of Reviews of Effects (DARE)	Cochrane Library/Wiley Interscience
Health Technology Assessment Database (HTA)	Cochrane Library/Wiley Interscience
NHS Economic Evaluation Database (NHS EED)	Cochrane Library/Wiley Interscience
EconLit	Ovid
Health Economic Evaluations Database (HEED)	Wiley Interscience
Research Papers in Economics (RePEc)	http://repec.org/
CEA Registry	https://research.tufts-nemc.org/cear4/

One reviewer applied the predefined inclusion criteria to select studies based on titles and abstracts. The selected records were then screened based on the full-text article by two independent researchers; any discrepancies were resolved through discussion or by consulting a third reviewer.

6.2 Study selection

6.2.1 Describe the inclusion and exclusion selection criteria, language restrictions and the study selection process. A justification should be provided to ensure that the rationale is transparent. A suggested format is provided below.

Studies needed to meet the inclusion and exclusion criteria detailed in Table 10 to be selected for the systematic review. The search strategy and inclusion criteria were designed to identify all studies in patients relevant to the submission including studies reporting on the efficacy and safety of both ranibizumab and relevant comparators in patients with CNV secondary to PM. Studies that specifically investigated ranibizumab were selected as being relevant for the assessment of the safety and efficacy of ranibizumab in this indication.

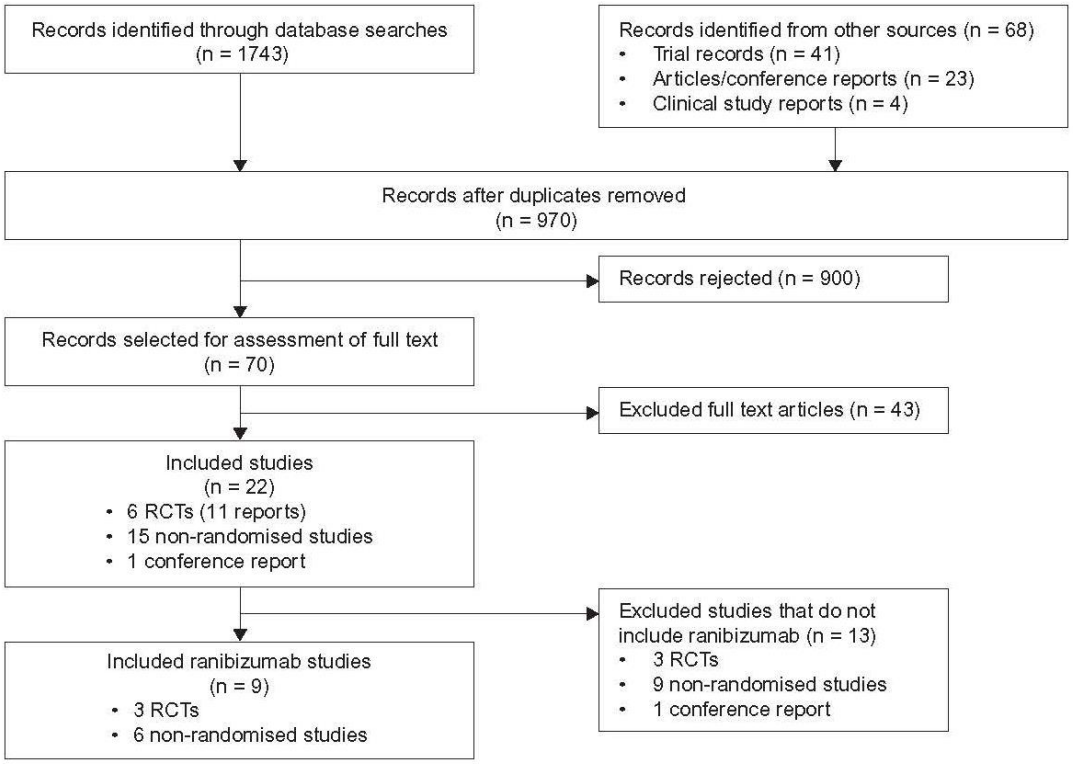
Table 10 Eligibility criteria used in search strategy

	Clinical effectiveness
Inclusion criteria	
Population	Patients of any age undergoing treatment for CNV secondary to PM, including patients with concomitant ocular disease
Intervention	Any types of treatment for CNV, including (but not restricted to) thermal laser photocoagulation therapy, surgery, vPDT and anti-VEGF therapy (e.g. bevacizumab and ranibizumab)
Comparator	'Standard care' defined as vPDT or laser treatment and other treatments identified in RCTs were eligible for inclusion
Outcomes	Visual acuity (ETDRS letters or logMAR); other measures of visual acuity such as blindness and lack of response; structural changes (e.g. foveal thickness and central retinal thickness), HRQoL, ocular and systemic AEs
Study design	RCTs of any duration; cross-over RCTs if data were presented at the time of cross-over; prospective randomised studies; open-label extension studies of RCTs; case series of ≥ 25 patients for ≥ 6 months
Language restrictions	None
Exclusion criteria	
Population	Patients with CNV secondary to causes other than PM (e.g. age-related macular degeneration)
Interventions	Treatments that are only used to correct vision (e.g. contact lenses, glasses, keratectomy)
Study design	Retrospective studies and analyses, dosing studies
AE, adverse event; CNV, choroidal neovascularisation; ETDRS, Early Treatment Diabetic Retinopathy Study; HRQoL, health-related quality of life; logMAR, logarithm of the minimum angle of resolution; PM, pathological myopia; RCT, randomised controlled trial, VEGF, vascular endothelial growth factor; vPDT, verteporfin photodynamic therapy	

6.2.2 A flow diagram of the numbers of studies included and excluded at each stage should be provided using a validated statement for reporting systematic reviews and meta-analyses such as the QUOROM statement flow diagram (www.consort-statement.org/?o=1065). The total number of studies in the statement should equal the total number of studies listed in section 6.2.4.

The review identified three RCTs and six non-RCTs that provide information on the efficacy and safety of ranibizumab in patients with CNV secondary to PM (Figure 7). The source for one of the RCTs, the Novartis phase III study, identified in the systematic literature review was a clinical study report (CSR). Results from this study were presented at the 2013 Annual meeting of the Association for Research in Vision and Ophthalmology (ARVO), held on 5th to 9th of May 2013 and these publications are included in this submission.

Figure 7 PRISMA diagram of included and excluded studies for the systematic review



PRISMA, preferred reporting items for systematic reviews and meta-analyses; RCT, randomised controlled trial

6.2.3 When data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or when trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Where data for a single RCT are taken from multiple sources these are clearly referenced. There were five reports of the Verteporfin in Photodynamic Therapy (VIP) study. Two were published papers, one which presented one-year results[26] and the other two-year results,[25] and are the main references used for this study. Two further sources were study reports reporting one- and two-year results,[81,82] and a third was an abstract.[83] Results of the Novartis phase III study have been published in two abstracts presented at ARVO 2013[33,35] and further details and data are described in the CSR.[32]

Complete list of relevant RCTs

6.2.4 Provide details of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the Evidence Review Group. This should be presented in tabular form. A suggested format is presented below.

Three RCTs were identified that report efficacy data for ranibizumab in the indication of interest: the Novartis phase III trial,[33,36] Iacono 2012[46] and Gharbiya 2010.[47] These are summarised in Table 11.

The Novartis trial was a phase III, randomised, double-blind, multicentre study that compared two different dosing regimens of ranibizumab 0.5 mg to vPDT in patients with visual impairment due to CNV secondary to PM.[33] The other two RCTs compared ranibizumab and bevacizumab in patients with CNV secondary to PM.

Table 11 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
Novartis phase III trial NCT01217944	Ranibizumab IVT injection (0.5 mg), two dosing regimens	vPDT[a]	Patients with visual impairment due to CNV secondary to PM	Bandello et al. ARVO 2013[33]
Iacono 2012	Ranibizumab IVT injection (0.5 mg)	Bevacizumab IVT injection (1.25 mg)	Patients with subfoveal CNV secondary to PM	Iacono P et al. *Retina* 2012; 32:1539–46[46]
Gharbiya 2010 ISRCTN 49803272	Ranibizumab IVT injection (0.5 mg)	Bevacizumab IVT injection (1.25 mg)	Patients with CNV secondary to PM	Gharbiya M et al. *Am J Ophthalmol* 2010;149:458–64.e1[47]

Bandello et al 2013;[33] Iacono et al., 2012;[46] Gharbiya et al., 2010[47]
CNV, choroid neovascularisation; IVT, intravitreal; PM, pathological myopia; RCT, randomised controlled trial; vPDT, verteporfin photodynamic therapy
[a]6 mg/m2 intravenously followed by a standard fluence rate of 600 mW/cm^2 delivered for 83 seconds with a light dose of 50 J/cm^2.

6.2.5 Please highlight which of the RCTs identified above compares the intervention directly with the appropriate comparator(s) with reference to the decision problem. If there are none, please state this.

The Novartis phase III trial is directly relevant to the decision problem because it compares the intervention of interest, ranibizumab, with the relevant comparator of interest, vPDT.[33] The patient population within the trial (described in section 0) is relevant to the decision problem because all these patients would be included within the licensed indication of ranibizumab for PM. In addition, vPDT is currently the only licensed treatment for CNV secondary to PM. This is the largest of the three RCTs identified, enrolling 277 patients who were followed up for 12 months (compared with 48 eyes[46] and 32 eyes[47] in the other two studies) and is the only multi-centre, RCT identified.

The Iacono 2012 and Gharbiya 2010 trials provide further evidence for the efficacy of ranibizumab in this indication.

6.2.6 When studies identified above have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. For example, when studies have been identified but there is no access to the level of trial data required, this should be indicated.

All three RCTs identified are discussed.

List of relevant non-RCTs

6.2.7 Please provide details of any non-RCTs (for example experimental and observational data) that are considered relevant to the decision problem and a justification for their inclusion. Full details should be provided in section 6.8 and key details should be presented in a table; the following is a suggested format.

Six relevant non-RCTs were identified by the systematic review: the REPAIR study,[39] Calvo-Gonzalez 2011,[41] Lalloum 2010,[42] Ouhadj 2010,[43] Silva 2010[44] and Vadala 2011.[45] These studies are summarised in Table 12. REPAIR was a 12-month, multicentre, single-arm, phase II study performed in 12 centres in the UK. The other five are prospective case series involving at least 25 patients followed for at least 6 months. All six studies report efficacy data for ranibizumab 0.5 mg in the relevant indication. In five of the studies patients receive a

single initial dose of ranibizumab followed by retreatment as needed, whereas in one study patients initially received three monthly doses followed by retreatment as needed.[41]

Table 12 List of relevant non-RCTs

Trial no. (acronym)	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
REPAIR 2011 NCT01037348	Ranibizumab, one dose then retreatment as needed	Patients with CNV secondary to PM	To evaluate the efficacy and safety of ranibizumab	Tufail A et al. *Eye* 2013;doi: 10.1038/eye.2013.8[39]	Reports efficacy and safety of ranibizumab in patients with CNV secondary to PM
Calvo-Gonzalez 2011	Ranibizumab, three monthly doses then retreatment as needed	Patients with CNV secondary to PM	To identify predictive factors for visual outcome and need for retreatment with ranibizumab	Calvo-Gonzalez C et al. *Am J Ophthalmol* 2011;151:529–34[41]	Reports efficacy and safety of ranibizumab in patients with CNV secondary to PM
Lalloum 2010	Ranibizumab, one dose then retreatment as needed	Patients with CNV secondary to PM	To evaluate the efficacy and safety of ranibizumab	Lalloum F et al. *Retina* 2010;30:399–406[42]	Reports efficacy and safety of ranibizumab in patients with CNV secondary to PM
Ouhadj 2010	Ranibizumab	Patients with CNV secondary to PM	To evaluate the efficacy and safety of ranibizumab	Ouhadj O et al. *J Fr Ophthalmol* 2010;33:649–54[43]	Reports efficacy and safety of ranibizumab in patients with CNV secondary to PM
Silva 2010	Ranibizumab, one dose then retreatment as needed	Patients with CNV secondary to PM	To evaluate the efficacy and safety of ranibizumab	Silva RM et al. *Retina* 2010;40:407–12[44]	Reports efficacy and safety of ranibizumab in patients with CNV secondary to PM
Vadala 2011	Ranibizumab, one dose then retreatment as needed	Patients with CNV secondary to PM	To evaluate the efficacy and safety of ranibizumab	Vadala M et al. *Br J Ophthalmol* 2011;95:657–61[45]	Reports efficacy and safety of ranibizumab in patients with CNV secondary to PM

REPAIR, Tufail et al. 2013;[39] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45]
CNV, choroidal neovascularisation; PM, pathological myopia; RCT, randomised controlled trial

6.3 Summary of methodology of relevant RCTs

6.3.1 As a minimum, the summary should include information on the RCT(s) under the subheadings listed in this section. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (www.consort-statement.org). It is expected that all key aspects of methodology will be in the public domain; if a manufacturer or sponsor wishes to submit aspects of the methodology in confidence, prior agreement must be requested from NICE. When there is more than one RCT, **the information should be tabulated**.

Methods

6.3.2 Describe the RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one RCT.

The comparative methodology for the three identified RCTs is summarised in Table 13.

The Novartis phase III trial was a 12-month, multicentre, international, double-blind trial in which 277 patients with visual impairment due to CNV secondary to PM were randomised 2:2:1 to receive ranibizumab, 0.5 mg (two groups with retreatment according to different predefined criteria) or vPDT (6 mg/m^2 intravenously followed by a standard fluence rate of 600 mW/cm^2 delivered for 83 seconds with a light dose of 50 J/cm^2).[32-34] All patients received initial treatment on day 1, were monitored at monthly intervals and received retreatment according to predefined criteria (Figure 8).

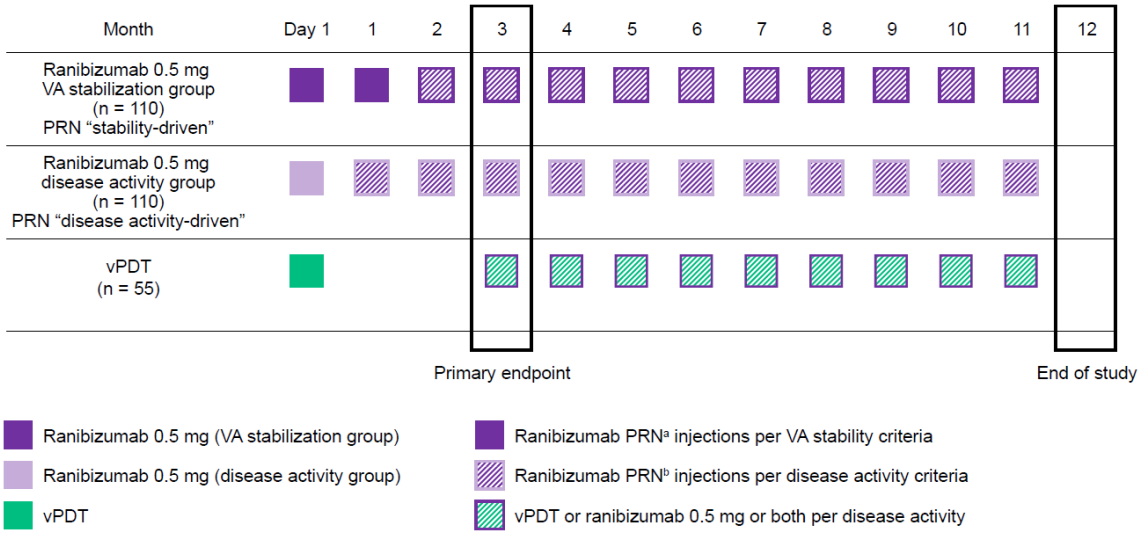
- In the ranibizumab disease activity group, patients received ranibizumab 0.5 mg on day 1. From month 1 onwards, dosing was stopped if no disease activity was seen (i.e. vision impairment, attributable to intra or subretinal fluid or active leakage secondary to PM as assessed by OCT and/or FA). Treatment was resumed when the disease activity criterion was fulfilled and continued until no disease activity was seen.
- In the ranibizumab stabilisation group, patients received ranibizumab 0.5 mg on day 1 and month 1. For the subsequent months, treatment was stopped if the stabilisation criterion for BCVA was fulfilled (i.e. no change in BCVA as compared with the two preceding monthly visits). Treatment was resumed

with monthly injections when there was a loss of BCVA due to disease activity and was continued until stable BCVA was reached again for three consecutive monthly assessments.

- In the vPDT group, patients received vPDT on day 1. For months 3 to 11, patients with disease activity could receive either ranibizumab 0.5 mg, vPDT or ranibizumab 0.5 mg plus vPDT. Treatment was stopped if no disease activity was seen. Treatment was resumed when the disease activity criterion was fulfilled (defined as for the ranibizumab group) and continued until no disease activity was seen.

To ensure blinding, on day 1 and months 1 and 2, all patients received ranibizumab or a sham ranibizumab procedure, and on day 1 all patients received vPDT or a sham vPDT procedure. There were at least two investigators involved in the study; the blinded (assessing) investigator who performed all assessments and an un-blinded (treating) investigator who administered the randomised study treatment when needed.

Figure 8 Design of Novartis phase III study



Ohno-Matsui et al., 2013[35]
PRN, pro re nata; VA, visual acuity; vPDT, vertefporfin photodynamic therapy
[a]Dosing was stopped if the VA stabilization criterion was fulfilled; treatment was resumed with monthly injections when there was a loss of visual acuity owing to disease activity and continued until stable visual acuity was reached again for three consecutive monthly assessments.
[b]Treatment was resumed when the disease activity criterion was fulfilled and continued until no disease activity was seen.

The Iacono 2012 study was a prospective, single-centre, randomised, double-blind trial in which 55 patients (55 eyes) were randomised 1:1 to treatment with ranibizumab 0.5 mg or bevacizumab 1.25 mg.[46] Both groups received an initial treatment on day 1 and were

retreated as needed if they met predefined criteria for disease progression at monthly examinations for a duration of 18 months.

The Gharbiya 2010 study was a prospective, randomised study in which 32 patients (32 eyes) were randomised 1:1 to treatment with ranibizumab 0.5 mg or bevacizumab 1.25 mg.[47] The treatment pattern was similar to that of the Iacono 2012 study, although the Gharbiya 2010 study had a shorter follow-up of 6 months.

Table 13 Comparative summary of methodology of the RCTs

Trial no. (acronym)	Novartis phase III[32-34]	Iacono 2012[46]	Gharbiya 2010[47]
Location	United Kingdom, Austria, Canada, France, Germany, Hong Kong, Hungary, India, Italy, Japan, Latvia, Lithuania, Poland, Portugal, Singapore, Slovakia, South Korea, Spain, Switzerland, Turkey	Italy	Italy
Design	Phase III, randomised, double-blind, multicentre, active-controlled study	Prospective, single-centre, randomised, double-blind clinical trial	Prospective, randomised, interventional study
Duration of study	12 months	18 months	6 months
Method of randomisation	A randomisation list (2:2:1 ratio) was produced using a validated system that automates the random assignment of treatment arms to randomisation numbers in the specified ratio	The patient randomisation was performed by means of sequentially numbered envelopes according to a computer-generated code list; a permuted block randomisation was performed with a final allocation ratio of 1:1	Eligible patients were randomly assigned in a 1:1 ratio to intravitreal injection of ranibizumab or bevacizumab. No details of the randomisation method were provided.
Method of blinding (care provider, patient and outcome assessor)	There were at least two investigators involved in the study: the blinded (assessing) investigator who performed all assessments and an un-blinded (treating) investigator who administered the randomised study treatment when needed; for blinding purposes there were both sham ranibizumab and sham vPDT applications	BCVA measurements were made at each visit by an expert examiner, unaware of the purpose of the study, and FA and OCT assessments were interpreted separately by two experienced ophthalmologists blinded to each other Study was described as double-blind, although it is unclear as no details are provided on blinding of patients or treating investigators	BCVA was measured by a single orthoptist, who was blinded to the study; all FA and OCT evaluations were interpreted by two retinal specialists in an un-blinded fashion It was unclear if patients or treating investigator were blinded to treatment
Intervention(s) (n =) and comparator(s) (n =)	Ranibizumab intravitreal injection, 0.5 mg • retreated based on disease activity criteria (n = 116)	Ranibizumab intravitreal injection 0.5 mg (n = 27) Bevacizumab intravitreal injection 1.25	Ranibizumab intravitreal injection 0.5 mg (n = 16) Bevacizumab intravitreal injection

Trial no. (acronym)	Novartis phase III[32-34]	Iacono 2012[46]	Gharbiya 2010[47]
	• retreated based on stabilisation criteria (n = 106) Verteporfin (6 mg/m^2 intravenously) followed by a standard fluence rate of 600 mW/cm^2 delivered for 83 seconds with light dose of 50 J/cm^2 (n = 55)	mg/0.05 mL (n = 28)	1.25 mg/0.05 mL (n = 16)
Primary outcomes (including scoring methods and timings of assessments)	Difference between the average level of BCVA (letters) over all monthly post-baseline assessments from month 1 to month 3 (endpoint) and the baseline level of BCVA	Change from baseline in the mean BCVA at the 18-month examination Change from baseline in the proportion of eyes improving in BCVA by > 5 and > 15 letters at the 18-month examination	Change from baseline in BCVA and FCT at 6 months
Secondary outcomes (including scoring methods and timings of assessments)	Average change in BCVA from month 1 to month 6 over baseline Mean change from baseline in BCVA at 3, 6 and 12 months Proportion of patients with ≥ 10 and ≥ 15 letters gain or reaching 84 letters, and ≥ 10 and ≥ 15 letters loss from baseline at months 3, 6 and 12 Change from baseline in CRT over time Proportion of patients with presence of active leakage Number of ranibizumab re-treatments from baseline to month 2, month 5 and month 11 Impact on HRQoL as assessed by NEI VFQ-25, EQ-5D and WPAI-	Change in the mean CMT and mean CNV area over time Mean number of injections received over 18 months	The proportions of eyes that gained ≥ 10 letters or ≥ 15 letters from baseline at 6 months Proportion of eyes losing or gaining ≥ 10% in FCT at 6 months Mean number of injections over 6 months

Trial no. (acronym)	Novartis phase III[32-34]	Iacono 2012[46]	Gharbiya 2010[47]
	GH instruments (exploratory analyses) Safety and tolerability		
Duration of follow-up	12 months	18 months	6 months

Bandello et al., 2013;[33,34] Novartis phase III study 12-month CSR;[32] Iacono et al., 2012;[46] Gharbiya et al., 2010[47]
BCVA, best corrected visual acuity; CMT, central macular thickness; CNV, choroidal neovascularisation; CRT, central retinal thickness; EQ-5D, 5-dimension EuroQol questionnaire; FA, fluorescein/fundus angiography; FCT, foveal centre thickness; IOP, intraocular pressure; HRQoL, health related quality of life; NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; OCT, optical/ocular coherence tomography; RCT, randomised controlled trial; vPDT, verteporfin photodynamic therapy; WPAI-GH, Work Productivity and Activity Impairment Questionnaire: General Health

Participants

6.3.3 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one RCT. Highlight any differences between the trials.

Inclusion and exclusion criteria for the three RCTs are listed in Table 14.

The Novartis phase III trial included male and female patients aged 18 years or more with active CNV secondary to PM and BCVA ≥ 24 and ≤ 78 letters on the Early Treatment Diabetic Retinopathy Study (ETDRS) chart.[32] Visual loss was required to be due to any CNV related to PM, and patients with any other ocular disorders were excluded. Patients with hypertension, a history of malignancy or stroke, prior treatment with laser photocoagulation, vPDT or anti-VEGF therapies, or known sensitivity to the study drugs were also excluded.

The Iacono 2012 study included patients with subfoveal CNV secondary to PM and a baseline BCVA between 20/32 and 20/400 (Snellen equivalent).[46] Patients were excluded if they had intraocular surgery of any kind within 6 months of the day of injection, any other ocular disease that could compromise vision, ocular hypertension or glaucoma as well as uncontrolled systemic hypertension, peripheral vascular disease or a history of cardiovascular disease.

Patients included in the Gharbiya 2010 study had subfoveal or juxtafoveal CNV secondary to PM, and evidence of leakage from the CNV lesion.[47] If patients had other ocular diseases that could affect vision, had received prior treatment for CNV, had a history of cerebrovascular

accident or venous thromboembolism, or had major surgery within the prior 6 weeks, they were excluded.

Table 14 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Novartis phase III trial[32]	Male or female patients ≥ 18 years of age Written informed consent given Diagnosis of active CNV secondary to PM in the study eye using the following criteria: • Presence of myopia greater than −6 D of spherical equivalence • Ocular ultrasonography or biometry demonstrating anterio-posterior elongation measurement ≥ 26 mm • Presence of posterior changes compatible with the PM seen by fundus ophthalmoscopy and fundus photography • Presence of active leakage from CNV seen by FA • Presence of intra- or subretinal fluid seen or increase of CRT by OCT At least one of the following lesion types present in the study eye: • Subfoveal (presence of abnormal neovasculature in the avascular central fovea) • Juxtafoveal (presence of abnormal neovasculature not under the centre of the fovea but < 200 µm from the centre) with involvement of the central macular area • Extrafoveal (presence of abnormal neovasculature more than 200 µm from the centre of the fovea) with involvement of the central macular area • Margin of the optic disc (presence of abnormal neovasculature at peripapilar area) with involvement of the central	Patients with inability to comply with the study or follow procedures SBP > 150 mmHg or DBP > 90 mmHg at the time of enrolment Use of anticoagulant medications (other than aspirin) at study entry and during the study Use of other investigational drugs at the time of enrolment, or within 30 days or 5 half-lives of enrolment, whichever was longer History of hypersensitivity to the study drugs or to drugs of similar chemical classes, and fluorescein or any other component of fluorescein formulation History of malignancy of any organ system (other than localised basal or squamous cell carcinoma of the skin), within the past 5 years History of stroke Any type of advanced, severe or unstable disease or its treatment, that could interfere with primary and/or secondary outcome evaluations Presence of CNV secondary to any cause other than PM Presence of active infectious disease or intraocular inflammation, active or suspected periocular infection in either eye at the time of enrolment IOP ≥ 25 mmHg for any reason in either eye at the time of enrolment

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	macular area BCVA ≥ 24 letters and ≤ 78 letters tested at 4 m starting distance using ETDRS-like BCVA chart Visual loss was to be only due to the presence of any eligible types of CNV related to PM based on clinical ocular findings (described at inclusion criteria of the study eye), FA and OCT	Ocular disorders in the study eye that could confound interpretation of study results Presence of iris neovascularisation in either eye at the time of enrolment Presence of amblyopia or ocular disorders with final BCVA < 20/200 or amaurosis in the fellow eye History of pan-retinal or focal/grid laser photocoagulation with involvement of the macular area in the study eye History of intraocular treatment with any anti-VEGF or vPDT at any time in the study eye History of intravitreal treatment with corticosteroids within 3 months prior to randomisation in the study eye History of intra-ocular surgery within 3 months prior to the randomisation in the study eye History or presence of porphyria Pregnant or nursing (lactating) women Women of child-bearing potential, unless they were: • post-menopausal • surgically sterile • using reliable contraception
Iacono 2012[46]	Spherical equivalent refractive error of −6.0 D or more (if < −6.0 D, eyes could be eligible if there were retinal abnormalities consistent with PM, such as lacquer cracks, chorioretinal atrophy or posterior staphyloma, and if the axial length of the eye was ≥ 26.5 mm)	Intraocular surgery of any kind within 6 months of the day of injection Any other ocular disease that could compromise vision in the study eye

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	Naïve subfoveal myopic CNV (subfoveal defined as the presence of CNV under the geometric centre of the foveal vascular zone, confirmed on FA) Baseline BCVA between 20/32 and 20/400 Women at least 12 months post-menopause or using standard forms of contraception	Ocular hypertension or glaucoma Uncontrolled systemic hypertension, peripheral vascular disease, and history of thromboembolism, ischaemic heart disease or stroke
Gharbiya 2010[47]	PM, defined as axial length > 26.5 mm Subfoveal or juxtafoveal CNV (CNV was classified as juxtafoveal if the lesion was closer than 200 μm but not under the geometric centre of the foveal avascular zone) Evidence of leakage from CNV on FA	Prior treatment for CNV Other ocular diseases that could affect the visual acuity, including angioid streaks, trauma, choroiditis, hereditary diseases in the study or the fellow eye, aphakia, previous vitreoretinal surgery Prior history of bleeding diathesis Prior cerebrovascular accident, pulmonary embolus or deep venous thrombosis Myocardial infarction or uncompensated coronary artery disease within the past 6 months Major surgery within the prior 6 weeks Ongoing uncontrolled hypertension
Novartis phase III study 12-month CSR;[32] Iacono et al., 2012;[46] Gharbiya et al., 2010[47] BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; CRT, central retinal thickness; D, dioptres; DBP, diastolic blood pressure; ETDRS, Early Treatment Diabetic Retinopathy Study; FA, fluorescein/fundus angiography; IOP, intraocular pressure; OCT, optical/ocular coherence tomography; PM, pathological myopia; RCT, randomised controlled trial; SBP, systolic blood pressure; VEGF, vascular endothelial growth factor; vPDT, verteporfin photodynamic therapy		

6.3.4 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one RCT.

Baseline demographics and disease-related characteristics for the three RCTs are summarised in Table 15 (Novartis phase III trial) and Table 16 (Iacono 2012 and Gharbiya 2010).

In the Novartis phase III trial, patient demographics and baseline disease characteristics were well-balanced between the treatment groups.[34] The majority (75.5%) were female, which is typical in patients with PM[26,84], and the mean age was 54 to 57 years across the three groups. Approximately two-thirds of lesions were subfoveal. The mean BCVA at baseline was 55 letters and approximately 60% of patients had a BCVA of more than 60 letters.[32]

In the Iacono 2012 trial, the mean age was 61 years in the bevacizumab group and 65 years in the ranibizumab group, 75% of patients were female and mean BCVA at baseline was 55 letters.[46] In the Gharbiya 2010 trial, the mean age was 60 years, 69% were female and the mean BCVA at baseline was 50 to 55 letters.[47]

Table 15 Characteristics of participants across randomisation groups in the Novartis phase III trial

Baseline characteristic	Ranibizumab 0.5 mg, retreatment by disease activity (n = 116)	Ranibizumab 0.5 mg, retreatment by stabilisation (n = 106)	Verteporfin PDT (n = 55)
Age, years, mean ± SD (range)	56.1 ± 14.4 (19–85)	54.0 ± 14.0 (18–87)	57.4 ± 12.8 (26–86)
Females, n (%)	87 (75.0)	82 (77.4)	40 (72.7)
Ethnic background, n (%)			
Caucasian	70 (60.3)	60 (56.6)	32 (58.2)
Asian	46 (39.7)	45 (42.5)	23 (41.8)
Other	0	1 (0.9)	0
Visual acuity, ETDRS letters, mean ± SD	55.8 ± 12.6	55.4 ± 13.4	54.7 ± 13.8
Visual acuity subgroup, n (%)			
< 45 letters	26 (22.4)	21 (19.8)	13 (23.6)
45– < 60 letters	42 (36.2)	47 (44.3)	21 (38.2)
60– < 73 letters	39 (33.6)	29 (27.4)	17 (30.9)
≥ 73 letters	9 (7.8)	9 (8.5)	4 (7.3)
IOP, mmHg, mean ± SD	15.1 ± 3.2	15.1 ± 2.8	14.8 ± 3.0
Axial length, mm, mean ± SD	28.8 ± 1.8	29.3 ± 1.9	29.4 ± 1.9
Refraction sphere, D, mean ± SD	11.6 ± 4.7	13.7 ± 5.2	12.2 ± 4.9
CRT, µm, mean ± SD	373.1 ± 127.44	350.2 ± 95.12	355.1 ± 102.35
CNV location subtype, n (%)			
Subfoveal	81 (69.8)	71 (67.0)	38 (69.1)
Juxtafoveal	24 (20.7)	26 (24.5)	16 (29.1)
Extrafoveal	3 (2.6)	7 (6.6)	1 (1.8)
Can't grade	5 (4.3)	1 (0.9)	0
Not applicable	2 (1.7)	1 (0.9)	0
Missing	1 (0.9)	0	0

Bandello et al., 2013;[34]; Ohno-Matsui et al., 2013;[35] Novartis phase III study 12 month CSR[32]
CNV, choroidal neovascularisation; CRT, central retinal thickness; D, dioptres; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; PDT, photodynamic therapy; RCT, randomised controlled trial; SD, standard deviation

Table 16 Characteristics of participants in the RCTs across randomisation groups for the Iacono 2012 and Gharbiya 2010 trials

Baseline characteristic	Ranibizumab 0.5 mg/0.05 mL	Bevacizumab 1.25 mg/0.05 mL
Iacono 2012[46] (n = 55)	*(n = 27)*	*(n = 28)*
Age, years, mean ± SD	65 ± 12	61 ± 11
Females, n (%)	20 (74.1)	22 (78.6)
Visual acuity, logMAR, mean ± SD	0.60 ± 0.29 (55 letters)	0.60 ± 0.26 (55 letters)
CMT, µm, mean ± SD	255 ± 88	221 ± 61
Gharbiya 2010[47] (n = 32)	*(n = 16)*	*(n = 16)*
Age, years, mean ± SD	60.6 ± 10.5	59.1 ± 11.4
Females, n (%)	12 (75.0)	10 (62.5)
Visual acuity, Snellen equivalent, mean	20/76	20/66
Axial length, mm, mean ± SD	29.4 ± 2.9	30.1 ± 2.5
FCT, µm, mean ± SD	251 ± 64.8	237 ± 40.8

Iacono et al., 2012;[46] Gharbiya et al., 2010[47]
CMT, central macular thickness; FCT, foveal centre thickness; logMAR, logarithm of the minimal angle of resolution; RCT, randomised controlled trial; SD, standard deviation

Outcomes

6.3.5 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life (HRQL), and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

The primary and secondary outcomes for the three identified trials are summarised in Table 17.

In the Novartis phase III trial, the primary outcome was the mean average change in BCVA measured using an ETDRS chart from baseline to month 3.[33,34] This is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.[85] The difference between the average level of BCVA over all monthly post-baseline assessments from month 1 to month 6 and from month 1 to month 12 and the baseline level of BCVA was included as a secondary outcome measure (see Table 17 for details of other secondary endpoints).

The primary outcomes in the Iacono 2012 and Gharbiya 2010 trials were the mean changes in BCVA and these studies also report the proportion of patients gaining 15 letters or more and reductions in retinal thickness.

Table 17 Primary and secondary outcomes of the RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
Novartis phase III trial[32-34,36]	The difference between the average level of BCVA (letters) over all monthly post-baseline assessments from month 1 to month 3 and the baseline level of BCVA	The change in BCVA using an ETDRS chart is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.[85]	The difference between the average level of BCVA (letters) over all monthly post-baseline assessments from month 1 to month 6 and the baseline level of BCVA The difference between the average level of BCVA (letters) over all monthly post-baseline assessments from month 1 to month 12 and the baseline level of BCVA and based on the time course of BCVA changes from baseline Proportion of patients with ≥ 10 and ≥ 15 letters gain or reaching 84 letters, and ≥ 10	As mentioned previously, the ETDRS chart is the gold standard measure for visual acuity in clinical practice.[85] A gain in BCVA of 10 letters has been shown to be associated with clinically relevant improvements in in vision-related quality of life.[78] Change in CRT from baseline provides a measure of the direct effect of treatment on the CNV lesion. The NEI VFQ-25 is a validated tool that uses 25 questions to elicit information on general health, quality of vision and vision-related quality of life[37] and has been used to demonstrate effects

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
			and ≥ 15 letters loss for each month between treatment groups The time course of CRT changes from baseline Proportion of patients with presence of active leakage over time up to month 12 Proportion of patients treated with ranibizumab by visit and the number of ranibizumab re-treatments from baseline to month 2, month 5 and month 11 in the 0.5 mg ranibizumab treatment groups Comparison of the safety and tolerability of each of the two regimens with 0.5 mg ranibizumab vs vPDT and between the two regimens of 0.5 mg ranibizumab at month 3, month 6 and month 12 Impact on HRQoL as assessed by NEI VFQ-25,	of treatment in various ocular diseases[86-88] The impact on absenteeism from work and daily activity impairment attributable to ocular health status was assessed using the Work Productivity and Activity Impairment: General Health Questionnaire (WPAI-GH)[89]

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
			EQ-5D and WPAI-GH instruments (exploratory analyses)	
Iacono 2012[46]	Change from baseline in the mean BCVA at the 18-month examination Change from baseline in the proportion of eyes improving in BCVA by > 5 and > 15 letters at the 18-month examination	See explanation for phase III study	Change in the mean CMT and mean CNV area over time Mean number of injections received over 18 months	Change from baseline in CMT and CNV area over time gives a measure of the effect of treatment on the CNV lesion
Gharbiya 2010[47]	Change from baseline in BCVA and FCT at 6 months	See explanation for phase III study	The proportions of eyes that gained ≥ 10 letters or ≥ 15 letters from baseline at 6 months Proportion of eyes losing or gaining ≥ 10% in FCT at 6 months Mean number of injections over 6 months	See explanation for phase III study Change in FCT is indicative of the effect of treatment on the CNV lesion
Bandello et al., 2013;[33,34] Ohno-Matsui et al., 2013;[36] Novartis phase III study 12 month CSR;[32] Iacono et al., 2012;[46] Gharbiya et al., 2010[47] BCVA, best corrected visual acuity; CMT, central macular thickness; CNV, choroidal neovascularisation; CRT, central retinal thickness; EQ-5D, 5-dimension EuroQol questionnaire; ETDRS, Early Treatment of Diabetic Retinopathy Study; FCT, foveal centre thickness; HRQoL, health-related quality of life; NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; RCT, randomised controlled trial; WPAI-GH, Work Productivity and Activity Impairment: General Health Questionnaire				

Statistical analysis and definition of study groups

6.3.6 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also

provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

The statistical analyses used in the three RCTs are summarised in Table 18.

The objective of the Novartis phase III trial was to demonstrate superior efficacy of ranibizumab 0.5 mg (either dosing regimen) compared with vPDT, based on the average change in BCVA from month 1 to month 3 over baseline.[32,33] A power calculation determined that 275 patients were required to detect superior efficacy for either ranibizumab regimen, defined as a treatment difference of 8 letters, with 91% power. All efficacy analyses were based on the full analysis set consisting of all randomised patients who received at least one application of study treatment and had at least one post-baseline BCVA measurement. An intent-to-treat principle was employed and a modified last observation carried forward (LOCF) approach was used to impute missing data, For the primary endpoint, a stratified Cochran–Mantel–Haenszel (CMH) test was used to compare the observed BCVA scores, and superiority was claimed according to the Hochberg principle if the one-sided p-value was less than or equal to 0.0005, or if both one-sided p-values were less than or equal to 0.001. For secondary endpoints, for continuous and ordered categorical variables, changes from baseline were compared between treatment arms using analysis of variance (ANOVA) models and/or stratified CMH/exact Fisher tests. The principal analysis was to be performed after 6 months and a further analysis was planned at a follow-up of 12 months.

The objective of the Iacono 2012 trial was to compare the effects of intravitreal ranibizumab and intravitreal bevacizumab in the treatment of subfoveal CNV secondary to PM during an 18-month follow-up.[46] A power calculation determined that approximately 44 patients were required to detect a difference in the BCVA of 10 ETDRS letters with 90% power (2-sided; 5% significance level). The main analysis was done on an intent-to-treat basis, with a Student paired and unpaired *t*-test used for continuous variables, and the Fisher exact test used for categorical variables.

The objective of the Gharbiya 2012 trial was to compare the efficacy and safety of intravitreal injection of ranibizumab versus bevacizumab in patients with CNV secondary to PM over 6

months.[47] No power calculation was reported, and it was unclear if an intent-to-treat analysis was used. Changes in BCVA and foveal centre thickness (FCT) between baseline and month 6 were analysed using a one-tailed, paired *t*-test and were the main outcome measures.
To compare treatment efficacy between the ranibizumab- and the bevacizumab-treated eyes during the 6-month follow-up period, an ANOVA was performed for continuous variables. ANOVA was also used to determine any difference between the groups in numbers of injections delivered during the 6-month period. Any differences between groups in baseline characteristics were assessed using the X^2 test for categorical variables and an ANCOVA for continuous variables.

Table 18 Summary of statistical analyses in RCTs

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Novartis phase III trial[32,33]	The primary objective was to demonstrate the superior efficacy of 0.5 mg ranibizumab driven by stabilisation and/or by disease activity re-treatment criteria vs vPDT as assessed by the difference between the average level of BCVA, (letters) over all monthly post-baseline assessments from month 1 to month 3 and the baseline level of BCVA.	For the primary endpoint, comparisons were performed using the stratified CMH test with the observed values as scores; according to the Hochberg procedure, superiority was to be claimed if the corresponding one-sided p-value was ≤ 0.001/2 ≤ 0.0005 or if both one-sided p-values were ≤ 0.001 For secondary endpoints, for continuous and ordered categorical variables, changes from baseline were compared between treatment arms using ANOVA models and/or stratified CMH/exact Fisher tests	With 110 patients in each of the ranibizumab groups and 55 patients in the vPDT group, based on pair-wise treatment group comparisons using CMH tests at multiple one-sided 0.001 (Hochberg procedure) assuming a treatment difference of 8 letters between each of the ranibizumab groups and vPDT and SD = 10 letters, the power to reject at least one of the hypotheses that vPDT is superior to either of the ranibizumab regimens is ≥ 91%	For the full analysis set, the analysis followed a modified LOCF approach with the specification that missing values occurring timely between observed values were to be replaced by the mean of the last observation before and the first observation after the missing time-point. For the primary and key secondary endpoints, no data after month 3 and month 6, respectively, were used for the mean imputation method In addition, in order to assess the impact of missing data, the following methods were used to replace missing data: 1) LOCF approach (standard), where missing values were replaced by carrying forward the previous, non-missing post-baseline value. 2) FOCB approach, where missing values were replaced by

Trial no. (acronym)	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
				carrying back the first available non-missing post-baseline value (only considering data prior to the cut-off date, if applicable).
Iacono 2012[46]	The aim of the study was to compare the effects of intravitreal ranibizumab and intravitreal bevacizumab in the treatment of subfoveal CNV secondary to PM during an 18-month follow-up	Statistical analyses were performed using Student's paired and unpaired *t*-tests for continuous variables and the Fisher exact test for categorical variables	The study was designed to detect a difference in the BCVA of 10 letters with a SD of 10 letters Approximately 44 patients (22 eyes in each arm per group) were required to detect this difference (90% power, two-sided with 5% significance level)	Analysis was done on an intent-to-treat basis
Gharbiya 2010[47]	The purpose of this study was to compare the efficacy and safety of intravitreal injection of ranibizumab versus bevacizumab in patients with CNV secondary to PM over 6 months	Changes in BCVA and FCT between baseline and month 6 were analysed with a one-tailed, paired *t*-test. Comparisons between treatment groups were analysed using ANOVA for continuous variables and the number of injections delivered	Not reported	Not reported
Bandello et al., 2013;[33] Novartis phase III study 12 month CSR;[32] Iacono et al., 2012;[46] Gharbiya et al., 2010[47] ANOVA, analysis of variance; BCVA, best corrected visual acuity; CMH, Cochran–Mantel–Haenszel; CNV, choroidal neovascularisation; ETDRS, Early Treatment Diabetic Retinopathy Study; FCT, foveal centre thickness; FOCB, first observation carried back; LOCF, last observation carried forward; PM, pathological myopia; RCT, randomised controlled trial; SD, standard deviation; vPDT, verteporfin photodynamic therapy				

6.3.7 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

[redacted]

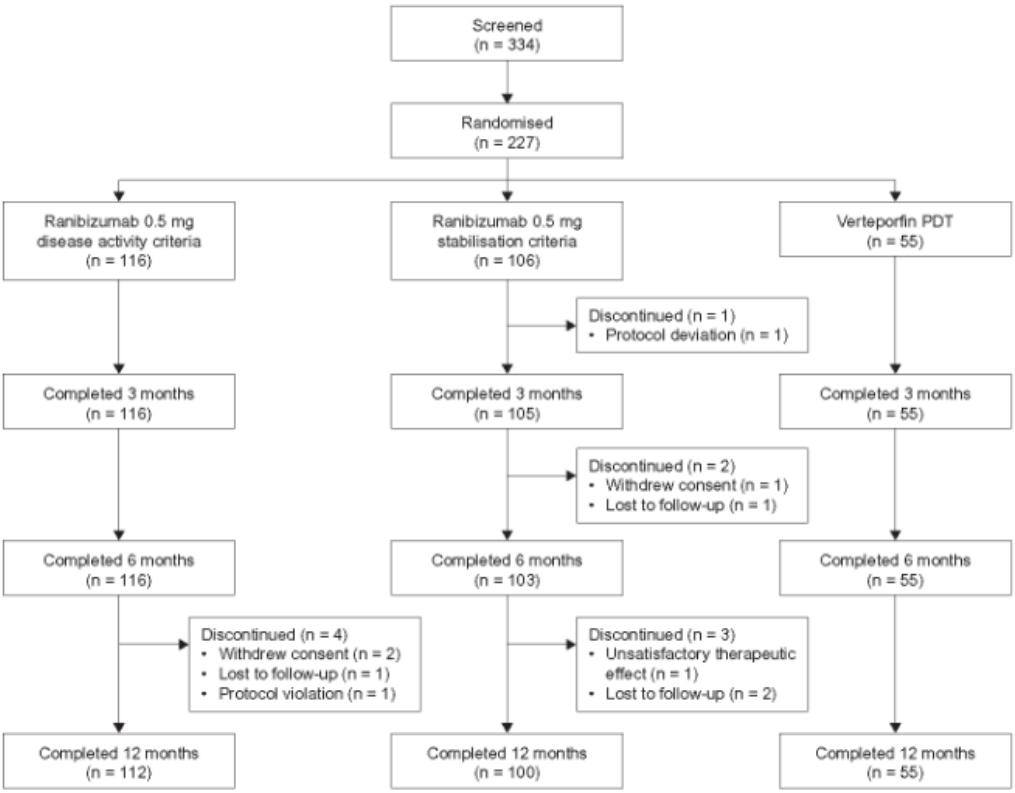
No subgroup analyses were reported in the Iacono 2012 and Gharbiya 2010 studies.

Participant flow

6.3.8 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

Figure 9 presents a CONSORT flow chart for the Novartis phase III study.[32,34] At 3 months, one patient had discontinued from the ranibizumab stabilisation group and no patients had discontinued from the other two groups. At 6 months a further two patients discontinued from the ranibizumab stabilisation group and no patients had discontinued from either of the other groups.[34] No patients discontinued due to AEs.

Figure 9 CONsolidated Standards of Reporting Trials (CONSORT) flow chart for the Novartis phase III study



Bandello et al., 2013;[34] Novatis phase III study 12-month CSR[32]
PDT, photodynamic therapy

In the Iacono study[46], overall, 55 subjects with subfoveal CNV secondary to PM were enrolled in the study, of whom 27 were randomly assigned to the intravitreal ranibizumab group and 28 to the intravitreal bevacizumab group. However, after randomisation and before the administration of the first injection, four patients in the intravitreal ranibizumab group and three patients in the intravitreal bevacizumab group refused to participate in the study because they were unable to follow the strict study protocol. Finally, 23 subjects in the intravitreal ranibizumab group and 25 subjects in the intravitreal bevacizumab group were considered for the analysis. There is no indication that any patients discontinued during the study.

In the Gharbiya study[47], 32 eyes from 32 patients with CNV secondary to PM were consecutively enrolled. All patients completed follow-up at 6 months.

6.4 Critical appraisal of relevant RCTs

6.4.1 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to

the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

- Was the method used to generate random allocations adequate?
- Was the allocation adequately concealed?
- Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?
- Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?
- Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?
- Is there any evidence to suggest that the authors measured more outcomes than they reported?
- Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

6.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 10.3, appendix 3 for a suggested format.

See Section 10.3, Appendix 3 for full details of quality assessment for each RCT.

6.4.3 If there is more than one RCT, tabulate a summary of the responses applied to each of the critical appraisal criteria. A suggested format for the quality assessment results is shown below.

Quality assessment of the three RCTs[32,46,47] is described in Table 19. The Novartis phase III study used a robust design with appropriate randomisation and blinding, and data were analysed using an intent-to-treat approach. The Iacono 2012 study used appropriate

randomisation and an intent-to-treat analysis, but methods used to account for missing data are not described in the paper and it is unclear if patients or the treating investigator were blinded to treatment. In the Gharbiya 2010 study, no details are provided regarding how randomisation was performed and it is unclear whether patients or the treating investigator were blinded to treatment. In addition it is unclear if an intent-to-treat approach was used for analyses.

Table 19 Quality assessment results for RCTs

Trial	Novartis phase III trial[32,34]	Iacono 2012[46]	Gharbiya 2010[47]
Was randomisation carried out appropriately?	Yes	Yes	Not clear
Was the concealment of treatment allocation adequate?	Yes	Yes	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Not clear	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Assessors were blinded to treatment but it is unclear if patients and treating investigators were blinded	No
Were there any unexpected imbalances in drop-outs between groups?	No	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	No	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes	Yes Not clear	Not clear Not clear

Bandello et al., 2013;[34] Novartis phase III study 12 month CSR;[32] Iacono et al., 2012;[46] Gharbiya et al., 2010[47]
RCT, randomised controlled trial

6.5 Results of the relevant RCTs

6.5.1 Provide the results for all relevant outcome measure(s) pertinent to the decision problem. Data from intention-to-treat analyses should be presented whenever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given. **If there is more than one RCT, tabulate the responses.**

6.5.2 The information may be presented graphically to supplement text and tabulated data. If appropriate, please present graphs such as Kaplan–Meier plots.

6.5.3 For each outcome for each included RCT, the following information should be provided.

- The unit of measurement.
- The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
- A 95% confidence interval.
- Number of participants in each group included in each analysis and whether the analysis was by ‘intention to treat’. State the results in absolute numbers when feasible.
- When interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustments should be described to cater for the interim nature of the data.
- Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.
- Discuss and justify definitions of any clinically important differences.
- Report any other analyses performed, including subgroup analysis and adjusted analyses, indicating those pre-specified and those exploratory.

Overview of efficacy

The Novartis phase III trial demonstrates that ranibizumab, administered according to disease activity or disease stabilisation criteria, significantly improves BCVA and provides greater reductions in CRT compared with vPDT, the only licensed treatment for CNV secondary to PM (Table 20).[32-34] At 3 months, patients achieved clinically meaningful gains in BCVA (10 letters) with ranibizumab whereas vPDT achieved only stabilisation of BCVA. [redacted]. The majority of gains in BCVA over baseline were achieved rapidly, in the first three months; however there continued to be small improvements in the ranibizumab groups at months 6 and 12. Gains in BCVA were accompanied by improvements in vision-related functioning, as assessed using the NEI VFQ-25.[35,36] Similar improvements in all BCVA outcomes measures were observed with both ranibizumab dosing regimens, but were achieved with fewer injections when retreatment was given according to the disease activity criteria rather than the disease stabilisation criteria.

Results from the two small RCTs provide additional evidence for the efficacy of ranibizumab with retreatment administered according to the presence of disease activity and report results for a follow-up of 6 or 18 months.[46,47]

Table 20 Summary of efficacy results from the Novartis phase III trial

	Months 0−3			**Months 0−6**		**Months 0−12**	
	Ranibizumab disease activity, n = 116	**Ranibizumab disease stabilisation, n = 105**	**vPDT, n = 55**	**Ranibizumab disease activity, n = 116**	**Ranibizumab disease stabilisation, n = 105**	**Ranibizumab disease activity, n = 116**	**Ranibizumab disease stabilisation, n = 105**
Mean average change in BCVA (letters) from baseline, mean (SD)	10.6 (7.26)***	10.5 (8.16)***	2.2 (9.47)	11.7 (8.24)	11.9 (8.81)	12.5 (8.83)	12.8 (9.48)
Change in BCVA (letters) from baseline, mean (SD)	12.5 (8.81)	12.1 (10.18)	1.4 (12.21)	12.7 (11.01)	13.7 (10.16)	14.4 (10.20)	13.8 (11.42)
Gain of ≥ 10 letters, n (%)	76 (65.5)***	65 (61.9)***	15 (27.3)	75 (64.7)	75 (71.4)	80 (69.0)	73 (69.5)
Gain ≥ 10 letters (versus vPDT), OR (95% CI)	5.07 (2.50–10.27)	4.33 (2.13–8.83)	NA	−	−	−	−
Gain ≥ 10 letters (versus vPDT), RR (95% CI)	2.40 (1.53–3.77)	2.27 (1.44–3.58)	NA	−	−	−	−
Gain of ≥ 15 letters, n (%)	50 (43.1)**	40 (38.1)**	8 (14.5)	52 (44.8)	49 (46.7)	60 (51.7)	56 (53.3)
Gain ≥ 15 letters (versus vPDT), OR (95% CI)	4.45 (1.93–10.26)	3.62 (1.55–8.43)	NA	−	−	−	−
Gain ≥ 15 letters (versus vPDT), RR (95% CI)	2.96 (1.51–5.81)	2.62 (1.32–5.20)	NA	−	−	−	−
Change from baseline in CRT (μm), mean (SD)	-77.6 (102.25)	-61.0 (67.46)	-12.0 (65.84)	-74.8 (97.05)	-66.1 (73.63)	-71.3 (100.91)	-66.6 (82.63)

No. of injections, mean (SD)	1.8 (0.8)	2.5 (0.6)	0 (0.0)	2.5 (1.6)	3.5 (1.5)	3.5 (2.9)	4.6 (2.6)
Change from baseline in NEI VFQ-25 composite score, mean (SD)	4.3 (10.09)*	5.3 (13.96)*	0.3 (12.63)	5.1 (14.38)	6.3 (13.98)	5.1 (15.83)	6.6 (15.66)

Bandello et al., 2013;[33,34] Ohno-Matsui et al., 2013;[35,36] Novartis phase III study 12 month CSR[32]
BCVA, best corrected visual acuity; CI, confidence interval; NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; OR, odds ratio; RR, risk ratio; SD, standard deviation; vPDT, verteporfin photodynamic therapy
*p < 0.05, **p < 0.01; ***p < 0.001 vs vPDT

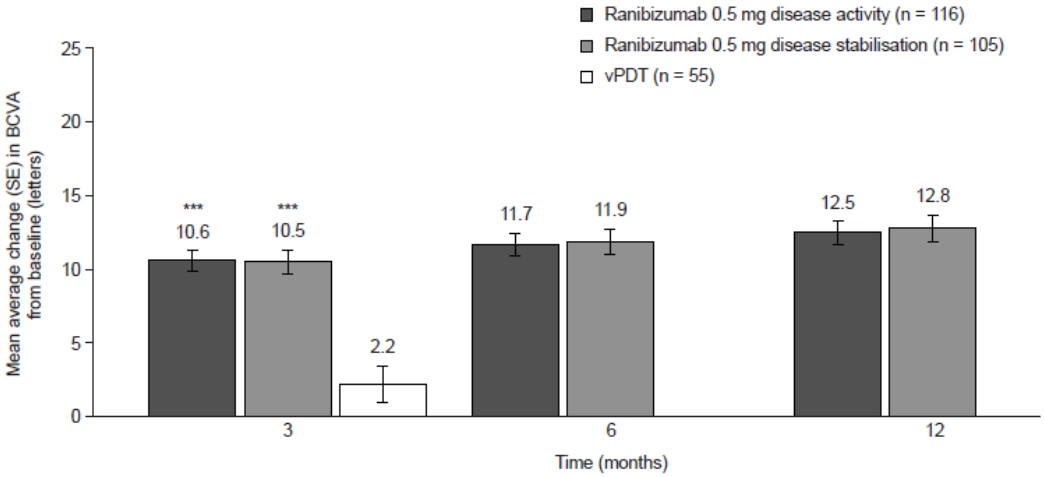
Novartis phase III trial

As described in section 6.3.2, this trial consisted of a 3-month double-blind phase during which patients received ranibizumab (with retreatment according to disease activity or disease stabilisation criteria) or vPDT, and from month 3 patients in the vPDT group were eligible to receive ranibizumab 0.5 mg according to disease activity criteria (in addition to or instead of retreatment with vPDT); the decision to treat with ranibizumab was at the physician's discretion. During months 3−11, 38 out of the 53 patients who received vPDT at baseline received treatment with ranibizumab. This treatment group is therefore referred to as the vPDT/ranibizumab group from month 4 onwards and results for this group should be interpreted with caution.

Gains in BCVA with ranibizumab were significantly greater than those achieved with vPDT over the double-blind treatment phase

The Novartis phase III study met its primary endpoint demonstrating a superior mean average change in BCVA from baseline to month 3 for both ranibizumab groups compared with vPDT. The mean (SD, SE) average gains in BCVA for this period were 10.6 (7.3, 0.67) letters in the ranibizumab disease activity group and 10.5 (8.2, 0.80) letters in the ranibizumab disease stabilisation group compared to 2.2 (9.5, 1.28) letters in the vPDT group, a difference that was highly statistically significant ($p < 0.00001$, i.e. below multiplicity adjusted critical values, for both comparisons, Figure 10). The mean (± SD) changes in BCVA from baseline at 3 months were 12.5 (8.8, 0.82) (ranibizumab disease activity), 12.1 (10.2, 0.99) (ranibizumab disease stabilisation) and 1.4 (12.2, 1.65) (vPDT).

Figure 10 Mean (± SE) average change in BCVA from baseline to months 3, 6 and 12 during treatment with ranibizumab or vPDT



Bandello et al 2013[33,34] and Novartis phase III study 12 month CSR[32]
BCVA, best corrected visual acuity; SD, standard deviation; vPDT, verteporfin photodynamic therapy
***p < 0.001 vs vPDT

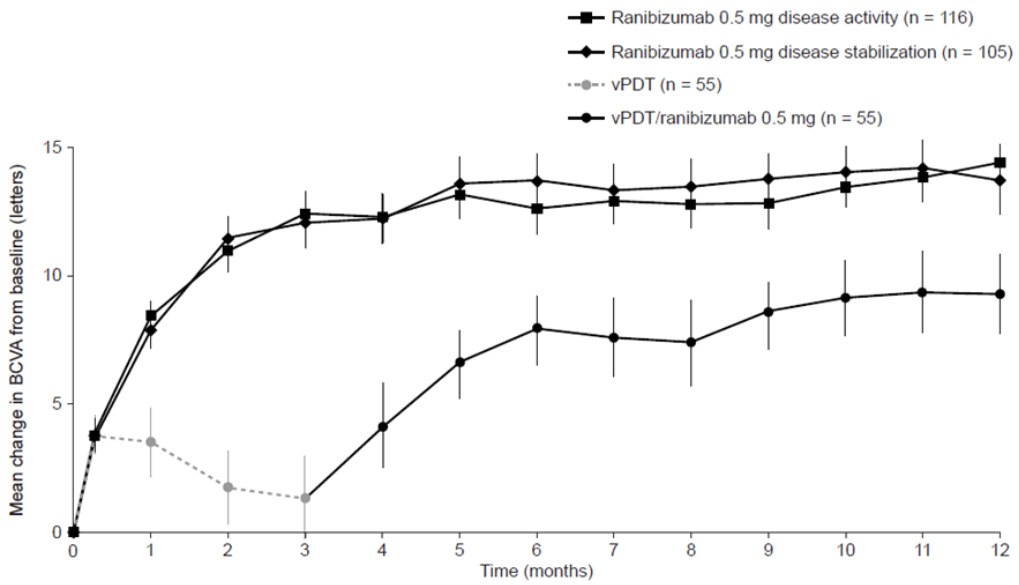
Gains in BCVA achieved with ranibizumab at 3 months were sustained at 6 and 12 months and there was no significant difference between the two ranibizumab regimens

Gains in BCVA over baseline achieved over the first 3 months were sustained in both ranibizumab groups at months 6 and 12. The mean (± SD) average gain from baseline in BCVA over 6 months was 11.7 ± 8.2 letters for the ranibizumab disease activity group and 11.9 ± 8.8 letters for the ranibizumab disease stabilisation group (Figure 10). From baseline to 12 months, the mean average gain in BCVA was 12.5 ± 8.8 letters for the ranibizumab disease activity group and 12.8 ± 9.5 letters for the ranibizumab disease stabilisation group (Figure 10). There was no significant difference between ranibizumab groups in gain in BCVA over 6 months in a non-inferiority comparison ($p < 0.00001$, i.e. below multiplicity adjusted critical values). Mean (± SD) changes from baseline at 6 months were 12.7 ± 11.0 letters (ranibizumab disease activity), 13.7 ± 10.2 letters (ranibizumab disease stabilisation), and, 14.4 ± 10.2 and 13.8 ± 11.4, respectively, at 12 months.

Improvements in BCVA from baseline achieved with ranibizumab were evident from month 1

In both of the ranibizumab groups, gains in BCVA over baseline were observed at month 1 and further gains were seen over months 2 and 3. Thereafter the gain in BCVA was sustained in both groups (Figure 11). In the vPDT group, BCVA remained stable over months 1 to 3 and improved thereafter when patients were able to receive ranibizumab. However gains in BCVA over baseline in the vPDT/ranibizumab group remained lower than in the ranibizumab groups throughout the study.

Figure 11 Mean (± SE) change in BCVA over time during treatment with ranibizumab or vPDT/ranibizumab



Bandello et al 2013;[33] Novartis phase III trial CSR[32]
BCVA, best-corrected visual acuity; SE, standard error; vPDT, verteporfin photodynamic therapy.
From month 3 to 11, the investigators had the option to treat the disease activity of patients randomised to vPDT with 0.5 mg ranibizumab, vPDT, or a combination of 0.5 mg ranibizumab and vPDT.

[redacted]

[redacted](Table 21). [redacted]

Table 21 Mean gain in BCVA from baseline to month 3 according to baseline demographics and disease characteristics

	Ranibizumab disease activity (N = 116)		Ranibizumab disease stabilisation (N = 105)		vPDT (N = 55)	
Subgroup category	**n**	**Mean letters gained (SD)**	**n**	**Mean letters gained (SD)**	**n**	**Mean letters gained (SD)**
Age category (years)						
< 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45–< 55	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
55–< 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 65	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Sex	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Male	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Female	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Race	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Caucasian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Asian	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline axial length	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
< 28 mm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
28–< 30 mm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 30 mm	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Location of CNV subtype	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Subfoveal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Juxtafoveal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrafoveal	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline BCVA						
< 45	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
45–< 60	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
60–< 73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
≥ 73	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Novartis phase III trial 12-month CSR[32]
BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; SD, standard deviation; vPDT, verteporfin photodynamic therapy
*p < 0.05; ***p < 0.001 vs vPDT

Greater proportions of patients gained ≥ 10 and ≥ 15 letters at 3 months with ranibizumab compared with vPDT

Approximately twofold more ranibizumab-treated patients gained at least 10 letters from baseline at month 3 compared with the vPDT group: ranibizumab disease activity, 65.5%; ranibizumab disease stabilisation, 61.9%; vPDT, 27.3% (Table 22). The difference in the proportion of patients gaining at least 10 letters was statistically significant for both ranibizumab groups compared with vPDT at 3 months (p < 0.00001 both comparisons,

Fisher's exact test, unstratified and CMH test, stratified) and the proportion of patients with this improvement in BCVA from baseline was sustained at 6 and 12 months for the two ranibizumab groups: ranibizumab disease activity, 64.7% (6 months) and 69.0% (12 months); ranibizumab disease stabilisation, 71.4% (6 months) and 69.5% (12 months).

The proportion of patients who gained at least 15 letters from baseline at month 3 was approximately threefold higher for both ranibizumab groups compared with the vPDT group: ranibizumab disease activity, 43.1%, p = 0.00002 (Fisher's exact test, unstratified) and p = 0.00001 (CMH test, stratified) versus vPDT; ranibizumab disease stabilisation, 38.1%, p = 0.00205 (Fisher's exact test, unstratified) and p = 0.00146 (CMH test, stratified) versus vPDT; vPDT, 14.5%. Almost half of patients in both ranibizumab groups gained at least 15 letters from baseline at 6 months (ranibizumab disease activity, 44.8%; ranibizumab disease stabilisation, 46.7%), and over half of patients had gained at least 15 letters at 12 months (ranibizumab disease activity, 51.7%; ranibizumab disease stabilisation, 53.3%.

Table 22 Proportion of patients gaining ≥ 10 or ≥ 15 letters from baseline at 3, 6 and 12 months during treatment with ranibizumab or vPDT

	Ranibizumab disease activity, n = 116	**Ranibizumab disease stabilisation, n = 105**	**vPDT, n = 55**
Patients gaining ≥ 10 letters, n (%)			
At 3 months	76 (65.5)***	65 (61.9)***	15 (27.3)
OR (95% CI), versus vPDT	5.07 (2.50–10.27)	4.33 (2.13–8.83)	NA
RR (95% CI), versus vPDT	2.40 (1.53–3.77)	2.27 (1.44–3.58)	NA
At 6 months	75 (64.7%)	75 (71.4%)	_
At 12 months	80 (69.0)	73 (69.5)	_
Patients gaining ≥ 15 letters, n (%)			
At 3 months	50 (43.1)***	40 (38.1)*	8 (14.5)
OR (95% CI), versus vPDT	4.45 (1.93–10.26)	3.62 (1.55–8.43)	NA
RR (95% CI), versus vPDT	2.96 (1.51–5.81)	2.62 (1.32–5.20)	NA
At 6 months	52 (44.8%)	49 (46.7%)	_
At 12 months	60 (51.7)	56 (53.3)	_

Bandello et al., 2013;[34] Novartis phase III study 12 month CSR[32]
CI, confidence interval; NA, not applicable; OR, odds ratio; RR, risk ratio; vPDT, verteporfin photodynamic therapy
*p < 0.05; ***p < 0.001 vs vPDT

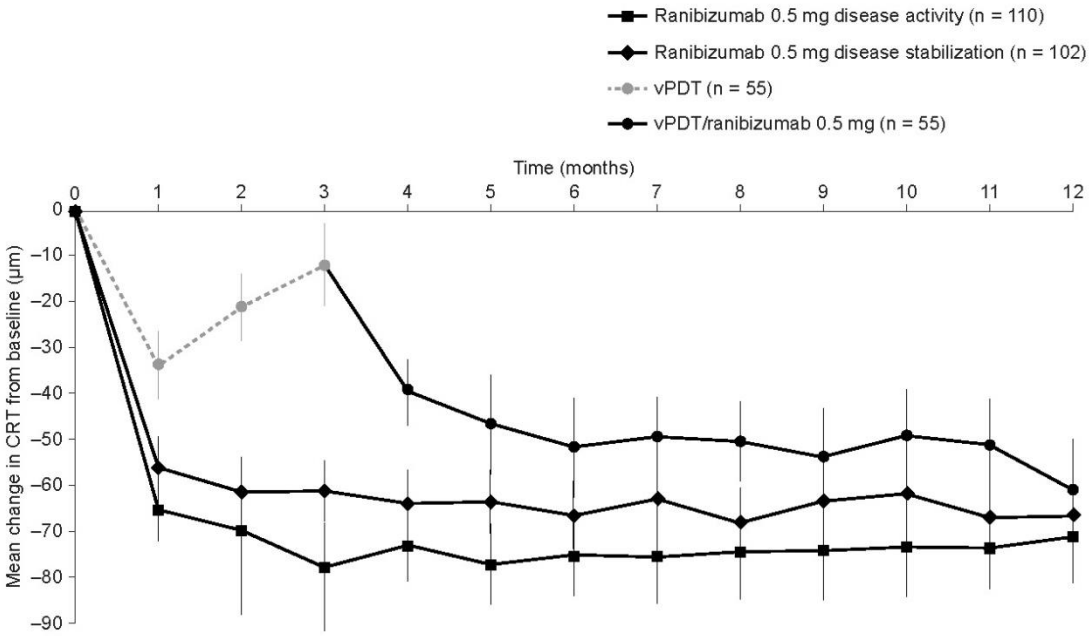
<u>Ranibizumab provided rapid and sustained reductions in central retinal thickness</u>

At baseline mean CRT was 349 to 373 µm across the three treatment groups. In both ranibizumab groups, a greater mean decrease in CRT from baseline was evident at month 1 compared with the vPDT group, and at 3 months the mean decrease in CRT was five- to sixfold greater in the ranibizumab groups compared with the vPDT group (mean change ± SE

in CRT from baseline to month 3: ranibizumab disease activity, −77.6 ± 9.75 µm; ranibizumab disease stabilisation, −61.0 ± 6.68 µm; vPDT, −12.0 ± 8.96 µm) (

Figure 12). Reductions in CRT achieved with ranibizumab at 3 months were sustained at 6 and 12 months, and throughout the study reductions in CRT were greater with the ranibizumab disease activity regimen compared with the disease stabilisation regimen. From month 3 onwards greater reductions in CRT from baseline were observed in the vPDT/ranibizumab group compared with months 1 to 3 as patients were allowed to receive ranibizumab.

Figure 12 Mean (± SE) change from baseline in central retinal thickness over time during treatment with ranibizumab or vPDT/ranibizumab



Novartis phase III study 12 month CSR[32]
CRT, central retinal thickness; SE, standard error; vPDT, verteporfin photodynamic therapy. From month 3 to 11, the investigators had the option to treat the disease activity of patients randomised to vPDT with 0.5 mg ranibizumab, vPDT, or a combination of 0.5 mg ranibizumab and vPDT.

Similar trends were observed in central foveal thickness (CFT). Mean (± SD) changes from baseline in CFT were −74.3 ± 105.08 µm (disease activity) and −62.6 ± 82.94 µm (disease stabilisation) for the two ranibizumab groups compared with −18.6 ± 83.52 for the vPDT group at month 3, −79.8 ± 111.47 µm, −68.2 ± 88.51 µm and −57.0 ± 91.79 µm, respectively, at month 6, and −75.1 µm ± 106.92, −68.4 µm ± 100.59 and −62.6 µm ± 99.23, respectively, at month 12.

Improvements in BCVA were achieved with fewer ranibizumab injections when therapy was given according to disease activity criteria

The mean (± SD) number of ranibizumab injections received over the first 3 months was slightly lower for patients treated according to disease activity compared to those treated according to disease stabilisation: 1.8 ± 0.8 versus 2.5 ± 0.6. This difference was also evident over months 1 to 6: 2.5 ± 1.6 versus 3.5 ± 1.5, and months 1 to 12: 3.5 ± 2.9 versus 4.6 ± 2.6. Over the first 3 months, 47% of the disease activity group received only one injection compared with 4% of the disease stabilisation group. Over the first 6 months, 59% of the disease activity group received 2 or fewer injections compared with 34% of the disease stabilisation group. Over the 12 month period, the proportion of patients receiving 4 or fewer injections was 72% in the disease activity group and 59% in the group treated with ranibizumab according to disease stabilisation.

Ranibizumab achieved superior improvements in visual functioning compared with vPDT

The NEI VFQ-25 is a validated tool which uses 25 questions to elicit information on general health, quality of vision and vision-related quality of life.[37] The NEI VFQ-25 provides a composite score, consisting of 11 vision-related constructs (general vision, ocular pain, near activities, distance activities, social function, mental health, role difficulties, dependency, driving, colour vision and peripheral vision) and a general health rating; scores can be determined for each subscale.[37] Higher scores represent better functioning on a 0 to 100 scale for the composite and each subscale. An analysis of AMD trial data suggests that a four- to six-point improvement in mean composite NEI VFQ-25 scores represents a clinically meaningful change corresponding to a gain in BCVA of at least 15 letters.[38]

In the phase III study, the NEI VFQ-25 was administered at baseline and months 3, 6 and 12.[35,36] At month 3, the improvement in mean composite score from baseline was significantly greater in both ranibizumab groups (4.3 points in the disease activity group and 5.3 points in the stabilisation group) compared with vPDT (0.3 points, $p < 0.05$) and the improvement from baseline for these two groups was maintained at 6 and 12 months (Table 23–Table 25). A 4−6 point improvement in mean composite NEI VFQ-25 scores is considered to represent a clinically meaningful change corresponding to at least a 15-letter change in BCVA ;[38] hence the improvements achieved with ranibizumab can be considered to be clinically meaningful. Statistically significant improvements from baseline compared with vPDT were also reported for both ranibizumab groups at 3 months for general vision, near activities (disease stabilisation group only), mental health and dependency ($p < 0.05$).

Effects on HRQoL were also assessed with the EQ-5D. Patients rated health status on a visual analogue scale where 100 represents best possible health and 0 represents worst possible health. Baseline scores ranged from 70.4 to 76.3 across the three treatment groups.

At 3, 6 and 12 months similar small improvements were seen in all three The change from baseline at 3, 6 and 12 months, respectively, was 2.3, 2.9 and 4.1 points for the ranibizumab disease activity group; 4.2, 4.1 and 5.7 for the ranibizumab disease stabilisation group and 2.1, 3.4 and 2.1 points for the vPDT group. The similar changes in EQ-5D scores between treatment groups were not unexpected as the EQ-5D is recognised as being insensitive to changes in vision and visual functioning.[90,91] Thus, the NEI VFQ-25 results provide a more accurate reflection of the treatments' effect on HRQoL.

Table 23 Mean (± SD) change from baseline in vision-related quality of life as assessed using the NEI VFQ-25 during treatment with ranibizumab or vPDT, month 0−3

NEI VFQ-25 score	Ranibizumab disease activity (n = 116)	Ranibizumab disease stabilisation (n = 105)	vPDT (n = 55)
Composite	**4.3 (10.09)***	**5.3 (13.96)***	**0.3 (12.63)**
General health	1.9 (19.80)	4.6 (21.74)	–0.6 (20.52)
General vision	7.3 (16.74)*	8.6 (18.64)*	–1.4 (19.48)
Ocular pain	3.4 (16.98)	–1.3 (19.52)	2.6 (15.15)
Near activities	5.3 (15.40)	11.5 (21.64)*	0.9 (15.48)
Mental health	4.9 (17.28)*	7.4 (20.80)*	–1.8 (20.51)
Dependency	3.1 (18.87)*	3.7 (21.10)*	–4.7 (19.39)
Distance activities	4.5 (16.55)	6.9 (17.16)	1.0 (19.63)
Driving	–0.2 (12.89)	14.1 (26.43)	2.6 (27.82)
Social functioning	4.7 (15.66)	4.8 (18.12)	1.1 (15.91)
Roles difficulties	6.5 (20.95)	4.5 (25.86)	4.5 (23.36)
Colour vision	1.1 (13.98)	0.0 (14.26)	1.1 (20.85)
Peripheral vision	3.0 (21.03)	4.0 (18.53)	0.6 (19.28)

Ohno-Matsui et al., 2013;[35,36] Novartis phase III study 12 month CSR[32]
NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; vPDT, verteporfin photodynamic therapy
All data are mean (SD); *p < 0.05 vs vPDT

Table 24 **Mean (± SD) change from baseline in vision-related quality of life as assessed using the NEI VFQ-25 during treatment with ranibizumab or vPDT/ranibizumab, months 0−6**

NEI VFQ-25 score	Ranibizumab disease activity (n = 116)	Ranibizumab disease stabilisation (n = 105)	vPDT/ranibizumab (n = 55)
Composite	**5.1 (14.38)**	**6.3 (13.98)**	**2.3 (13.86)**
General health	0.8 (21.52)	2.3 (23.70)	–2.7 (25.66)
General vision	8.3 (19.76)	12.7 (19.22)	4.7 (20.52)
Ocular pain	4.7 (20.66)	–0.1 (16.68)	4.8 (17.00)
Near activities	6.5 (20.57)	10.0 (21.64)	4.8 (18.12)
Mental health	8.9 (21.33)	10.3 (22.71)	1.3 (21.09)
Dependency	2.8 (22.39)	5.6 (25.95)	–5.9 (20.99)
Distance activities	3.5 (19.34)	6.0 (18.72)	3.2 (22.49)
Driving	–3.0 (23.14)	14.5 (26.94)	6.0 (17.91)
Social functioning	2.4 (20.27)	6.0 (17.78)	3.7 (17.66)
Roles difficulties	9.6 (24.49)	8.4 (26.31)	4.3 (22.31)
Colour vision	0.8 (14.41)	–0.3 (15.48)	0.5 (19.15)
Peripheral vision	3.7 (23.17)	2.8 (22.24)	1.6 (22.61)

Ohno-Matsui et al., 2013;[35,36] Novartis phase III study 12 month CSR[32]
NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; vPDT, verteporfin photodynamic therapy
All data are mean (SD)

Table 25 **Mean (± SD) change from baseline in vision-related quality of life as assessed using the NEI VFQ-25 during treatment with ranibizumab or vPDT, months 0−12**

NEI VFQ-25 score	Ranibizumab disease activity (n = 116)	Ranibizumab disease stabilisation (n = 105)	vPDT/ranibizumab (n = 55)
Composite	**5.1 (15.83)**	**6.6 (15.66)**	**4.9 (11.91)**
General health	2.9 (22.32)	2.6 (25.30)	1.1 (23.86)
General vision	9.8 (19.47)	13.2 (18.91)	7.7 (21.08)
Ocular pain	4.7 (19.97)	–1.3 (19.70)	2.7 (16.68)
Near activities	5.6 (22.49)	12.1 (24.82)	6.4 (18.73)
Mental health	8.9 (21.36)	9.0 (24.23)	4.0 (18.54)
Dependency	4.0 (25.01)	6.3 (23.86)	1.8 (14.94)
Distance activities	5.3 (21.58)	6.0 (20.05)	6.5 (22.55)
Driving	–1.3 (23.22)	14.1 (29.31)	8.9 (17.89)
Social functioning	3.3 (19.22)	7.0 (18.56)	4.8 (17.40)
Roles difficulties	9.8 (26.61)	6.8 (28.80)	9.8 (22.41)
Colour vision	0.0 (19.19)	1.4 (14.94)	4.8 (16.18)
Peripheral vision	2.1 (24.24)	6.0 (20.76)	1.6 (19.29)

Ohno-Matsui et al., 2013;[35,36] Novartis phase III study 12 month CSR[32]
NEI VFQ-25, 25-item National Eye Institute Visual Functioning Questionnaire; vPDT, verteporfin photodynamic therapy
All data are mean (SD)

Effects on absenteeism and loss of productivity due to health impairment were assessed using the WPAI-GH.[89] Scores are presented as a percentage of overall work impairment and high scores reflect greater impairment and less productivity. Mean (± SD) reductions from baseline in WPAI-GH Total score of 22.0 ± 55.0 (disease activity) and 21.9 ± 75.2 (disease stabilisation) were observed at 3 months in the ranibizumab groups compared with a mean reduction of 10.2 ± 59.9 in the vPDT group. These corresponded to percentage reductions of 27.6%, 29.4% and 13.4%, respectively.[32] A 20% reduction in work productivity impairment can be interpreted as equivalent to the productivity lost by many patients with health problems, thereby suggesting productivity may have been regained for both ranibizumab treated groups.

Small RCTs comparing ranibizumab versus bevacizumab

The Iacono 2012[46] and Gharbiya 2010[47] studies provide further evidence for the efficacy of ranibizumab based on 18 months of follow-up of 27 patients and 6 months of follow-up of 16 patients, respectively. In both studies, patients received an initial injection and were then retreated as needed (based on monthly examinations) if the presence of persistent leakage was detected on FA or if intraretinal or subretinal fluid was detected on OCT, or a new haemorrhage was detected (Iacono 2012 only). These criteria correspond to the retreatment criteria used for the ranibizumab disease activity group in the Novartis phase III trial. Both studies report the effects of ranibizumab on BCVA and CRT (Table 26).

Table 26 Comparison of efficacy results for ranibizumab administered according to disease activity criteria from the Novartis phase III trial and two small RCTs

	Novartis phase III trial[32-34] n = 116		**Gharbiya 2010[47] n = 16**	**Iacono 2012[46] n = 23**
Follow-up duration, months	6	12	6	18
Mean (± SD) change from baseline in BCVA, letters	12.7 ± 11.0	14.4 ± 10.2	17.31 ± 11.10	9 (NR)
Patients gaining ≥ 10 letters, n (%)	75 (64.7)	80 (69.0)	12 (75)	NR
Patients gaining ≥ 15 letters, n (%)	52 (44.8)	60 (51.7)	9 (56.2)	7 (30.4)
Mean (± SD) change from baseline in CRT, µm	−74.8 ± 97.05	−71.3 ± 100.91	−45 (NR)	NR
Mean (± SD) number of ranibizumab injections	2.5 ± 1.6	3.5 ± 2.9	2.81 ± 1.17	2.56 ± 1.61

Bandello et al., 2013;[33,34] Novartis phase III study 12-month CSR;[32] Iacono et al;, 2012;[46] Gharbiya et al., 2010[47]
BCVA, best corrected visual acuity; CRT, central retinal thickness; NR, not reported; RCT, randomised controlled trial; SD, standard deviation

Improvements in BCVA achieved with ranibizumab in a small RCT were in agreement with those reported for the Novartis phase III study

In the Gharbiya 2010 study,[47] 12 (75%) patients on ranibizumab achieved an improvement of at least 10 letters and 9 (56.2%) patients gained at least 15 letters at 6 months. This compares to 64.7% and 44.8%, respectively, for the ranibizumab disease activity regimen of the Novartis phase III study.[32] The mean (± SD) gain in BCVA at 6 months in the ranibizumab group of the Gharbiya 2010 study was 17.31 ± 11.10 letters.[47] (The greater improvement in BCVA in this study compared with the Novartis phase III study could be due to the lower BCVA at baseline in the Gharbiya 2010 study (Gharbiya 2010, 26 letters; Novartis phase III study, approximately 55 letters).

In both the Gharbiya 2010 and Novartis phase III studies, ranibizumab treatment resulted in a reduction in CRT at 6 months. This was greater in the Novartis phase III trial (74.8 µm and 66.1 µm in the disease activity and stabilisation groups, respectively) than in the Gharbiya 2010 trial (45 µm) and may reflect the fact that the mean (± SD) baseline CRT was lower in the latter study (251 ± 64.8 µm compared to 373 µm and 349 µm in the two ranibizumab groups, respectively, in the Novartis phase III trial).[32,47]

The mean number of ranibizumab injections was similar in the Novartis phase III and Gharbiya 2010 trials. At 6 months, patients had received a mean (± SD) of 2.81 ± 1.17 injections in the Gharbiya 2010 trial compared to 2.5 injections in the ranibizumab disease activity group in the Novartis phase III trial.[34,47]

Results from a second small RCT indicate that improvements in BCVA with ranibizumab are sustained during therapy for up to 18 months

In the Iacono 2012[46] study, a statistically significant improvement in BCVA from baseline was observed at 1 month with ranibizumab (p = 0.007) and was then sustained, giving an overall mean improvement in BCVA from baseline of 9 letters at 18 months; 30% of eyes achieved a BCVA gain of at least 15 letters and 65% gained at least 5 letters from baseline at 18 months. The gain in BCVA is less than that reported for the Novartis Phase III study at 12 months or the Gharbiya 2010 study at 6 months which could be due to the higher mean BCVA at baseline in this study (70 letters compared to 55 letters in the Novartis phase III study). The gain in BCVA was achieved with a mean (± SD) of 2.56 ± 1.61 injections over the 18 months.

The ranibizumab group showed a statistically significant (p = 0.002) reduction in the mean (± SD) CRT from baseline (257 ± 96 µm) at 1 month (192 ± 98 µm). The mean CRT reduction was consistently maintained over the subsequent follow-up period.[46]

6.6 Meta-analysis

When more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.9 to 5.3.12.

6.6.1 The following steps should be used as a minimum when presenting a meta-analysis.

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.

- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

A meta-analysis was not performed.

6.6.2 If a meta-analysis is not considered appropriate, a rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal.

The systematic review identified only one RCT comparing the treatments of interest.

6.6.3 If any of the relevant RCTs listed in response to section 6.2.4 (Complete list of relevant RCTs) are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored.

A meta-analysis was not performed.

6.7 *Indirect and mixed treatment comparisons*

Data from head–to–head RCTs should be presented in the reference-case analysis, if available. If data from head–to–head RCTs are not available, indirect treatment comparison methods should be used. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.3.13 to 5.3.22.

6.7.1 Describe the strategies used to retrieve relevant clinical data on the comparators and common references both from the published literature and from unpublished data. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in section 10.4, appendix 4.

vPDT was the comparator used in the model. Head-to-head data for ranibizumab compared with vPDT were available from the Novartis phase III trial for months 1 to 3.[33] There are no head-to-head data available for ranibizumab compared with vPDT beyond 3 months. However, the systematic searches described in sections 6.1 and 6.2 identified one additional RCT that provided data for vPDT beyond 3 months, the Verteforfin in Photodynamic Therapy (VIP) trial.[25] Data from the VIP trial were used in the economic model for vPDT for cycles 2−4 (see section 7.3.2). An overview of the VIP trial is provided in Table 27. No indirect comparisons were performed.

Table 27 Details of the VIP 2001 trial

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
VIP 2001[26]	vPDT[a]	Placebo + PDT	Patients with subfoveal CNV secondary to PM	VIP Study Group. *Am J Ophthalmol* 2001;131:541–60[26]
VIP Study Group, 2001[26] CNV, choroid neovascularisation; IVT, intravitreal; PDT, photodynamic therapy; PM, pathological myopia; VIP, Verteforfin in Photodynamic Therapy; vPDT, verteporfin PDT [a]6 mg/m^2 intravenously followed by standard fluence rate of 600 mW/cm^2 delivered for 83 seconds with a light dose of 50 J/cm^2.				

6.7.2 Please follow the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 10.5, appendix 5, a complete quality assessment for each comparator RCT identified.

Methodology of the RCT

The methodology for the VIP 2001 trial is summarised in Table 28. VIP 2001 was a randomised, double-blind, multicentre trial involving 120 patients; all patients had CNV secondary to PM and specifically involved patients with subfoveal lesions.[25,92] Patients were randomised 2:1 to received vPDT or placebo and were followed for 24-months. Categorical change in BCVA (loss of less than 8 letters from baseline at 12 months) was the primary outcome of VIP 2001. Secondary outcomes included median change in BCVA and the proportion of patients gaining 15 letters or more in BCVA from baseline.

Table 28 Details of methodology for the VIP 2001 trial

Trial no. (acronym)		**VIP 2001**[25,26,93]
Design		Multicentre, double-blind, placebo-controlled, randomised clinical trial
Patients, n		120
Intervention(s) and comparator(s)		Verteporfin (IV 6 mg/m^2) followed by a standard fluence rate of 600 mW/cm^2 intensity for 83 seconds with a light dose of 50 J/cm^2 (n = 81) Placebo IV infusion followed by light application as for verteporfin (n = 39)
Outcomes	Primary	Proportion of patients losing < 8 letters from baseline at 12 months
	Secondary	Median change in BCVA Contrast sensitivity Visual performance Lesion size CNV progression Fluorescein leakage Number of re-treatments HRQoL AEs
Duration of follow-up		24 months
VIP Study Group, 2001;[26] Blinder et al., 2001;[25] VIP 24-months CSR[93] AE, adverse event; BCVA, best corrected visual acuity; CNV, choroid neovascularisation; HRQoL, health-related quality of life; IV, intravenous; PDT, photodynamic therapy; VA, visual acuity; VIP, Verteporfin in Photodynamic Therapy		

Critical appraisal of the RCT

Quality assessment of the VIP 2001 trial is described in Table 29.

In the VIP 2001 trial, randomisation, treatment allocation and blinding were carried out appropriately. There was little evidence of outcome reporting bias.

Table 29 Quality assessment of the VIP 2001 trial

Quality assessment element	VIP 2001[25,26,93]
Was randomisation carried out appropriately?	Yes
Was the concealment of treatment allocation adequate?	Yes
Were the groups similar at the onset of the study in terms of prognostic factors?	No
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes
Were there any unexpected imbalances in dropouts between groups?	No
Is there any evidence to suggest that authors measured more outcomes than they reported?	No
Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Yes
VIP Study Group 2001;[26] Blinder et al., 2001;[25] VIP 24-month CSR[93]	

Results of the VIP study

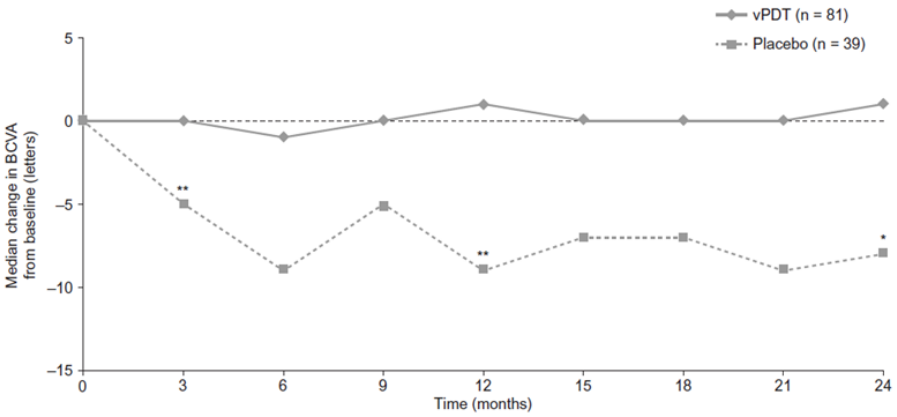
The main results for the visual acuity assessments in the VIP 2001 trial are described in Table 30. The study showed that BCVA was maintained over 24 months in patients treated with vPDT compared to a decrease in BCVA in patients in the placebo group (Figure 13).[25,92] However, the proportion of patients with stable BCVA (defined as losing less than 8 letters of BCVA relative to baseline), although significantly greater at 12 months in patients receiving vPDT did not differ significantly between treatment groups at 24 months (p = 0.11), and only 12% of patients receiving vPDT had an increase of 15 letters or more at 24 months.[25]

Table 30 Summary of visual acuity results from the VIP 2001 trial

Follow-up, months	Patients with stable BCVA, %		Change in median BCVA, letters		Patients gaining ≥ 15 letters, n (%)	
	vPDT n = 81	Placebo n = 39	vPDT n = 81	Placebo n = 39	vPDT n = 81	Placebo n = 39
0	–	–	–	–	–	–
3	77*	56	0	−5	2 (2.5)**	0
12	72**	44	1**	−9	5 (6.2)**	1 (2.6)
24	64	49	1*	−8	10 (12.3)*	0

*p < 0.05; **p < 0.01 versus placebo.
BCVA, best corrected visual acuity; VIP, verteporfin in photodynamic therapy; vPDT, verteporfin photodynamic therapy.
VIP Study Group 2001;[92] Blinder et al., 2003[25]

Figure 13 Change in median BCVA over time during treatment with vPDT or placebo in the VIP study[a]



VIP trial, Blinder et al 2003[25]
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; VIP, verteporfin in photodynamic therapy
[a]The change in median BCVA letter score was a secondary endpoint. The primary endpoint was the proportion of eyes with fewer than 8 letters of BCVA loss at 12 months.
*p < 0.05; **p < 0.01 versus placebo.
Statistical analyses are presented for all time points reported in the original publications.

6.8 Non-RCT evidence

Non-RCT, both experimental and observational, evidence will be required, not just for those situations in which RCTs are unavailable, but also to supplement information from RCTs when they are available. This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 3.2.8 to 3.2.10.

6.8.1 If non-RCT evidence is considered (see section 6.2.7), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.6 and 10.7, appendices 6 and 7.

A systematic literature review was performed to identify all studies evaluating the clinical effectiveness and safety of treatment for CNV secondary to PM. The search is described in further detail in section 6.1.1.

The systematic literature search identified six relevant non-RCTs (see section 6.2.7).

Summary of methodology of relevant non-RCTs

6.8.2 As a minimum, the summary should include information on the non-RCT(s) under the subheadings listed in this section. When there is more than one non-RCT, **the information should be tabulated**.

The methodology of the six included non-randomised trials is summarised in Table 31.

The REPAIR study was a phase II, open-label, multicentre study based in the UK.[39] Five additional prospective case series were included as they met the criteria of evaluating at least 25 patients for 6 months or longer and reporting adverse events.[41-45]

Table 31 Summary of methodology of included non-randomised studies

Study	Design and treatment	Participants	Outcomes
REPAIR 2011[39]	Phase II, open-label, single-arm multicentre, 12-month, UK-based study Ranibizumab IVT 0.5 mg at baseline, then PRN (monthly assessment)	Patients with active primary or recurrent subfoveal or juxtafoveal CNV secondary to PM, high myopia diagnosis and BCVA 78–24 letters (n = 48 eyes/48 patients)	Primary Mean change in BCVA from baseline to month 12 Secondary Mean change in BCVA from baseline to month 6 Mean change in CRT from baseline to months 6 and 12 Time to first retreatment and total number of retreatments Change in lesion size and morphology from baseline to months 6 and 12 HRQoL (Macular Disease Treatment Satisfaction Questionnaire and Well Being Questionnaire) Safety Follow-up: 12 months
Calvo-Gonzalez 2011[41]	Prospective case series Ranibizumab IVT 0.5 mg at baseline, 1 and 2 months, then PRN (monthly assessment)	Patients with CNV secondary to PM (n = 67 eyes/67 patients)	Mean change in BCVA, CMT and GLD from baseline Proportion of patients with BCVA gain or loss of ≥ 15 letters from baseline Proportion of patients with retinochoroidal atrophy Number of injections AEs Follow-up: mean 15.9 months (range, 6–27 months)
Lalloum 2010[42]	Prospective single-centre case series Ranibizumab IVT 0.5 mg at baseline, then PRN (monthly assessment)	Patients with subfoveal or juxtafoveal CNV secondary to PM (n = 32 eyes/32 patients)	Mean change in BCVA and CMT from baseline Proportion of patients with BCVA gain or loss of ≥ 15 letters from baseline Number of injections AEs Follow-up: median, 17 months (range, 7−29 months)
Ouhadj 2010[43]	Prospective case series Ranibizumab IVT 0.5 mg at baseline, then PRN (monthly assessment)	Patients with subfoveal or juxtafoveal CNV secondary to PM (n = 40 eyes/40 patients)	Mean change in BCVA and CMT Proportion of patients with BCVA gain of 3 lines or more Number of injections AEs

Study	Design and treatment	Participants	Outcomes
			Follow-up: mean 8 months (range, 3–15 months)
Silva 2010[44]	Prospective, multicentre, case series Ranibizumab IVT 0.5 mg at baseline, then PRN (monthly assessment)	Patients with subfoveal or juxtafoveal CNV secondary to PM (n = 34 eyes/32 patients)	Mean change in BCVA and CMT from baseline Proportions of patients with BCVA gain of ≥ 5, ≥ 10 and ≥ 15 letters Number of injections AEs Follow-up: 12 months
Vadala 2011[45]	Prospective, multicentre case series Ranibizumab IVT 0.5 mg at baseline, then PRN (monthly or quarterly assessment)	Patients with subfoveal or juxtafoveal CNV secondary to PM (n = 40 eyes/39 patients)	Mean change in BCVA and CRT from baseline Proportion of patients with BCVA gain of ≥ 5 letters Number of injections AEs Follow-up: mean 13.3 months (range, 12–18 months)

Tufail et al., 2013;[39] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45]
AE, adverse event; BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; CMT, central macular thickness; CRT, central retinal thickness; GLD, greatest linear dimension; IVT, intravitreal; PM, pathological myopia; PRN, pro re nata (as needed)

Methods

6.8.3 Describe the non-RCT(s) design (for example, duration, degree and method of blinding, and randomisation) and interventions. Include details of length of follow-up and timing of assessments. The following tables provide a suggested format for when there is more than one non-RCT.

The REPAIR study is a phase II, open-label, single-arm, multicentre, 12-month, UK-based study evaluating the efficacy and safety of intravitreal ranibizumab (0.5 mg) using an as-needed (PRN) dosing schedule in patients with CNV secondary to PM (Table 31).[39] Retreatment was given if there was evidence of sub- or intraretinal fluid on OCT; or evidence for leakage on FA together with a decrease in BCVA of 5 letters or more, or increased blurring or metamorphopsia. These retreatment criteria are similar to those employed in the ranibizumab disease activity arm of the Novartis phase III trial (vision impairment attributable to intra or subretinal fluid or active leakage secondary to PM as assessed by OCT and/or FA). Patients were assessed for efficacy and safety outcomes on a monthly basis. A planned interim analysis was to be performed when 75% of patients had completed 6 months on study.

The five additional studies identified were all prospective case series (Table 31). The average follow-up across these studies ranged from 8 to 17 months.

Participants

6.8.4 Provide details of the eligibility criteria (inclusion and exclusion) for the trial. The following table provides a suggested format for the eligibility criteria for when there is more than one non-RCT. Highlight any differences between the trials.

Inclusion and exclusion criteria for the REPAIR study and the five other non-RCTs are shown in Table 32. In the REPAIR study, patients were included if they were 18 years or older, had active primary or recurrent subfoveal or juxtafoveal CNV secondary to PM, a diagnosis of high myopia of at least −6 D in the study eye, and a BCVA of between 78 and 24 letters measured by ETDRS chart in the study eye.[39]

Patients in the REPAIR study were excluded if they were receiving or had received treatment in the study eye such as PDT, anti-VEGF agents, macular laser photocoagulation, intravitreal steroids, external-beam radiation therapy, vitrectomy or transpupillary thermotherapy, or had a history of any surgical intervention in the study eye within the past 2 months. Patients with

CNV of causes other than PM or any other ocular disorders in the study eye that may confound interpretation of study results were also excluded.[39]

The five case series studies included patients with CNV secondary to PM.[41-45] These studies generally had similar inclusion and exclusion to those for REPAIR except that patients who had received treatment in the study eye (e.g. vPDT) could be included.

Table 32 Eligibility criteria in the non-RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
REPAIR [39,94]	Provision of written informed consent Male or female outpatients of any race, aged 18 years or older Diagnosis of active primary or recurrent subfoveal or juxtafoveal CNV secondary to PM Diagnosis of high myopia of at least –6 D in the study eye spherical equivalent. For subjects who had undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye had to be at least −6 D[65,39] BCVA score between 78 and 24 letters in the study eye using ETDRS-like grading charts (approximately 6/9–6/96 Snellen equivalent) Willing and able to comply with all study procedures	History of any surgical intervention in the study eye within two months preceding Visit 1 (screening) Previous macular laser photocoagulation, treatment with intravitreal steroids, verteporfin with photodynamic therapy (Visudyne®) or anti-VEGF agents ranibizumab, bevacizumab or pegaptanib sodium (Macugen®) in the study eye Previous treatment with intravenously administered bevacizumab (Avastin®) Prior treatment in the study eye with external-beam radiation therapy, vitrectomy, or transpupillary thermotherapy Previous participation in any studies of investigational drugs within one month preceding Visit 1 (excluding vitamins and minerals) History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes History of allergic reaction to fluorescein Concurrent use of systemic anti-VEGF agents Current use of or likely need for systemic medications known to be toxic to the lens, retina or optic nerve, including deferoxamine, chloroquine/ hydroxychloroquine (Plaquenil), tamoxifen, phenothiazines and ethambutol Concomitant use of chronic NSAIDs for more than seven consecutive days or systemic or topical ocular corticosteroids for three or more consecutive days within six months prior to Visit 1. Note that aspirin taken as ‘low dose’ up to 100 mg qd for prophylaxis of myocardial infarction and/or stroke was permitted during the study

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Calvo-Gonzalez 2011[41]	Minimum spherical equivalent of –6 D Retinal signs of PM BCVA of 24 letters or more Active myopic CNV, defined as angiographic leakage and/or intraretinal oedema and/or subretinal fluid determined by OCT Patients who had been treated a minimum of 3 months previously with PDT or 2 months previously with sodium pegaptanib were also included.	Presence of active CNV secondary to a disease other than PM Concomitant disease in the study eye that could compromise the patient's vision or fixation Patients with previous thromboembolic episodes, allergy to fluorescein, and fertile women not using contraception.
Lalloum 2010[42]	PM (refractive error > –6 D) complicated by CNV associated with recent (<1 month) loss of vision and metamorphopsia Myopic CNV eyes treated successfully by PDT at least 1 year previously before inclusion and showing evidence of recurrence were included in this study	Presence of other retinal diseases (e.g., AMD, diabetic retinopathy, retinal dystrophies) Previous intravitreal injections of antiangiogenic drugs Previous laser photocoagulation for CNV PDT within the last 12 months Myopic CNV refractory to PDT, fibrous lesions after PDT, or atrophy after PDT Previous surgical removal of CNV or macular translocation History of retinal detachment Media opacities Presence of a Fuchs' spot related to the fibrous evolution of CNV Patients with advanced glaucoma Premenopausal women not using adequate contraception
Ouhadj 2010[43]	Subfoveal or juxtafoveal CNV secondary to PM and not previously treated for this	Not reported

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	condition	
Silva 2010[44]	PM with axial length ≥ 25 mm and spherical equivalent at least –8 D Subfoveal or juxtafoveal CNV With or without previous PDT Visual acuity ≥ 20/400 Age ≥ 21 years; signature required on a written informed consent form	CNV resulting from causes other than myopic CNV, including ocular histoplasmosis syndrome, angioid streaks, multifocal choroiditis, and choroidal rupture Any retinal vasculopathies, including diabetic retinopathy, retinal vein occlusions, etc., in the study eye Previous treatment with other antiangiogenic drugs (such as bevacizumab or pegaptanib), intravitreal triamcinolone; or radiation; also, PDT with Visudyne administered < 3 months before the inclusion Subfoveal or juxtafoveal laser scar Concomitant disease in the study eye, including uveitis, presence of pigment epithelial tears or rips, acute ocular or periocular infection, and central serous chorioretinopathy Advanced glaucoma (> 0.8 cup-to-disk ratio) or intraocular pressure > 21 mmHg in the study eye despite adequate treatment with medication Pregnancy or potential pregnancy (premenopausal women not using adequate contraception)
Vadala 2011[45]	Highly myopic eyes, spherical equivalent > –6 D Posterior pole myopic retinal changes (lacquer cracks, chorioretinal atrophy, papillary crescent, posterior staphyloma); FA detection of the subfoveal or juxtafoveal CNV BCVA >20/400 at baseline Duration of symptoms no longer than 4 weeks before enrolment	Post inflammatory macular changes Extrafoveal CNV Age-related macular alterations Refractive media opacities Presence of other maculopathies as diabetic retinopathy or retinal vascular occlusion History of recent myocardial infarction or other thromboembolic events Other previous intravitreal drugs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
	Minimum follow-up of 12 months Clear ocular media	injections Ocular hypertension or glaucoma
Tufail et al., 2013;[39] REPAIR study 12 month CSR;[94] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45] BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; D, dioptres; ETDRS, Early Treatment Diabetic Retinopathy Study; NSAID, nonsteroidal anti-inflammatory drugs; PDT, photodynamic therapy; PM, pathological myopia; RCT, randomised controlled trial; VEGF, vascular endothelial growth factor		

6.8.5 Describe the patient characteristics at baseline. Highlight any differences between study groups. The following table provides a suggested format for the presentation of baseline patient characteristics for when there is more than one non-RCT.

The REPAIR study recruited 65 patients;[39] over 90% were Caucasian and approximately 70% were female.[40,94] Patients had a mean age of 55.5 years, and the majority (66.2%) had subfoveal CNV lesions. Mean (± SD) BCVA at baseline was 59.5 ± 13.6 letters and mean duration of CNV was approximately 2 months. Further details of baseline characteristics of the REPAIR study population are provided in Table 33.

A summary of key baseline characteristics for patients in the additional five case series studies is provided in Table 34.

Table 33 Characteristics of patients in the non-randomised phase II REPAIR trial

Baseline characteristic	**REPAIR phase II** **Ranibizumab 0.5 mg (n = 65)**
Mean (± SD) age, years	55.5 ± 14.97
Proportion of patients aged:	
< 50 years, n (%)	21 (32.3)
50–64 years, n (%)	29 (44.6)
65–74 years, n (%)	10 (15.4)
75–84 years, n (%)	3 (4.6)
≥ 85 years, n (%)	2 (3.1)
Female, n (%)	46 (70.8)
Caucasian, n (%)	59 (90.8)
Mean ± SD (median) PM duration, years	39.89 ± 20.5 (20.52)
Mean (median) CNV duration, years	1.78 (0.56)
Mean ± SD (median) BCVA, letters	59.5 ± 13.6 (60.0)
Proportion of patients with BCVA of:	
23–37 letters, n (%)	6 (6.2)
38–52 letters, n (%)	16 (24.6)
53–67 letters, n (%)	25 (38.5)
68–82 letters, n (%)	19 (29.2)
> 82 letters, n (%)	1 (1.5)
Mean (median) CRT, µm	384.7 ± 130.8 (393.0)
Proportion of patients with BCVA in study eye worse than fellow eye at start of treatment, %	75.4
Proportion of patients with subretinal or intraretinal haemorrhage, n (%)	41 (63.1)
CNV location, n (%)	
Subfoveal	43 (66.2)
Juxtafoveal	17 (26.2)
Probably subfoveal/juxtafoveal	5 (7.7)
Mean (median) lesion area, mm^2	1.46 ± 1.35 (1.01)
Proportion of patients with:	
Intraretinal oedema with centre involvement, n (%)	57 (87.7)
Intraretinal cysts, n (%)	34 (52.3)
Subretinal fluid, n (%)	44 (67.7)
Tufail et al 2012;[40] REPAIR study 12 month CSR[94] BCVA, best corrected visual acuity; CNV, choroidal neovascularisation, CRT, central retinal thickness; PM, pathological myopia; SD, standard deviation	

Table 34 Baseline characteristics of included non-randomised, case series studies

Study reference	Number of patients (eyes)	Age (years), mean ± SD (range)	Female, n (%)	CNV location, n (%)	Patients received prior vPDT, n (%)	Refractive error (D), mean ± SD (range)	BCVA, mean ± SD	CFT, CMT or CRT (µm), mean ± SD (range)
Calvo-Gonzalez 2011[41]	67 (67)	59 ± 13	50 (74.6)	Subfoveal: 40 (59.7)	42 (62.7)	−11.1 ± 3.3	53.4 ± 12.4 letters	308.5 ± 87.4
Lalloum 2010[42]	32 (32)	57[a] (26–86)	25 (78.1)	Subfoveal: 28 (87.5) Juxtafoveal: 4 (12.5)	13 (40.6)	−13.5 (−6 to −23)	0.2 logMAR[a] (SD NR)	336[a] (179−663)
Ouhadj 2010[43]	40 (40)	40 ± 11 (20–55)	33 (82.5)	Subfoveal: 21 (52.5) Juxtafoveal: 19 (42.5)	NR	−14.1 ± 4.7	NR (range 20/400 to 20/50 Snellen)	NR
Silva 2010[44]	32 (34)	54 ± 17	20 (62.5)	NR	13 (38.2)	NR	51.8 ± 18.1 letters	307.6 ± 79.2
Vadala 2011[45]	39 (40)	53 ± 13 (32–80)	27 (69.2)	Subfoveal: 29 (72.5) Juxtafoveal: 11 (27.5)	15 (37.5)	−13.5 ± 6.5 (−6 to −28)	0.7 ± 0.3 logMAR; 21 ± 16 letters	218.9 ± 7.0

Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45]
BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; CFT, central foveal thickness; CMT, central macular thickness; CRT, central retinal thickness; D, dioptres; logMAR, logarithm of the minimal angle of resolution; NR, not reported; SD, standard deviation; vPDT, verteporfin photodynamic therapy
[a]Median

Outcomes

6.8.6 Provide details of the outcomes investigated and the measures used to assess those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of health-related quality of life, and any arrangements to measure compliance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. When appropriate, also provide evidence of reliability or validity, and current status of the measure (such as use within UK clinical practice). The following table provides a suggested format for presenting primary and secondary outcomes when there is more than one RCT.

In the phase II REPAIR study, the primary outcome was the mean change in BCVA from baseline to month 12.[39] The change in BCVA using an ETDRS chart is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.[85] Secondary outcomes included the mean change in BCVA from baseline to month 6, the mean change in CRT from baseline to months 6 and 12, time to first retreatment and total number of retreatments, change in lesion size and morphology from baseline to months 6 and 12, and the safety of intravitreal injections of ranibizumab (Table 35).

For the additional five case series, all assessed mean change in BCVA at their respective endpoints and the proportion of patients who gained at least 15 letters of visual acuity (see Table 35 for details).[41-45]

Table 35 Primary and secondary outcomes of the non-RCTs

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
REPAIR [39]	Mean change in BCVA from baseline to month 12	The change in BCVA using an ETDRS chart is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.[85]	Mean change in BCVA from baseline to month 6 Mean change in retinal thickness from baseline to months 6 and 12 Time to the first retreatment and the total number of treatments Change in lesion size and morphology from screening to months 6 and 12 Safety of intravitreal injections of ranibizumab Effects of ranibizumab on patient-reported outcomes from baseline to month 12, assessed by the MacTSQ and the W-BQ12	The ETDRS chart is the gold standard measure for visual acuity in clinical practice[85] Change from baseline in CRT over time gives a measure of the effect of treatment on the CNV lesion
Calvo-Gonzalez 2011[41]	No outcomes defined as primary endpoint		Mean change in BCVA, CMT and GLD from baseline Proportion of patients with BCVA gain or loss of ≥ 15 letters from baseline	See explanation for REPAIR study A gain in BCVA of 10 letters has been shown to be associated with clinically relevant improvements in vision-related quality of life and hence is

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
			Proportion of patients with retinochoroidal atrophy Number of injections Ocular or systemic adverse effects	considered to be clinically relevant.[78]
Lalloum 2010[42]	No outcomes defined as primary endpoint		Mean change in BCVA and CMT from baseline Proportion of patients with BCVA gain or loss of ≥ 15 letters from baseline Number of injections AEs	See explanation for REPAIR and Calvo-Gonzalez studies
Ouhadj 2010[43]			Mean change in BCVA and CMT Proportion of patients with BCVA gain of 3 lines or more Number of injections Injection or drug-related adverse events	See explanation for REPAIR and Calvo-Gonzalez studies
Silva 2010[44]	No outcomes defined as primary endpoint		Mean change in BCVA and CMT from baseline Proportions of patients with	See explanation for REPAIR and Calvo-Gonzalez studies

Trial no. (acronym)	Primary outcome(s) and measures	Reliability/validity/ current use in clinical practice	Secondary outcome(s) and measures	Reliability/validity/ current use in clinical practice
			BCVA gain of ≥ 5, ≥ 10 and ≥ 15 letters Number of injections Ocular or systemic adverse effects	
Vadala 2011[45]	Proportion of patients gaining ≥ 5 letters and proportion of patients with stable BCVA	The change in BCVA using an ETDRS chart is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice .[61]	Proportion of patients losing ≥ 5 letters Final BCVA Changes in CRT assessed by OCT Number of injections	See explanation for REPAIR study
Tufail et al., 2013;[39] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45] AE, adverse event; BCVA, best corrected visual acuity; CMT, central macular thickness; CNV, choroidal neovascularisation; CRT, central retinal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; GLD, greatest linear dimension; MacTSQ, Macular Disease Treatment Satisfaction Questionnaire; OCT, optical coherence tomography; RCT, randomised controlled trial; W-BQ12, Well-Being Questionnaire				

Statistical analysis and definition of study groups

6.8.7 State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). The following table provides a suggested format for presenting the statistical analyses in the trials when there is more than one RCT.

In the REPAIR study, the hypothesis objective was to evaluate the mean change in BCVA from baseline to month 12 (Table 36).[39,94] For this primary efficacy variable, a sample size of 58 was calculated to have 90% power to detect a difference in mean BCVA from baseline of 10 letters. To allow for non-completing patients, a recruitment target of 64 patients (one eye per patient) was set and 65 patients were recruited.

Three sets of patients were analysed. The Full Analysis set consisted of all patients who received at least one application of study treatment and had at least one post-baseline assessment for BCVA. Following the intent-to-treat principle, patients were analysed according to the treatment assigned. No data were excluded from the Full Analysis set analyses because of protocol deviations. The Per Protocol set consisted of all patients in the Full Analysis set who completed the treatment phase of the trial without clinically significant protocol deviations. If deviations occurred, then the data from specific patients, visits, or evaluations could be excluded. The Safety set consisted of all patients who received at least one application of study treatment and had at least one post-baseline safety assessment. Patients were analysed according to treatment received. The statement that a patient had no AEs also constituted a safety assessment.

The primary variable was the difference from baseline to Month 12 in the level of BCVA. Efficacy endpoints (change in BCVA, CRT and lesion area) were reported as mean with 95% CI derived from a t-distribution; p-values are reported from a paired t-test. For the Full Analysis set, the analysis followed a last observation carried forward approach.

Table 36 Summary of statistical analyses in non-RCTs

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
REPAIR [39]	The primary objective was to evaluate the mean change in BCVA from baseline to month 12. The key secondary objectives were to evaluate: Mean change in BCVA from baseline to month 6 Mean change in retinal thickness from baseline to months 6 and 12 Time to the first retreatment and the total number of treatments Change in lesion size and morphology from screening to months 6 and 12 Safety of intravitreal injections of ranibizumab. Exploratory objectives were to evaluate the effects on patient-reported outcomes, assessed by the MacTSQ and W-BQ12 instruments.	The null hypothesis that visual acuity at 12 months was equal to that at baseline was tested using a paired t-test.	For the primary efficacy variable (change in BCVA from baseline to 12 months), a sample size of 58 was calculated to have 90% power to detect a difference in mean BCVA of 10 letters. Therefore, to allow for non-completing patients a recruitment target of 64 patients (one eye per patient) was set and 65 patients were recruited.	For the Full Analysis set, the analysis followed a LOCF approach. In the event that a subject received rescue medication and continued in the study, the last observed value prior to receipt of rescue medication was used in the LOCF procedure.

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Calvo-Gonzalez 2011[41]	This prospective study evaluates the treatment of myopic CNV with ranibizumab by identifying possible predictive factors that could affect final visual acuity and the need for retreatment.	The Student paired t test or multivariate analysis of variance were used to compare continuous variables Categorical variables were compared using the Chi-squared test or McNemar test	NR	For the intent-to-treat population, a LOCF approach was followed.
Lalloum 2010[42]	Analysis was initially performed on the entire cohort with measurements of visual acuity variations and macular thickness. A secondary analysis compared the eyes without previous PDT with the eyes with previous PDT treatment.	Visual acuity and macular thickness at baseline were compared with that observed at final examination using the Wilcoxon matched-pairs signed-rank test. Factors potentially associated with visual acuity improvement and macular thickness reduction were assessed using the Mann–Whitney test and Spearman Rho correlation, respectively	NR	NR
Ouhadj 2010[43]	The primary reported outcome was the proportion of patients with an improvement in visual acuity.	NR	NR	NR

Trial acronym	Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Silva 2010[44]	Outcomes assessed statistically were BCVA and CRT.	BCVA and CRT were assessed using a Wilcoxon signed-ranks test and a two-tailed t-test, respectively	NR	NR
Vadala 2011[45]	The primary outcome was the improvement (by a minimum of 5 letters) or stabilisation of BCVA. The secondary outcome was the change in CRT.	BCVA and CRT were assessed using a non-parametric Wilcoxon signed-ranks test and a two-tailed t-test, respectively. The influence of age, previous PDT and lesion size on BCVA change were analysed by means of multivariate linear regression.	NR	NR

Tufail et al., 2013;[39] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45]
BCVA, best-corrected visual acuity; CRT, central retinal thickness; LOCF, last observation carried forward; MacTSQ, Macular Disease Treatment Satisfaction Questionnaire; NR, not reported; PDT, photodynamic therapy; RCT, randomised controlled trial; W-BQ12, Well-Being Questionnaire.

6.8.8 Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

No subgroup analyses were performed in the REPAIR study.

Four of the prospective case series included analyses of improvement in BCVA according to factors such as prior vPDT, age and baseline BCVA (Table 37).

Table 37 Details of subgroup analyses in non-RCTs

Trial no. (acronym)	Subgroups analysed	Rationale	Pre-planned or post-hoc
Calvo-Gonzalez 2011[41]	Age, gender, refractive error, prior vPDT or pegaptanib, myopic foveal atrophy, foveal pigment, fibrosis, myopic CNV GLD and area, CNV location, initial cystoid macular oedema, baseline BCVA and CMT	These factors may influence response to ranibizumab therapy	Pre-planned
Lalloum 2010[42]	Prior vPDT, sex, age, initial visual acuity, and retinal thickness	These factors may influence response to ranibizumab therapy	Unclear if pre-planned
Silva 2010[44]	Prior vPDT	Prior treatment with vPDT may influence response to ranibizumab therapy	Unclear if pre-planned
Vadala 2011[45]	Prior vPDT, age, lesion size	These factors may influence response to ranibizumab therapy	Pre-planned

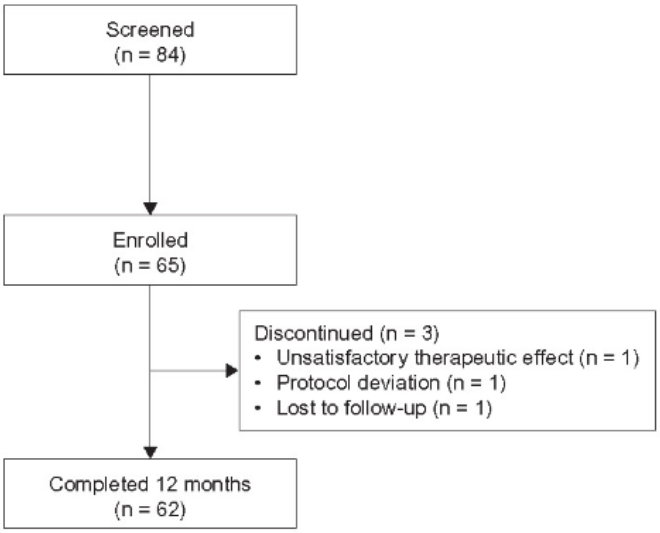
Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Silva et al., 2010;[44] Vadala et al., 2011[45]
BCVA, best corrected visual acuity; CMT, central macular thickness; CNV, choroidal neovascularisation; GLD, greatest linear dimension; RCT, randomised controlled trial; vPDT, verteporfin photodynamic therapy

Participant flow

6.8.9 Provide details of the numbers of patients who were eligible to enter the RCT(s), randomised, and allocated to each treatment. Provide details of, and the rationale for, patients who crossed over treatment groups and/or were lost to follow-up or withdrew from the RCT. This information should be presented as a CONSORT flow chart.

In the phase II REPAIR trial, 65 patients were recruited and 62 completed the full 12 months of follow-up (Figure 14).[94]

Figure 14 CONSORT flow chart of patients in REPAIR[94]



REPAIR 12-month CSR[94]

Critical appraisal of relevant non-RCTs

6.8.10 The validity of the results of an individual study will depend on the robustness of its overall design and execution, and its relevance to the decision problem. Each study that meets the criteria for inclusion should therefore be critically appraised. Whenever possible, the criteria for assessing published studies should be used to assess the validity of unpublished and part-published studies. The critical appraisal will be validated by the ERG. The following are the minimum criteria for assessment of risk of bias in RCTs, but the list is not exhaustive.

A detailed critical appraisal of the included non-randomised studies is provided in Table 38.

Table 38 Quality assessment of included non-randomised, case series studies

Study reference	Checklist components (Case series, CRD Report 4, 2001) (Yes/No/Unclear)					
	Is the study based on a representative sample selected from a relevant population?	**Are the criteria for inclusion explicit?**	**Did all individuals enter the survey at a similar point in their disease progression?**	**Was follow-up long enough for important events to occur?**	**Were outcomes assessed using objective criteria or was blinding used?[b]**	**If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?**
REPAIR 2012[39,94]	Unclear	Yes	Unclear	Yes	Yes/No	Not applicable
Calvo-Gonzalez 2011[41]	Yes	Yes	Unclear	Yes/No[a]	Yes/No	No
Lalloum 2010[42]	Unclear	Yes	Unclear	Yes/No[a]	Unclear	Yes
Ouhadj 2010[43]	Yes	Unclear	Unclear	No	Unclear	Not applicable
Silva 2010[44]	Unclear	Yes	Unclear	Yes	Unclear	Yes
Vadala 2011[45]	Yes	Yes	Yes	No	Unclear	No

Tufail et al., 2013;[39] REPAIR study 12 month CSR;[94] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45]

[a]Denotes that the duration of follow-up would be long enough in some patients but not in others.

[b]Yes/No denotes outcomes measured using objective (intraocular pressure, central retinal thickness etc) and subjective (eg Early Treatment of Diabetic Retinopathy Study charts, self-report) criteria.

Results of the relevant non-RCT

6.8.11 Provide the results for all relevant outcome measure(s) pertinent to the decision problem.

The results for the non-RCTs are summarised in Table 39.

Table 39 Summary of efficacy results for non-RCTs

Reference	N (eyes)	Time point at which efficacy assessed or mean ± SD (range) duration of follow-up	Number of injections, mean± SD	Change in BCVA (letters), mean ± SD (range)	Gained ≥ 15 letters at follow-up, %
REPAIR[40,94]	65 (65 eyes)	12 months	3.6 ± 2.6	13.76 ± 13.9** (range NR)	37%
Calvo-Gonzalez 2011[41]	67 (67 eyes)	12 months (59 eyes), SD and range NR 16 (6−27) months, SD NR	3.9 ± 1.1 4.2 ± 1.7[b]	12.4 ± 13.0* (range NR) 12.0 ± 14.6* (range NR)	 40%
Lalloum 2010[42]	32 (32 eyes)	17 (7−29)[a] months	3.0 (1–12)[a]	9.5***, SD and range NR	47%
Ouhadj 2010[43]	40 (40 eyes)	8 (3–15) months, SD NR	2.2, SD NR	15.0 (5–45), SD NR	NR
Silva 2010[44]	32 (34 eyes)	12 months, SD and range NR	3.6 ± 1.8	8.0**, SD and range NR	24%
Vadala 2011[45]	39 (40 eyes)	13 ± 2 (12−18) months	2.8 ± 1.2	14.5 (5–40)[a] for 32 eyes with improvement	60% for 32 eyes with improvement

Tufail et al 2012;[40] REPAIR 12-month CSR;[94] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43]
Silva et al., 2010;[44] Vadala et al., 2011[45]
BCVA, best corrected visual acuity; NR, not reported; RCT, randomised controlled trial; SD, standard deviation
[a]Median (range); [b]Patients scheduled to receive three monthly injections followed by retreatment as needed.
*p < 0.05; **p < 0.001;***p < 0.0001 vs baseline

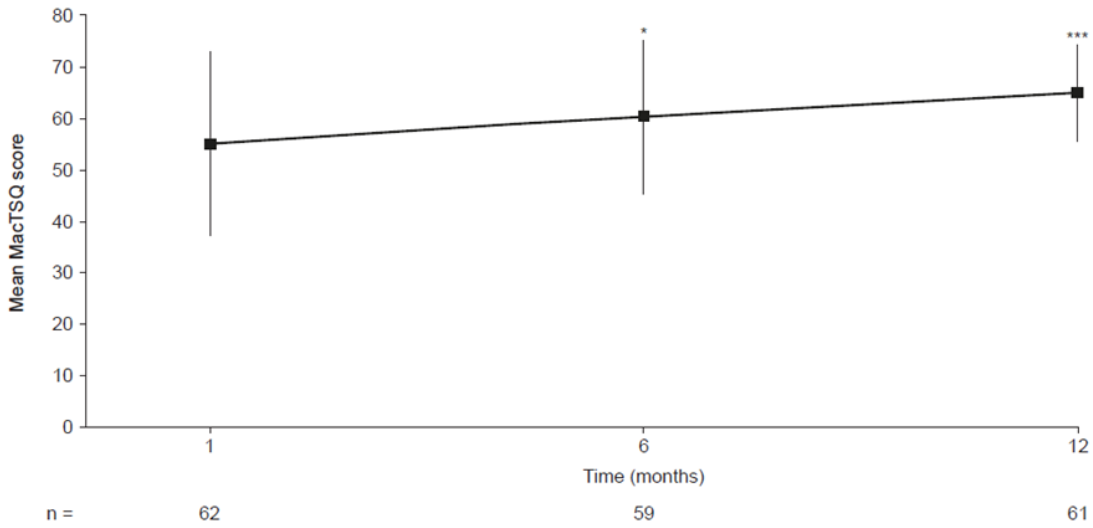
Efficacy results from REPAIR are in good agreement with those reported for the Novartis phase III study

In the phase II REPAIR study, mean BCVA improved from baseline by 12.2 letters at 6 months and 13.76 letters at 12 months, comparable to that achieved in the Novartis phase III study. This was accompanied by a mean reduction in CRT of 108 µm at 6 months and 135.16 µm at 12 months. [39,40] As in the Novartis phase III study, improvements in BCVA were evident at month 1 and further improvements were evident throughout the study. The improvements

in BCVA were achieved with a mean (± SD) of 3.6 ± 2.57 ranibizumab injections over 12 months and 21.5% of patients required no further treatment beyond the initial injection.[40,94]

As an exploratory objective, the REPAIR study also evaluated the effects of ranibizumab on patient-reported outcomes.[39,95] Treatment satisfaction was measured using the 13-item Macular Disease Treatment Satisfaction Questionnaire (MacTSQ; scores range from 0 to 72), which includes subscales on the impact of treatment and information provision and convenience. Well-being was assessed using the 12-item Well-Being Questionnaire (W-BQ12; scores range from 0 to 36), which produces measures of negative well-being, positive well-being, energy and a composite general well-being score. The W-BQ12 was administered at baseline, and both instruments were completed at months 1, 6 and 12. The mean (± SD) overall MacTSQ score increased from 55.0 ± 17.9 at month 1 to 58.8 ± 16.2 at month 6 and 64.9 ± 9.2 at month 12 (p = 0.005 and 0.0001 vs month 1, respectively; Figure 15). At month 12, both patients treated in their better-seeing eye (BSE) and worse-seeing eye (WSE) groups had improvements of 9.5–10.0 points. Patients had significantly higher mean (± SD) W-BQ12 general well-being scores at month 12 compared with baseline (27.3 ± 6.4 vs 25.6 ± 7.0, p = 0.03) and numerical improvements were seen in all subscales.[94]

Figure 15 Mean (± SD) MacTSQ score following treatment with ranibizumab in the REPAIR study



REPAIR 12-month CSR[94]
MacTSQ, Macular Disease Treatment Satisfaction Questionnaire
*p = 0.005, ***p = 0.0001 vs vPDT

Results from prospective cases series studies are in good agreement with those of the phase II and phase III studies

The findings from the five prospective case series agree with those of the Novartis phase III study and the REPAIR phase II study. The five studies reported gains in BCVA of 8 to 19.1 letters over mean durations of follow-up ranging 8 to 16 months, and the proportion of patients that gained at least 15 letters ranged from 24 to 40% over mean follow-ups of 12 to 17 months in the three studies that reported this endpoint (Table 39).[41,42,44] . In the four studies where patients received a single initiation injection and were then treated PRN, the mean number of injections ranged from 2.2 (over 8 months)[43] to 3.6 (over 12 months)[44].

The benefits of ranibizumab treatment were reported to be independent of age, lesion size or refractive error

Four studies[41,42,44,45] analysed changes in BCVA according to baseline characteristics. The benefits of ranibizumab were found be independent of age[41,42,45], sex[42], lesion size[41,45] or refractive error[45]. Two studies reported that improvements in BCVA achieved with ranibizumab were similar in treatment-naïve patients and those who had previously received vPDT,[41,44,45] while a further two studies reported better responses in treatment-naïve patients[42,44]. One study reported greater improvements in BCVA in patients with a lower BCVA at baseline (in agreement with the Novartis phase III study),[41] while two further studies reported no effect of baseline BCVA on the improvement in BCVA in response to ranibizumab.[42,45]

6.9 Adverse events

This section should provide information on the adverse events experienced with the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, post-marketing surveillance data may demonstrate that the technology shows a relative lack of adverse events commonly associated with the comparator, or the occurrence of adverse events is not significantly associated with other treatments.

6.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 6.1 to 6.5 for the identification, selection, methodology and quality of the trials, and the presentation of results. Examples for search strategies for specific adverse effects and/or generic adverse-effect terms and key aspects of quality criteria for adverse-effects data can found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 10.8 and 10.9, appendices 8 and 9.

No studies were identified that specifically aimed to capture safety evidence. Detailed safety data are reported in section 6.9.2 for the Novartis phase III study, and the other RCTs and non-RCTs also provide limited safety data.

6.9.2 Please provide details of all important adverse events for each intervention group. For each group, give the number with the adverse event, the number in the group and the percentage with the event. Then present the relative risk and risk difference and associated 95% confidence intervals for each adverse event. A suggested format is shown below.

Ranibizumab is generally well tolerated in patients with CNV secondary to PM

Results from the Novartis phase III study indicate that ranibizumab is generally well tolerated in patients with visual impairment due to CNV secondary to PM.[33,34] Most AEs were mild or moderate in severity[34] in all treatment groups and no patients discontinued therapy due to an AE.

Table 40 and Table 41 summarise the ocular and non-ocular AEs reported over months 1 to 3, 1 to 6 and 1 to 12 in the phase III study.[32-34] Only two severe ocular AEs were reported during the trial: allergic conjunctivitis was reported over months1−3 in a patient in the ranibizumab disease activity group and dacryocystitis was reported over months 4−6 in a patient in the ranibizumab disease stabilisation group. Eleven severe non-ocular AEs were reported in 9 patients over the 12 month period, seven events in the ranibizumab disease activity group and four in the ranibizumab disease stabilisation group. None of the ocular or non-ocular severe AEs were suspected to be related to the study drug or ocular injection. Only two serious ocular AEs were reported during the trial, one in the first 3 months (corneal erosion in a patient in the ranibizumab stabilisation group), and one after month 6 (retinoschisis in the ranibizumab disease activity group). The latter was not suspected to be related to the study medication or ocular injection. Serious non-ocular AEs were reported in 5 patients in the ranibizumab disease activity group and 6 patients in the stabilisation group over the 12 month period; none were related to study medication.

Table 40 Summary of AEs in the Novartis phase III study reported in at least two patients in any treatment group and all AEs related to ocular safety concerns: baseline to month 3

	AEs, n (%)			OR (95% CI) vs vPDT		RR (95% CI) vs vPDT	
	Ranibizumab disease activity (N = 118)	Ranibizumab disease stabilisation (N = 106)	vPDT (N = 53)	Ranibizumab disease activity (N = 118)	Ranibizumab disease stabilisation (N = 106)	Ranibizumab disease activity (N = 118)	Ranibizumab disease stabilisation (N = 106)
Ocular AEs, n (%)[a]							
Any	16 (13.6)	29 (27.4)	5 (9.4)	1.51 (0.52–4.35)	3.61 (1.31–9.98)	1.44 (0.56–3.72)	2.90 (1.19–7.06)
Severe	0	0	0	NA	NA	NA	NA
Conjunctival haemorrhage	6 (5.1)	10 (9.4)	0	NA	NA	NA	NA
Punctate keratitis	3 (2.5)	6 (5.7)	2 (3.8)	0.67 (0.11–4.10)	1.50 (0.31–7.18)	0.67 (0.12–3.91)	1.53 (0.30–7.85)
Intraocular pressure increased	2 (1.7)	2 (1.9)	1 (1.9)	0.44 (0.06–3.21)	0.49 (0.07–3.58)	0.45 (0.07–3.10)	0.50 (0.07–3.45)
Eye pain	1 (0.8)	2 (1.9)	0	NA	NA	NA	NA
Dry eye	0	3 (2.8)	0	NA	NA	NA	NA
Injection site haemorrhage	0	0	0	NA	NA	NA	NA
Vitreous floaters	0	0	0	NA	NA	NA	NA
Retinal tear	0	0	0	NA	NA	NA	NA
Conjunctivitis allergic	0	0	0	NA	NA	NA	NA
Metamorphopsia	0	0	0	NA	NA	NA	NA
Retinal haemorrhage	0	0	0	NA	NA	NA	NA
Blepharitis	0	0	0	NA	NA	NA	NA
Conjunctivitis	0	0	0	NA	NA	NA	NA
Eyelid oedema	0	0	0	NA	NA	NA	NA
Cataract	0	1 (0.9)	0	NA	NA	NA	NA
Ocular hyperaemia	0	0	0	NA	NA	NA	NA
Ocular AEs related to study medication or ocular injection, or both, n (%)							
Any, n (%)	10 (8.5)	19 (17.9)	3 (5.7)	1.54 (0.41–5.85)	3.64 (1.03–12.91)	1.50 (0.43–5.22)	3.17 (0.98–10.23)

	AEs, n (%)			OR (95% CI) vs vPDT		RR (95% CI) vs vPDT	
	Ranibizumab disease activity (N = 118)	**Ranibizumab disease stabilisation (N = 106)**	**vPDT (N = 53)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**
Conjunctival haemorrhage	5 (4.2)	8 (7.5)	0	NA	NA	NA	NA
Punctate keratitis	2 (1.7)	3 (2.8)	2 (3.8)	0.44 (0.06–3.21)	0.74 (0.12–4.59)	0.45 (0.07–3.10)	0.75 (0.13–4.35)
Eye pain	1 (0.8)	2 (1.9)	0	NA	NA	NA	NA
Intraocular pressure increased	1 (0.8)	2 (1.9)	1 (1.9)	0.44 (0.03–7.24)	1.00 (0.09–11.28)	0.45 (0.03–7.05)	1.00 (0.09–10.78)
Conjunctival oedema	0	1 (0.9)	0	NA	NA	NA	NA
Corneal erosion	1 (0.8)	1 (0.9)	0	NA	NA	NA	NA
Retinal tear	0	1 (0.9)	0	NA	NA	NA	NA
Vitreous floaters	1 (0.8)	1 (0.9)	0	NA	NA	NA	NA
Vitreous prolapse	0	1 (0.9)	0	NA	NA	NA	NA
Conjunctival hyperaemia	0	0	1 (1.9)	NA	NA	NA	NA
Injection site haemorrhage	1 (0.8)	1 (0.9)	0	NA	NA	NA	NA
Intracranial pressure increased	0	1 (0.9)	0	NA	NA	NA	NA
Uveitis	0	1 (0.9)	0	NA	NA	NA	NA
Ocular hyperaemia	0	0	0	NA	NA	NA	NA
Iridocyclitis	0	0	0	NA	NA	NA	NA
Drug hypersensitivity	0	0	0	NA	NA	NA	NA
Injection site pain	0	0	0	NA	NA	NA	NA
Adenoviral conjunctivitis	0	0	0	NA	NA	NA	NA
Eye irritation	0	0	0	NA	NA	NA	NA
Metamorphopsia	0	0	0	NA	NA	NA	NA
Non-ocular AEs, n (%)[b]							
Any	30 (25.4)	27 (25.5)	6 (11.3)	2.67 (1.04–6.87)	2.68 (1.03–6.96)	2.25 (0.99–5.07)	2.25 (0.99–5.11)
Severe	1 (0.8)	0	0				

	AEs, n (%)			OR (95% CI) vs vPDT		RR (95% CI) vs vPDT	
	Ranibizumab disease activity (N = 118)	**Ranibizumab disease stabilisation (N = 106)**	**vPDT (N = 53)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**
Nasopharyngitis	6 (5.1)	5 (4.7)	1 (1.9)	2.79 (0.33–23.73)	2.57 (0.29–22.61)	2.69 (0.33–21.83)	2.50 (0.30–20.86)
Headache	4 (3.4)	4 (3.8)	0	NA	NA	NA	NA
Intervertebral disc protrusion	0	2 (1.9)	0	NA	NA	NA	NA
Pharyngitis	0	2 (1.9)	0	NA	NA	NA	NA
Upper respiratory tract infection	3 (2.5)	1 (0.9)	0	NA	NA	NA	NA
Back pain	3 (2.5)	1 (0.9)	0	NA	NA	NA	NA
Hypertension	3 (2.5)	1 (0.9)	1 (1.9)	1.36 (0.14–13.35)	0.50 (0.03–8.08)	1.35 (0.14–12.66)	0.50 (0.03–7.84)
Fatigue	2 (1.7)	0	0	NA	NA	NA	NA
Haemorrhoids	2 (1.7)	0	0	NA	NA	NA	NA
Tooth disorder	2 (1.7)	0	0	NA	NA	NA	NA
Migraine	0	0	0	NA	NA	NA	NA
Pain in extremity				NA	NA	NA	NA
Hypercholesterolaemia	1 (0.8)	0	0	NA	NA	NA	NA
Urinary tract infection	1 (0.8)	0	0	NA	NA	NA	NA
Bronchitis	1 (0.8)	0	0	NA	NA	NA	NA
Influenza	0	0	0	NA	NA	NA	NA
Tendonitis	0	0	0	NA	NA	NA	NA
Abdominal pain	0	0	0	NA	NA	NA	NA
Bacteriuria	0	0	0	NA	NA	NA	NA
Diabetes mellitus	0	0	0	NA	NA	NA	NA
Nausea	0	0	0	NA	NA	NA	NA
Osteoporosis	0	0	0	NA	NA	NA	NA
Toothache	0	0	0	NA	NA	NA	NA
Vomiting	0	0	0	NA	NA	NA	NA

	AEs, n (%)			OR (95% CI) vs vPDT		RR (95% CI) vs vPDT	
	Ranibizumab disease activity (N = 118)	**Ranibizumab disease stabilisation (N = 106)**	**vPDT (N = 53)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**
Arthralgia	0	0	0	NA	NA	NA	NA
Cough	0	0	0	NA	NA	NA	NA
Cystitis	0	0	0	NA	NA	NA	NA
Sciatica	0	0	0	NA	NA	NA	NA
Dental caries	0	0	0	NA	NA	NA	NA
Hyperglycaemia	0	0	0	NA	NA	NA	NA
Hyperlipidaemia	0	0	0	NA	NA	NA	NA
Seasonal allergy	0	0	0	NA	NA	NA	NA
Tinnitus	0	0	0	NA	NA	NA	NA
Urticaria	0	0	0	NA	NA	NA	NA
Serious AEs, n (%)	**0**	**2 (1.9)**	**0**	NA	NA	NA	NA

Novartis phase III study 12-month CSR[32]
AE, adverse event; CI, confidence interval; NA, not applicable; NR, not reported; OR, odds ratio; RR, risk ratio; vPDT, verteporfin photodynamic therapy
[a]Reported in at least 2 patients in any treatment group and all AEs related to ocular safety concerns; [b]Reported in at least 2 patients in any treatment group

Table 41 Summary of AEs in the Novartis phase III study reported in at least two patients in any treatment group and all AEs related to ocular safety concerns: baseline to months 6 and 12

	Baseline to month 6		Baseline to month 12	
	Ranibizumab disease activity (N = 118)	**Ranibizumab disease stabilisation (N = 106)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**
Ocular AEs, n (%)[a]				
Any	31 (26.3)	38 (35.8)	44 (37.3)	46 (43.4)
Severe	1 (0.8)	0	1 (0.8)	1 (0.9)
Conjunctival haemorrhage	11 (9.3)	10 (9.4)	12 (10.2)	12 (11.3)
Punctate keratitis	3 (2.5)	6 (5.7)	3 (2.5)	8 (7.5)
Intraocular pressure increased	3 (2.5)	2 (1.9)	7 (5.9)	3 (2.8)
Eye pain	3 (2.5)	3 (2.8)	4 (3.4)	4 (3.8)
Dry eye	0	4 (3.8)	2 (1.7)	4 (3.8)
Injection site haemorrhage	3 (2.5)	3 (2.8)	3 (2.5)	3 (2.8)
Vitreous floaters	1 (0.8)	3 (2.8)	1 (0.8)	5 (4.7)
Retinal tear	0	2 (1.9)	1 (0.8)	2 (1.9)
Conjunctivitis allergic	2 (1.7)	0	5 (4.2)	1 (0.9)
Metamorphopsia	2 (1.7)	0	3 (2.5)	0
Retinal haemorrhage	2 (1.7)	0	3 (2.5)	1 (0.9)
Blepharitis	0	0	2 (1.7)	2 (1.9)
Conjunctivitis	0	0	1 (0.8)	2 (1.9)
Eyelid oedema	0	0	0	2 (1.9)
Cataract	0	2 (1.9)	2 (1.7)	1 (0.9)
Ocular hyperaemia	0	0	2 (1.7)	1 (0.9)
Ocular AEs related to study medication or ocular injection, or both, n (%)				
Any, n (%)	19 (16.1)	21 (19.8)	24 (20.3)	26 (24.5)
Conjunctival haemorrhage	9 (7.6)	8 (7.5)	10 (8.5)	10 (9.4)
Punctate keratitis	2 (1.7)	3 (2.8)	2 (1.7)	5 (4.7)
Eye pain	3 (2.5)	2 (1.9)	3 (2.5)	3 (2.8)
Intraocular pressure increased	1 (0.8)	2 (1.9)	5 (4.2)	3 (2.8)
Conjunctival oedema	0	1 (0.9)	0	1 (0.9)
Corneal erosion	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Retinal tear	0	1 (0.9)	0	1 (0.9)
Vitreous floaters	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Vitreous prolapse	0	1 (0.9)	0	1 (0.9)
Conjunctival hyperaemia	0	0	0	0
Injection site haemorrhage	3 (2.5)	3 (2.8)	3 (2.5)	3 (2.8)

	Baseline to month 6		Baseline to month 12	
	Ranibizumab disease activity (N = 118)	**Ranibizumab disease stabilisation (N = 106)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**
Intracranial pressure increased	0	1 (0.9)	0	1 (0.9)
Uveitis	1 (0.8)	1 (0.9)	1 (0.8)	1 (0.9)
Ocular hyperaemia	0	1 (0.9)	1 (0.8)	1 (0.9)
Iridocyclitis	1 (0.8)	0	1 (0.8)	0
Drug hypersensitivity	0	0	0	1 (0.9)
Injection site pain	0	0	0	1 (0.9)
Adenoviral conjunctivitis	0	0	1 (0.8)	0
Eye irritation	0	0	1 (0.8)	0
Metamorphopsia	0	0	1 (0.8)	0
Non-ocular AEs, n (%)[b]				
Any	42 (35.6)	38 (35.8)	51 (43.2)	48 (45.3)
Severe	3 (2.5)	1 (0.9)	6 (5.1)	3 (2.8)
Nasopharyngitis	7 (5.9)	7 (6.6)	12 (10.2)	12 (11.3)
Headache	7 (5.9)	6 (5.7)	11 (9.3)	8 (7.5)
Intervertebral disc protrusion	0	2 (1.9)	0	2 (1.9)
Pharyngitis	0	2 (1.9)	0	2 (1.9)
Upper respiratory tract infection	4 (3.4)	1 (0.9)	4 (3.4)	3 (2.8)
Back pain	3 (2.5)	1 (0.9)	4 (3.4)	2 (1.9)
Hypertension	3 (2.5)	2 (1.9)	5 (4.2)	3 (2.8)
Fatigue	2 (1.7)	0	2 (1.7)	0
Haemorrhoids	2 (1.7)	0	2 (1.7)	0
Tooth disorder	2 (1.7)	0	2 (1.7)	0
Migraine	0	2 (1.9)	1 (0.8)	2 (1.9)
Pain in extremity	0	2 (1.9)	1 (0.8)	2 (1.9)
Hypercholesterolaemia	2 (1.7)	1 (0.9)	2 (1.7)	1 (0.9)
Urinary tract infection	4 (3.4)	1 (0.9)	3 (2.5)	3 (2.8)
Bronchitis	2 (1.7)	1 (0.9)	4 (3.4)	1 (0.9)
Influenza	2 (1.7)	0	4 (3.4)	2 (1.9)
Tendonitis	2 (1.7)	0	2 (1.7)	1 (0.9)
Abdominal pain	0	0	1 (0.8)	3 (2.8)
Bacteriuria	0	0	0	2 (1.9)
Diabetes mellitus	0	0	1 (0.8)	2 (1.9)
Nausea	0	0	1 (0.8)	2 (1.9)
Osteoporosis	0	0	0	2 (1.9)
Toothache	0	0	1 (0.8)	2 (1.9)
Vomiting	0	0	1 (0.8)	2 (1.9)
Arthralgia	0	0	2 (1.7)	1 (0.9)
Cough	0	0	2 (1.7)	1 (0.9)

	Baseline to month 6		Baseline to month 12	
	Ranibizumab disease activity (N = 118)	**Ranibizumab disease stabilisation (N = 106)**	**Ranibizumab disease activity (N = 118)**	**Ranibizumab disease stabilisation (N = 106)**
Cystitis	0	0	1 (0.8)	1 (0.9)
Sciatica	0	0	2 (1.7)	1 (0.9)
Dental caries	0	0	2 (1.7)	0
Hyperglycaemia	0	0	2 (1.7)	0
Hyperlipidaemia	0	0	2 (1.7)	0
Seasonal allergy	0	0	2 (1.7)	0
Tinnitus	0	0	2 (1.7)	0
Urticaria	0	0	2 (1.7)	0
Serious AEs, n (%)	**2 (1.7)**	**3 (2.8)**	**6 (5.1)**	**7 (6.6)**
Bandello et ao., 2013;[33,34] Novartis phase III 12 month CSR[32] [a]Reported in at least 2 patients in any treatment group and all AEs related to ocular safety concerns; [b]Reported in at least 2 patients in any treatment group.				

6.9.3 Give a brief overview of the safety of the technology in relation to the decision problem.

Ranibizumab was well tolerated and associated with few treatment-related ocular AEs

The results of the Novartis phase III trial provide a comprehensive assessment of the safety profile of ranibizumab over 12 months, with retreatment given according to disease activity and disease stabilisation criteria.[32-34]

In the ranibizumab disease activity group, over the first 3 months, there were 16 (13.6%) ocular AEs, of which 10 (8.5%) were considered related to treatment. The incidence of ocular AEs over the first 3 months was higher in the ranibizumab disease stabilisation group than the disease activity group (any ocular AE, 29 [27.4%]; treatment-related ocular AEs, 19 [17.9%]) and the difference was also apparent at 6 and 12 months (Table 41). In contrast, the incidence of non-ocular AEs was similar for both ranibizumab groups (43.2% and 45.3% for the disease activity and stabilisation groups, respectively over 12 months) and all except three AEs in the ranibizumab disease activity group were not considered to be related to study medication. The incidence of ocular AEs and non-ocular AEs was lower in the vPDT group than in either ranibizumab group as assessed over the first 3 months of the study.

Conjunctival haemorrhage was the only treatment-related ocular AE reported in more than 2% of patients receiving ranibizumab with retreatment according to disease activity over the first 3 months

Conjunctival haemorrhage was the most frequent treatment-related ocular AE in both ranibizumab groups, reported in 4.2% of patients in the disease activity group and 7.5% of patients in the disease stabilisation group over the first 3 months, and 8.5 and 9.4% of

patients, respectively, over the 12 months. In the ranibizumab disease activity group, eye pain, injection site haemorrhage and increased intraocular pressure were the only other treatment-related ocular AEs reported in at least 2% of patients over the 12 month trial period (n = 3, 2.5%; n = 3, 2.5%; n = 5, 4.2%; respectively), whereas in the ranibizumab disease stabilisation group, punctate keratitis, eye pain, injection site haemorrhage and intraocular pressure increased were the only other treatment-related ocular AEs reported in at least 2% of patients (n = 5, 4.7%; n = 3, 2.8%; n = 3, 2.8%; n = 3, 2.8%; respectively) over this period. Punctate keratitis was also the only treatment-related ocular AE reported in at least 2% of patients in the vPDT group (n = 2, 3.8%) over months 1 to 3.

No cases of retinal detachment were reported. Retinal tear possibly related to study medication was reported for 1 (0.9%) patients in the ranibizumab disease stabilisation group. There were no endophthalmitis events reported in the study.

Few non-ocular AEs were reported and most were considered to be not related to study medication

The most frequent non-ocular AEs (occurring in at least 4% of patients) over 12 months were nasopharyngitis, headache and hypertension for the ranibizumab disease activity group and nasopharyngitis and headache in the ranibizumab disease stabilisation group. Only three of the non-ocular AEs, all in the ranibizumab disease activity group, were considered to be related to study medication (headache, hepatic function abnormal and nausea). There were few AEs relating to possible systemic effects of ranibizumab; non-ocular haemorrhage was reported in seven patients (disease activity group, n = 5 [4.2%]; disease stabilisation group, n = 2 [1.9%]), hypertension was reported in nine patients (disease activity group, n = 5 [4.2%]; disease stabilisation group, n = 4 [3.8%]) and one other arterial thromboembolic event was reported in the disease stabilisation group.

Results of non-RCTs and two small RCTs were in agreement with those of the Novartis phase III study

Limited safety data were reported for the two small RCTs and four of the non-RCTs. Both RCTs reported that no systemic AEs or significant ocular AEs were reported during the follow-up period in either group.[46,47] Calvo-Gonzalez et al.[41] reported that two eyes developed anterior uveitis after the second and third injections and that these AEs responded well to topical anti-inflammatory treatment; no other ocular or systemic complications were recorded. The four non-RCTs reported that no ocular or systemic AEs were observed.[42-45]

Table 42 summarises the AEs reported in the REPAIR study.[94] Ocular AEs were reported by 29 (44.6%) of patients; only four events in four patients were considered to be possibly related to ranibizumab. The only ocular AEs reported in 3 (4.5%) or more patients were eye

pain, vitreous floaters, conjunctival haemorrhage and foreign body sensation in the eye. Non-ocular AEs occurred in 39 (60%) patients; none of these were considered to be related to ranibizumab. Retinal detachment, retinal tear and endophthalmitis were reported in one patient each; only the case of endophthalmitis was considered possibly related to ranibizumab and was considered a serious AE. Two further serious AEs were reported; neither were considered related to ranibizumab.

Table 42 Summary of adverse events reported in ≥ 2 patients in the REPAIR study

Adverse event	Number (%) of patients (N = 65)
Any adverse event	46 (70.8)
Any ocular adverse event	29 (44.6)
Eye pain	7 (10.8)
Conjunctival hemorrhage	4 (6.2)
Vitreous floaters	4 (6.2)
Foreign body sensation in eyes	3 (4.6)
Intraocular pressure increased	2 (3.1)
Metamorphopsia	2 (3.1)
Vision blurred	2 (3.1)
Visual acuity reduced	2 (3.1)
Any non-ocular adverse events	39 (60.0)
Nasopharyngitis	6 (9.2)
Lower respiratory tract infection	5 (7.7)
Back pain	4 (6.2)
Cough	4 (6.2)
Fall	4 (6.2)
Headache	4 (6.2)
Hypertension	3 (4.6)
Arthralgia	2 (3.1)
Dizziness	2 (3.1)
Gout	2 (3.1)
Influenza	2 (3.1)
Migraine	2 (3.1)
Musculoskeletal pain	2 (3.1)
Procedural nausea	2 (3.1)
Sinusitis	2 (3.1)
Tooth extraction	2 (3.1)
Upper respiratory tract infection	2 (3.1)
Tufail et al 2012;[40] REPAIR 12-month CSR[94]	

6.10 Interpretation of clinical evidence

6.10.1 Please provide a statement of principal findings from the clinical evidence highlighting the clinical benefit and harms from the technology.

Efficacy

Ranibizumab provides clinically meaningful improvements in BCVA in patients with visual impairment due to CNV secondary to PM

The only currently approved treatment for CNV secondary to PM, vPDT, generally achieves stabilisation of BCVA and few patients achieve a clinically meaningful improvement in BCVA of 10 to 15 letters over two to three years.[25,26,96] In contrast, the Novartis phase III study demonstrated that ranibizumab achieves a mean improvement in BCVA of 10 to 12 letters with approximately two-thirds of patients achieving a gain in BCVA of at least 10 letters and over half achieving a gain of at least 15 letters at 12 months.[34] Gains in BCVA of approximately 10 letters were achieved with ranibizumab, [redacted].[32]

Additional evidence for the efficacy of ranibizumab is provided by results from two small RCTs comparing ranibizumab and bevacizumab, a phase II study (REPAIR) and five prospective case series studies.[32,41-47,97] These studies reported gains in BCVA from baseline of 8 to 14 letters over follow-ups ranging from 6 to 24 months and the proportion of patients gaining at least 15 letters over follow-up ranged from 24% to 40% in the six studies reporting this endpoint.

Ranibizumab provides rapid and sustained improvements in BCVA

Results from the Novartis phase III study indicate gains in BCVA are evident from 1 month. BCVA increased rapidly up to three months after the first ranibizumab injection, and improvement continued up to 12 months with retreatment as needed in the phase III study.[33,34] A similar pattern of rapid improvement in BCVA was observed in the four other studies which reported improvements in BCVA at 1- to 3-month intervals over the follow-up period.[41,46,47,97] Indeed results from the Iacono 2012 and Calvo-Gonzalez 2011 studies indicate that improvements in BCVA achieved with ranibizumab are sustained at 18 and 24 months, respectively, with retreatment based on disease activity criteria.

Ranibizumab, administered as a single initiation dose followed by retreatment according to disease activity, provides sustained improvements in BCVA and CRT

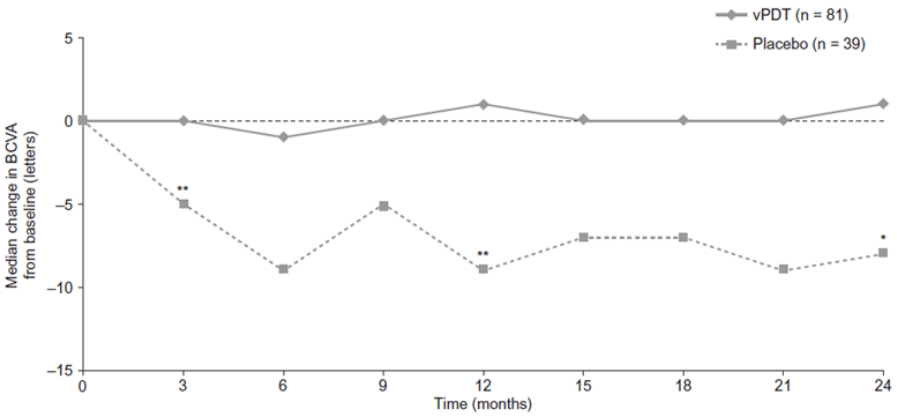
The Novartis phase III study investigated two different ranibizumab dosing regimens, one in which retreatment was given according to disease activity criteria and the other in which retreatment was given according to disease stabilisation criteria. Analysis of the mean average change from baseline in BCVA at 6 months indicated that there was no significant difference between the two regimens. This is in agreement with all other BCVA outcome measures. However, the reduction in CRT from baseline at 6 months was greater for the ranibizumab disease activity group compared with the disease stabilisation group, suggesting a possible advantage for this regimen.

In addition, the mean number of injections required over the 12-month period was lower in the ranibizumab disease activity group compared with the disease stabilisation group (3.5 versus 4.6) and 50% of patients in this group compared with 26% of the ranibizumab disease stabilisation group received two or less injections. Retreatment according to disease activity is the anticipated dosing regimen for ranibizumab as per the SmPC.[1]

Gains in BCVA achieved with ranibizumab were significantly superior to those achieved with vPDT, the only licensed treatment for this indication

The Novartis phase III trial assessed the efficacy and safety of ranibizumab compared with vPDT. The efficacy of vPDT has been established in the VIP study, a 2-year, placebo-controlled RCT (see section 6.7 for details). In the VIP study patients treated with vPDT gained a median of 0 letters from baseline at 3 months and 1 letter from baseline at both 12 and 24 months (Figure 16). A gain of at least 15 letters was achieved by 2%, 6% and 12% of patients at 3, 12 and 24 months, respectively.[25,26] The results for vPDT from the Novartis phase III study are in reasonable agreement with, or better than, those of the VIP study, reporting a median change in BCVA from baseline to month 3 of 1.0 letter and 14.5% of patients achieved a gain of at least 15 letters at this time point.

Figure 16 Change in median BCVA letter score from baseline following therapy with vPDT or placebo in the VIP study[a]



VIP trial, Blinder et al 2003[25]
BCVA, best corrected visual acuity; ETDRS, early treatment diabetic retinopathy study; VIP, verteporfin in photodynamic therapy
[a]The change in median BCVA letter score was a secondary endpoint. The primary endpoint was the proportion of eyes with fewer than 8 letters of BCVA loss at 12 months.
*p < 0.05; **p < 0.01 versus placebo.
Statistical analyses are presented for all time points reported in the original publications

In the Novartis phase III study, highly statistically significant differences (p < 0.0001) were observed between ranibizumab (either regimen) and vPDT for all BCVA endpoints (mean average change from baseline for months 1 to 3; proportion of patients gaining at least 10 letters at 3 months; proportion of patients gaining at least 15 letters at 3 months).[32,33] These results suggest that ranibizumab offers substantial therapeutic benefits over vPDT for the management of visual impairment due to CNV secondary to PM.

Ranibizumab provides superior improvements in visual functioning compared with vPDT

The phase III study assessed vision-related functioning using the NEI VFQ-25, a validated patient-reported outcome questionnaire which provides a measure of the effect of treatment on vision-related activities such as general vision, near activities, distant activities, driving, dependency and social function. A change of 4 to 6 points on the NEI VFQ-25 composite score is considered to correspond to a clinically meaningful change.[38]

At month 3, a clinically meaningful improvement in mean composite score from baseline was observed in both ranibizumab groups (4.3 and 5.3) compared to a minimal change in the vPDT group (0.3) and the difference between ranibizumab and vPDT was statistically significant (p < 0.05). Statistically significant (p < 0.05) differences between ranibizumab and vPDT were also observed for general vision, near activities (disease stabilisation group only),

mental health and dependency. The improvement in visual functioning observed at 3 months in the ranibizumab groups was maintained at 6 and 12 months.[32,35,36]

Safety

Ranibizumab treatment is generally well-tolerated and is associated with few treatment-related AEs

Results from the phase III study indicate that ranibizumab is generally well tolerated. Most AEs were mild or moderate in severity in both ranibizumab groups, with only two severe ocular events – allergic conjunctivitis in a patient in the disease activity group and dacryocystitis in a patient in the stabilisation group – being reported over the 12-month study period; these events were not suspected to be related to the study drug or ocular injection. Conjunctival haemorrhage was the most frequently reported treatment-related ocular AE in both ranibizumab groups, and was the only AE reported in more than 5% of patients in either group over the 12-month follow-up period.[33,34] Only two ocular serious adverse events − corneal erosion in a patient in the disease stabilisation group and retinoschisis in a patient in the disease activity group − were reported.

Non-ocular events were reported in approximately 40% of patients over the 12-month follow-up (disease activity, 43.2%; disease stabilisation, 45.3%); most were considered to be not related to study medication. The most frequent non-ocular AEs (occurring in at least 4% of patients) in the ranibizumab groups over the 12-month follow-up were nasopharyngitis, headache and hypertension.[34] Only three non-ocular AEs were suspected to be related to treatment (headache, hepatic function abnormal, and nausea); all occurred in the ranibizumab disease activity group within the first 6 months on study.[32]

These results are in agreement with the established safety profile of ranibizumab in other approved indications, namely wet AMD, diabetic macular oedema and retinal vein occlusion.[1] No new safety signals were identified.

Fewer AEs were reported for ranibizumab retreatment according to disease activity compared with retreatment according to disease stabilisation

Over the 12-month follow-up in the phase III study, there were fewer ocular AEs (37% versus 43%) and fewer ocular AEs considered to be related to treatment (20% versus 25%) in the ranibizumab disease activity group compared with the ranibizumab stabilisation group.[32,34] This may reflect the lower mean number of injections (3.5 versus 4.6 over 12 months). The incidence of non-ocular AEs was similar for the two ranibizumab groups (disease activity, 43%; disease stabilisation, 45%).

6.10.2 Please provide a summary of the strengths and limitations of the clinical-evidence base of the intervention.

Strengths

Evidence for the efficacy and safety of ranibizumab is based on results from the Novartis phase III trial, a 12-month, randomised, double-blind, multicentre, active-controlled study.[32,34] The results of this study provide robust evidence for the clinical efficacy and safety of ranibizumab in patients with visual impairment due to CNV secondary to PM based on the rigorous design of the study, inclusion of appropriate endpoints, the duration of follow-up and inclusion of vPDT, the only licensed treatment for this indication as the comparator for the double-blind phase of the trial.

The study consisted of a 3-month, double-blind phase during which the efficacy and safety of ranibizumab was compared with vPDT, and a 9-month phase that provided data on the efficacy and safety of ranibizumab treatment for up to 1 year. The study involved 277 patients randomised 2:2:1 to the two ranibizumab groups and vPDT, and was powered to detect a difference of 8 letters in average mean change in BCVA from baseline over months 1 to 3 between either ranibizumab group and vPDT with a power of at least 91%. Patients and the assessing investigators were blinded to treatment. BCVA was assessed monthly using the EDTRS BCVA testing protocol, which is considered the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.[85] CRT was assessed monthly by OCT. The primary efficacy variable was the mean average change from baseline in BCVA over the double-blind phase of the study (i.e. months 1 to 3). Secondary efficacy parameters included both the proportion of patients gaining at least 10 letters or at least 15 letters from baseline; these categorical gains are considered to correspond to clinically meaningful improvements in vision. The study also included assessment of the impact of treatment on patient-reported visual function, as assessed using the validated NEI VFQ-25. Safety data were collected throughout the study. Results are available for the full 12 months study duration.

Further evidence for the efficacy and safety of ranibizumab are provided by two small RCTs with durations of follow-up of 6 months and 18 months,[46,47] and 6 non-RCTs,[39,41-45,98] one of which was performed at 12 centres in the UK.[39]

Limitations

Although the Novartis phase III study provides robust evidence for the safety and efficacy of ranibizumab in this indication, the study has several limitations.

Firstly, the total planned duration of follow-up of the Novartis phase III trial is 12 months. The trial therefore does not provide information on the long-term efficacy and safety of ranibizumab. However, one of the non-RCTs identified reports on the efficacy of ranibizumab at 24 months,[41] and one of the RCTs reports a follow-up of 18 months.[46] The results of both of these studies suggest that the improvement in BCVA achieved at 3 months with ranibizumab can be sustained with retreatment based on disease activity. Both studies also suggest that long-term therapy with ranibizumab is well tolerated.

Secondly, patients randomised to vPDT in the Novartis phase III trial were able to receive ranibizumab after month 3. The design of the study reflects the fact that ranibizumab was expected to provide clinically relevant improvements in BCVA after a single injection, based on data from previous studies, and 12-month results from the VIP study indicated that the effects of vPDT on BCVA are observed at 3 months after therapy. Ethical considerations therefore meant that it was necessary to make the expected benefits of ranibizumab available to patients in the vPDT arm of the study after the evaluation of the primary comparison which could be performed at month 3. Thus, the Novartis phase III study only provides a fully intact randomised comparison of the efficacy and safety of ranibizumab and vPDT monotherapy for 3 months since few (28%) patients remained on monotherapy at 12 months. However, the placebo-controlled Verteporfin in Photodynamic Therapy (VIP) study (the seminal study of vPDT in this indication) provides a rigorous assessment of the efficacy and safety of vPDT in this patient population over a 2-year period (see section 7**Error! Reference source not found.** for details).[38,39] Efficacy data for vPDT from the VIP study are therefore used in the economic model for months 4−12 (i.e. the period for which fully randomised and double-blind data are not available from the Novartis phase III study).

6.10.3 Please provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Data from the Novartis phase III trial are directly relevant to the decision problem. The study provides evidence for the comparative efficacy and safety of ranibizumab (the therapy of interest) and the only licensed comparator for the indication, vPDT, which is the comparator included in the cost-utility model. Patients in the phase III trial are representative of those who would be eligible to receive ranibizumab in clinical practice in the UK andincluded three centres in the UK. The outcome measure, change in BCVA measured using an ETDRS chart, provides an accurate assessment of the clinical benefit of therapy and is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.[85] Change in BCVA and safety data from the phase III study are used in the cost-

utility model; see Section 7 for further details. Supporting evidence for the clinical benefit of ranibizumab in this indication is provided by data from additional studies including the phase II REPAIR study which was performed in 12 UK centres.

6.10.4 Identify any factors that may influence the external validity of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select patients for whom treatment would be suitable based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the SPC?

The findings of the Novartis phase III study have high external validity. The criteria used in clinical practice to select patients for whom ranibizumab would be suitable are similar to the inclusion and exclusion criteria of the phase III study, i.e. diagnosis of active CNV (any location) secondary to PM and presence of visual impairment due to CNV secondary to PM (i.e. BCVA of 74 letters or less). In the phase III study ranibizumab was given as a single initiation dose with retreatment according to either disease activity or disease stabilisation criteria. The disease activity criteria used in the study correspond to the anticipated licensed regimen as per the Summary of Product Characteristics.[1] Thus the data reported for this treatment group reflect what would be anticipated in clinical practice. Treatment is initiated with a single injection. If monitoring reveals signs of activity, further treatment is recommended. Monitoring for disease activity may include clinical examination, OCT or FA. Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year, the frequency of monitoring should be determined by the treating physician.

All evidence for the efficacy of ranibizumab for the treatment of CNV secondary to PM is based on the licensed dose of 0.5 mg. The ranibizumab disease activity group from the phase III study and evidence from the phase II study, two RCTs, and four of the five non-RCTs are all for a treatment regimen consisting of an initial dose followed by retreatment based on disease activity criteria.

7 Cost-effectiveness

7.1 Published cost-effectiveness evaluations

Identification of studies

7.1.1 Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided as in section 10.10, appendix 10.

Search strategy

The search strategy used to identify studies was the same as the one designed for the review of clinical effects. The strategy was sensitive enough to retrieve economic studies (economic evaluations and costs studies) as well as studies with other designs. No search filters specifically to retrieve economic evaluations were applied. No language or date limits were applied. Animal studies, news articles and editorials were excluded by the strategy where possible. Searches were conducted in several databases as described in section 10.10. Additional efforts to identify studies included assessing papers in the reference lists of all eligible studies. Recent reviews were also checked for additional studies not identified by the electronic searches.

Study selection

Initial record selection, on the basis of title and abstract, was undertaken by one reviewer. Obvious false positives were removed at this stage. The full papers were then assessed for relevance by one reviewer and checked by a second reviewer. Discrepancies were resolved through discussion or by consulting a third reviewer.

Inclusion and exclusion criteria

Participants

Studies that evaluate the costs and benefits of patients undergoing treatment for PM or CNV secondary to PM, including patients refractory to other therapies, were considered to be eligible for inclusion.

Interventions and comparators

Economic evaluations of any treatments for PM or CNV secondary to PM were considered to be eligible for inclusion in the review.

Outcomes

The outcomes of interest included total, direct and indirect costs; summary health outcomes; utility values; cost-effectiveness ratios and number of cases of blindness.

Study types

Economic evaluations of the cost-effectiveness of any treatments for PM or CNV secondary to PM were considered to be eligible for inclusion in the review. In addition to full publications, studies published as abstracts or conference presentations were considered for inclusion if costs and outcomes were sufficiently disaggregated.

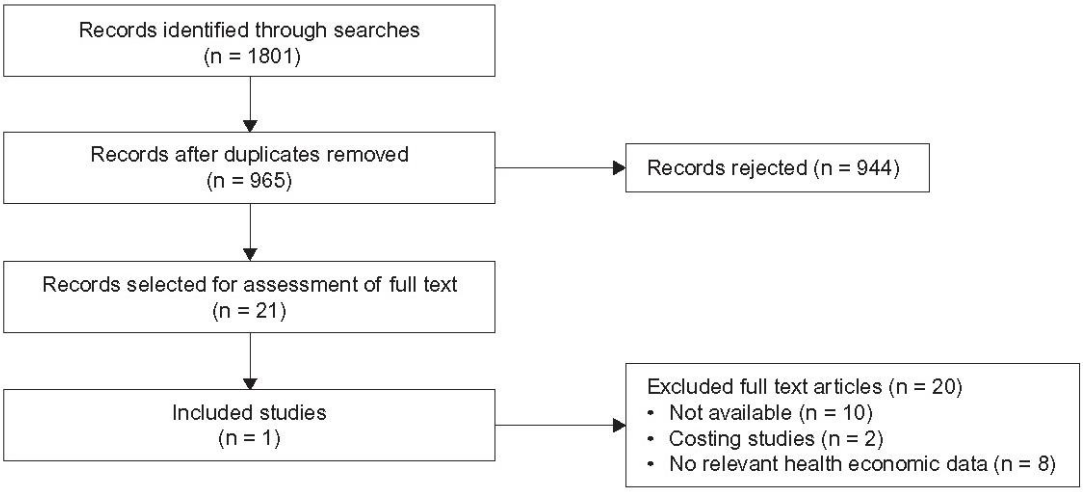
Description of identified studies

7.1.2 Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. When studies have been identified and not included, justification for this should be provided. If more than one study is identified, please present in a table as suggested below.

Search results

The search strategy identified 1801 records. After removal of duplicates, 965 records were screened for relevance based on titles and abstracts, and of these, 21 records were selected for full text review. Figure 17 shows a flow diagram of the screening.

Figure 17 Flow chart of the study selection process for the systematic review



Only one study was considered to be relevant; a summary of the relevant data from the study is provided in Table 43. Sharma & Bakal (2002)[99] is a cost-utility study based on data from the VIP trial.[26] The study aimed to determine the improvement in quality of life that patients with PM gained from vPDT relative to the resources expended, from the perspective of the patient and insurer. It estimated the 1-year costs and health outcomes associated with treating PM patients with vPDT. Quality-adjusted life-years (QALYs) were estimated by converting disease-specific scores (based on BCVA) into utilities, using a pre-established algorithm.[100] The study estimated that the use of vPDT would lead to a gain of 0.037 QALYs, at a net cost increase of approximately $8,000, corresponding to an incremental cost-effectiveness ratio (ICER) of $214,085 per QALY. Sensitivity analyses demonstrated that the model outcomes were sensitive to the duration of treatment effect and to the link between BCVA gain and utility increase.

This study is of limited relevance to the decision problem given that it considered the cost-effectiveness of vPDT from the patient and insurer perspective in the US and was based on costs for 1 year.

Table 43 Summary list of other cost-effectiveness evaluations

Study	Year	Country(ies) where study was performed	Summary of model	Patient population (average age in years)	QALYs (intervention, comparator)	Costs (currency) (intervention, comparator)	ICER (per QALY gained)
Sharma & Bakal[99]	2002	USA	Decision analysis with an assumption of 3.4 treatments during the 1-year time-frame of analysis for the base case of the model	A 50-year old male with monocular vision and PM who develops a subfoveal CNV lesion	0.037 additional QALYs for vPDT vs no-treatment	US Dollars ($) Total incremental cost of vPDT: $1,998 per treatment	$214,085 per QALY for base case
Sharma & Bakal, 2002[99] CNV; choroidal neovascularisation; ICER, incremental cost-effectiveness ratio; PM, pathological myopia; QALY, quality-adjusted life-year; vPDT, verteporfin photodynamic therapy							

7.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

A quality assessment of the single included study is shown in Table 44.

[1] Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83.

[2] Philips Z, Ginnelly L, Sculpher M, et al. (2004) Quality assessment in decision-analytic models: a suggested checklist (Appendix 3). In: Review of guidelines for good practice in decision-analytic modelling in health technology assessment. Health Technology Assessment 8: 36.

Table 44 Quality assessment of Sharma & Bakal[99]

Study design	
Was the research question stated?	Yes
Was the economic importance of the research question stated?	Yes
Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes
Was a rationale reported for the choice of the alternative programmes or interventions compared?	No
Were the alternatives being compared clearly described?	No
Was the form of economic evaluation stated?	Yes
Was the choice of form of economic evaluation justified in relation to the questions addressed?	No
Data collection	
Was/were the source(s) of effectiveness estimates used stated?	Yes
Were details of the design and results of the effectiveness study given (if based on a single study)?	No
Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	No
Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes
Were the methods used to value health states and other benefits stated?	No
Were the details of the subjects from whom valuations were obtained given?	No
Were productivity changes (if included) reported separately?	No
Was the relevance of productivity changes to the study question discussed?	No
Were quantities of resources reported separately from their unit cost?	No
Were the methods for the estimation of quantities and unit costs described?	No
Were currency and price data recorded?	No
Were details of price adjustments for inflation or currency conversion given?	No
Were details of any model used given?	Yes
Was there a justification for the choice of model used and the key parameters on which it was based?	No
Analysis and interpretation of results	
Was time horizon of cost and benefits stated?	Yes
Was the discount rate stated?	Yes
Was the choice of rate justified?	Yes
Was an explanation given if cost or benefits were not discounted?	NA
Were the details of statistical test(s) and confidence intervals given for stochastic data?	No
Was the approach to sensitivity analysis described?	Yes
Was the choice of variables for sensitivity analysis justified?	No
Were the ranges over which the parameters were varied stated?	Yes
Were relevant alternatives compared? (i.e. Were appropriate comparisons made when conducting the incremental analysis?)	NA
Was an incremental analysis reported?	Yes
Were major outcomes presented in a disaggregated as well as aggregated form?	No
Was the answer to the study question given?	Yes
Did conclusions follow from the data reported?	Yes
Were conclusions accompanied by the appropriate caveats?	No
Were generalisability issues addressed?	No

Sharma & Bakal, 2002[99] NA, not applicable

7.2 De novo analysis

Patients

7.2.1 What patient group(s) is(are) included in the economic evaluation? Do they reflect the licensed indication/CE marking or the population from the trials in sections 1.3 and 6.3.3, respectively? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem? For example, the population in the economic model is more restrictive than that described in the (draft) SPC/IFU and included in the trials.

The patient population described in the decision problem matches the anticipated licensed indication for ranibizumab, i.e. patients with visual impairment due to CNV secondary to PM (as described in section 1.5). The base case uses data from the Novartis phase III trial, as described in section 6.3; this cohort is considered to be representative of the licensed population and patients who would receive ranibizumab in the UK.

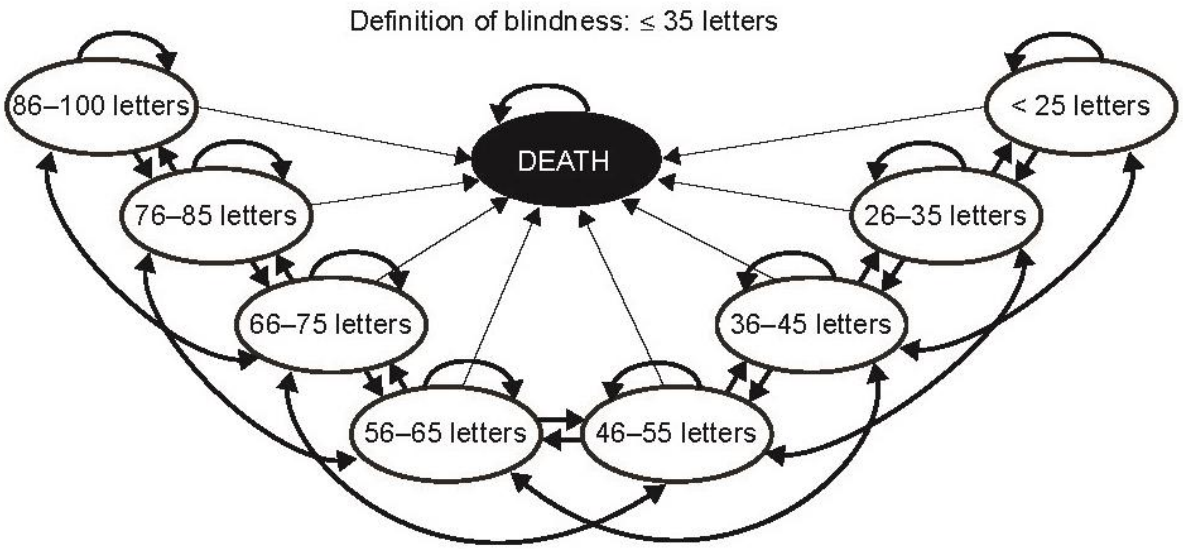
Model structure

7.2.2 Please provide a diagrammatical representation of the model you have chosen.

A state transition Markov model was developed in Microsoft® Excel. It comprises nine mutually exclusive health states, eight of which are defined by ranges of BCVA and one is an absorbing state, 'death' (Figure 18**Error! Reference source not found.**). The eight BCVA health states correspond to levels of BCVA defined according to the ETDRS scale. The approximate equivalent Snellen values are also given in Figure 18.

The model follows a cohort of 1,000 hypothetical generated patients. Each patient may experience a different health pathway over the course of the model. Patients enter the model at a BCVA level as defined by the baseline distribution of BCVA levels in the Novartis phase III trial. Using 3-monthly cycles, the model predicts changes in each patient's health status, quality of life, resource use and associated costs.

Figure 18 Model structure



BCVA	
EDTRS letters	Snellen equivalents
86–100	20/16–20/10
76–85	20/32–20/20
66–75	20/64–20/40
56–65	20/80–20/50
46–55	20/125–20/80
36–45	20/200–20/125
26–35	20/320–20/200
< 25	< 20/320

The arrows shown in this figure apply to the transition probability sensitivity analyses. **For transition probabilities based on current BCVA (base case), patients may move between any two states, so the arrows as depicted on this schematic would extend to all other states.** The arrows have not been completed here for every possible state to maintain legibility.
BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study

7.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.5.

Treatment in patients with visual impairment due to CNV secondary to PM aims to improve or stabilise BCVA. The model structure therefore fits the care pathway as the effectiveness of interventions is determined by their impact on BCVA.

This Markov approach has successfully been employed in other economic assessments of interventions used to treat conditions associated with deterioration in BCVA.[48-53] The model therefore represents an appropriate approach to modelling the impact of changes in BCVA on costs and quality of life over time.

In the model, the BCVA health states are defined by a 10-letter range in BCVA. A range of 10 letters (2 lines) was chosen because a change of 10 letters is considered to be clinically significant. For example, in a study of vision loss in patients with diabetic retinopathy, a decrease in BCVA of 10 letters was associated with a substantial decline in HRQoL (eg inability to drive, increased dependency, role limitations, impaired mental health), and was correlated with a significant change in vision related quality of life as measured with the NEI VFQ-25.[78]

7.2.4 Please define what the health states in the model are meant to capture.

The BCVA health states in the model are based on the BCVA in the treated eye and thus capture the effects of disease progression over time.

There is currently a lack of consensus about how an individual's visual acuity relates to their quality of life, specifically whether HRQoL is determined solely by BCVA in the BSE, or WSE, or the combination of BCVA in both eyes. In the model, the maximum gain in utilities relating to BCVA in the WSE is 0.1 (i.e. the difference between the worst to the best BCVA states and this was tested in scenario analyses. A weighted approach based on the number of patients whose BCVA represents the BSE and WSE respectively was used to determine utilities (see section 7.4.9 for details). This proportion was derived from the Novartis phase III study (i.e BSE for 20.8% of patients at baseline).

7.2.5 How does the model structure capture the main aspects of the condition for patients and clinicians as identified in section 2 (Context)? What was the underlying disease progression implemented in the model? Or what treatment was assumed to reflect underlying disease progression? Please cross-reference to section 2.1.

The main aspect of CNV secondary to PM for patients and clinicians is loss of vision (see section 2.1). This is captured directly in the model in the health states, as described in sections 7.2.3 and 7.2.4. A change in

BCVA has implications for HRQoL as well as for the type and frequency of healthcare provided, and these aspects of the condition are captured in the model.

In the first year of the model, disease progression for treatment with ranibizumab is modelled based on the efficacy results for the ranibizumab disease activity arm from the Novartis phase III trial. For treatment with vPDT, disease progression over the first year is modelled based on the efficacy results for the vPDT group of the Novartis phase III trial for the first 3 months (cycle 1) and results for vPDT in the VIP study for the following 9 months (cycles 2, 3 and 4). Data from the VIP study were used for months 4−12 for vPDT because in the Novartis phase III trial, patients in the vPDT arm could receive ranibizumab from month 4 onwards and 72% of patients did so. For year 2, disease progression is modelled based on data derived from a natural history study that reports the decline in BCVA over time in patients not receiving treatment (base case)[22] or from multiple natural history studies from different countries (scenario analysis, see section 7.3.2 and Table 46 for further details)..[14,16,18-22]

7.2.6 Please provide a table containing the following information and any additional features of the model not previously reported. A suggested format is presented below.

Table 45 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	Lifetime	Effects of CNV secondary to PM on BCVA, including the risk of recurrence, are expected to continue for the remainder of the patient's life; patients have an average age of 55 years at the start of the model	Novartis phase III trial,[32] VIP study[81]
Cycle length	3 months	This allows sufficient time to capture movement between health states on a regular basis and allows for the regular treatment and follow-up frequency in this condition. Furthermore, patient level data were reported for 3-month intervals in the VIP trial which provides the transition probabilities for vPDT for cycles 2−4 (months 4−12).	Novartis phase III trial,[32] VIP study[81]
Half-cycle correction	Yes	NICE reference case	NICE methods guide
Were health effects measured in QALYs; if not, what was used?	Yes, QALYs	NICE reference case	NICE methods guide
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	NICE methods guide
Perspective (NHS/PSS)	NHS and PSS	NICE reference case	NICE methods guide
Novartis phase III 12 month CSR,[32] VIP trial[81] BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; NHS, National Health Service; PM, pathological myopia; PSS, personal social services; QALY, quality-adjusted life-year; vPDT, verteporfin photodynamic therapy			

Technology

7.2.7 Are the intervention and comparator(s) implemented in the model as per their marketing authorisations/CE marking and doses as stated in sections 1.3 and 1.5? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specified decision problem?

Both ranibizumab and vPDT are implemented as per their marketing authorisations.

7.2.8 Please note that the following question refers to clinical continuation rules and not patient access schemes. Has a treatment continuation rule been assumed? If the rule is not stated in the (draft) SPC/IFU, this should be presented as a separate scenario by considering it as an additional treatment strategy

alongside the base-case interventions and comparators. Consideration should be given to the following.

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.
- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Based on the SPC, ranibizumab treatment for patients with visual impairment due to CNV secondary to PM is initiated with a single injection. As described in section 1.13, treatment is initiated with a single injection. If monitoring reveals signs of activity, further treatment is recommended. Monitoring for disease activity may include clinical examination, OCT or FA. Monitoring is recommended monthly for the first two months and at least every three months thereafter during the first year. After the first year the frequency of monitoring should be determined by the treating physician.[1]

In the Novartis phase III trial, the ranibizumab disease activity group was treated according to the SPC (see section 6.3.2). The use of ranibizumab within the model is based on data from this treatment arm in the phase III trial.

After initial vPDT administration, patients should be re-evaluated every 3 months. In the event of recurrent CNV leakage, vPDT may be given up to 4 times a year, according to the SPC.[101] The use of vPDT in the VIP study adheres to this treatment strategy, and data from this study were used in the economic model (see section 6.7.2 for clinical data and Table 55 for model details).

7.3 Clinical parameters and variables

When relevant, answers to the following questions should be derived from, and be consistent with, the clinical-evidence section of the submission (section 6). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided as well as a justification for the approach.

7.3.1 Please demonstrate how the clinical data were implemented into the model.

Clinical data regarding the effectiveness of the interventions and the incidence of AEs were used in the model.

Clinical effectiveness

The effectiveness of the treatments in the model is expressed as the probability of moving between health states based on the change in BCVA in the treated (study) eye, as described in detail in section 7.3.2. Effectiveness data were populated using patient level data for the study eye from the Novartis phase III trial and the VIP trial for year 1 (Table 46). Data from a number of natural history studies were then used to model disease progression beyond year 1 in both treatment groups (Table 46).

Table 46 Sources of clinical effectiveness data used in the model

	Ranibizumab	vPDT
Year 1 (baseline to month 3)	Novartis phase III trial	Novartis phase III trial
Year 1 (month 3 to month 12)	Novartis phase III trial	VIP trial
Year 2+ (beyond month 12 onwards)	Yoshida et al., 2002 (base case)[22] Multiple natural history studies (scenario analysis)[14,16,18-22]	Yoshida et al., 2002 (base case)[22] Multiple natural history studies (scenario analysis)[14,16,18-22]

Adverse events

A number of AEs were included in the model as described in Table 47. The rationale for inclusion of each adverse event was based on a combination of the relative prevalence and severity of each event (that is, infrequent and non-severe events and adverse events that were not associated with increased health resource utilisation were not included.)

The rates for ranibizumab were selected from the clinical study report (CSR) for the Novartis Phase III trial and the rates for vPDT and observation were selected from the CSR for the VIP trial.[81] The model included the events that occurred in at least five patients, and the AEs that are suspected to be related to the study drug and/or ocular injection. There were no non-ocular adverse events relating to the study drug and/or the ocular injection that occurred in at least five patients for ranibizumab.

Table 47 Adverse events included in the model

Events per patient (%)	Ranibizumab[34]	vPDT[81]
Conjunctival haemorrhage	8.5%	-
Intraocular pressure increased	4.2%	-
Visual Disturbance	-	14.8%
Injection site AEs	-	9.9%
AE, adverse event; vPDT, verteporfin photodynamic therapy Bandello et al 2013;[34] VIP trial[81]		

7.3.2 Demonstrate how the transition probabilities were calculated from the clinical data. If appropriate, provide the transition matrix, details of the transformation of clinical outcomes or other details here.

Transition probabilities for Year 1 from Novartis phase III trial and VIP trial

Three sets of transition probabilities were developed based on data from the Novartis phase III trial (for baseline to month 3 for ranibizumab and vPDT and months 3 to 12 for ranibizumab) and the VIP trial (for months 3 to 12 for vPDT). Effectiveness data were available from the monthly follow-up visits from month 1 to month 12 in the Novartis phase III trial and from 3-monthly follow-up visits in the VIP trial. Thus monthly data were available for ranibizumab for the first year and for vPDT from month 1 to month 3, and 3-monthly data were available for vPDT from month 4 to month 12.

Transition probabilities for the first year on treatment were calculated using the last observation carried forward (LOCF) data for the following four time periods:

- baseline to month 3
- month 3 to month 6
- month 6 to month 9
- month 9 to month 12.

A cycle length of three months was chosen to allow for the inclusion of patient-level data from the VIP trial, in which patients were assessed at three-monthly intervals. Furthermore, this cycle length allows sufficient time to capture changes in BCVA.

Transition probabilities were calculated from clinical trial data as follows:

i. All BCVA scores for the study eye were assigned to one of the BCVA health states specified in the model structure
ii. For each patient at each time point, the change in health state was determined: gaining two health states (i.e. at least 4 lines), gaining one health state (i.e. gaining between 2 and 4 lines), no change in health state (i.e. gaining of losing less than 2 lines), losing one health state (i.e. losing between 2 and 4 lines), or losing two health states (i.e. losing at least 4 lines)
iii. The probability (by treatment) of moving between groups was then determined for each month
iv. Where probabilities were calculated over longer periods (i.e. month 2 to 6), the probability of changing each month was used to derive the overall probabilities, as opposed to the probability of

having changed between months 2 and 6 only. For example, if a patient started in the third health state, moved to the second after one month, and then moved back to the third, this would impact on the probability of gaining and losing a group during that time period;

Three different methods of calculating the probabilities were used to derive alternative sets of transition probabilities, which are presented in scenario analyses (section 7.7.9).

Scenario 1: Dependent on current BCVA level (full 8x8 matrix). The probability of change was considered to depend upon the patient's current BCVA level (i.e. the patient's visual acuity at $month_N$ determines their likelihood of change by $month_{N+1}$) and a patient could move from any health state to any other health state. **This was used for the base case**.

Scenario 2: Dependent on current BCVA level (split for top two levels). The probability of change was considered to depend upon the patient's current BCVA level (i.e. the patient's BCVA at $month_N$ determines their likelihood of change by $month_{N+1}$) for the **top two health states** only, combined with the probability of change being independent of the patient's current BCVA level for the rest of the health states. A patient could only gain or lose up to 2 health states (i.e. 4 lines) between any consecutive cycles. Thus the probabilities (for all but the top 2 states) were then calculated for the following outcomes: gaining at least 4 lines, gaining between 2 and 4 lines, no change in BCVA, losing between 2 and 4 lines, and losing at least 4 lines. This was used as a scenario analysis.

Scenario 3: Constant across all BCVA levels. The probability of change was considered irrespective of the patient's current BCVA level (i.e. constant transition probabilities across BCVA levels) and a patient could only gain or lose up to 2 health states (i.e. 4 lines, as for scenario 2) between any consecutive cycles. This was also used as a scenario analysis.

Table 48, Table 49 and Table 50 give examples of the transition probability matrices for the three scenarios (see Section 11.1, Appendix 14 for the full set of matrices).

In the base case (Scenario 1 − dependent on current BCVA level), transition probability matrices were calculated where patients may move from any one of the eight health states (other than death) to any other health state, resulting in 64 (8x8) unique transition probabilities. These probabilities are based on the change between two specific health states (e.g. the probability of moving from the 86- to 100-letter health state to the 55- to 46-letter health state) and not the change in number of health states (e.g. gaining one health state corresponding to gaining at 2 to 4 lines). Also, patients are not restricted to losing or gaining less than 4 lines between any two consecutive cycles. Using a complete 8x8 transition matrix (Scenario 1) with fully unique values is a more sophisticated strategy which represents the clinical trial data more accurately as fewer assumptions are made. However, as transition probabilities are calculated for moving between each health state, there are instances where there are few or no real observations for some transitions – this may lead to counter-intuitive or unrealistic scenarios.

The two alternative methods of deriving transition probabilities – Scenarios 2 and 3 − were tested in scenario analyses. Scenario 3 – constant across all BCVA levels − allows for a larger number of observations to be included in the calculation of transition probabilities. However, this approach leads to a ceiling effect because patients in the highest BCVA group will be unable to achieve a higher health state in the model, even though clinical data suggest that a percentage of patients with a high BCVA do achieve an improvement in BCVA. The resulting ceiling effect means that the average BCVA score in the model will, over time, gradually fall below the observed value.

Scenario 2 – current BCVA split for top two levels – aims to reduce this potential ceiling effect in that transition probabilities for the top two levels – those most affected by the ceiling effect – are considered dependent on the current BCVA level, whereas transition probabilities for the lower BCVAs are not dependent on current BCVA. This method makes fewer assumptions about the transition probabilities compared to scenario 3 and can be viewed as a compromise between Scenario 1 and 3.

Table 48 State transition probability matrix for ranibizumab based on trial data (full matrix) (Scenario 1)

0 to 3 m		Before							
		100–86	**85–76**	**75–66**	**65–56**	**55–46**	**45–36**	**35–26**	**< 25**
After	**100–86**	1.00*	0.00	0.18	0.00	0.00	0.00	0.00	0.00
	85–76	0.00	1.00	0.68	0.24	0.13	0.00	0.00	0.00
	75–66	0.00	0.00	0.09	0.59	0.31	0.23	0.00	0.00
	65–56	0.00	0.00	0.05	0.12	0.25	0.31	0.44	0.00
	55–46	0.00	0.00	0.00	0.06	0.25	0.31	0.33	0.00
	45–36	0.00	0.00	0.00	0.00	0.06	0.15	0.00	0.00
	35–26	0.00	0.00	0.00	0.00	0.00	0.00	0.22	0.00
	< 25	0.00	0.00	0.00	0.00	0.00	0.00	0.00	1.00*
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**0**	**3**	**22**	**34**	**16**	**13**	**9**	**0**
	*In some instances, a small sample size meant that no patients provided data for a particular column. In those instances, it was assumed that the patient would remain in the same health state. These cases are marked with an asterisk (*).								

Table 49 State transition probability matrix for ranibizumab based on trial data (split for top two levels) (Scenario 2)

0 to 3 m		Before							
		100–86	**85–76**	**75–66**	**65–56**	**55–46**	**45–36**	**35–26**	**< 25**
After	**100–86**	1.0000*	0.0000	0.3365 (0.046)					
	85–76	0.0000	1.0000*	0.4904 (0.049)	0.3365 (0.046)				
	75–66	0.0000	0.0000	0.1442 (0.034)	0.4904 (0.049)	0.3365 (0.046)			
	65–56		0.0000	0.0288 (0.016)	0.1442 (0.034)	0.4904 (0.049)	0.3365 (0.046)		
	55–46			0.0000 (0.000)	0.0288 (0.016)	0.1442 (0.034)	0.4904 (0.049)	0.3365 (0.046)	-
	45–36				0.0000 (0.000)	0.0288 (0.016)	0.1442 (0.034)	0.4904 (0.049)	0.3365 (0.046)
	35–26					0.0000 (0.000)	0.0288 (0.016)	0.1442 (0.034)	0.4904 (0.049)
	< 25						0.0000 (0.000)	0.0288 (0.016)	0.1731 (0.037)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**0**	**3**	**104**	**104**	**104**	**104**	**104**	**104**
	*standard deviation 0.000								

Table 50 Transition probabilities based on trial data constant across baseline BCVA level, baseline to month 3 (Scenario 3)

	Probability (standard deviation)	
Effectiveness progression rates	**Ranibizumab**	**vPDT**
Gain at least 4 lines	0.327 (0.045)	0.073 (0.035)
Gain between 2 and 4 lines	0.477 (0.048)	0.273 (0.060)
No change	0.168 (0.036)	0.364 (0.064)
Lose between 2 and 4 lines	0.028 (0.016)	0.236 (0.057)
Lose at least 4 lines	0.000 (0.000)	0.055 (0.030)
n	107	55
BCVA, best-corrected visual acuity; vPDT, verteporfin photodynamic therapy		

Transition probabilities for Year 2 onwards (12 months onwards)

Transition probabilities were also derived from a number of studies that have reported the decline in BCVA over time in individuals with PM in the absence of treatment (Table 51). These studies report baseline BCVA and the proportion of patients that experience a worsening, improvement or stabilisation of their BCVA at the end of a follow-up period. To translate these data into transition probabilities for use in the model, it was assumed that BCVA does not change significantly in a 3-month cycle; it either remains stable or deteriorates by no more than two lines. The duration of follow-up varies between patients and studies, and in each study, the overall probability of a patient's vision deteriorating over the follow-up period was converted to a monthly rate, using the following equation:

$$Rate = - \ln(1 - probability) / follow\text{-}up\ time$$

Each of these rates was then converted into a three-monthly probability of deterioration in BCVA using the following equation:

$$Probability = 1 - \exp(\ln[1 - rate] / 3)$$

The mean probability of a patient experiencing deterioration in BCVA was then weighted based on the number of eyes in each study.

Table 51 Studies reporting disease progression in the absence of treatment and used to derive transition probabilities beyond year 1.

Study	Eyes in study	Follow up (months)	Probability of decrease in BCVA during follow up period	Rate of BCVA loss (per month)	% patients with BCVA deterioration (per cycle)
Hotchkiss & Fine, 1981[18]	27	25.2	0.54	0.029	0.010
Hampton et al. 1983[16]	42	40.8	0.71	0.030	0.010
Secretan et al. 1997[20]	50	60	0.62	0.016	0.005
Tabandeh et al. 1999[21]	22	12	0.36	0.037	0.013
Bottoni & Tilanus, 2001[14]	31	46.8	0.58	0.019	0.006
Yoshida et al. 2002[22]	47	86.4	0.51	0.008	0.003
Kojima et al. 2006[19]	54	60	0.85	0.032	0.011

Hotchkiss & Fine, 1981;[18] Hampton et al., 1983;[16] Secretan et al., 1997;[20] Tabandeh et al., 1999;[21] Bottoni & Tilanus, 2001;[14] Yoshida et al., 2002;[22] Kojima et al., 2006[19]
BCVA, best corrected visual acuity

The base case analysis incorporates data from Yoshida et al. 2002[22] as this study reported follow up data for the longest duration (86.4 months). The transition probabilities are summarised in Table 52. As a scenario analysis, data from all studies were pooled and incorporated into the model as described previously. It is assumed that BCVA declines at the same rate, irrespective of initial treatment. This represents a conservative approach since clinical opinion from a UK advisory board suggests that the decline in BCVA after treatment (i.e. from the second year onwards) is likely to be more rapid in the vPDT group.

Table 52 Transition probabilities derived from Yoshida et al 2002[22] and used in the base case analysis

		Before							
	BCVA	**86-100**	**76-85**	**66-75**	**56-65**	**46-55**	**36-45**	**26-35**	**<25**
After	**86-100**	0.9972	0.000	0.000	0.000	0.000	0.000	0.000	0.000
	76-85	0.0028	0.9972	0.000	0.000	0.000	0.000	0.000	0.000
	66-75	0.000	0.0028	0.9972	0.000	0.000	0.000	0.000	0.000
	56-65	0.000	0.000	0.0028	0.9972	0.000	0.000	0.000	0.000
	46-55	0.000	0.000	0.000	0.0028	0.9972	0.000	0.000	0.000
	36-45	0.000	0.000	0.000	0.000	0.0028	0.9972	0.000	0.000
	26-35	0.000	0.000	0.000	0.000	0.000	0.0028	0.9972	0.000
	<25	0.000	0.000	0.000	0.000	0.000	0.000	0.0028	0.9972

Yoshida et al., 2002[22]
BCVA, best corrected visual acuity

Mortality

In addition to moving between the BCVA health states, patients may also die. The probability of all-cause mortality was therefore included in the model, using annual rates based on life tables for England and

Wales.[102] The rates for males and females were calculated as an average, and were converted to monthly rates using the following formula:

$$Monthly\ rate\ (age_n) = 1 - \exp\left[\ln\left(\frac{Annual\ rate\ (age_n)}{12}\right)\right]$$

In addition, as per the models for AMD[103] and RVO,[53] an increased mortality risk was applied according to BCVA in all All situations (base case and all scenarios/sensitivity analyses tested). This was based on evidence for a relationship between BCVA and risk of mortality.[55] Although this evidence was not specific to PM, it seems reasonable to assume that the worsening of BCVA associated with CNV secondary to PM may lead to similar increases in mortality. The relative risk (RR) applied to each BCVA level is shown in Table 53.

Table 53 Relative risk for mortality by BCVA level in the BSE or WSE

BCVA level (letters)	RR of mortality (BSE)	RR of mortality (WSE)
86 to 100	1.00	1.00
76 to 85	1.00	1.00
66 to 75	1.00	1.00
56 to 65	1.00	1.00
46 to 55	1.23	1.00
36 to 45	1.23	1.00
26 to 35	1.54	1.23
<25	1.54	1.23
BCVA, best corrected visual acuity; BSE, better-seeing eye; RR, relative risk; WSE, worse-seeing eye		

The relative risk of death was applied to patients based on a weighted average of those treated in the WSE or BSE. Thus if 10% of patients had the disease in the BSE, then the risk of mortality would be calculated as:

Mortality risk = (0.10 x risk associated with BSE) + (0.90 x risk associated with WSE)

In the economic model, the increase in mortality (i.e. the RR minus 1) was multiplied by the proportion of patients treated in the BSE at that time point.

7.3.3 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

The transition probabilities are expected to vary over time. This has been included in the model as described in section 7.3.2.

7.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so,

how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No, the final outcome used in the model was change in BCVA and this was measured directly in the clinical trials.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[3]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two ophthalmologists in the UK were selected and invited to participate in face-to-face interviews to discuss clinical assumptions applied to the economic model. Both were acknowledged experts in the treatment of PM, are practicing at NHS teaching and general hospitals and were investigators in the phase 2 study (REPAIR) performed in the UK which investigated the efficacy and safety of ranibizumab for the treatment of CNV secondary to PM (see section 6.2.7) and were aware of the results from this trial. At each interview the expert was presented with all aspects of the model in a presentation (see Section 11.3, Appendix 16). Two members of the Novartis Medical team and one health economist attended the interviews. During the interview, a member of the Novartis team presented each slide, explaining the methodology, and then asked the clinical expert an open question about their thoughts and opinions following each slide. No iteration was used in the collation of opinions.

Additionally, an international advisory board was held on 13th December 2012 in Hong Kong, attended by eleven experts in retinal medicine from the Asia-Pacific region. The Novartis phase III and REPAIR trials

[3] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

were discussed, as well as current treatment practices for CNV secondary to PM, bilateral disease, recurrence, unanswered questions from clinical studies and patient information and education.

Summary of selected values

7.3.6 Please provide a list of all variables included in the cost-effectiveness analysis, detailing the values used, range (distribution) and source. Provide cross-references to other parts of the submission. Please present in a table, as suggested below.

Variables not yet presented in previous sections are included in Table 54.

Table 54 Summary of UK base case variables applied in the economic model

Variable	Value	Reference to section in submission
Population		
Comparator	vPDT	Table 15
Starting age, mean	55	
Data source	Trial data (Novartis phase III and VIP studies)	
Transition probabilities	Based on current BCVA	Section 7.3.2
Natural progression	From year 2 onwards	Section 7.3.1
Eye involvement		
BSE/WSE split	20.8% of the cohort (both groups) had the study eye as the BSE at baseline (79.2% WSE at baseline) 32.4% of the ranibizumab cohort had the study eye as the BSE at 12 months compared to 22.4% of the vPDT cohort	Section 7.2.4
Recurrence	Yes, 6% annually	Section 7.3.7
Bilateral disease	Yes, 15% at baseline	Section 7.5.5
Results		
Time horizon	Lifetime	Section 7.3.7
Discounting	3.5% (costs and outcomes)	Section 7.3.8
Willingness to pay threshold	£20,000	Not applicable
Perspective	Health care	Not applicable
Quality of life		
Utility, BSE	Czoski-Murray, 2009[56] values	Section 7.4.9
Utility, WSE	0.1 maximum utility gain	
Unit costs		
Ranibizumab	£742.17; [redacted]	Section 7.5.1
vPDT	£850	
Ophthalmologist	£123.62	
OCT	£51.27	
Injection visit	£117.26	
Cost of Blindness	Year 1: £17,325.94; Year 2+: £17,244.67	
Resource use		
Ranibizumab: Treatment visits Monitoring visits	 Year 1: 3.5; Year 2: 1; Year 3+: 0 Year 1: 8.5; Year 2: 4; Year 3+: 0	Section 7.5.5
vPDT: Treatment visits Monitoring visits	 Year 1: 3.4; Year 2: 1.7; Year 3+: 0 Year 1: 4; Year 2: 4; Year 3+: 0	
Recurrence treatment and monitoring visits	As above, for each comparator	
Adverse events		
Rates: Conjunctival haemorrhage Intraocular pressure	 Ranibizumab: 8.5% Ranibizumab: 4.2%	Section 7.3.1

increased Visual Disturbance Injection site AEs (non-ocular)	 vPDT: 14.8% vPDT: 9.9%	
Disutilities: Conjunctival haemorrhage Intraocular pressure increased Visual Disturbance Injection site AEs (non-ocular)	 0.02 0.01 0.00 0.1336	Section 7.4.8
Costs: Conjunctival haemorrhage Intraocular pressure increased Visual Disturbance Injection site AEs (non-ocular)	 £1,234.31 £31.67 £0 £100	Section 7.5.7
Baseline distribution of visual acuity in Novartis phase III trial[32]		
BCVA level (letters)	**Proportion of all patients**	
86–100	0%	Not applicable
76–85	4%	
66–75	20%	
56–65	33%	
46–55	20%	
36–45	13%	
26–35	9%	
< 25	1%	
Proportion of patients whose treated eye is their BSE		
BCVA level	**Proportion of all patients**	
86–100	50%[a]	Not applicable
76–85	50%	
66–75	28%	
56–65	20%	
46–55	26%	
36–45	19%	
26–35	17%	
< 25	0%	
Novartis phase III study 12 month CSR[32] AE, adverse event; BCVA, best corrected visual acuity; BSE, better-seeing eye; OCT, optical coherence tomography; PAS, patient access scheme; vPDT, verteporfin photodynamic therapy; WSE, worse-seeing eye [a]Assumption; no patients had a BCVA level of between 86 and 100 at baseline.		

7.3.7 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the

longer term difference in effectiveness between the intervention and its comparator? For the extrapolation of clinical outcomes, please present graphs of any curve fittings to Kaplan–Meier plots.

Costs and clinical outcomes have been extrapolated to a lifetime time horizon. This time period was chosen because CNV secondary to PM is generally diagnosed in a younger population than other eye diseases (e.g. the mean age at baseline in the Novartis phase III trial was 54 to 57 years) and the benefits of improved BCVA are likely to extend for the lifetime of patients. Patients have an average age of 55 years at the start of the model, and effects of the interventions on BCVA are expected to be experienced over two years, as evident from clinical data. Thereafter due to an absence of any robust longer-term data, BCVA in the model declines according to the natural history in this population and this is integrated into the model as described in section 7.3.2. Costs are extrapolated beyond the trial follow-up period as described in sections 7.5.5 and 7.5.6.

A further reason for considering a lifetime horizon is that patients may experience a recurrence of CNV secondary to PM after they have been treated. This recurrence may manifest as either the same lesion that the patient was originally treated for or as a new lesion. Based on recommendations from an advisory board, the rate of recurrence was assumed to be approximately 30% over 5 years, resulting in an annual prevalence of 6%. The impact of recurrence on costs was included in the model (see section 7.5.5). Due to a lack of evidence, additional potential gains in vision (and therefore QALYs) were not accounted for; a conservative approach was therefore adopted.

7.3.8 Provide a list of all assumptions in the de novo economic model and a justification for each assumption.

Table 55 Assumptions within the model

Parameter	Assumptions	Justification
Time horizon	Lifetime	Effects of CNV secondary to PM on BCVA, including the risk of recurrence, are expected to continue for the remainder of the patient's life; patients have an average age of 55 years at the start of the model. The scope states that the time horizon should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared.
Health states	Eight BCVA health states defined by a BCVA range of 10 letters (2 lines) and death	A change in BCVA of 10 letters is considered to be clinically meaningful and confers sufficient granularity to model incremental differences in BCVA between treatments
BCVA at baseline	Distributed as in Novartis phase III trial for the ranibizumab disease activity and vPDT arms	Reflects the baseline health states of the population from the key study used in the model
Treated eye	Distribution between BSE and WSE according to distribution at baseline in the Novartis phase III trial	Reflects the treated eye in the population from the key study used in the model
Progression in year 1	For ranibizumab: based on data from Novartis phase III trial for the ranibizumab disease activity group. For vPDT: based on Novartis phase III trial for months 1 to 3 (cycle 1) and from the VIP study for months 4 to 12 (cycles 2, 3 and 4).	Based on data from large randomised studies for the interventions of interest
Progression in years 2+	Based on decline in BCVA due to natural history for this population	Data indicate that BCVA stabilisation is achieved after 1 year in patients with CNV secondary to PM and that progressive decline in BCVA occurs due to natural history
Utilities	Utilities according to BCVA were applied. WSE utilities were assumed to have a maximum 10% gain from the lowest (<25 letters) to the highest (86–100 letters) health state in the base case analysis.	In the base case, utilities for the BSE were taken from Czoski-Murray,[56] a study performed in a representative sample of the UK general population in which visual acuity levels were simulated using contact lenses. The gain in utilities for the WSE was based on an approach as advised by NICE for ranibizumab for age-related macular degeneration.[48] This takes into account the relative benefits of binocular and monocular vision, with a difference in utility value of approximately 0.1 between people with good visual acuity in

Parameter	Assumptions	Justification
		both eyes and people with good vision in only on eye.
Mortality	An increase in mortality according to BCVA in the BSE and WSE was applied	A decrease in BCVA has been associated with an increased risk of mortality, with blindness increasing the risk by a factor of 1.54 relative to those without visual impairment[55]
Adverse events	Adverse event rates for ranibizumab and vPDT were based on data from the Novartis phase III trial and VIP trials, respectively. Disutilities were applied to each patient experiencing an adverse event and costs of managing the adverse event were applied.	Based on data from large randomised studies for the interventions of interest.
Treatment duration	The maximum duration of initial treatment was assumed to be 2 years in the base case analysis.	The UK experts and an international advisory board consider two years to be the maximum plausible time a patient should be on treatment before being discharged from services
Number of treatments and follow-up visits	Patients treated with ranibizumab were assumed to receive 3.5 treatment visits in year 1 and 1 treatment in year 2. Patients treated with vPDT were assumed to have 3.4 treatment visits in year one and 1.7 in year 2. Patients treated with ranibizumab were assumed to be monitored 8.5 times in year 1 and 4 times in year 2, whereas patients treated with vPDT were monitored quarterly in years 1 and 2. Patients were assumed to experience recurrence at an annual rate of 6%. The injection treatment and monitoring frequency for recurrence is assumed to be the same as for year 1 of initial treatment. These patients are set up so they start treatment again as per year 1.	For ranibizumab, the mean number of injections for year 1 was taken from the Novartis phase III trial and the assumption of one injection in year 2 is based on recommendations from a UK advisory board. The treatment schedule for years 1 and 2 for vPDT was based on the VIP study. For both treatments, based on advisory board recommendations, patients are assumed to be discharged after 2 years; hence, no treatment is given from year 3 onwards.
Cost of blindness	Annual costs of blindness applied to the patients in the model as they move in and out of blindness health state for their BSE	Blindness has been shown to be associated with significant lifetime costs[104] (Table 61). The cost of blindness is higher during the first year after diagnosis, so the additional cost of the first year was assigned as an extra cost during the cycle that the patient becomes blind.
Fellow eye involvement	The model allows for fellow eye involvement and was built to capture both the cost and quality of life of bilateral disease. For	Two studies informed the assumed prevalence of bilateral disease at baseline of 15%.[49,68]

Parameter	Assumptions	Justification
	patients where the fellow eye also experiences CNV secondary to PM, the cost of treatment, including drug costs, administration costs and costs associated with monitoring visits, was doubled. To account for the difference in quality of life between the BSE and WSE, the utility values were taken from the BSE curve for the study eye. The impact on costs and quality of life is only assessed from baseline, as it is assumed that the fellow eye will be free from disease at the same rate as the study eye, after which time neither eye will be treated or monitored. The prevalence of bilateral disease was assumed to be approximately 15% at baseline.	
Discounting	Costs and benefits were both discounted at 3.5% per annum	This is in line with the NICE methods guidelines
BCVA, best corrected visual acuity; BSE, better-seeing eye; CNV, choroidal neovascularisation; PM, pathological myopia; vPDT, verteporfin photodynamic therapy; WSE, worse-seeing eye		

7.4 Measurement and valuation of health effects

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.4.

The HRQL impact of adverse events should still be explored regardless of whether they are included in cost-effectiveness analysis.

All parameters used to estimate cost effectiveness should be presented clearly in tabular form and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

Patient experience

7.4.1 Please outline the aspects of the condition that most affect patients' quality of life.

CNV secondary to PM is characterised by visual impairment. Loss of vision is associated with decreased HRQoL and disabilities in performing everyday tasks such as working, reading, driving, recognising faces and detail on television, and participating in many sports and hobbies.[9,105,106] There are only limited data on the effect of PM on HRQoL. A Japanese study involving 200 patients with bilateral PM reported that,

compared with controls, patients with PM had significantly lower QoL scores for vision-related daily tasks, social handicap, emotional handicap, cognition of disease and eye satisfaction.[107]

7.4.2 Please describe how a patient's HRQL is likely to change over the course of the condition.

If CNV secondary to PM is not treated, BCVA generally initially stabilises and then gradually decreases over time due to chorioretinal atrophy around regressed CNV.[65] CNV due to PM is associated with an increased risk of blindness. Evidence from seven studies showed that 53 to 96% of patients with the condition were legally blind after a mean follow-up ranging from 1 to 11 years (see section 2.1).[13,16,17,19,21-23] As visual impairment and blindness significantly impact on HRQoL, as described in section 7.4.1, HRQoL is expected to decrease over time, especially over the first year, if the condition is not treated.

HRQL data derived from clinical trials

7.4.3 If HRQL data were collected in the clinical trials identified in section 6 (Clinical evidence), please comment on whether the HRQL data are consistent with the reference case. The following are suggested elements for consideration, but the list is not exhaustive.

- Method of elicitation.
- Method of valuation.
- Point when measurements were made.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.

HRQoL data were collected in the Novartis phase III study using the EQ-5D, NEI VFQ-25 and WPAI-GH instruments (see section 6.5.3). The EQ-5D is a preference-based instrument, but has been shown to be largely insensitive to changes in BCVA and vision-related QoL.[108,109] However, a modified version of the EQ-5D (vision bolt-on) which includes an assessment of effects of visual impairment is currently in development was discussed at the European ISPOR 2012 conference. The NEI VFQ-25 is a validated, vision-specific QoL measure, but is not preference-based and is therefore not consistent with the NICE reference case. The WPAI-GH was used to assess effects on absenteeism from work and daily activity impairment, and is also not a preference-based instrument. Consequently the HRQoL data collected in the Novartis phase III study were not deemed relevant to the economic model.

Mapping

7.4.4 If mapping was used to transform any of the utilities or quality-of-life data in clinical trials, please provide the following information.

- Which tool was mapped from and onto what other tool? For example, SF-36 to EQ-5D.
- Details of the methodology used.
- Details of validation of the mapping technique.

No mapping was undertaken.

HRQL studies

7.4.5 Please provide a systematic search of HRQL data. Consider published and unpublished studies, including any original research commissioned for this technology. Provide the rationale for terms used in the search strategy and any inclusion and exclusion criteria used. The search strategy used should be provided in section 10.12, appendix 12.

A systematic review was undertaken to identify studies reporting utilities for patients with visual impairment due to CNV secondary to PM. Because few relevant studies were anticipated, the review also aimed to identify studies of utilities for patients with AMD and with CNV due to AMD.

The following were eligible for inclusion in the review:

- reports of utility elicitation exercises
- reports of utility validation exercises
- reports of economic evaluations using utility measures gathered during the studies
- reviews of utility studies
- data from unpublished studies.

To be eligible, a utility report was required to include details regarding:

- mean or median utility values at different disease levels (if available)
- the country/perspective
- a standard method of utility assessment (eg standard gamble, TTO, rating scale)
- a description of the health state valuation instrument (eg a generic preference-based measure such as the EQ-5D or a bespoke instrument).

No date or language limits were applied during the search. The search involved combining terms for CNV or AMD or PM with search terms for utilities and specific ocular QoL instruments. The full search strategy used can be found in Section 10.12, Appendix 12. Searches were undertaken in April 2012.

The following databases were searched:

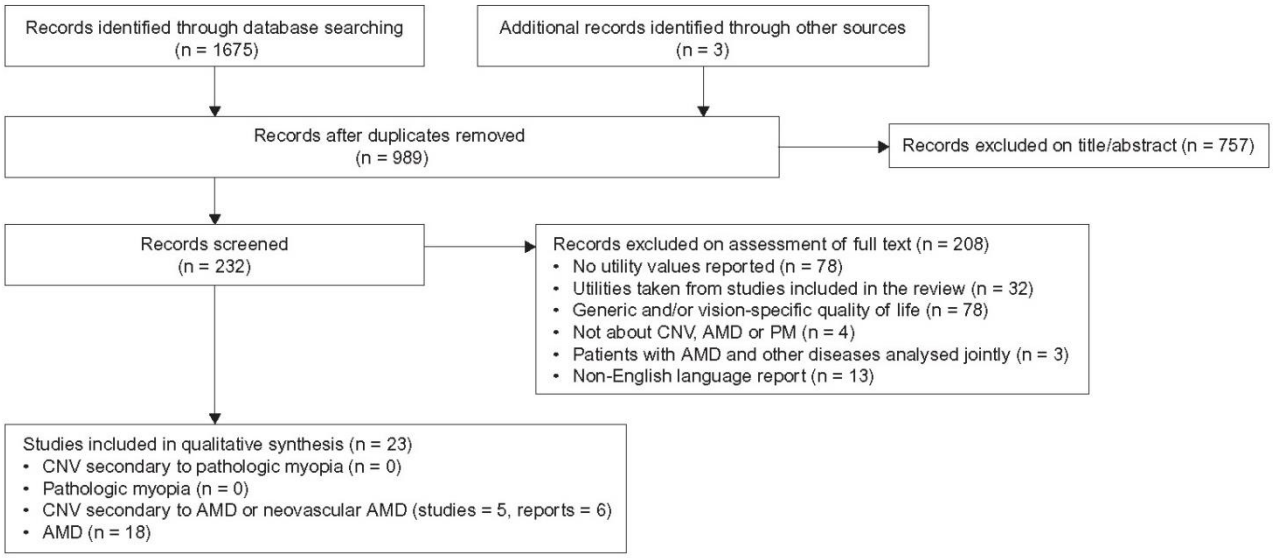
- NHS Economic Evaluation Database (NHS EED) at http://www.crd.york.ac.uk/crdweb/
- Health Economic Evaluation Database (HEED) at http://www.crd.york.ac.uk/crdweb/

- Cost-Effectiveness Analysis (CEA) Registry produced by Tufts University
- Patient-Reported Outcome and Quality of Life Instruments Database (PROQOLID)
- MEDLINE
- EMBASE
- HTA database; (http://www.crd.york.ac.uk/crdweb/)
- NICE submissions.

Initial selection was based on the title and abstract, and full papers for potentially relevant studies were screened for relevance by one reviewer and checked by a second. Discrepancies were resolved through discussion or by consulting a third reviewer.

In total, 1,675 records were retrieved and 989 remained after removal of duplicates. A total of 232 records were obtained for full-text assessment, and of these, 24 papers reporting 23 studies were identified as being relevant (Figure 19).

Figure 19 Flow of studies in the systematic review to identify studies reporting health state utility values



7.4.6 Provide details of the studies in which HRQL is measured. Include the following, but note that the list is not exhaustive.

- Population in which health effects were measured.
- Information on recruitment.
- Interventions and comparators.
- Sample size.
- Response rates.
- Description of health states.
- Adverse events.

- Appropriateness of health states given condition and treatment pathway.
- Method of elicitation.
- Method of valuation.
- Mapping.
- Uncertainty around values.
- Consistency with reference case.
- Appropriateness for cost-effectiveness analysis.
- Results with confidence intervals.
- Appropriateness of the study for cost-effectiveness analysis.

No studies were identified that provided utility values for patients with PM or patients with CNV secondary to PM. Five studies provided utility values for CNV secondary to AMD (see Section 11.2, Appendix 15, Table 96) and 18 studies provided utility values for AMD (see Section 11.2, Appendix 15, Table 97).

Studies of CNV Secondary to AMD

All five CNV secondary to AMD studies had quality concerns. Inclusion and exclusion criteria were poorly reported in three studies.[90,110,111] No study reported that their approach had been piloted, and only Bass (2004)[112] reported using a set script to reduce interviewer bias. No quantitative assessment was made on how representative the sample population was of the population with CNV as a whole in any of the studies. Three studies[90,110,113] noted that their population sample may be healthier than the total target population as people living in nursing homes had been excluded.

Four of the studies (involving between 67 and 401 subjects each) used the EQ-5D to measure utilities and reported overall mean values of 0.64 to 0.68 (see Section 11.2, Appendix 15, Table 96).[90,110,111,113] Three of these reported utilities values according to BCVA level,[90,111,113] and all found the EQ-5D to be insensitive to changes in BCVA. A fifth study, Bass (2004)[112], used a bespoke tool that measured utility based on a preference scale and involved 792 patients with AMD. This study reported mean utility values of 0.53 to 0.69 according to BCVA in the BSE. Again, no significant difference in utility was observed for the three BCVA groups investigated. In this study, 46% of patients had subfoveal CNV due to the ocular histoplasmosis syndrome or an unknown cause and thus may not correspond to the target population for the decision problem. Utility values from these five studies were therefore considered to be inappropriate for use in the decision problem given their lack of sensitivity to BCVA.

Studies of AMD

There were similar quality concerns with regard to the 18 studies of utilities for AMD as with the studies of CNV secondary to AMD. Several studies did not adequately report the inclusion and exclusion criteria. Au Eong (2012)[114] was the only study that reported that they had piloted their approach. Only four studies[114-117]

reported taking steps to limit interviewer bias. Espallargues (2005)[116] and Bansack (2007)[115] reported the potential for selection bias.

None of the studies reported quantitative assessment to determine whether the study population was representative of the entire AMD population. Three studies[118-120] acknowledged that their population was not representative of the population with AMD as a whole. Czoski-Murray(2009)[56] used a general sample of the UK population, but noted that the significantly lower age of the study population compared with the general population coupled with the exclusion of participants with a range of ocular conditions may limit the generalisability of study findings.

Of the 18 studies, only 9 reported utility values according to BCVA level (Section11.2, Appendix 15, Table 97).[56,100,116,118,120-124] Of these, seven used TTO techniques,[56,100,116,120-123] three used the standard gamble (SG) method[100,120,122] and two used indirect means to determine utilities for AMD.[118,124] Three-quarters of the studies involved patients with AMD or visual impairment,[114-123,125-128] one involved ophthalmologists[100] and one involved a representative sample of the UK general population.[56] A further study was a meta-analysis of 24 studies performed in Thailand, 21 of which involved patients with AMD.[124]

The study performed in the UK general population[56] was considered to be the most appropriate for use in the economic model given that the study population was representative of the general population, as recommended by NICE. In addition, in this study the BCVA health states were simulated in subjects by wearing special contact lenses that created the effects of AMD. Subjects then provided a utility for this condition by TTO. Additional advantages of the utility values derived in this study are that data include adjustment to control for important factors known to affect utility (including age and sex) and that BCVA was defined for the BSE. Utility values for the BSE by health state from this study are summarised in Table 57 (see section 7.4.9).

7.4.7 Please highlight any key differences between the values derived from the literature search and those reported in or mapped from the clinical trials.

Not applicable.

Adverse events

7.4.8 Please describe how adverse events have an impact on HRQL.

Disutilities were applied to each patient experiencing an AE (Table 56). Incidence rates are available for the 12-month trial period but without a detailed breakdown of the timing of events. Therefore the disutilities were calculated as one-off events per patient, weighted by the expected duration of the impact on HRQoL.

Table 56 Adverse event disutilities

Adverse event	Disutility	Source	Duration (months)	Source
Conjunctival haemorrhage	0.02	Brändle et al. 2007[129]	1	Assumption
Intraocular pressure increased	0.01	Vaahtoranta-Lehtonen et al. 2007[130]	0.03	Vaahtoranta-Lehtonen et al. 2007[130]
Visual Disturbance	0.00	Assumption	0	Assumption
Injection site AEs	0.1336	Brown et al. 2005[131]	0.2696	Brown et al. 2005[131]
Brändle et al., 2007;[129] Vaahtoranta-Lehtonen et al., 2007;[130] Brown et al., 2005[131] AE, adverse event				

Quality-of-life data used in cost-effectiveness analysis

7.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 7.4.3 to 7.4.8. Justify the choice of utility values, giving consideration to the reference case.

Utilities were applied to each health state in order to generate QALYs. Czoski-Murray et al., 2009,[56] a study performed in the UK general population, was considered to be the most appropriate for use in the economic model given that the study population was representative of the general population patient (see section 7.4.6). Furthermore it was used in the recent 2013 resubmission of ranibizumab for branch RVO.[53] Additional advantages of the utility values derived in this study are that data include adjustment to control for important factors known to affect utility (including age and sex) and that BCVA was defined for the BSE. Utility values for the BSE by health state from this study are summarised in Table 57.

For completeness, utilities based on two further studies which have been used for utilities in previous NICE submissions for ocular indications are also available in the model.[132,133] Sharma (2000)[99] developed a univariate mapping equation to transform logMAR visual acuity levels to utilities and a bivariate equation that took time since diagnosis into account, and Brown (1999)[132] published utilities related to WSE. (Brown (1999)[132] was not identified in the systematic review because it did not include utility values specific to CNV, AMD or PM which were specified in the search strategy). However, the results of the latter appear illogical (eg in some cases utilities increased as the vision deteriorated) and were based on a small sample of individuals per level of BCVA.

Table 57 Summary of quality-of-life values for cost-effectiveness analysis

Health state	Czoski-Murray 2009[56]	Czoski-Murray 2009[56]	Utility (Brown 1999)[132]	Utility (Sharma 2000, univariate)[99]	Utility (Sharma 2000, bivariate)[99]
	BSE	**WSE**	**BSE**	**BSE**	**BSE**
BCVA 86 to 100 letters	**0.850**	**0.850**	0.920	0.991	0.931
BCVA 76 to 85 letters	**0.758**	**0.836**	0.880	0.818	0.704
BCVA 66 to 75 letters	**0.685**	**0.821**	0.770	0.666	0.557
BCVA 56 to 65 letters	**0.611**	**0.807**	0.755	0.636	0.528
BCVA 46 to 55 letters	**0.537**	**0.793**	0.670	0.591	0.484
BCVA 36 to 45 letters	**0.464**	**0.779**	0.665	0.563	0.457
BCVA 26 to 35 letters	**0.390**	**0.764**	0.645	0.544	0.440
BCVA <25 letters	**0.353**	**0.750**	0.510	0.537	0.433
Death	**0.000**	**0.000**	0.000	0.000	0.000

Brown et al., 1999;[132] Sharma et al., 2000;[133] Czoski-Murray et al., 2009[56]
BCVA, best corrected visual acuity; BSE, better-seeing eye; WSE, worse-seeing eye

Utility values given in Czoski-Murray (2009)[56] only relate to the BSE. An assumption was therefore required for the utility values for the WSE. The assumption used was that the maximum gain (the difference between the best and worst possible health states for the WSE) was 0.1 in the base case (based on 2013 NICE recommendations[61]). In order to accomplish this, the utility for the WSE at the highest health state was anchored to the utility for the same health state in patients who were treated in their BSE. In the base case analysis, this was a value of 0.85. A calculation was performed for the other seven health states to allow a linear decline in utility. For example, the utility value for the 76-85 letter health state was calculated by subtracting 10% divided by 7 (to allow all remaining 7 health states to decline evenly and result in a total 10% decline) from the utility value in the next highest health state. **Table 57 includes utility values used in the base case from Czoski-Murray (for BSE) and derived values for the WSE**.

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[4]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought
- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions

[4] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two clinical experts were interviewed; see Section 7.3.5 for details.

7.4.11 Please define what a patient experiences in the health states in terms of HRQL. Is it constant or does it cover potential variances?

HRQoL changes according to health state. The higher the level of BCVA, the better the patient's HRQoL. Lower health states represent worse BCVA, and therefore patients are expected to experience worse HRQoL. Within each health state, HRQoL remains constant.

7.4.12 Were any health effects identified in the literature or clinical trials excluded from the analysis? If so, why were they excluded?

All AEs that occurred in more than 5 patients and that were suspected to be related to study drug and/or ocular injection, as reported in the Novartis phase III trial (for ranibizumab) or VIP trial (for vPDT) were included in the analysis. Less frequent AEs and those not considered to be related to study drug and/or ocular injection were not included.

7.4.13 If appropriate, what was the baseline quality of life assumed in the analysis if different from health states? Were quality-of-life events taken from this baseline?

Not applicable.

7.4.14 Please clarify whether HRQL is assumed to be constant over time. If not, provide details of how HRQL changes with time.

HRQoL is assumed to be constant over time and dependent on the health state based on BCVA. The utilities used in the base case analysis were based on the Czoski-Murray study; these utilities are adjusted for the age of the patient.

7.4.15 Have the values in sections 7.4.3 to 7.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

7.5 Resource identification, measurement and valuation

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.5.

All parameters used to estimate cost effectiveness should be presented clearly in a table and include details of data sources. For continuous variables, mean values should be presented and used in the analyses. For all variables, measures of precision should be detailed.

NHS costs

7.5.1 Please describe how the clinical management of the condition is currently costed in the NHS in terms of reference costs and the payment by results (PbR) tariff. Provide the relevant Healthcare Resource Groups (HRG) and PbR codes and justify their selection. Please consider in reference to section 2.

vPDT is the current standard of care for vision impairment due to CNV secondary to PM in the NHS. The HRG descriptions for vPDT (including administration) and administration of ranibizumab used for NHS costing are given in Table 58.

Table 58 HRG codes

HRG code	HRG name
RA23Z	Ultrasound scan less than 20 minutes
BZ23Z	Vitreous Retinal Procedures – category 1
HRG, Healthcare Resource Groups	

They have been selected because the respective OPCS codes fall within each of the HRG codes:

- Photodynamic therapy to subretinal lesion (C88.2) – vitreous retinal (VR) banding of 1
- Injection of therapeutic substance into posterior segment of eye NEC (C89.3) – VR banding of 2 (for ranibizumab).

Monotherapy with either vPDT or ranibizumab would be costed as a Category 1 procedure (sum of VR bands from 0 to 2).

7.5.2 Please describe whether NHS reference costs or PbR tariffs are appropriate for costing the intervention being appraised.

The NHS reference costs and the British National Formulary (BNF) are used to cost resources associated with ranibizumab treatment.

The NHS reference costs are more appropriate because they represent the actual national average costs that have already been incurred as a result of delivering care. These costs take into account staff time, event-based time and standard equipment time. Thus, they include opportunity costs, whereas the PbR

Tariffs are prices (or prospective costs), which are prone to adjustment in the future. Thus at point of use in the model, costs based on the PbR Tariff will not reflect opportunity costs of delivering care.

Resource identification, measurement and valuation studies

7.5.3 Please provide a systematic search of relevant resource data for the UK. Include a search strategy and inclusion criteria, and consider published and unpublished studies. The search strategy used should be provided as in section 10.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

- country of study
- date of study
- applicability to UK clinical practice
- cost valuations used in study
- costs for use in economic analysis
- technology costs.

The systematic review to identify relevant resource use data for the UK was performed alongside the review to identify relevant cost-effectiveness studies and the same methods and search strategy were used (see Section 10.10, Appendix 10).

No UK-specific resource use data was identified. Two costing studies were obtained in full, but were excluded because they did not relate to the UK. One study estimated the consumption of resources and direct costs for Italian patients with macular degeneration associated with PM,[134] and one estimated the direct costs of myopia in children in Singapore[135].

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[5]:

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical specialist whose opinion was sought

[5] Adapted from Pharmaceutical Benefits Advisory Committee (2008) Guidelines for preparing submissions to the Pharmaceutical Benefits Advisory Committee (Version 4.3). Canberra: Pharmaceutical Benefits Advisory Committee.

- the background information provided and its consistency with the totality of the evidence provided in the submission
- the method used to collect the opinions
- the medium used to collect opinions (for example, was information gathered by direct interview, telephone interview or self-administered questionnaire?)
- the questions asked
- whether iteration was used in the collation of opinions and if so, how it was used (for example, the Delphi technique).

Two clinical experts were interviewed; see Section 7.3.5 for details.

Intervention and comparators' costs

7.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example, drugs costs should be cross-referenced to sections 1.10 and 1.11. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Total costs for each treatment were determined from the unit costs for a treatment (ie ranibizumab and vPDT), administration and a monitoring visit, multiplied by the number of treatment and monitoring visits. Unit costs were obtained from published sources and are summarised in Table 59.

Ranibizumab and vPDT both incur administration costs each time the patient receives treatment. The administration cost for ranibizumab was assumed to consist of the cost of OCT and the injection visit, and that for vPDT was assumed to consist of OCT plus an ophthalmologist consultation visit. The cost of OCT was estimated to be the same as an outpatient diagnostic procedure coded as an ultrasound scan of less than 20 minutes, i.e. £51.27 (RA23Z).[57] The ranibizumab injection administration visit was costed as an office-based outpatient procedure (£117.26) (BZ23Z, Vitreous Retinal Procedures - category 1),[57] and the cost of an ophthalmologist consultation was costed as a consultant led multi-professional face-to-face follow-up visit for ophthalmology (£123.62).[57]

There are some concomitant treatments that are associated with the administration of vPDT, including phenylephrine, amethocaine and tropicamode. These have a very low associated cost per dose (~£0.01) and are excluded from the analysis as they are very unlikely to impact upon results.

In addition to the treatment and administration costs, patients also require follow-up visits to monitor their disease status. In many cases, such follow-up visits can be combined with a treatment visit and, as such, would not incur any additional costs. However, there will be some occasions when a patient requires follow-up without treatment and these costs are included in the model. The cost of a monitoring visit (irrespective of

the treatment being received at other times) is assumed to correspond to the cost of OCT plus an ophthalmologist consultation visit, and is shown in Table 59.

Table 59 Unit costs associated with the technology in the economic model

Items	Ranibizumab	Reference in submission	vPDT	Reference in submission
Treatment costs	£742.17	1.10	£850.00	NA
Administration costs	£168.53[a]	NA	£174.89[b]	NA
Monitoring visit costs	£174.89[b]	NA	£174.89[b]	NA

NA, not applicable; vPDT, verteporfin photodynamic therapy
[a]Cost of optical coherence tomography (£51.27) + injection visit (£117.26)[57]
[b]Cost of optical coherence tomography (£51.27) + ophthalmologist (£123.62)[57]

Total costs were obtained by multiplying the costs for treatments and follow-up by the frequency of treatment visits and monitoring visits. The frequency of treatment and monitoring visits are summarised in Table 60. For ranibizumab, the mean number of injections for year 1 was taken from the number of injections in the disease activity arm of the Novartis phase III trial, and it was assumed that these patients would receive one injection in the second year. For vPDT, the number of injections for year 1 and year 2 was based on treatment schedule in the VIP trial. Patients were assumed to be monitored quarterly as per the UK label. Also based on recommendations from a UK advisory board, it was assumed that patients would be discharged from services after a maximum of 2 years and therefore would no longer be treated or monitored after this time, unless they experience a recurrence, assumed to occur in 6% of patients per year.

Table 60 Frequency of treatment and monitoring visits

	Year 1		Year 2		Year 3	
Treatment	**Injection visits**	**Monitoring visits**	**Injection visits**	**Monitoring visits**	**Injection visits**	**Monitoring visits**
Ranibizumab	3.5[a]	8.5[c]	1[c]	4[c]	0[d]	0[d]
vPDT	3.4[b]	4[c]	1.7[b]	4[c]	0[d]	0[d]

[a]Bandello et al., 2013[34]
[b]VIP study group 2001[26]
[c]Assumption based on posology for vPDT
[d]Assumption (patients are considered to be “cured” after their course of treatment) (advisory board)
vPDT, verteporfin photodynamic therapy

Fellow eye involvement

The model was built to capture both the cost and HRQoL implications of bilateral CNV secondary to PM. For patients with bilateral disease, the cost of treatment, including drug costs, administration costs and costs associated with monitoring visits, was doubled since the fellow eye would incur additional treatment and monitoring visits. This was a conservative approach as some patients with bilateral disease, according to external advisory board input, would be able to receive treatment in both eyes at the same visit. Furthermore, the costs of OCT should be applied only once for the two eyes. To account for the difference in HRQoL, the utility values were taken from the BSE data for the study eye. The impact on costs and HRQoL

was only assessed from baseline, as it was assumed that the fellow eye would be free from disease at the same rate as the study eye, after which time neither eye would be treated or monitored.

The prevalence of bilateral disease was assumed to be approximately 15% at baseline. Two sources were identified to support this: one study[136] involving 269 patients referred to a single centre in the USA reported that Fuchs' spot was bilateral in 4 of 24 patients (16.7%). A second study[84] involving 225 patients under the age of 50 years with confirmed CNV secondary to PM, who were referred to a French tertiary centre, reported that the lesion was bilateral in 32 individuals (14.2%). Bilateral disease was only modelled as a prevalence as patients entered the model. An incidence rate was not modelled as the lack of long-term natural history data means an accurate estimation could not be determined. Bilateral disease was not assumed to impact upon the effectiveness of treatment, since there are no data to indicate the likely relationship between the outcome in each individual eye.

Recurrence

The model also considered the cost of retreatment for recurrence. It was assumed that the rate of recurrence is 30% over 5 years (i.e. an annual prevalence of 6%, based on recommendations of the international advisory board) and recurrence could occur at any time after initial treatment. Patients who experienced recurrence received treatment and monitoring as per year 1 of initial treatment. This was a conservative approach since feedback from a UK advisory board suggested that only one additional injection would be administered in this situation.

Health-state costs

7.5.6 Please summarise, if appropriate, the costs included in each health state. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model. The health states should refer to the states in section 7.2.4.

Based on a systematic review, no data were found to link disease severity with resource use in PM. However, patients considered to be blind (VA ≤ 35 letters) have been shown to incur significant lifetime costs associated with factors including residential care, community care and the need for hip replacement.[137] Previous appraisals of interventions for ocular conditions have used this reference as a source of costs of blindness; this model included these costs inflated to 2010 prices, as summarised in Table 61.

In the base case, the model applies the annual cost of blindness to patients as they move in and out of the blindness health states when both eyes have a BCVA of ≤ 35 letters. If a patient's study eye is their BSE and that is blind, it is assumed their WSE is also blind. Costs of low vision aids and low vision rehabilitation are assumed to be incurred only during the first year of blindness. These additional costs were thus only included during the cycle in which the patient becomes blind.

Table 61 Cost of blindness

Blindness resource use	Cost	Patients	Notes
Residential care	£51,090[a]	30%	-
Community care	£10,006[b]	6%	-
Depression	£2,291[c]	39%	-
Hip replacement	£6,617[d]	5%	-
Low vision aids	£167[e]	33%	Inflated cost is divided by two, assuming that the service applies every two years.
Low vision rehabilitation	£303[f]	11%	Inflated cost is divided by two, assuming that the service applies every two years.
Blind registration	£86[g]	94.5%	A one-off cost is applied to the first year of severe visual impairment only.
First year cost	**£17,325.94**		
Subsequent annual costs	**£17,244.67**		

[a]PSSRU 2011.[138] Health authority residential care for older people. £982.50 establishment cost per permanent resident week. Costs assumed 52 weeks per year.
[b]PSSRU 2011.[138] Home care worker. Typical home care package = 12.4 hours per week. Based on a study of community care packages, it has been estimated that on average 6.6 hours are worked weekdays between 9 a.m. and 5 p.m., 0.16 hours weekdays after 5 p.m., and 0.55 hours each on Saturday and Sunday. Costs = £22 per hour face-to-face weekday contact (£27 per hour weekday evenings; £33 per hour Saturdays; £45 per hour Sundays). Total per care package = £192.42 per week x 52 weeks per year.
[c]McCrone 2008.[139] Cost per patient aged 65-74 = £2,000 per annum (estimated from figure 15) 2005/6 cost inflated to 2010/11 cost using Hospital & Community Health Services (HCHS) index.
[d]NHS Reference Costs 2010/11.[140] NHS Trusts Elective Inpatient HRG Data. HRG HB12B Major Hip Procedures for Category 1 with CC.
[e]2003/4 cost inflated to 2010/11 cost using Hospital & Community Health Services (HCHS) index
[f]PSSRU 2011.[138] Community occupational therapist (local authority). Cost per hour of client contact including training = £82. Length of contact per care episode = 5.2 hours (PSSRU 2003).
[g]PSSRU 2011.[138] NHS community occupational therapist. Cost per hour of client contact including qualifications = £82. Mean duration of visit = 40 minutes. General practitioner. Per surgery consultation lasting 11.7 minutes including qualification costs, excluding direct staff care costs = £31.

Adverse-event costs

7.5.7 Please summarise the costs for each adverse event listed in section 6.9 (Adverse events). These should include the costs of therapies identified in sections 2.7 and 2.8. Cross-reference to other sections of the submission for the resource costs. Provide a rationale for the choice of values used in the cost-effectiveness model discussed in section 7.2.2.

Patients experiencing AEs were assumed to incur the cost of managing those events. These costs are shown in

Table 62.

Table 62 Cost of adverse events

Adverse event	Cost	Source
Conjunctival haemorrhage	£1,234.31	Brändle et al. 2007[129]
IOP increased	£31.67	See Table 63
Visual Disturbance	£0	Assumption
Injection site AEs	£100	Assumption
Brändle et al., 2007[129] AE, adverse event; IOP, intraocular pressure		

Costs for drug treatments for management of elevated intraocular pressure (IOP) were determined from unit costs for possible treatments (beta-blockers, prostaglandins, carbonic anhydrase inhibitors, brimonidine and combination therapy), the likely number of units treatment required and the proportion of patients likely to receive each therapy (see Table 63). The figures were drawn from the NICE STA for Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion (September 2010).[53] Specifically, the calculations are an average of the cost per patient reported for the first six months and for the second six months. In that document, the costs are reported across *all* patients, irrespective of whether or not they have an event. In the ranibizumab model described in this report, the costs were converted to the rate per event (as opposed to average per patient in the whole trial).

Table 63 Cost of IOP treated with drug

Drug	% of use	Unit cost	Units	Total cost	Weight	Total
Beta-blockers	14%	£1.55	4.5	£6.98	30%	£2.07
Prostaglandins	9%	£12.48	4.5	£56.16	18%	£10.23
CA inhibitors	5%	£6.56	3.5	£22.96	10%	£2.38
Combination	10%	£10.05	5	£50.25	21%	£10.61
Brimonidine	10%	£6.85	4.5	£30.83	21%	£6.38
Total	48%[a]					**£31.67**
CA, carbonic anhydrase; IOP, intraocular pressure [a]Reported for all patients (regardless of event rate), so total does not necessarily sum to 100%						

Miscellaneous costs

7.5.8 Please describe any additional costs that have not been covered anywhere else (for example, PSS costs). If none, please state.

No additional costs are included.

7.6 Sensitivity analysis

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', sections 5.1.11, 5.8, and 5.9.4 to 5.9.12.

Sensitivity analysis should be used to explore uncertainty around the structural assumptions used in the analysis. Analysis of a representative range of plausible scenarios should be presented and each alternative analysis should present separate results.

The uncertainty around the appropriate selection of data sources should be dealt with through sensitivity analysis. This will include uncertainty about the choice of sources for parameter values. Such sources of uncertainty should be explored through sensitivity analyses, preferably using probabilistic methods of analysis.

All inputs used in the analysis will be estimated with a degree of imprecision. Probabilistic sensitivity analysis (PSA) is preferred for translating the imprecision in all input variables into a measure of decision uncertainty in the cost effectiveness of the options being compared.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

7.6.1 Has the uncertainty around structural assumptions been investigated? Provide details of how this was investigated, including a description of the alternative scenarios in the analysis.

Sensitivity analysis, including assessment of uncertainty around appropriate data sources and structure of the model, was explored using deterministic and probabilistic methods of analysis together with several scenario analyses. (section 7.6.2 and 7.6.3).

7.6.2 Which variables were subject to deterministic sensitivity analysis? How were they varied and what was the rationale for this? If any parameters or variables listed in section 7.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

One-way sensitivity analyses were carried out where there was substantial uncertainty around a key parameter value in order to estimate the impact of different parameter values on the costs and effects of each treatment. Table 64 lists the base case value for each of these parameters and the range by which they were varied in the sensitivity analyses.

Table 64 Summary of parameters in sensitivity analysis

	Base case value	Range
Cost of treatment drug	£742.17	£0–£3750
Cost of comparator drug	£850.00	£0–£3750
Frequency of treatment (treatment year 1)	3.5	0–12
Frequency of treatment (treatment year 2)	1	0–12
Frequency of treatment (comparator year 1)	3.4	0–12
Frequency of treatment (comparator year 2)	1.7	0–12
Monitoring frequency (treatment year 1)	8.5	0–12
Monitoring frequency (treatment year 2)	4	0–12
Monitoring frequency (comparator year 1)	4	0–12
Monitoring frequency (comparator year 2)	4	0–12
Cost of administration visit (treatment)	£168.53	£0–£1500
Cost of administration visit (comparator)	£174.89	£0–£1500
Cost of monitoring visit	£174.89	£0–£1500
Cost of blindness (multiplier)	1	0.5–2
Probability that the study eye is the better-seeing eye	1	0.5–2
Starting age	55	35–95
Baseline prevalence of bilateral disease	15%	0%–30%
Rate of recurrence	6%	0%-12%
Utility curve for BSE (multiplier)	1	0.3–1.3
Utility curve for WSE	0.1	0.05–0.8
Treatment transition probabilities (multiplier: 0-3)	1	0.5–2
Treatment transition probabilities (multiplier: 3-6)	1	0.5–2
Treatment transition probabilities (multiplier: 6-9)	1	0.5–2
Treatment transition probabilities (multiplier: 9-12)	1	0.5–2
Comparator transition probabilities (multiplier: 0-3)	1	0.5–2
Comparator transition probabilities (multiplier: 3-6)	1	0.5–2
Comparator transition probabilities (multiplier: 6-9)	1	0.5–2
Comparator transition probabilities (multiplier: 9-12)	1	0.5–2
Natural progression (multiplier)	1	0.5–2
Discount rate - costs	3.5%	0–6%
Discount rate - benefits	3.5%	0–6%
BSE, better-seeing eye; WSE, worse-seeing eye		

7.6.3 Was PSA undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated if different from those in section 7.3.6, including the derivation and value of ‘priors’. If any parameters or variables were omitted from sensitivity analysis, please provide the rationale for the omission(s).

PSA was conducted in the model to take account of the simultaneous effect of uncertainty relating to model parameter values. Distributions were fitted to key parameters within the model. Beta distributions were used

for probabilities and gamma distributions were used for cost parameters (beta distributions are bound between the values of zero and one, whereas gamma distributions produce only non-negative values). Normal distributions were assumed for parameters such as age where non-negative values were very unlikely, and lognormal distributions were used for risk ratios.

The parameters assessed in the probabilistic sensitivity analyses are presented in Table 65.

Table 65 Parameters varied in probabilistic sensitivity analyses

Parameter	Mean	Variation	Type	Alpha	Beta	PSA value
General						
Starting age	55	15	Normal	NA	NA	59.4
Baseline prevalence of bilateral PM	0.1500	0.0050	Lognormal	NA	NA	0.15
Annual rate of recurrence	0.0600	0.0050	Lognormal	NA	NA	0.06
Clinical effectiveness						
Treatment transition probabilities (months 0–3)	1	0.1	Lognormal	NA	NA	0.80
Treatment transition probabilities (months 3–6)	1	0.1	Lognormal	NA	NA	1.03
Treatment transition probabilities (months 6–9)	1	0.1	Lognormal	NA	NA	1.00
Treatment transition probabilities (months 9–12)	1	0.1	Lognormal	NA	NA	0.90
Comparator transition probabilities (months 0–3)	1	0.1	Lognormal	NA	NA	0.90
Comparator transition probabilities (months 3–6)	1	0.1	Lognormal	NA	NA	1.31
Comparator transition probabilities (months 6–9)	1	0.1	Lognormal	NA	NA	1.01
Comparator transition probabilities (months 9–12)	1	0.1	Lognormal	NA	NA	0.97
Natural history	1	0.1	Gamma	100	0.01	0.906
Quality of life						
Utilities (BSE)	1	0.05	Normal	NA	NA	1.062
Utility (WSE relative to BSE)	0.30	0.05	Beta	25.2	58.8	0.304
Costs						
Administration costs (ranibizumab)	£168.53	£65.70	Gamma	6.58	25.61	£211.96
Administration costs (vPDT)	£174.89	£64.68	Gamma	7.31	23.92	£202.65
Follow up costs (all treatments)	£174.89	£64.68	Gamma	7.311	23.921	£81.12
Treatment visits year 1 (ranibizumab)	1	0.05	Gamma	400	0.0025	1.041
Treatment visits year 2 (ranibizumab)	1	0.05	Gamma	400	0.0025	0.943
Treatment visits year 1	1	0.05	Gamma	400	0.0025	0.900

(vPDT)						
Treatment visits year 2 (vPDT)	1	0.05	Gamma	400	0.0025	1.081
Monitoring visits year 1 (ranibizumab)	1	0.05	Gamma	400	0.0025	0.959
Monitoring visits year 2 (ranibizumab)	1	0.05	Gamma	400	0.0025	1.039
Monitoring visits year 1 (vPDT)	1	0.05	Gamma	400	0.0025	1.011
Monitoring visits year 2 (vPDT)	1	0.05	Gamma	400	0.0025	0.985
Cost of blindness	1	0.05	Gamma	400	0.0025	1.003
BSE, better-seeing eye; NA, not applicable; PM, pathological myopia; PSA, probabilistic sensitivity analysis; WSE, worse-seeing eye; vPDT, verteporfin photodynamic therapy						

For transition probability rates, the beta distribution was determined by the trial results. The ‘alpha’ input for each probability was represented by the number of patients who moved health state, whilst the ‘beta’ value was determined by the number who did not move states. This allowed the level of uncertainty to be accurately quantified by way of a mean and standard deviation input. For cost data, no estimates of the magnitude of uncertainty were available, so the standard deviation was assumed to be equivalent to 20% of the total cost.

In cases where probabilities were required to sum to 1.000, such as for transition probabilities, probabilities were randomly sampled and then manipulated in sequence to ensure that the total was 1.000

7.7 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following.

- Link between clinical- and cost-effectiveness results.
- Costs, QALYs and incremental cost per QALY.
- Disaggregated results such as LYG, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment.
- A statement as to whether the results are based on a PSA.
- Cost-effectiveness acceptability curves, including a representation of the cost-effectiveness acceptability frontier.
- Scatter plots on cost-effectiveness quadrants.
- A tabulation of the mean results (costs, QALYs, ICERs), the probability that the treatment is cost effective at thresholds of £20,000–£30,000 per QALY gained and the error probability.

Clinical outcomes from the model

7.7.1 For the outcomes highlighted in the decision problem (see section 5), please provide the corresponding outcomes from the model and compare them with clinically important outcomes such as those reported in clinical trials. Discuss reasons for any differences between modelled and observed results (for example, adjustment for cross-over). Please use the following table format for each comparator with relevant outcomes included.

Data from the model for the first year closely match clinical data from the Novartis phase III study

The mean BCVA at baseline and months 3, 6, 9 and 12 for ranibizumab, and at baseline and month 3 for vPDT from the Novartis phase III trial are compared with the data from the model in Table 66. The data from the model closely match the data from the clinical trial. The mid-point visual acuity value of the health state is used to calculate the mean visual acuity in the model; this therefore may have contributed to small differences between the modelled and trial outcomes. Visual acuity at baseline in the trial was very similar for the ranibizumab and the vPDT arms. In the model, it was assumed that both groups were from the same population and, as such, data from both of these arms were used to calculate the baseline visual acuity inputs.

Table 66 Comparison of model results and clinical trial data

Outcome	Clinical trial result	Model result
Ranibizumab		
Visual acuity at baseline	55.8	55.6
Visual acuity at 3 months	68.4	67.6
Visual acuity at 6 months	68.6	67.6
Visual acuity at 9 months	69.1	68.5
Visual acuity at 12 months	70.6	69.8
Verteporfin photodynamic therapy		
Visual acuity at baseline	54.7	55.6
Visual acuity at 3 months	56.5	55.0

Progression of visual acuity over the first year of the model is presented in Figure 20. The model demonstrates that visual acuity tends to improve immediately in the ranibizumab arm due to treatment. Patients in the vPDT arm experience a small initial worsening of visual acuity in the model. However, these patients in the trial actually experienced a small increase in visual acuity. The model values for BCVA for both vPDT and ranibizumab are slight underestimates; the differences between the modelled and trial outcomes may be attributed to the small differences in the baseline visual acuity values. Thereafter, the level of visual acuity remains relatively constant over time, which is in line with the results seen in the VIP study (Figure 22).

Figure 20 Comparison of model results and clinical trial data for mean visual acuity

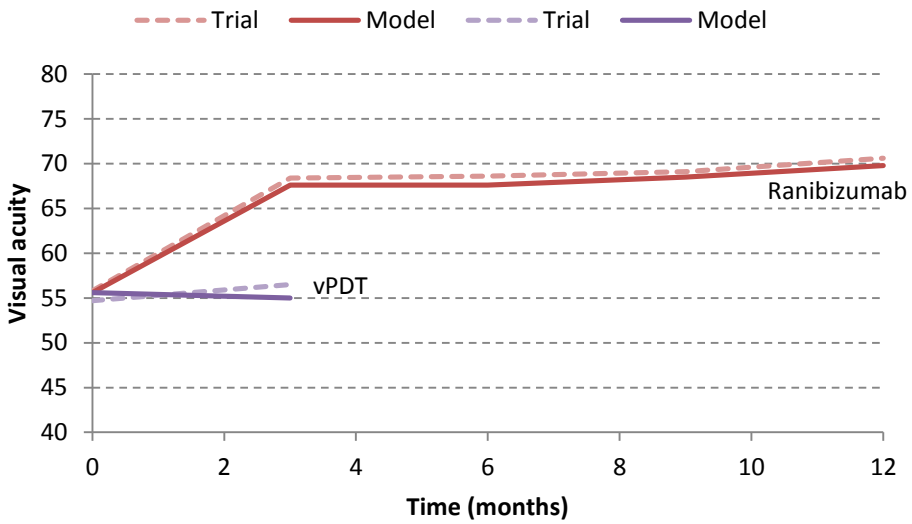
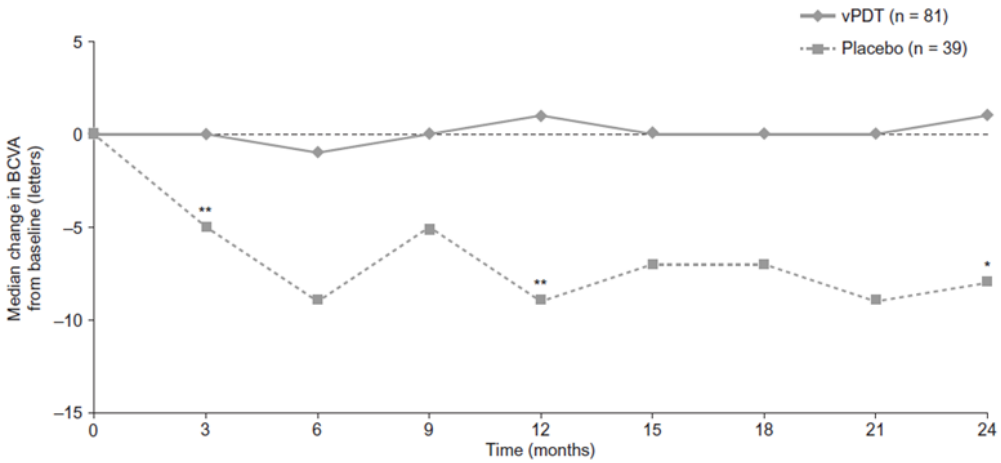


Figure 21 Change in median BCVA letter score from baseline following therapy with vPDT or placebo in the VIP study[a]

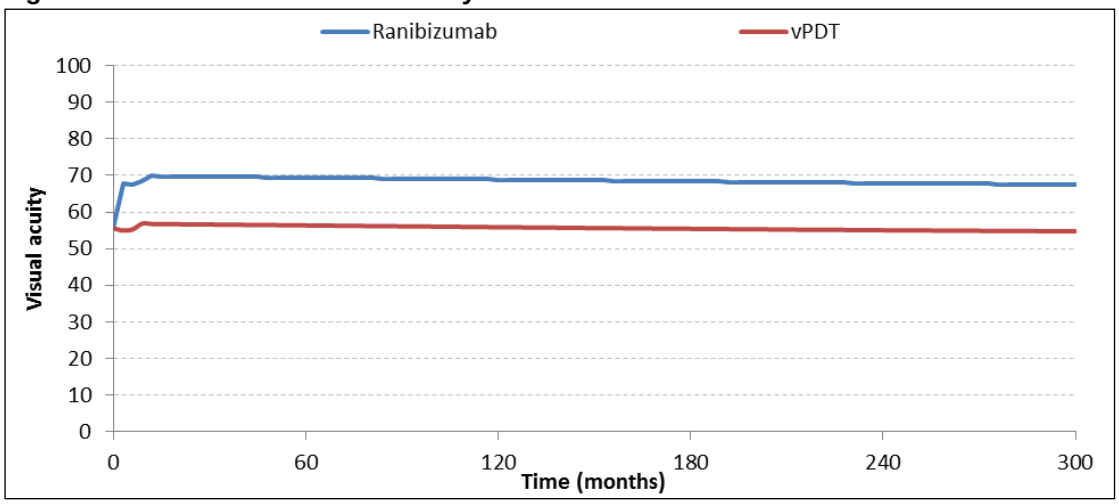


Blinder et al., 2003[25]
BCVA, best-corrected visual acuity; VIP, Verteporfin in Photodynamic Therapy; vPDT, verteporfin photodynamic therapy
Statistical analyses are presented for all time points reported in the original publications
[a]The change in median BCVA letter score was a secondary endpoint. The primary endpoint was the proportion of eyes with fewer than 8 letters of BCVA loss at 12 months.
*p < 0.05; **p < 0.01 versus placebo.

The model predicts a small decrease in visual acuity over time beyond the first year as reported in natural history studies

After the first year, there is a small decrease in mean visual acuity due to natural worsening of visual acuity over time as reported in the natural history studies described earlier (section 6.2.2).[14,16,18-22] It is important to note that as mortality increases with declining visual acuity,[55] and this effect is included in the model (see section 7.3.2), patients with higher visual acuity are slightly more likely to survive each cycle in the model. This effect offsets the decrease in visual acuity over time resulting from natural progression and means the modelled decrease in visual acuity over time is slightly less than would be observed if the effect of visual acuity on mortality was not included. The progression of visual acuity over the model time horizon is presented in Figure 22.

Figure 22 Modelled visual acuity over time



7.7.2 Please provide (if appropriate) the proportion of the cohort in the health state over time (Markov trace) for each state, supplying one for each comparator.

The Markov traces for each comparator in the model up to 36 months are provided below in Table 67 and Table 68.

Table 67 Markov trace of ranibizumab

Month	Health state (letters)								
	86–100	76–85	66–75	56–65	46–55	36–45	26–35	< 25	Death
0	18	159	252	256	170	84	53	7	1
3	46	287	300	183	113	38	25	7	2
6	42	278	312	196	100	36	25	7	3
9	36	304	300	240	57	26	26	7	4
12	44	348	267	277	0	20	31	7	5
15	44	347	266	277	1	20	31	7	7
18	44	346	266	276	2	20	31	7	8
21	44	344	266	276	3	20	31	7	9
24	43	343	266	275	3	20	31	8	11
27	43	342	266	275	4	20	31	8	12
30	43	340	266	275	5	20	30	8	13
33	43	339	266	274	6	20	30	8	15
36	43	338	265	274	6	20	30	8	16

Table 68 Markov trace of vPDT

Month	Health state (letters)								
	86–100	76–85	66–75	56–65	46–55	36–45	26–35	< 25	Death
0	12	41	213	308	175	151	92	7	1
3	25	39	215	272	172	119	127	28	2
6	24	52	193	273	196	123	106	29	3
9	24	77	208	246	204	162	43	31	4
12	24	87	229	209	210	149	32	53	6
15	24	87	229	209	210	149	33	53	7
18	24	86	228	209	209	149	33	53	8
21	24	86	227	208	209	149	33	53	10
24	24	86	227	208	209	149	33	53	11
27	24	86	226	208	209	149	34	53	12
30	24	85	225	208	208	149	34	53	14
33	24	85	225	207	208	149	34	53	15
36	24	85	224	207	208	149	35	53	16

7.7.3 Please provide details of how the model assumes QALYs accrued over time. For example, Markov traces can be used to demonstrate QALYs accrued in each health state over time.

The number of life-years (after half-cycle correction) in each health state was multiplied by QALY weights and discounted at a rate of 3.5% in the base case (Table 69 and Table 70).

Table 69 Markov trace for ranibizumab (QALYs)

Month	Health state (letters)							
	86–100	**76–85**	**66–75**	**56–65**	**46–55**	**36–45**	**26–35**	**< 25**
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
3	0.004	0.032	0.050	0.048	0.031	0.015	0.009	0.001
6	0.010	0.056	0.058	0.034	0.020	0.007	0.004	0.001
9	0.009	0.054	0.060	0.037	0.018	0.006	0.004	0.001
12	0.007	0.059	0.057	0.045	0.009	0.004	0.005	0.001
15	0.009	0.066	0.050	0.051	0.000	0.004	0.005	0.001
18	0.009	0.066	0.050	0.050	0.000	0.003	0.005	0.001
21	0.009	0.065	0.050	0.050	0.000	0.003	0.005	0.001
24	0.009	0.064	0.049	0.049	0.000	0.003	0.005	0.001
27	0.009	0.063	0.049	0.049	0.001	0.003	0.005	0.001
30	0.008	0.062	0.048	0.048	0.001	0.003	0.005	0.001
33	0.008	0.062	0.048	0.048	0.001	0.003	0.005	0.001
36	0.008	0.061	0.047	0.047	0.001	0.003	0.005	0.001

Table 70 Markov trace for vPDT (QALYs)

Month	Health state (letters)							
	86–100	**76–85**	**66–75**	**56–65**	**46–55**	**36–45**	**26–35**	**< 25**
0	0.000	0.000	0.000	0.000	0.000	0.000	0.000	0.000
3	0.003	0.008	0.042	0.058	0.032	0.028	0.017	0.001
6	0.005	0.008	0.042	0.051	0.032	0.021	0.023	0.005
9	0.005	0.010	0.037	0.051	0.035	0.023	0.018	0.005
12	0.005	0.015	0.040	0.045	0.037	0.028	0.007	0.006
15	0.005	0.017	0.043	0.038	0.037	0.026	0.006	0.010
18	0.005	0.016	0.043	0.038	0.037	0.026	0.006	0.009
21	0.005	0.016	0.042	0.038	0.036	0.026	0.006	0.009
24	0.005	0.016	0.042	0.037	0.036	0.025	0.006	0.009
27	0.005	0.016	0.041	0.037	0.036	0.025	0.006	0.009
30	0.005	0.016	0.041	0.036	0.035	0.025	0.006	0.009
33	0.005	0.015	0.041	0.036	0.035	0.025	0.006	0.009
36	0.005	0.015	0.040	0.036	0.035	0.025	0.006	0.009

7.7.4 Please indicate the life years and QALYs accrued for each clinical outcome listed for each comparator. For outcomes that are a combination of other states, please present disaggregated results. For example:

Gains in QALYs for both treatments largely reflect gains in patients with visual acuity greater than 35 letters

Table 71 presents disaggregated costs and health outcomes according to a cut-off point where visual acuity of 35 or fewer letters in the BSE would be regarded as legally partially sighted or severely visually impaired (blind) and for AEs.

Table 71 Model outputs by clinical outcomes

Outcome	QALY	Cost (£)
Ranibizumab		
Visual acuity > 35 letters	12.703	8415.02
Visual acuity ≤ 35 letters	0.479	1173.07
Loss due to AEs	-0.00010	106.24
Total	13.182	9694.33
vPDT		
Visual acuity > 35 letters	11.485	9902.46
Visual acuity ≤ 35 letters	1.264	2532.71
Loss due to AEs	-0.00003	9.90
Total	12.750	12,445.07
AE, adverse event; QALY, quality-adjusted life-year; vPDT, verteporfin photodynamic therapy		

7.7.5 Please provide details of the disaggregated incremental QALYs and costs by health state, and of resource use predicted by the model by category of cost. Suggested formats are presented below.

Cost savings provided by ranibizumab compared with vPDT largely represent reductions in costs of treatment and costs of blindness which are partly offset by increased costs of monitoring

Table 72 and Table 73 present disaggregated incremental QALYs and costs by health state, and Table 74 summarises resource use predicted by the model by category of cost.

Table 72 Summary of QALY gain by health state

Health state (letters)	QALY intervention (X)	QALY comparator (Y)	Increment	Absolute increment	% absolute increment
86–100	0.55981	0.31033	0.24948	0.24948	2.61%
76–85	4.17724	1.05248	3.12477	3.12477	32.75%
66–75	3.68189	2.84313	0.83876	0.83876	8.79%
56–65	3.54585	2.77188	0.77398	0.77398	8.11%
46–55	0.46484	2.59882	-2.13398	2.13398	22.36%
36–45	0.27318	1.90869	-1.63550	1.63550	17.14%
26–35	0.34947	0.57968	-0.23021	0.23021	2.41%
< 25	0.12923	0.68455	-0.55532	0.55532	5.82%
Loss due to AEs	-0.00014	-0.00003	-0.00011	0.00011	0.001%
Total	13.18151	12.74955	0.43196	9.54211	100%
AE, adverse event; QALY, quality-adjusted life-year					

Table 73 Summary of costs by health state

Health state (letters)	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
86–100	£335.12	£245.70	£89.42	£89.42	1.30%
76–85	£2560.12	£774.24	£1785.87	£1785.87	26.00%
66–75	£2467.98	£2380.69	£87.29	£87.29	1.27%
56–65	£2199.42	£2643.82	-£444.40	£444.40	6.47%
46–55	£567.53	£2221.61	-£1654.07	£1654.07	24.08%
36–45	£284.85	£1636.39	-£1351.54	£1351.54	19.68%
26–35	£1098.37	£2067.58	-£969.21	£969.21	14.11%
< 25	£74.71	£465.14	-£390.43	£390.43	5.68%
Cost of AEs	£106.25	£9.90	-£96.35	£96.35	1.40%
Total	£9694.34	£12,445.07	-£2943.43	£6868.58	100%
AE, adverse event					

Table 74 Summary of predicted resource use by category of cost

Item	Cost intervention (X)	Cost comparator (Y)	Increment	Absolute increment	% absolute increment
Treatment costs	£1939.81	£4177.91	-£2238.10	£2238.10	49.95%
Admin. costs	£734.15	£859.62	-£125.47	£125.47	2.80%
Monitoring	£2108.21	£1339.61	£768.60	£768.60	17.15%
Bilateral costs	£717.33	£956.57	-£239.24	£239.24	5.34%
Recurrence costs	£3258.34	£3724.11	-£465.77	£465.77	10.40%
Cost of AEs	£106.25	£9.90	£96.35	£96.35	2.15%
Cost of blindness	£830.25	£1377.35	-£547.10	£547.10	12.21%
Total	£9694.34	£12,445.07	-£2750.73	£4480.64	100%
AE, adverse even					

Base-case analysis

7.7.6 Please present your results in the following table. List interventions and comparator(s) from least to most expensive and present ICERs in comparison with baseline (usually standard care) and then incremental analysis ranking technologies in terms of dominance and extended dominance.

The ICER is calculated as the ratio of the mean incremental cost and the mean incremental QALY, in line with section 5.9.3 of the NICE guide to the methods of technology appraisal for the presentation of results from a non-linear model.

Ranibizumab provides a cost saving of £2751 and a QALY gain of 0.43 over the patient's lifetime compared with vPDT and therefore dominant

The deterministic results are reported in Table 75.

Table 75 Base-case results using deterministic values

Technology	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	9694	16.85	13.18	-2751	0.11	0.43	Dominant
vPDT	12,445	16.75	12.75				
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; vPDT, verteporfin photodynamic therapy							

In order to account for the variance in the model inputs (and because the model is not linear), the base case results using probabilistic values are reported in Table 76.

Table 76 Results using probabilistic values

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	9422	16.02	12.53	-2691	0.09	0.42	Dominant
vPDT	12,113	15.93	12.11				
ICER, incremental cost-effectiveness ratio; LYG, life-years gained; QALYs, quality-adjusted life-years; vPDT, verteporfin photodynamic therapy							

Sensitivity analyses

7.7.7 Please present results of deterministic sensitivity analysis. Consider the use of tornado diagrams.

Deterministic sensitivity analysis

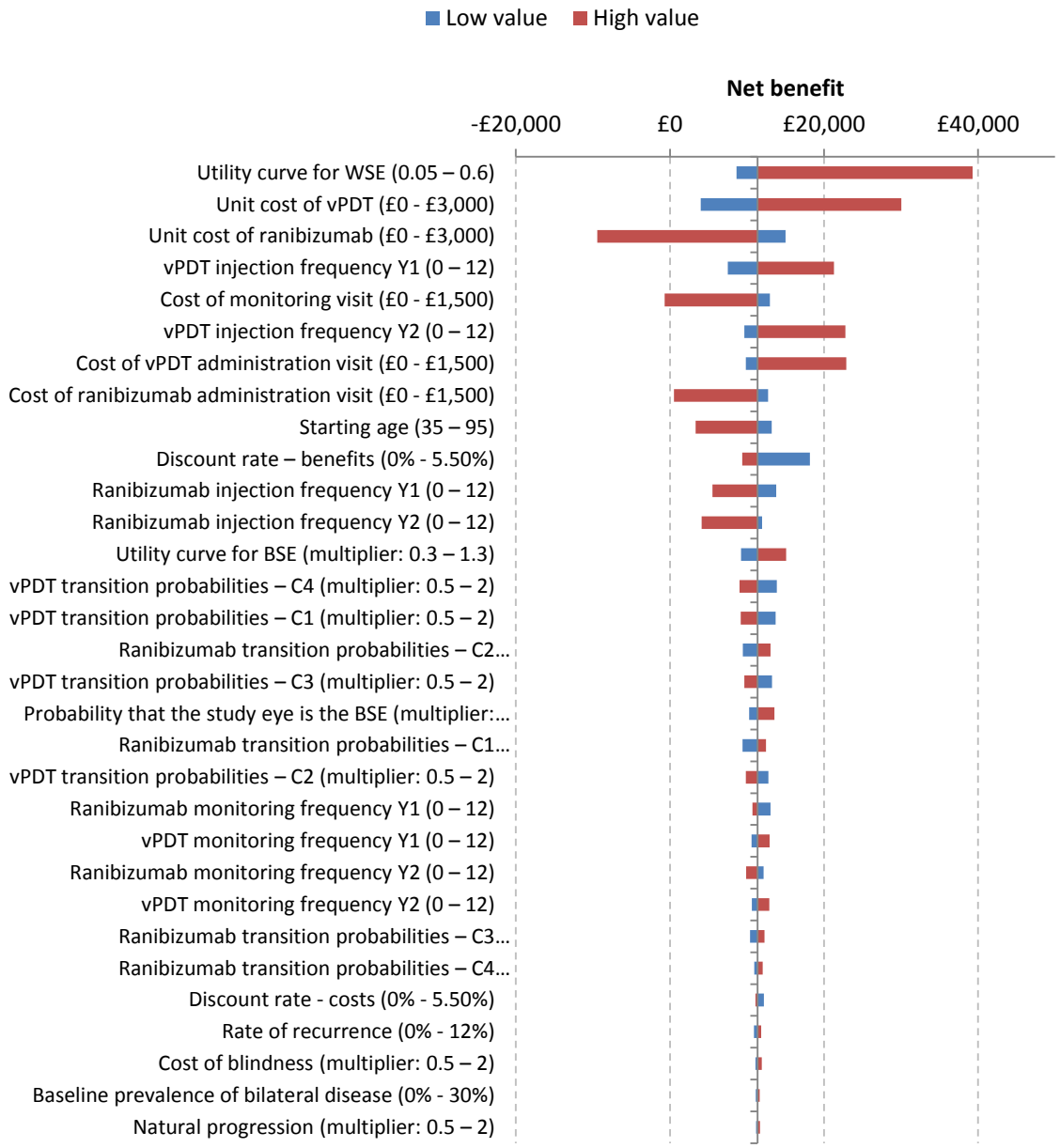
A range of parameters were varied in one-way sensitivity analysis to test the robustness of the model. All varied parameters and the range of variation (high and low values for each input) are shown in Table 77, together with the incremental costs and QALYs and net benefit, with a net benefit of greater than £0 being equivalent to an ICER of less than £20,000/QALY. These results are also summarised in a tornado diagram (see Figure 23). Deterministic sensitivity analysis charts for each of the inputs in Table 77 are given in Figure 24–Figure 29 and Figure 31–Figure 33. These report the change in net benefit since, in the majority of cases, the ICER is dominant.

Ranibizumab is cost-effective compared with vPDT for the majority of scenarios considered

Ranibizumab is cost-effective compared with vPDT for the majority of scenarios considered and is dominant in most situations (see Table 77 and Figure 23). For the base-case the net benefit is £11,389.92. The model is sensitive to changes in:

- unit costs of ranibizumab and vPDT (treatment, administration and monitoring),
- injection frequency for ranibizumab and vPDT
- the starting age of the patient cohort,
- the discount rate for benefits, and
- the maximum utility gain in the WSE.

Figure 23 Deterministic sensitivity analysis – tornado diagram of net benefit



BSE, better-seeing eye; C, cycle; WSE, worse-seeing eye; vPDT, vPDT, verteporfin photodynamic therapy; Y, year

Table 77 Deterministic sensitivity analysis

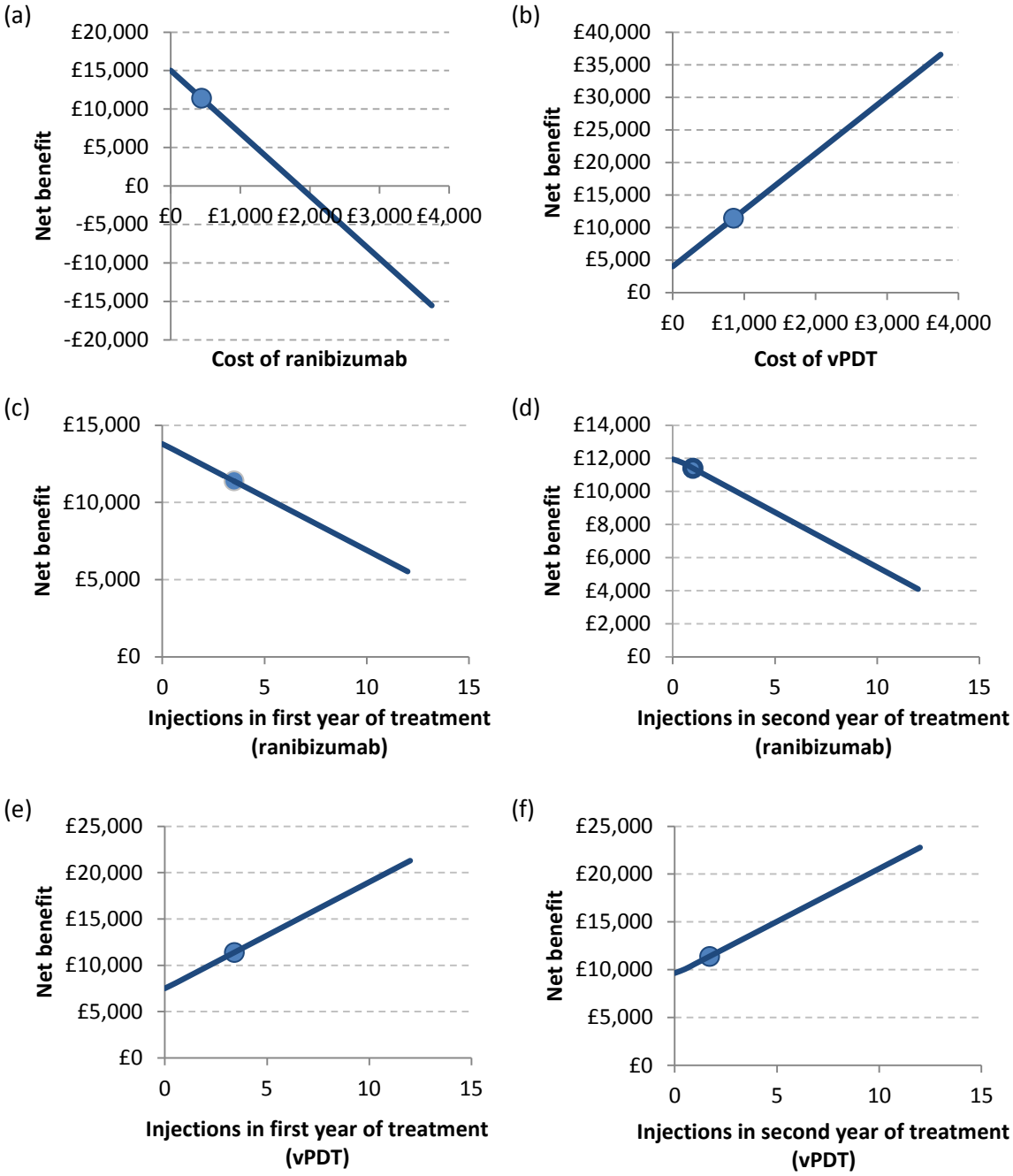
	Low value			High value		
	Incremental costs	**Incremental QALYs**	**Net benefit**	**Incremental costs**	**Incremental QALYs**	**Net benefit**
Ranibizumab injection frequency Y1 (0–12)	-£5,148.11	0.43	£13,787.30	£3,107.97	0.43	£5,531.22
Ranibizumab injection frequency Y2 (0–12)	-£3,307.15	0.43	£11,946.34	£4,538.42	0.43	£4,100.77
vPDT injection frequency Y1 (0–12)	£1,127.39	0.43	£7,511.80	-£12,647.41	0.43	£21,286.60
vPDT injection frequency Y2 (0–12)	-£1,007.35	0.43	£9,646.53	-£14,144.49	0.43	£22,783.68
Ranibizumab monitoring frequency Y1 (0–12)	-£4,419.98	0.43	£13,059.16	-£2,063.40	0.43	£10,702.58
Ranibizumab monitoring frequency Y2 (0–12)	-£3,505.94	0.43	£12,145.12	-£1,240.33	0.43	£9,879.52
vPDT monitoring frequency Y1 (0–12)	-£1,965.24	0.43	£10,604.43	-£4,321.72	0.43	£12,960.90
vPDT monitoring frequency Y2 (0–12)	-£1,995.68	0.43	£10,634.86	-£4,260.85	0.43	£12,900.04
Cost of monitoring visit (£0–1,500)	-£4,344.53	0.43	£12,983.71	£9,325.02	0.43	-£685.04
Cost of ranibizumab administration visit (£0–1,500)	-£4,123.74	0.43	£12,762.93	£8,096.65	0.43	£542.53
Cost of vPDT administration visit (£0–1,500)	-£1,232.92	0.43	£9,872.10	-£14,250.83	0.43	£22,890.02
Unit cost of ranibizumab (£0–3,000)	-£6,378.58	0.43	£15,017.77	£18,062.22	0.43	-£9,423.03
Unit cost of vPDT (£0–3,000)	£4,626.08	0.43	£4,013.10	-£21,409.74	0.43	£30,048.93
Cost of blindness (multiplier: 0.5–2)	-£2,477.19	0.43	£11,116.37	-£3,297.83	0.43	£11,937.02
Starting age (35 – 95)	-£3,294.78	0.50	£13,200.67	-£1,334.47	0.10	£3,337.09
Rate of recurrence (0–12%)	-£2,284.96	0.43	£10,924.15	-£3,216.51	0.43	£11,855.69
Baseline prevalence of bilateral disease (0–30%)	-£2,511.49	0.43	£11,150.68	-£2,989.18	0.43	£11,648.53
Probability that the study eye is the BSE (multiplier: 0.5–2)	-£2,485.70	0.39	£10,271.36	-£3,271.82	0.51	£13,557.34
Discount rate – costs (0–5.50%)	-£3,565.37	0.43	£12,204.56	-£2,478.49	0.43	£11,117.68
Discount rate – benefits (0–5.50%)	-£2,750.73	0.77	£18,168.02	-£2,750.73	0.33	£9,385.42
Utility curve for BSE (multiplier: 0.3–1.3)	-£2,750.73	0.32	£9,247.70	-£2,750.73	0.62	£15,098.80
Utility curve for WSE (0.05–0.6)	-£2,750.73	0.29	£8,660.48	-£2,750.73	1.83	£39,284.29
Ranibizumab transition probabilities – C1 (multiplier: 0.5–2)	-£2,351.41	0.35	£9,408.26	-£2,968.20	0.47	£12,463.83
Ranibizumab transition probabilities – C2 (multiplier: 0.5–2)	-£2,351.10	0.35	£9,448.51	-£3,038.39	0.50	£13,075.36
Ranibizumab transition probabilities – C3 (multiplier: 0.5–2)	-£2,669.49	0.39	£10,414.40	-£2,811.56	0.47	£12,280.01
Ranibizumab transition probabilities – C4 (multiplier: 0.5–2)	-£2,749.56	0.41	£10,936.61	-£2,752.14	0.47	£12,056.36
vPDT transition probabilities – C1 (multiplier: 0.5–2)	-£3,004.91	0.54	£13,732.97	-£2,543.69	0.33	£9,180.91

vPDT transition probabilities – C2 (multiplier: 0.5–2)	-£2,921.49	0.49	£12,781.43	-£2,561.06	0.37	£9,873.48
vPDT transition probabilities – C3 (multiplier: 0.5–2)	-£2,934.80	0.52	£13,267.01	-£2,591.39	0.35	£9,645.19
vPDT transition probabilities – C4 (multiplier: 0.5–2)	-£3,383.66	0.52	£13,862.43	-£2,227.79	0.34	£9,035.49
Natural progression (multiplier: 0.5–2)	-£2,554.69	0.43	£11,198.59	-£3,095.63	0.43	£11,693.51
BSE, better-seeing eye; C, cycle; QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy; WSE, worse-seeing eye; Y, year						

Ranibizumab is dominant compared with vPDT for unit costs up to £782.95

The model is sensitive to the unit cost of ranibizumab. Increasing the unit cost of ranibizumab decreased net benefit, with the net benefit being greater than £0 for unit costs less than £1843.50 (see Figure 24a). The model is also sensitive to the number of ranibizumab injections in the first year (see Figure 24c), with the net benefit decreasing with an increase in the number of injections, but the net benefit remains positive (£5,531) for the maximum number of injections. A similar effect is observed for the number of injections in year 2 (see Figure 24d). Increasing the cost of an administration visit for ranibizumab reduces the net benefit but ranibizumab remains cost effective compared with vPDT for all unit costs considered in the model (Figure 25e). (In the base case the cost is £169.)

Figure 24 **Deterministic sensitivity analyses: Net benefit according to: unit cost of treatment (a, b) and frequency of treatment (c−f)**

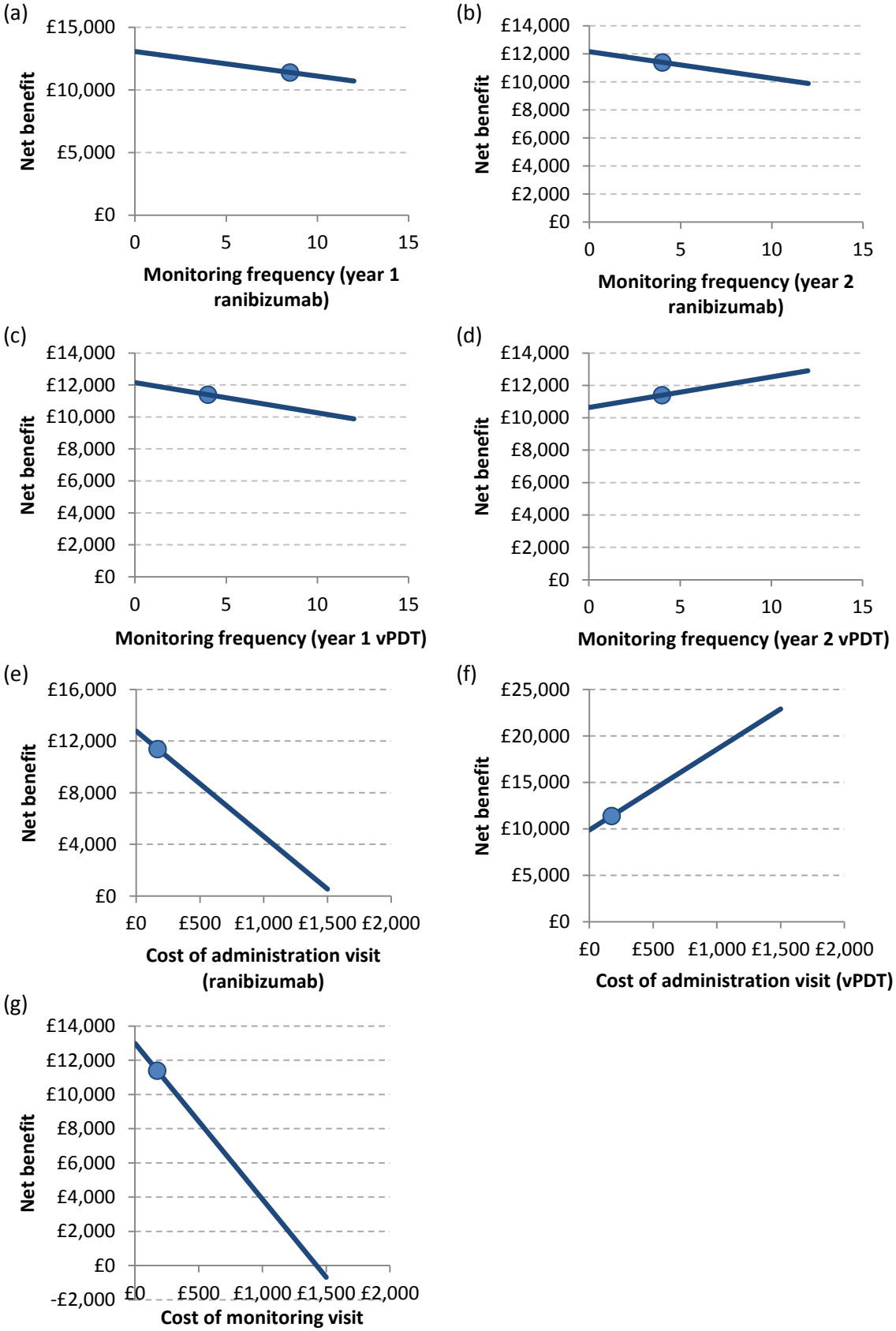


vPDT, verteporfin photodynamic therapy

Net benefit decreases with increasing cost of monitoring but ranibizumab remains cost effective over vPDT for unit costs of monitoring of up to £1425

The frequency of monitoring has minimal effect on the net benefit with ranibizumab remaining dominant under all scenarios considered for the frequency of monitoring of both ranibizumab and vPDT (see Figure 25a–d). As ranibizumab requires a greater number of monitoring visits than vPDT, the net benefit decreases when the unit cost of a monitoring visit is increased (Figure 25g). However, the net benefit remains positive for unit costs of up to approximately £1425. (The maximum unit cost considered is £1500.)

Figure 25 **Deterministic sensitivity analyses: Net benefit according to: monitoring frequency (a−d), cost of administration (e and f) and cost of monitoring (g)**



vPDT, verteporfin photodynamic therapy

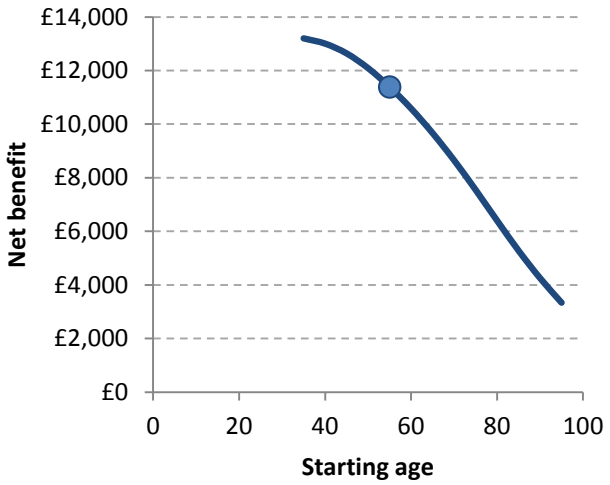
Ranibizumab is cost effective over vPDT for all unit costs considered for vPDT

The model is sensitive to the unit costs of vPDT and frequency of treatment. As predicted, increasing the unit cost of vPDT results in an increase in net benefit to a maximum of £30,049 for the upper unit cost considered (£3,000; see Figure 24b), and increases in net benefit are observed for increases in the number of treatments in year 1 and year 2 (see Figure 24e–f). Increasing the cost of an administration visit also increases the net benefit (Figure 25f). The frequency of monitoring has minimal effect on the net benefit (see Figure 25c–d).

Net benefit increases with decreasing age of patients at the start of treatment; ranibizumab is dominant for all starting ages considered

The sensitivity analysis considered a mean starting age for treatment ranging from 35 to 95 years (see Figure 26). As the mean age of the cohort increases, the net benefit decreases but remains positive for all ages evaluated; furthermore ranibizumab is dominant for all starting ages considered. This reflects the fact that in a younger cohort, patients live for longer with the benefits of treatment. Ranibizumab provides cost savings compared with vPDT across all areas, the largest being from savings in the costs of recurrence and blindness, which accumulate over the patient's lifetime. Younger patients therefore accumulate greater cost savings for recurrence and blindness. Moreover, a large proportion of costs are related to treatment (57% for ranibizumab and 76% for vPDT) and occur in the first 2 years of the model, while QALY gains are experienced over the remaining lifespan of the patient. As such, the cost-savings and QALY gain achieved with ranibizumab over vPDT over a patient's lifespan are greater in patients starting treatment at a younger age compared with older patients.

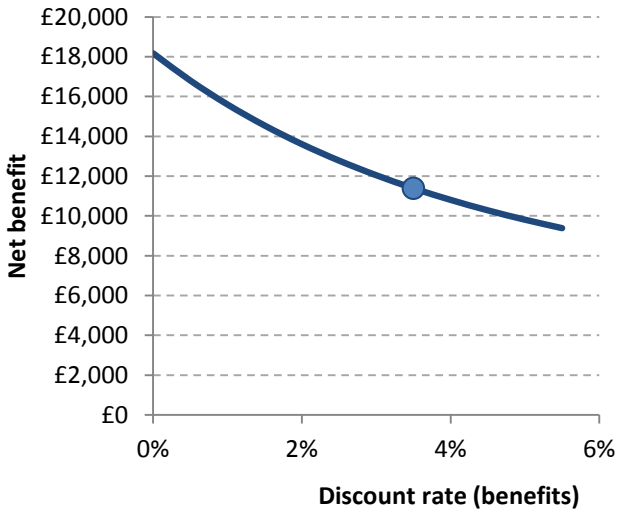
Figure 26 Deterministic sensitivity analysis: Net benefit according to age of starting treatment



The model is sensitive to the discount rate used for benefits but not costs

For all discount rates considered for benefits and costs, a (positive) net benefit was observed for ranibizumab over vPDT (see Figure 27).

Figure 27 Deterministic sensitivity analysis: Net benefit according to the discount rate for benefits



The model is sensitive to changes in the utilities for the BSE and WSE

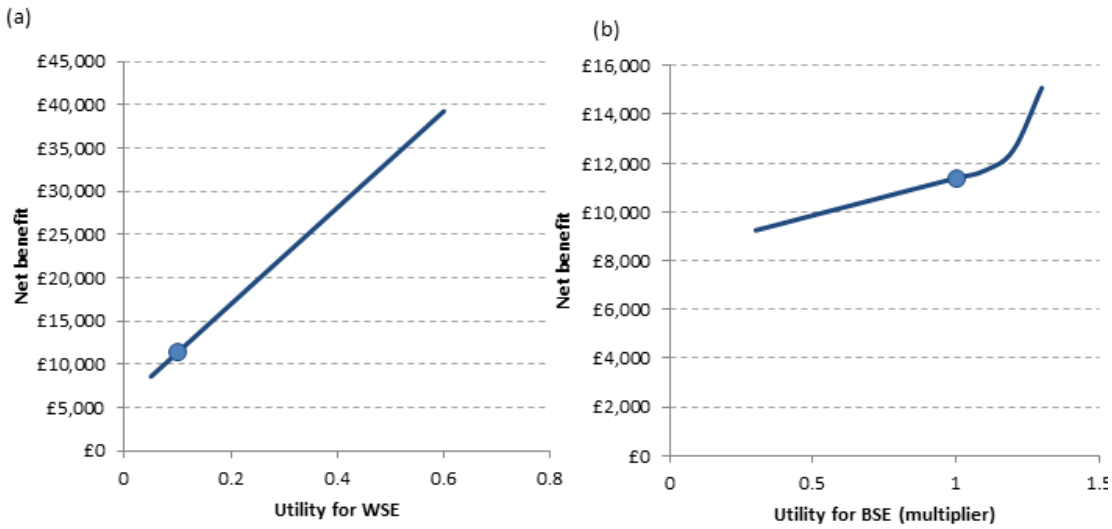
The model is sensitive to the maximum gain in utilities for the WSE, with the net benefit increasing from £8660 for the lower value considered to £39,284 for the highest value considered in the sensitivity analysis (see Figure 28a). This reflects the effect of utility values on the incremental gains in QALYs. In the base case, the maximum gain in utility for the WSE is 0.1 and the utility for the WSE at the highest health state is anchored to the utility for this state in the BSE (Figure 30a). Increasing the maximum utility gain in the WSE (i.e. the difference between the best and worst possible health states) leads to lower utility values on the WSE curve (although higher incremental utility in favour of ranibizumab), and thus a decrease in QALYs in both the ranibizumab and vPDT arms, as shown in Table 78. Higher utility gains for the WSE therefore result in greater **incremental** gains in QALYs for ranibizumab over vPDT and hence greater net benefits. Furthermore over time, ranibizumab has a higher proportion of patients whose study eye is the BSE and thus fewer patients taking their values from the WSE curve (see Section 7.4.9 for an explanation of how utilities are calculated). Varying the WSE maximum utility gain was evaluated in a scenario analysis reported in section 7.7.11).

Table 78 Changes in health benefits linked to maximum utility gain in the WSE

Maximum utility gain for WSE	Total QALYs		
	Ranibizumab	vPDT	Incremental
0.1 (base case)	13.18	12.75	0.43
0.2	12.78	12.07	0.71
0.3	12.38	11.39	0.99
0.4	11.98	10.71	1.27
QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy; WSE, worse-seeing eye			

The model is also sensitive to changes in the utilities for the BSE, but the effect on net benefit is less marked than that for changes in the utilities for the WSE (see Figure 28b). Increasing utility values on the BSE curve results in a more cost-effective scenario for ranibizumab. In the ranibizumab cohort, more study eyes are the BSE over time, and therefore more patients benefit from these higher utility values.

Figure 28 Deterministic sensitivity analysis: Net benefit according to utilities for the WSE (a) and BSE (b)

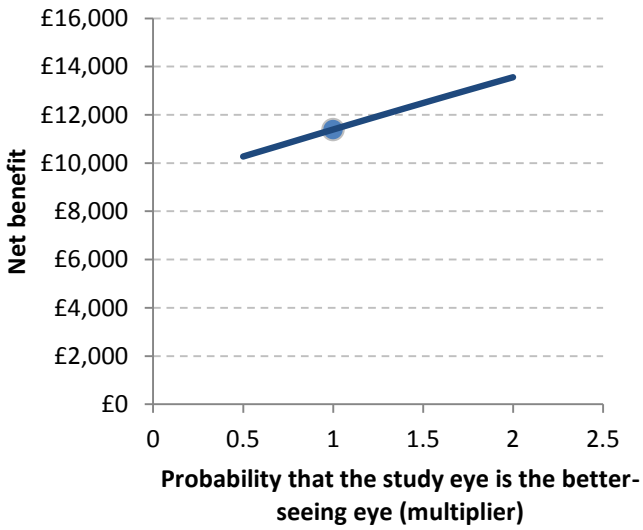


BSE, better-seeing eye; WSE, worse-seeing eye

Net benefit increases with increasing probability that the study eye is the BSE

Changes in the probability that the treated eye is the BSE also affect the net benefit, though to a lesser extent than changes in utilities. In the base case, the proportion of study eyes being the BSE was 20.8%. Net benefit increases with increasing the probability that the study eye is the BSE (see Figure 29). This reflects the fact that, as the probability that the study eye is the BSE increases, the incremental benefit in QALYs for ranibizumab over vPDT also increases. However, counter-intuitively, patients accrue less QALYs due to the fact that utility is calculated using a weighted approach to account for visual acuity in the BSE and the WSE and utilities on the WSE curve are higher than on the BSE curve (see Figure 30a).

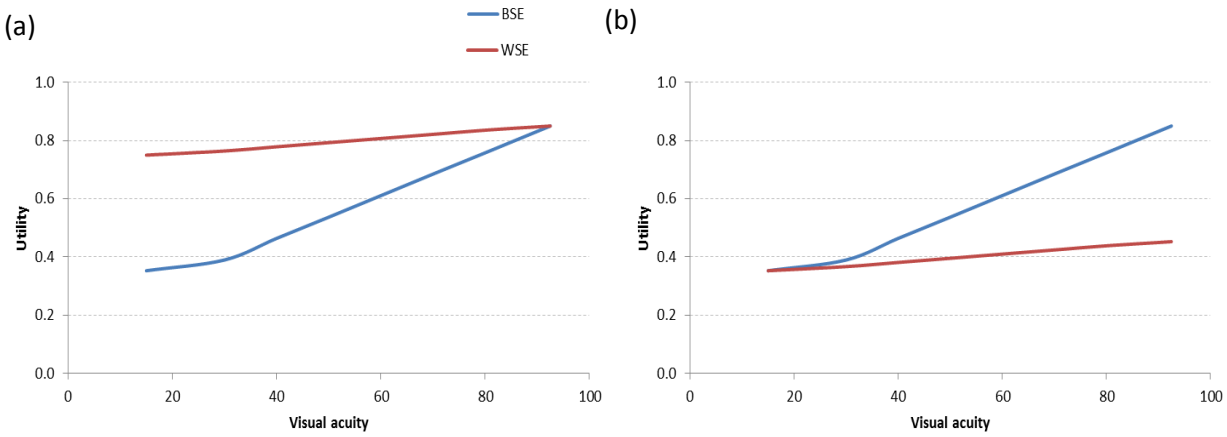
Figure 29 **Deterministic sensitivity analysis: Net benefit according to: the probability that the study eye is the BSE**



Anchoring the utility slope for the WSE at the lower end of the BSE curve (see Figure 30b) leads to more intuitive results, i.e. improving vision yields increases in incremental utility (although the overall QALYs accrued would be much lower). Likewise, a model based only on the BSE also yields improved incremental utility for ranibizumab as BCVA improves as compared with vPDT.

Table 79 below demonstrates the effects of these scenarios on the base case. Net benefits for ranibizumab over vPDT for these scenarios are approximately 2- and 3-fold greater than for the base case and hence illustrate that the base case uses a conservative estimate of the effect of improvements in visual acuity on utilities.

Figure 30 **Utility slopes/values for BSE and WSE anchored at upper (a) and lower end (b)**



BSE, best-seeing eye; WSE, worse-seeing eye

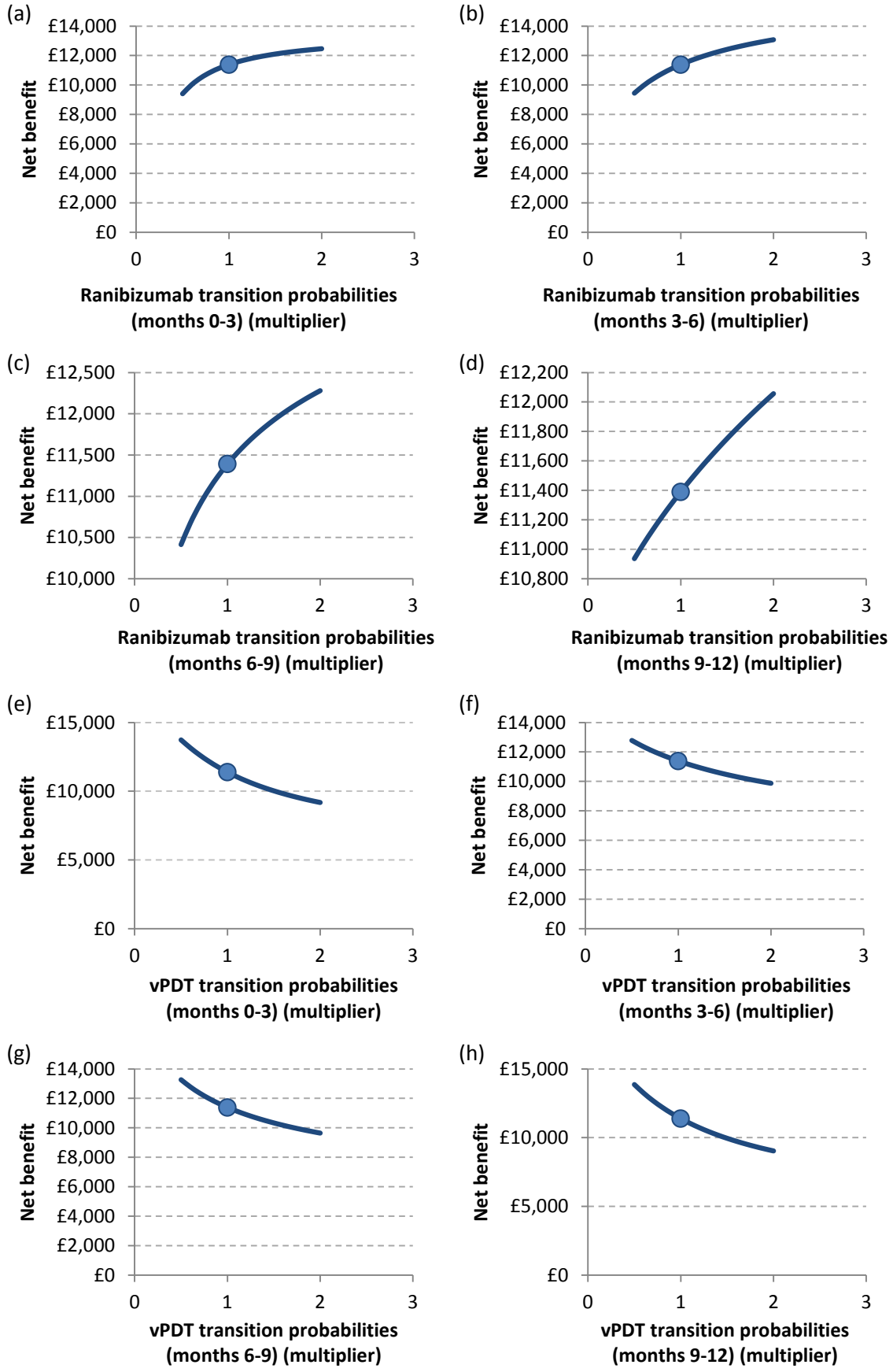
Table 79 Sensitive analysis based on different utility curves for the WSE

	Base Case			Lower Anchor			BSE Only		
	Ranibizumab	**vPDT**	**Incremental**	**Ranibizumab**	**vPDT**	**Incremental**	**Ranibizumab**	**vPDT**	**Incremental**
Total QALYS	13.18	12.75	0.43	8.57	7.55	1.02	11.32	9.72	1.59
Net Benefit			£11,390			£23,102			£34,616
BSE, best-seeing eye; QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy									

There is negligible impact in the sensitivity analyses evaluating changes in the transition probabilities for ranibizumab and vPDT and for natural progression

Transition probabilities for ranibizumab and vPDT were determined for four cycles in year 1 (months 0−3, 3−6, 6−9 and 9−12) (see section 7.3.2). For all four time periods and for both ranibizumab and vPDT, changes in the transition probabilities had relatively little impact on the net benefit for ranibizumab over vPDT (Figure 31). As expected, increasing the effectiveness of ranibizumab treatment (i.e. by raising the probability of gaining 2 or more lines and reducing the probability of losing 2 or more lines) results in a higher net benefit, and increasing the effectiveness of vPDT results in a lower net benefit. For all scenarios ranibizumab is dominant over vPDT.

Figure 31 **Deterministic sensitivity analyses: Net benefit according to transition probabilities for ranibizumab (a–d) and vPDT (e–h)**

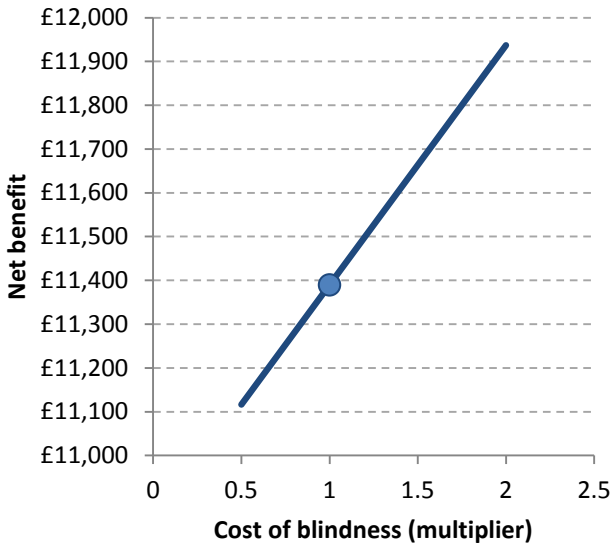


Transition probabilities for year 2 onwards in the model were derived from a study of the natural history of CNV secondary to PM (i.e. in the absence of treatment) for the base case.[22] When transition probabilities for year 2 onwards (i.e. natural deterioration of vision over time) are increased (with an increased multiplier), a small gain in net benefit for ranibizumab over vPDT is observed. In this scenario, the costs of blindness will be increased over the model time horizon, with larger cost gains for the vPDT arm due to a greater proportion of patients being in these health states after completing treatment.

The model is relatively insensitive to changes in the cost of blindness, the prevalence of bilateral disease and the rate of recurrence

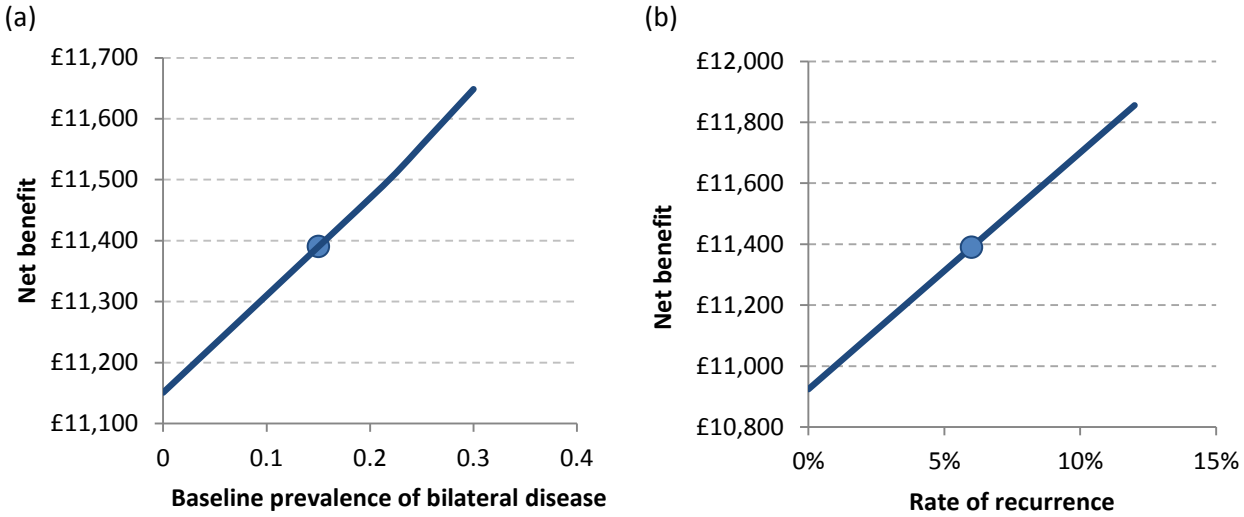
The model is relatively insensitive to the cost associated with blindness (i.e. when the patient's visual acuity in the BSE falls below 35 letters). Again, this is to be expected, since relatively few patients go blind. Cost of blindness (incurred by those patients whose visual acuity falls below 35 letters in the BSE) is incurred to a greater extent in the vPDT cohort, and thus the difference between ranibizumab and vPDT widens over time (see Figure 32). As a result, the net benefit for ranibizumab over vPDT increases as the time horizon increases or the starting age of the population decreases.

Figure 32 Deterministic sensitivity analysis: Net benefit according to the cost of blindness



Net benefit increases with increasing prevalence of bilateral disease and rate of recurrence (see Figure 33). This reflects the fact that it is more costly to treat a patient with vPDT than with ranibizumab (despite the increased monitoring requirements for ranibizumab) so, as expected, as the rate of recurrence and the baseline prevalence of bilateral disease increase, ranibizumab becomes more cost-effective.

Figure 33 Deterministic sensitivity analyses: Net benefit according to baseline prevalence of bilateral disease (a) and rate of recurrence (b)



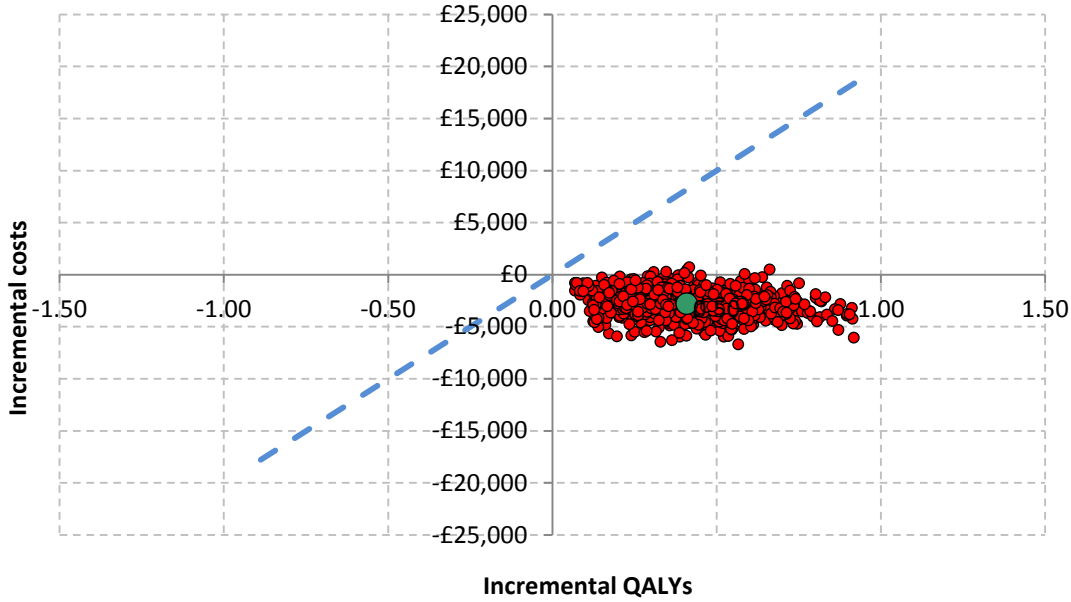
7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probability that ranibizumab is cost-effective when compared to vPDT is 100.0% at WTP thresholds of £20,000 and £30,000 per QALY

The probabilistic analysis allows an overall assessment of the uncertainty within the model. When run, the probabilistic sensitivity analysis generates a scatter plot (Figure 34), which is observed to have a very small downward-sloping pattern. This is to be expected, since there is likely to be an inverse relationship between incremental cost and incremental effectiveness. For example, if the probabilistic sensitivity analysis distributions randomly generate a 'favourable' iteration, (i.e. where the treatment is more effective than the comparator), then this is likely to have two effects. Firstly, the patient will gain QALYs through improved quality of life and, to a much lesser extent, through increased survival. Secondly, the patient will be more likely to avoid costly complications such as blindness and, as such, will see their incremental cost reduced. Similarly, a 'less favourable' iteration will see reduced QALYs and increased long-term costs, thus generating a very slightly downward-sloping scatter plot.

Table 80 and Figure 35 summarise the results of the probabilistic sensitivity analysis, indicating that the probability that ranibizumab is cost-effective when compared to vPDT is 100.0% at willingness-to-pay (WTP) thresholds of £20,000 and £30,000.

Figure 34 Cost-effectiveness plane for ranibizumab versus vPDT

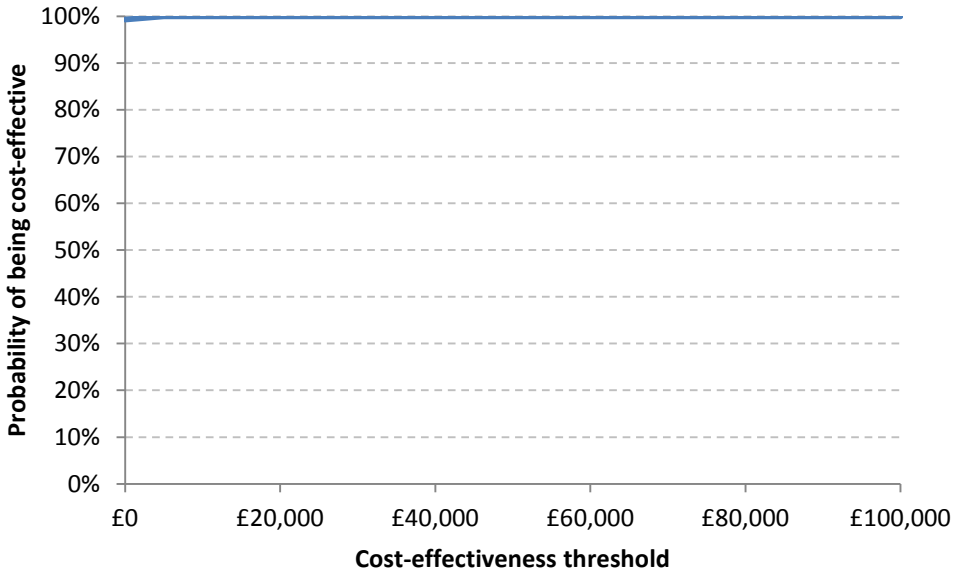


QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy

Table 80 Probability of cost-effectiveness for ranibizumab versus vPDT

	WTP = £0	WTP = £20,000	WTP = £30,000
Probability of cost-effectiveness	99.3%	100%	100%
WTP, willingness-to-pay			

Figure 35 Cost-effectiveness acceptability curve for ranibizumab versus vPDT for a WTP threshold of £20,000 per QALY



vPDT, verteporfin photodynamic therapy

7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The model is robust to changes in the methods used for calculating transition probabilities for the first year

Three different methods of calculating transition probabilities from patient-level data (see Section 7.3.2 for further details on the methodology) were explored to investigate which most accurately predicted the results from the trial data and adequately addressed the ceiling effect in the BCVA scale. As a result, the base case employed the "based on current visual acuity" method because it most accurately replicated the trial data and circumvented any ceiling effect issues. Scenarios using the two other methods are presented below in Table 81 and Table 82. These results demonstrate that the alternative methods for calculating transition probabilities have little effect on the outcomes of the model.

Table 81 Scenario analysis using transition probabilities split for top two levels only (scenario 2)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	£9,576	16.78	13.14	-£4,078	0.13	0.43	Dominant
vPDT	£13,654	16.65	12.71				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy							

Table 82 Scenario analysis using transition probabilities constant across all visual acuity levels (scenario 3)

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	£9,840	16.76	13.15	-£4,032	0.13	0.42	Dominant
vPDT	£13,872	16.63	12.73				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy							

The model is stable to changes in the sources used for calculating transition probabilities for beyond year 1

In the scenario analysis presented in Table 83, all seven sources for natural history are used to calculate long-term transition probabilities. In the base case, patients have a 0.28% chance of visual acuity deterioration per 3-month cycle; using pooled data from all studies, patients have a 0.78% chance of visual acuity deterioration per 3-month cycle. The scenario analysis demonstrates that this input has little effect on the outcomes of the model.

Table 83 Scenario analysis using transition probabilities for year 2 onwards based on pooled data from natural history studies

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	£9,710	16.78	13.09	-£3,330	0.13	0.43	Dominant
vPDT	£13,040	16.65	12.67				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy							

Ranibizumab remains dominant over vPDT when the maximum gain in utility for WSE is increased to 0.2 or 0.3

A major source of uncertainty is the relationship between utility and visual acuity in the WSE. There is little published evidence regarding this. Thus scenario analyses were undertaken for different values for the maximum utility gains for the WSE (difference between the best and worst possible health states). Table 84 and
Table 85 summarise the results of scenarios for a maximum WSE utility gain of 0.2 and 0.3 respectively (base case is 0.1). Ranibizumab is dominant compared with vPDT for both scenarios.

Table 84 Scenario analysis using a maximum gain in utilities for the WSE of 0.2

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	£9,694	16.80	12.78	-£2,751	0.11	0.71	Dominant
vPDT	£12,445	16.70	12.07				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy; WSE, worse-seeing eye							

Table 85 Scenario analysis using a maximum gain in utilities for the WSE of 0.3

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Ranibizumab	£9,694	16.80	12.38	-£2,751	0.11	0.99	Dominant
vPDT	£12,445	16.70	11.39				
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALY, quality-adjusted life year; vPDT, verteporfin photodynamic therapy; WSE, worse-seeing eye							

7.7.10 What were the main findings of each of the sensitivity analyses?

This economic assessment provides a robust comparison of ranibizumab and vPDT for the treatment of visual impairment due to CNV secondary to PM. The analysis demonstrates that ranibizumab is dominant compared with vPDT as it is associated with lower lifetime costs and an incremental QALY gain.

Extensive deterministic sensitivity analyses demonstrate that the base case results are robust, with ranibizumab remaining cost-effective compared with vPDT for almost all scenarios considered. The maximum utility gain in the WSE has the biggest impact on the results but ranibizumab is dominant over vPDT for all values considered. As expected, the unit cost of ranibizumab has a strong effect on the cost-effectiveness as does the frequency of injections and follow up visits. However, even assuming 12 injections per year in either year 1 or year 2, ranibizumab remains cost-effective compared with vPDT given 3.4 times per year and is also dominant at a unit cost for ranibizumab of up to £783. Net benefit decreases with increasing cost of monitoring but ranibizumab remains cost effective compared with vPDT for unit costs of monitoring up to £1425. Neither variations in the rate of recurrence nor the baseline prevalence of bilateral disease affect the dominance of ranibizumab over vPDT. As the mean age of the cohort increases, ranibizumab becomes less cost-effective as cost savings from avoidance of blindness are not accumulated but ranibizumab is dominant for all starting ages considered. Changes in the transition probabilities for the first year of treatment or for natural progression have negligible impact and the model is relatively insensitive to changes in the cost of blindness.

Scenario analyses further demonstrate that the model is robust to changes in the methods for calculating transition probabilities for the first year and for the sources for natural history used to calculate transition probabilities beyond the first year. Increasing the maximum gain in utilities for the WSE increases the QALYs gained with ranibizumab compared with vPDT and for all values considered ranibizumab is dominant.

PSA, undertaken to obtain an overall measure of uncertainty within the model, demonstrated that ranibizumab has a 100% probability of being cost-effective compared with vPDT at WTP thresholds of both £20,000 and £30,000 per QALY.

Ranibizumab thus represents a clinically important improvement in the management of CNV secondary to PM and an efficient use of NHS resources compared with vPDT, providing a cost saving of £2751 and a QALY gain of 0.43 over the patient's lifetime.

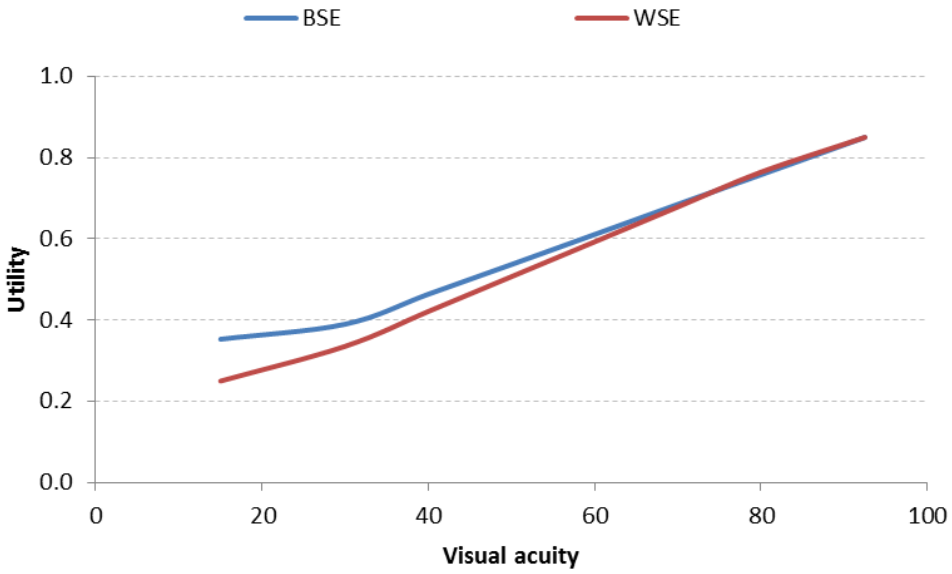
7.7.11 What are the key drivers of the cost-effectiveness results?

The unit costs for ranibizumab and vPDT and the treatment frequency for both year 1 and year 2 are both key drivers of the model. The majority of costs in the model occur in the treatment period (the first 2 years of the model) and so the unit costs and treatment frequency have a large impact on total costs. Recurrence costs also account for a large proportion of the total costs as these are applied over the model time horizon, so an increase in unit costs for

ranibizumab and vPDT and treatment frequency impacts on the cost of recurrence as well initial treatment costs.

QALYs in the model are driven by the visual acuity-utility relationship for the BSE and the maximum utility gain in the WSE, and also by the probability that the study eye is the BSE. The latter has less of an impact on cost-effectiveness, while the maximum utility gain in the WSE has one of the biggest impacts on the model. There is much uncertainty in this parameter as there is little published evidence in utility relating to visual acuity in the WSE. In the base case, the utility for the WSE was conservatively assumed to have a maximum QALY gain of 0.1, resulting in the WSE curve having a greater utility value than the BSE curve. For utility values of 0.5 and above (see Figure 36), the WSE actually has worse utility values than the BSE, which results in a counterintuitive scenario. This has been shown to be disadvantageous to vPDT, which has a greater proportion of patients whose study eye is their WSE.

Figure 36 Utility slopes/values for BSE and WSE for a maximum utility gain in the WSE of 0.6



BSE, better seeing eye; WSE, worse seeing eye

7.8 Validation

7.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The economic model has been validated by an external expert health economist at Oxford University, who undertook extensive analyses to assess the model for internal and external

validity. The review report is available upon request, along with a commentary to justify any areas where the reviewer's comments were not addressed (for example, due to a lack of suitable data). Furthermore, the model was validated by two consultant ophthalmologists – a presentation of the meeting discussions is provided in Appendix 16, section 11.3.

7.9 Subgroup analysis

For many technologies, the capacity to benefit from treatment will differ for patients with differing characteristics. This should be explored as part of the reference-case analysis by providing separate estimates of clinical and cost effectiveness for each relevant subgroup of patients.

This section should be read in conjunction with NICE's 'Guide to the methods of technology appraisal', section 5.10.

Types of subgroups that are not considered relevant are those based solely on the following factors.

- Individual utilities for health states and patient preference.
- Subgroups based solely on differential treatment costs for individuals according to their social characteristics.
- Subgroups specified in relation to the costs of providing treatment in different geographical locations within the UK (for example, when the costs of facilities available for providing the technology vary according to location).

7.9.1 Please specify whether analysis of subgroups was undertaken and how these subgroups were identified. Were they identified on the basis of an a priori expectation of differential clinical or cost effectiveness because of known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 6.3.7.

No clinically relevant subgroups were identified.

7.9.2 Please clearly define the characteristics of patients in the subgroup.

Not applicable.

7.9.3 Please describe how the statistical analysis was undertaken.

Not applicable.

7.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 7.7.6 (Base-case analysis).

Not applicable.

7.9.5 Were any obvious subgroups not considered? If so, which ones, and why were they not considered? Please refer to the subgroups identified in the decision problem in section 5.

Not applicable.

7.10 Interpretation of economic evidence

7.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Not applicable. The literature search for cost-effectiveness studies did not identify analyses suitable for comparison with the de novo analysis.

7.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 5?

Yes, the model is applicable to all groups of patients who could potentially use the technology.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

The model has a number of strengths. Firstly the economic model has been built to be as flexible as possible in order to assess multiple different scenarios and sensitivity analyses, based on various inputs and assumptions. This reflects the fact that, as is the case with the majority of diseases, there is some debate regarding the factors that should be accounted for within an assessment of the treatment pathway, and there are likely to be minor differences of opinion as to what assumptions should be made in the base case analysis. Results of the different scenarios and sensitivity analyses demonstrate that the model is robust and ranibizumab remains cost-effective compared with vPDT in all but the most extreme scenarios tested.

Secondly, the baseline characteristics of patients entering the model and the transitions between health states for the first year for ranibizumab were based on clinical trial data from the 12-month Novartis phase III study. This study involved patients who are likely to be representative of patients in England and Wales who would be eligible to receive ranibizumab for this indication and treatment was given according to the anticipated posology for ranibizumab and the approved posology for vPDT. Patient-level data from the phase III study were used to calculate transition probabilities for the first year of treatment with ranibizumab and for the first 3 months for vPDT. Transition probabilities for months 4−12 for vPDT were calculated from patient-level data from the VIP trial, another large study in patients representative of those who would be eligible to receive treatment in England and Wales. These two studies provide reliable evidence for the efficacy of the two treatments.

Thirdly, the model uses a dynamic approach to model the proportion of patients who are treated in their BSE. Previous ranibizumab models using BCVA health states have maintained a constant proportion of patients whose treated eye is their BSE over the period of the model. The current model is dynamic in that, although the proportion of patients whose treated eye is their BSE is fixed within a health state (and matched at baseline), as patients transition across health states, the overall proportion whose treated eye is their BSE can change over time in the model. Thus, if treatment improves the visual acuity of the treated eye to such an extent that it exceeds the BCVA of the fellow eye, the treated eye becomes the

BSE. This allows more accurate estimations of utility for the patient, rather than just the eye, reflecting the relative gain from binocular vision.

Fourthly, in addition to considering initial treatment for CNV in the study eye, the model also accounts for bilateral disease and recurrences. The latter in particular is found to account for a significant proportion of costs over a patient's life time. The model also includes costs for managing AEs relating to treatment, although these were found to be minimal for both treatments. The model thus provides an accurate real-world assessment of the costs and health outcomes of treatment in a UK setting. Furthermore, the model was validated by UK-based ophthalmologists.

Fifthly, costs included in the model are largely based on NHS costs. Unit costs for treatment, administration and monitoring were taken from NHS sources and the frequency of treatment is largely based on data from the Novartis phase III study for ranibizumab and the VIP trial for vPDT. Costs of blindness are included in the model, based a recent review of resource use and unit costs drawn largely from PSSRU sources.

Limitations exist within the model, largely due to scarce clinical trial data supporting some of the modelling assumptions. Firstly, head-to-head data (from the Novartis phase III study) were available for ranibizumab and vPDT only for the first 3 months of the model as after 3 months, due to ethics considerations, patients in the vPDT arm were able to receive ranibizumab. As a result, for months 4−12 a naïve comparison using VIP data for vPDT was employed. Ideally, the model would have been populated with a randomised, double blinded, head-to-head study for the entire first year but in the absence of such data the naïve comparison was considered the best available option.

Secondly, there remains some uncertainty over the long-term impact of treatment with ranibizumab or vPDT. It was therefore assumed that after the first year of the model, the rates of decline in BCVA would be the same for both treatment groups and this is modelled based on data from a published study which followed 47 eyes that received no treatment for a mean duration of 86 months.[22] This was considered a conservative assumption by the two UK consultant ophthalmologists who reviewed the model and stated that they anticipated the rate of decline in visual acuity after vPDT would be faster than after ranibizumab. The model makes the assumption that the benefits of treatment are maintained beyond the 2-year treatment period; there are few data to support any claims otherwise. This was investigated in sensitivity analyses using a range of transition probabilities for natural history which observed negligible impact of natural progression on the model.

Thirdly, the relationship between utility and BCVA in the WSE is a major source of uncertainty. Utility data were not obtained directly from the Novartis phase III or VIP studies as they did not employ appropriate assessments. Instead utility estimates for the BSE were obtained from a published study which had simulated visual impairment associated with AMD using specially designed contact lenses.[56] BCVA was defined for the BSE and the 'health states' were valued by a representative sample of the UK population. (These utilities have been used in the recent 2013 NICE resubmission of ranibizumab for RVO.[53]) However, there are no published studies that can be used to estimate utilities in the WSE. Utilities for the WSE were therefore assumed to be proportional but higher than utilities for patients treated in the BSE. In the base case, there was a 0.1 maximum difference in utility values for the WSE between the best and worst possible health states. This assumption was based on the 2013 NICE recommendations issued for ranibizumab for the treatment of RVO.[61] Sensitivity analyses indicate that utility in the WSE is a key driver of the model, so future analyses would benefit from more accurate assessments of utilities for the WSE as well as data to allow simultaneous modelling of both eyes. However, for all scenarios considered in this model regarding the utilities for the BSE and WSE, ranibizumab is cost-effective compared with vPDT.

Furthermore, utilities based only on BCVA may not fully capture the impact of vision loss. Impaired contrast sensitivity and loss of visual field are also important factors in determining visual function. For patients with monocular vision loss, these factors may be especially important as aspects of visual functioning such as depth perception and reading speed may impact on utility, but are not captured when utility is mapped solely to visual acuity. Thus this model may underestimate the full benefits of treatment with ranibizumab.

In conclusion, ranibizumab directly addresses the urgent need for an effective treatment for visual impairment due to CNV secondary to PM, a leading cause of blindness. Ranibizumab has been shown to significantly improve BCVA compared with vPDT, the only treatment currently licensed for this condition and provides clinically meaningful improvements in BCVA and HRQoL that are sustained with as needed treatment according to disease activity. Economic modelling has demonstrated that ranibizumab is dominant compared with vPDT under extensive sensitivity analyses. These results are highly relevant to the UK as the patient population considered in the model is representative of patients likely to be eligible for treatment in England and Wales. The comparator, vPDT, is the only available licensed treatment for this indication, and costs are generally drawn from relevant NHS and PSSRU sources. Ranibizumab thus represents a clinically important improvement in the management of CNV secondary to PM and an efficient use of NHS resources in England and Wales compared with vPDT, providing a cost saving of £2751 and a QALY gain of 0.43 over the patient's lifetime.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

One of the limitations of the model is the lack of data on utilities in patients based on their WSE. Ideally, it would be useful to be able to accurately model the patients' BSEs and WSEs simultaneously, without making assumptions about visual acuity in the fellow eye as was the case with the model in this evaluation. A patient-level simulation would allow the modelling of each eye, and account for the relationship of visual acuity between the two eyes. Such a model would require data on the natural progression of visual acuity in an unaffected eye as well as detailed data on the complex relationship between visual acuity in each eye. Data for visual acuity in the fellow eye were collected in the Novartis phase III trial, albeit at less frequent intervals than for the study eye, however currently the evidence for the relationship between the two eyes is sparse. Therefore this approach was not possible in this analysis, but could be considered in the future when appropriate data are available.

Section C – Implementation

8 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will allow the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers.

8.1 How many patients are eligible for treatment in England and Wales? Present results for the full marketing authorisation/CE marking and for any subgroups considered. Also present results for the subsequent 5 years.

Epidemiological data were taken from published sources, where available. The total population reflected the Novartis phase III population, from the Office for National Statistics for England and Wales.

Table 86 Epidemiological inputs

Total population (over 40 years of age)	30,647,713[141]
Prevalence of PM in population	1.20%[24]
Incidence of CNV in patients with PM	0.98%[66]
Patients eligible for pharmacotherapy	81.00%[16]
Treatment rate	80.00%
Prevalence of bilateral disease	5.50%[66]
Office for National Statistics;[141] Vongphanit et al., 2002;[24] Ohno-Matsui et al., 2003;[66] Hampton et al., 1983[16] CNV, choroid neovascularisation; PM, pathological myopia	

Table 87 Mean diagnosis rate over 5-year time horizon

	Year 1	Year 2	Year 3	Year 4	Year 5
Mean diagnosis rate	83%	84%	85%	86%	86%

The inputs in Table 86 and Table 87 were used to calculate the total number of patients eligible for treatment each year of the 5-year time horizon (Table 88).

Table 88 Patients eligible for treatment

	Year 1	Year 2	Year 3	Year 4	Year 5
Patients starting treatment	2045	2070	2094	2119	2119

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

It was assumed that all patients in the baseline cohort (current forecast of market share) were treated with vPDT. In the predicted forecast of market share, uptake of ranibizumab was assumed to come proportionally from the patients treated with vPDT (Table 89). No other comparators were considered to be relevant.

Table 89 Uptake rate of ranibizumab

Year 1	Year 2	Year 3	Year 4	Year 5
7%	16%	26%	32%	32%

8.3 What assumption(s) were made about market share (when relevant)?

The indication for treatment of myopic CNV was assumed to be unaffected by the availability of ranibizumab treatment, ie all patients treated with ranibizumab would be treated with pre-specified market share if ranibizumab was not an option.

8.4 In addition to technology costs, please consider other significant costs associated with treatment that may be of interest to commissioners (for example, procedure codes and programme budget planning).

The analysis of budget impact also considers costs associated with the administration of the technologies and monitoring of the patient during the treatment period. The costs of treating bilateral disease and recurrence after the treatment period are also considered in the analysis.

8.5 What unit costs were assumed? How were these calculated? If unit costs used in health economic modelling were not based on national reference costs or the PbR tariff, which HRGs reflected activity?

A healthcare payer perspective (NHS) on costs was adopted and as such national reference costs were deemed appropriate for use in the analysis. The model takes a cumulative cohort approach based on costs directly calculated from the cost-effectiveness model.

The estimate of budget impact includes costs relating to bilateral disease and recurrence, and uses the same assumptions as the cost-effectiveness analysis.

In addition to the drug costs, the unit costs that were included in the analysis relate to monitoring of the patient and administration of the treatment (Table 90). Clinical expert opinion was elicited in determining the resources for each item.

Table 90 Unit costs for monitoring and administration

Resource	Cost	Visit	Reference
OCT	£51.27	Monitoring, administration (ranibizumab and vPDT)	NHS reference costs 2011–2012 Estimated to be the same as an outpatient procedure coded as ultrasound scan less than 20 minutes (RA23Z)
Ophthalmologist	£123.62	Monitoring, vPDT administration	NHS reference costs 2011–2012 Unit cost for a consultant-led multi-professional face-to-face follow-up visit for ophthalmology
Injection visit cost	£117.26	Ranibizumab administration	NHS reference costs 2011–2012 BZ23Z: Outpatient procedures (office based) = £117 (minor vitreous retinal procedures)

8.6 Were there any estimates of resource savings? If so, what were they?

The budget impact model does not include costs relating to treating blindness. Any treatment that improves visual acuity will reduce the number of patients becoming legally blind in the long term, and will avert additional resources associated with caring for patients with blindness. In the cost-effectiveness model it has been demonstrated that ranibizumab is associated with reductions in the cost of blindness that occur steadily over the time horizon of the model.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

Total costs for the two scenarios over the 5-year time horizon are presented in Table 91. It is estimated that the introduction of ranibizumab to the market in England and Wales will results in cost savings of approximately £227,354 over 5 years.

Table 91 Annual budget impact

	World without ranibizumab					
Year	Drugs	Admin	Monitoring	Recurrence	Bilateral	Total
1	£5,895,707	£1,213,070	£1,427,141	£0	£1,280,388	£9,816,305
2	£8,899,554	£1,831,126	£2,864,195	£0	£2,039,231	£15,634,106
3	£9,005,922	£1,853,011	£2,898,497	£506,769	£2,063,614	£16,327,813
4	£9,112,290	£1,874,897	£2,932,798	£1,016,653	£2,087,998	£17,024,635
5	£9,147,625	£1,882,167	£2,949,905	£1,529,338	£2,096,954	£17,605,989
Total	£42,061,097	£8,654,271	£13,072,535	£3,052,760	£9,568,185	**£76,408,849**
	World with ranibizumab					
Year	Drugs	Admin	Monitoring	Recurrence	Bilateral	Total
1	£5,853,967	£1,212,392	£1,539,538	£0	£1,290,885	£9,896,781
2	£8,703,166	£1,811,265	£3,124,216	£0	£2,045,797	£15,684,444
3	£8,616,212	£1,808,118	£3,326,074	£510,936	£2,062,561	£16,323,900
4	£8,534,836	£1,802,106	£3,465,255	£1,030,441	£2,070,330	£16,902,967
5	£8,477,038	£1,792,312	£3,482,379	£1,558,914	£2,062,759	£17,373,403
Total	£40,185,219	£8,426,193	£14,937,462	£3,100,290	£9,532,331	**£76,181,495**
	Incremental costs					
Year	Drugs	Admin	Monitoring	Recurrence	Bilateral	Total
1	-£41,740	-£678	£112,397	£0	£10,497	£80,476
2	-£196,388	-£19,860	£260,021	£0	£6566	£50,338
3	-£389,710	-£44,893	£427,577	£4167	-£1054	-£3914
4	-£577,454	-£72,791	£532,457	£13,787	-£17,668	-£121,668
5	-£670,586	-£89,856	£532,475	£29,576	-£34,195	-£232,586
Total	-£1,875,878	-£228,078	£1,864,927	£47,530	-£35,854	**-£227,354**

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

Generally it would be expected that patients with worse visual acuity score would have higher associated resource use and costs (other than for support of blindness), such as to account for the increased risk of accidents associated with poor vision, and general comorbidities that are associated with limited mobility. However it is not possible to include this in the analysis as there are no published data on the relationship between visual acuity and additional background costs. Ranibizumab is associated with improving visual acuity so it would be expected that these costs would be lower than for vPDT, and the estimated value of cost-effectiveness may be an underestimate.

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10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts.

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

10.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The systematic literature review was performed in the following databases:

- MEDLINE and MEDLINE In-Process
- EMBASE
- Cumulative Index to Nursing and Allied Health Literature (CINAHL)
- Science Citation Index (SCI)
- Latin American and Caribbean Health Sciences (LILACS)
- Cochrane Database of Systematic Reviews (CDSR)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- DARE Database of Abstracts of Reviews of Effects (DARE)
- Health Technology Assessment Database (HTA)
- NHS Economic Evaluation Database (NHS EED)
- EconLit
- Health Economic Evaluations Database (HEED)
- Research Papers in Economics (RePEc)
- CEA Registry

Information on ongoing or recently completed trials, unpublished research, and research reported in the grey literature were identified by searching trials registers and conference proceedings (from the last three years) from specific organisations, as follows:

- ClinicalTrials.gov
- International Clinical Trials Registry Platform (ICTRP)
- EU Clinical Trials Register

- Conference Proceedings Citation Index – Science (CPCI-S)
- Association of Research in Vision and Ophthalmology (ARVO) annual meeting
- European Association for Vision and Eye Research (EVER) congress
- Royal College of Ophthalmologists (RCO) congress
- American Academy of Ophthalmology (AAO) annual meeting
- World Ophthalmology Congress (WOC)
- Retina International World Congress
- EURETINA Congress (European Society of Retina Specialists)
- APAO Congresses
- The Macula Society annual meeting
- Eye Complications Study Group of the EASD (EASDec)
- ISPOE annual meeting
- HTAi annual meetings
- National Institute for Health and Clinical Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Food and Drug Administration (FDA)
- European Medicines Agency (EMA)
- UK Department of Health

10.2.2 The date on which the search was conducted.

Database searches were conducted on 16 March 2012 (MEDLINE and MEDLINE In-Process, EMBASE, CINAHL and SCI), 19 March 2012 (LILACS, CDSR, DARE and CENTRAL), 20 March 2012 (CPCI-S), and 4 April 2012 (NHS EED, HTA, EconLit, HEED, CEA Registry and RePEc).

Searches of conference proceedings and ongoing trials were conducted on 19 March 2012 (ARVO, Clinicaltrials.gov, ICTRP and EU Clinical Trials Register), 20 March 2012 (EVER and RCO), 23 March 2012 (AAO, WOC, Retina International World Congress, EURETINA, APAO, Macula Society, EASDec, ISPOR, HTAi, NICE, SMC, PBAC, FDA, EMA and UK Department of Health).

10.2.3 The date span of the search.

The date spans of the various database searches are listed below:

- MEDLINE and MEDLINE In-Process: 1946–2012/Mar week 1
- EMBASE: 1974–2012/week 10
- Cumulative Index to Nursing and Allied Health Literature (CINAHL): 1982–09 March 2012
- Science Citation Index (SCI): 1889–14 Mar 2012
- Latin American and Caribbean Health Sciences (LILACS): 1982–2012 16 Feb
- Cochrane Database of Systematic Reviews (CDSR): 2012:Issue 3/1

- Cochrane Central Register of Controlled Trials (CENTRAL): 2012:Issue 3/1
- DARE Database of Abstracts of Reviews of Effects (DARE): 2012:Issue 3/1
- Health Technology Assessment Database (HTA): 2012:Issue 3/1
- NHS Economic Evaluation Database (NHS EED): 2012:Issue 3/1
- EconLit: 1961–2012/Mar
- Health Economic Evaluations Database (HEED): 2012/Mar
- Research Papers in Economics (RePEc): 2012/Mar
- CEA Registry: 2012/Mar

Congress abstracts from 2009 onwards were searched. No date limits were applied to searches of clinical trial registries or other sources of grey literature.

10.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE and MEDLINE In-Process (OvidSP)

1 Choroidal Neovascularization/ (3411)
2 ((choroid$ adj3 neovascular$) or CNV or mCNV).ti,ab. (5802)
3 ((subretinal or sub-retinal) adj3 choroid$).ti,ab. (194)
4 or/1-3 (6674)
5 exp Myopia/ (12464)
6 myopi$.ti,ab. (12217)
7 5 or 6 (15835)
8 4 and 7 (437)
9 animals/ not (animals/ and humans/) (3590935)
10 (editorial or news).pt. (427343)
11 8 not (9 or 10) (426)

EMBASE (OvidSP)

1 subretinal neovascularization/ (5433)
2 ((choroid$ adj3 neovascular$) or CNV or mCNV).ti,ab. (7408)
3 ((subretinal or sub-retinal) adj3 choroid$).ti,ab. (234)
4 or/1-3 (9194)
5 exp myopia/ (15544)
6 myopi$.ti,ab. (14689)
7 5 or 6 (19349)
8 4 and 7 (610)
9 animal/ (1680533)

10 nonhuman/ (3806919)

11 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. (4787614)

12 or/9-11 (6405137)

13 exp Human/ or Human Experiment/ (13076254)

14 12 not (12 and 13) (5059114)

15 editorial.pt. (396665)

16 8 not (14 or 15) (595)

CINAHL (EBSCO)

1 TI (choroid* N3 neovascular* or CNV or mCNV) or AB (choroid* N3 neovascular* or CNV or mCNV) (142)

2 TI (subretinal N3 choroid* or sub-retinal N3 choroid*) or AB (subretinal N3 choroid* or sub-retinal N3 choroid*) (2)

3 1 or 2 (144)

4 (MH "Myopia") (432)

5 TI (myopi*) or AB (myopi*) (344)6 4 or 5 (582)7 3 AND 6 (14)

SCI (Web of Science)

Databases=SCI-EXPANDED Timespan=All Years

Lemmatization=Off

1 TS=((choroid* NEAR/3 neovascular*) or CNV or mCNV) (8,428)

2 TS=((subretinal or sub-retinal) NEAR/3 choroid*) (281)

3 #2 OR #1 (8,527)

4 TS=myopi* (14,274)

5 #3 AND #4 (517)

6 TS=(rat or rats or mouse or mice or murine or hamster or hamsters or animal or animals or dogs or dog or pig or pigs or cats or bovine or cow or sheep or ovine or porcine or monkey) (3,673,080)

7 #5 NOT #6 (495)

CPCI-S (Web of Science)

Databases=CPCI-S Timespan=All Years

Lemmatization=Off

1 TS=((choroid* NEAR/3 neovascular*) or CNV or mCNV) (1,147)

2 TS=((subretinal or sub-retinal) NEAR/3 choroid*) (38)

3 #2 OR #1 (1,160)

4 TS=myopi* (1,921)

5 #3 AND #4 (67)

6 TS=(rat or rats or mouse or mice or murine or hamster or hamsters or animal or animals or dogs or dog or pig or pigs or cats or bovine or cow or sheep or ovine or porcine or monkey) (284,434)

7 #5 not #6 (67)

LILACS (BIREME)

(MH:"choroidal neovascularization" OR "choroidal neovascularization" OR "neovascularization choroidal" OR "coroidal neovascularizacion" OR "neovascularizacion coroidal" OR "neovascularizacao de coroide" OR CNV OR mCNV) AND (MH:"myopia" OR myop$ or miopí$)

CDSR, DARE and CENTRAL: Cochrane Library (Wiley interscience)

1 MeSH descriptor Choroidal Neovascularization explode all trees (253)

2 (choroid* NEAR/3 neovascular*) or CNV or mCNV:ti,ab,kw (796)

3 (subretinal or sub-retinal) NEAR/3 choroid*:ti,ab,kw (0)

4 (#1 OR #2 OR #3) (796)

5 MeSH descriptor Myopia explode all trees (571)

6 (myopi*):ti,ab,kw (1220)

7 (#5 OR #6) (1220)

8 (#4 AND #7) (35)

NHS EED and HTA: Cochrane Library (Wiley interscience)

1 MeSH descriptor Myopia explode all trees (571)

2 (myopi*):ti,ab,kw (1220)

3 (#1 OR #2) (1220)

EconLit (OvidSP)

(pathologic$ adj3 myopi$).ti,ab (0)

HEED (Wiley interscience)

AX=myopia or myopic or myopically (8)

CEA Registry (www.cearegistry.org)

myopia

RePEc (repec.org/)

pathologic + myopia

pathological + myopia

Association of Research in Vision and Ophthalmology annual meeting

2010 and 2011 meetings:

Boolean Search:

"choroidal neovascularization" [Abstract Body]

AND

myopi*

2009 meeting:

Available via IOVS journal:

Year: 2009

Abstract | Title : choroidal neovascularisation [phrase]

Text |Abstract | Title: myopi* [all]

European Association for Vision and Eye Research congress (www.ever.be/)

Abstract books in pdf:

'choroidal neovascularization'

Royal College of Ophthalmologists congress (www.rcophth.ac.uk/)

Final Programme and Abstract book available in pdf for 2011 congress (not available online for 2010 or 2009):

'choroidal neovascularisation'

American Academy of Ophthalmology annual meeting (www.aao.org/)

'choroidal neovascularization'

World Ophthalmology Congress (WOC) (www.woc2012.org/)

'choroidal neovascularization'

Retina International World Congress (http://www.retina-international.org/)

No abstracts or final programme available online.

EURETINA Congress (European Society of Retina Specialists) congress (www.euretina.org/)

2009 meeting:

'choroidal neovascularization'

2010 and 2011 meetings:

No abstracts or final programme available online for the 10th and 11th congresses.

APAO Congresses (http://www.apaophth.org/)

2011 meeting:

'choroidal neovascularization'

2009 and 2010 meetings:

No abstracts or final programme available online for the 24th and 25th congresses.

The Macula Society annual meeting (http://www.maculasociety.org/)
'choroidal neovascularization'

Eye Complications Study Group of the EASD (EASDec) (www.easdec.org)
'choroidal neovascularization'

ISPOR annual meeting (www.ispor.org/)
'choroidal neovascularization'

HTAi annual meetings (www.htai.org/)
'choroidal neovascularization'

ClinicalTrials.gov (ClinicalTrials.gov)
(choroidal neovascularisation OR CNV OR mCNV) AND (myopia OR myopic)
(choroidal neovascularisation OR CNV OR mCNV) AND (myopia OR myopic) AND (cost* OR economic*)

International Clinical Trials Registry Platform (ICTRP)
(ICTRP/http://apps.who.int/trialsearch/). Searched 19 March 2012.
choroid* AND myopi*

EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)
choroid* AND myopi*
choroid* AND myopi* AND cost*
choroid* AND myopi* AND economic*

National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk/)
choroidal neovascularization
choroidal neovascularisation

Scottish Medicines Consortium (SMC) (www.scottishmedicines.org.uk/)
choroidal neovascularization
choroidal neovascularisation

Pharmaceutical Benefits Advisory Committee (PBAC) (www.health.gov.au)
choroidal neovascularization
choroidal neovascularisation

Food and Drug Administration (FDA) (www.fda.gov/)
choroidal neovascularization
choroidal neovascularisation

European Medicines Agency (EMA) (www.ema.europa.eu/)
choroidal neovascularization
choroidal neovascularisation

UK Department of Health (www.dh.gov.uk/)
choroidal neovascularization
choroidal neovascularisation

10.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No additional searches were undertaken.

10.2.6 The inclusion and exclusion criteria.

Participants

Eligible participants were patients of any age undergoing treatment for myopic CNV. Participants could present with concomitant ocular disease such as cataract or diabetic retinopathy.

Patients with CNV secondary to causes other than pathologic myopia (e.g. age-related macular degeneration) were excluded from the review, although studies reporting results for mixed populations were eligible for inclusion if the outcome data for patients with myopic CNV and CNV due to other causes were sufficiently disaggregated.

Interventions

Eligible interventions were any types of treatment for CNV. These included, but were not restricted to, thermal laser photocoagulation therapy, surgery, PDT and anti-VEGF therapy (e.g. bevacizumab and ranibizumab).

Any treatments that are only used to correct vision (e.g. contact lenses, glasses, keratectomy) were excluded from the review.

Comparators

The key comparator was standard care defined as verteporfin PDT. Any other treatments used in RCTs identified in the literature were also eligible for inclusion.

Outcomes

For the review of clinical efficacy, studies that evaluated any of the following outcomes were eligible for inclusion:

- Visual acuity (measured using the ETDRS or log MAR charts)
- Other measures of visual acuity such as blindness and lack of response
- Structural changes (e.g. foveal thickness, central retinal thickness)
- Health-related quality of life (HRQoL)

Study type

RCTs of any duration were eligible for inclusion in this systematic review. In studies where a crossover design was used, only data from the first intervention phase after randomisation and before cross-over was eligible for inclusion. Studies published as abstracts or conference presentations were included in the primary analysis of clinical effectiveness if adequate data were provided and if no associated full published papers were available.

For adverse effects, eligible study designs were RCTs, prospective non-randomised studies (e.g. comparative studies and single-arm observational studies), open-label extension studies of treatments identified in the RCT literature, and case series that evaluated at least 25 patients for six months or more. Studies published as abstracts or conference presentations were excluded from the evaluation of adverse effects.

There were no restrictions on country or language. Unpublished data were also eligible for inclusion.

Retrospective studies and analyses were not eligible for inclusion because of the potential bias arising from retrospective approaches where the data were not necessarily collected for the purpose of the study or by the investigators of the retrospective study. Dosing studies were also excluded from the review.

10.2.7 The data abstraction strategy.

One reviewer screened records of potential relevance to the planned review, based on the abstracts alone, to remove duplicates and other studies that were obvious false positives. The selected records were then screened by two independent researchers using the inclusion criteria for participants, interventions, comparators (where applicable), outcomes and study design: full papers were obtained and assessed for relevance by two reviewers independently.

One reviewer extracted the data from the full papers of each of the included studies using a standardised template/form into an Excel spreadsheet. A second reviewer checked the data extraction. In the absence of full paper copies, data were extracted from the abstracts alone. Any discrepancies were resolved through discussion or by consulting a third reviewer. The various outcomes extracted are summarised in Table 92.

If available, data were collected for both the best seeing eye and the worst seeing eye.

Table 92 Outcomes extracted from included studies

Subheading	Information required
Study details	Trial number or acronym Author and year Full citation Country Single or multi centre
Methods/Interventions	Study design Phase of trial Study objective Inclusion/exclusion criteria Primary and secondary outcomes of the study Numbers randomised/enrolled Intervention group description (dose, regimen, duration) Comparator group description Trial duration Number of treatments Any cross-over Withdrawals and losses to follow-up Study conclusions
Participants	Number of patients (eyes) Age Gender Ethnic background Symptom duration Refractive error Lens status CNV features (size, thickness, stage, location) Axial length Visual acuity Central foveal or retinal thickness Prior treatment Concomitant ocular disease.
Clinical efficacy outcomes[a]	Visual acuity (BCVA, Snellen, ETDRS, logMAR) Categorised changes in visual acuity Contrast sensitivity Blindness Lack of response Central foveal or retinal thickness CNV or lesion size CNV leakage or progression HRQoL
Adverse effects	Non-specific ocular/systemic complications Non-specific treatment complications Myopic foveoschisis Cataracts Intraocular pressure

Subheading	Information required
	Retinal detachment Retinal tears Haemorrhage Retinal vascular occlusion Visual disturbances and loss of vision Endophthalmitis Occluded choroidal vessels Post-laser scar enlargement New lacquer cracks Injection-site reaction Drug-related inflammation and pain Inadvertent photocoagulation (extra-foveal) Allergic reactions Photosensitivity Other adverse effects or complications Deaths
Study quality	See Section 2.4
BCVA, best corrected visual acuity; CNV, choroidal neovascularisation; ETDRS, Early Treatment Diabetic Retinopathy Study; HRQoL, health related quality of life; logMAR, logarithm of the minimal angle of resolution [a]Clinical efficacy outcomes extracted from RCTs only	

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

10.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table 93 Quality assessment of included RCTs

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Novartis phase III study[32]		
Was randomisation carried out appropriately?	The authors stated that "A randomisation list was produced by or under the responsibility of Novartis DSM using a validated system that automates the random assignment of treatment arms to randomisation numbers in the specified ratio."	Yes
Was the concealment of treatment allocation adequate?	The authors stated that "The randomisation numbers were generated using the following procedure to ensure that treatment assignment was unbiased and concealed from patients and investigator staff"	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline characteristics appear to be balanced across groups.	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The authors stated that "To fulfil the masking, there were at least two investigators involved into the study: the masked (assessing) investigator who performed all assessments and captured data in the eCRFs and an unmasked (treating) investigator who administered the randomised study treatment."	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Only one of the three groups had patients drop out, but there were very few; overall no imbalances.	No

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Secondary efficacy endpoints such parameters based on FA as assessed by the Central Reading Centre (e.g. CNV leakage, area of lesion, area of CNV) do not appear to have been reported	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Authors stated that "Following the intent to treat principle, patients were analyzed according to the treatment assigned. No data were excluded from the FAS analyses because of protocol deviations." "For the full analysis set, the analysis followed a modified LOCF approach."	Yes Yes
Iacono 2012[46]		
Was randomisation carried out appropriately?	The authors stated that "patient randomisation to either IVR or IVB was performed by means of sequentially numbered envelopes according to a computer-generated code list"	Yes
Was the concealment of treatment allocation adequate?	The authors stated that "patient randomisation to either IVR or IVB was performed by means of sequentially numbered envelopes according to a computer-generated code list *and stored by an investigator, unaware of the purpose of the study*"	Yes

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There was no statistically significant difference between the groups in age, gender, refractive error, mean BCVA, mean CMT, mean CNV areas, and lens status (p=0.11 to p=0.99). Although not stated by the authors, the groups appear comparable in terms of mean age, gender distribution, mean BCVA, mean refractive error (and range), lens status and anatomical measures.	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Assessors and treating investigators were blinded to treatment; study was described as double-blind but not clearly stated whether or not patient were blind	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No patients dropped out (not counting patients who discontinued prior to administration of first injection	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes appear to have been reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The authors stated that "after randomisation and before the administration of the first injection, four patients in the IVR group and three patients in the IVB group refused to participate in the study because they were unable to follow the strict study protocol. Finally, 23 subjects in the IVR group and 25 subjects in the IVB group were considered for the analysis"	Yes Not clear
Gharbiya 2010[47]		
Was randomisation carried out appropriately?	No mention of randomisation method	Not clear

Study question	How is the question addressed in the study?	Grade (yes/no/not clear/NA)
Was the concealment of treatment allocation adequate?	Not reported	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The authors stated that there was no significant difference in major baseline characteristics (p=0.44 to p=0.69), but did not comment on how comparable the patients groups were.	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	The authors stated that "BCVA was measured by a single orthoptist, who was masked to the study. All FA and OCT evaluations were interpreted by 2 retinal specialists in an unmasked fashion."	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No patients dropped out	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	All outcomes appear to have been reported	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The authors did not specifically report an ITT analysis.	Not clear Not clear
Novartis phase III study 12 month CSR;[32] Iacono et al., 2012;[46] Gharbiya et al., 2010[47] BCVA, best corrected visual acuity; CMT, central macular thickness; CNV, choroidal neovascularisation; eCRF, electronic Case Report Form; FA, fluorescein angiography; FAS, full analysis set; ITT, intention-to-treat; IVB, intravitreal bevacizumab; IVR, intravitreal ranibizumab; LOCF, last observation carried forward; NA, not applicable; OCT, optical coherence tomography; RCT, randomised controlled trial		

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

Head-to-head data for ranibizumab compared with vPDT were available from the Novartis phase III trial[32] and the VIP study,[25] and hence indirect comparisons were not performed.

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

Not applicable

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

The following information should be provided.

10.6.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

Non-RCT evidence was identified from the systematic searches described in section 10.2.

10.6.2 The date on which the search was conducted.

Search dates are described in detail in section 10.2.2.

10.6.3 The date span of the search.

The date spans of the searches are described in detail in section 10.2.3.

10.6.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategies are described in section 10.2.4.

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.6.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria are described in detail in section 10.2.6.

In addition to RCTs, prospective non-randomised studies (e.g. comparative studies and single-arm observational studies), open-label extension studies of treatments identified in the RCT literature, and case series that evaluated at least 25 patients for six months or more were included if they reported adverse events. Retrospective studies and analyses were excluded.

10.6.7 The data abstraction strategy.

The data abstraction strategy is described in detail in section 10.2.7.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

10.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

Table 94 Quality assessment of included non-RCT studies

Study question	How is the question addressed in the study?	Grade (yes, no, not clear, NA)
REPAIR 2011[94]		
Is the study based on a representative sample selected from a relevant population?	Insufficient detail provided	Unclear
Are the criteria for inclusion explicit?	Detailed inclusion and exclusion criteria are provided	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Insufficient detail provided	Unclear
Was follow-up long enough for important events to occur?	12-month follow-up	Yes
Were outcomes assessed using objective criteria or was blinding used?	Study was open-label and contained a mix of objective an subjective outcomes	Yes/No
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	No sub-series was compared	NA
Calvo-Gonzalez 2011[41]		
Is the study based on a representative sample selected from a relevant population?	Patients were consecutive; presumed to be from a single centre	Yes
Are the criteria for inclusion explicit?	Detailed inclusion and exclusion criteria are provided	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Insufficient detail provided	Unclear
Was follow-up long enough for important events to occur?	Mean follow-up was 15.9 months; range was 6–27 months	Yes/No[a]
Were outcomes assessed using objective criteria or was blinding used?	The authors stated that “monthly follow-up examinations consisted of BCVA and IOP determination, retinography and OCT”, and “OCT and FA were performed and the data interpreted by 2 retinal specialists in an unmasked fashion”	Yes/No
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Eyes treated previously were compared with eyes that received no treatment; insufficient detail provided regarding distribution of prognostic factors	No
Lalloum 2010[42]		
Is the study based on a representative sample selected from a relevant population?	Insufficient detail provided	Unclear
Are the criteria for inclusion explicit?	Detailed inclusion and exclusion criteria are provided	Yes
Did all individuals enter the	Insufficient detail provided	Unclear

survey at a similar point in their disease progression?		
Was follow-up long enough for important events to occur?	The median follow-up was 17 months; range was 7–29 months	Yes/No[a]
Study question	**How is the question addressed in the study?**	**Grade (yes, no, not clear, NA)**
Were outcomes assessed using objective criteria or was blinding used?	Insufficient detail provided	Unclear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	The authors stated that "Subgroup analysis was also performed between eyes with and without PDT before treatment by ranibizumab and between sex, age, initial visual acuity, and retinal thickness"	Yes
Ouhadj 2010[43]		
Is the study based on a representative sample selected from a relevant population?	Study included consecutive patients from a single centre	Yes
Are the criteria for inclusion explicit?	Insufficient detail provided	Unclear
Did all individuals enter the survey at a similar point in their disease progression?	Insufficient detail provided	Unclear
Was follow-up long enough for important events to occur?	Mean follow-up was 8 months; range 3–15 months	No
Were outcomes assessed using objective criteria or was blinding used?	Insufficient detail provided	Unclear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	No sub-series was compared	NA
Silva 2010[44]		
Is the study based on a representative sample selected from a relevant population?	Insufficient detail provided	Unclear
Are the criteria for inclusion explicit?	Detailed inclusion and exclusion criteria are provided	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Insufficient detail provided	Unclear
Was follow-up long enough for important events to occur?	Follow-up was 12 months	Yes
Were outcomes assessed using objective criteria or was blinding used?	Insufficient detail provided	Unclear
If sub-series compared, was there sufficient description of	Study compared eyes that previously underwent PDT with those that did not	Yes

the series and distribution of prognostic factors?		
Vadala 2011[45]		
Is the study based on a representative sample selected from a relevant population?	Patients were consecutively enrolled in a multicentre trial	Yes
Are the criteria for inclusion explicit?	Detailed inclusion and exclusion criteria are provided	Yes
Did all individuals enter the survey at a similar point in their disease progression?	Patients were required to have symptoms for no longer than 4 weeks (inclusion criteria)	Yes
Was follow-up long enough for important events to occur?	All patients completed a 12-month follow-up	Yes
Were outcomes assessed using objective criteria or was blinding used?	Insufficient detail provided	Unclear
If sub-series compared, was there sufficient description of the series and distribution of prognostic factors?	Study compared eyes that previously underwent PDT with those that did not; insufficient detail provided regarding distribution of prognostic factors	No
REPAIR study 12 month CSR;[94] Calvo-Gonzalez et al., 2011;[41] Lalloum et al., 2010;[42] Ouhadj et al., 2010;[43] Silva et al., 2010;[44] Vadala et al., 2011[45] BCVA, best corrected visual acuity; FA, fluorescein angiography; NA, not applicable; OCT, optical coherence tomography; PDT, photodynamic therapy; RCT, randomised controlled trial [a]Denotes that the duration of follow-up would be long enough in some patients but not in others [b]Yes/No denotes outcomes measured using objective (IOP, CRT etc.) and subjective (e.g. ETDRS charts, self-report) criteria		

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

The following information should be provided.

10.8.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

AEs data were identified from the systematic searches described in section 10.2.

10.8.2 The date on which the search was conducted.

Search dates are described in detail in section 10.2.2.

10.8.3 The date span of the search.

The date spans of the searches are described in detail in section 10.2.3.

10.8.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategies are described in section 10.2.4.

10.8.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.8.6 The inclusion and exclusion criteria.

The inclusion and exclusion criteria are described in detail in section 10.2.6.

For the review of adverse effects, the eligible outcomes included, but were not restricted to:

- Cataracts
- Intraocular pressure
- Endophthalmitis
- Iris neovascularisation
- Any vascularisation
- Retinal detachment
- Vitreous haemorrhage
- Permanent lesion to retinal epithelium
- Loss of vision
- Surgical complications

Other systemic adverse events, such as arterial thromboembolic events and stroke, were also considered eligible.

AEs were extracted from RCTs, prospective non-randomised studies (e.g. comparative studies and single-arm observational studies), open-label extension studies of treatments identified in the RCT literature, and case series that evaluated at least 25 patients for six months or more.

10.8.7 The data abstraction strategy.

The data abstraction strategy is described in detail in section 10.2.7.

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

10.9.1 Please tabulate the quality assessment of each of the non-RCTs identified.

The quality assessments of the studies included in the review of adverse events are described in sections 10.3.1 and 10.7.1.

10.10 Appendix 10: Search strategy for cost-effectiveness studies (section 7.1)

The following information should be provided.

10.10.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- EconLIT
- NHS EED.

Cost-effectiveness studies were identified from the systematic searches described in section 10.2. Separate economic search strings were used in MEDLINE and MEDLINE In-Process, as well as EMBASE.

10.10.2 The date on which the search was conducted.

Search dates are described in detail in section 10.2.2. The specific economic searches in MEDLINE, MEDLINE In-Process and EMBASE were conducted on 4 April 2012.

10.10.3 The date span of the search.

The date spans of the searches are described in detail in section 10.2.3. The specific economic searches were for the date ranges of 1946–2012/Mar week 3 in MEDLINE and MEDLINE In-Process, and 1974–2012/week 3 in EMBASE.

10.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategies are described in section 10.2.4. Specific economic searches conducted in MEDLINE, MEDLINE In-Process and EMBASE are shown below.

MEDLINE and MEDLINE In-Process

1 Myopia, Degenerative/ (357)
2 (pathologic$ adj3 myopi$).ti,ab. (292)
3 or/1-2 (542)
4 economics/ (26193)
5 exp "costs and cost analysis"/ (162116)
6 economics, dental/ (1836)
7 exp "economics, hospital"/ (17730)
8 economics, medical/ (8429)
9 economics, nursing/ (3855)
10 economics, pharmaceutical/ (2307)
11 (economic$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (354269)
12 (expenditure$ not energy).ti,ab. (14854)
13 (value adj1 money).ti,ab. (17)
14 budget$.ti,ab. (15096)
15 or/4-14 (469401)
16 ((energy or oxygen) adj cost).ti,ab. (2393)
17 (metabolic adj cost).ti,ab. (629)
18 ((energy or oxygen) adj expenditure).ti,ab. (13763)
19 or/16-18 (16150)
20 15 not 19 (465739)
21 3 and 20 (13)

EMBASE

1 degenerative myopia/ (90)
2 (pathologic$ adj3 myopi$).ti,ab. (388)
3 1 or 2 (460)
4 Health Economics/ (31457)
5 exp Economic Evaluation/ (182384)
6 exp Health Care Cost/ (174601)

7 exp PHARMACOECONOMICS/ (151721)

8 or/4-7 (420143)

9 (econom$ or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic$).ti,ab. (500766)

10 (expenditure$ not energy).ti,ab. (20150)

11 (value adj2 money).ti,ab. (1077)

12 budget$.ti,ab. (20801)

13 or/9-12 (521842)

14 8 or 13 (768182)

15 (metabolic adj cost).ti,ab. (740)

16 ((energy or oxygen) adj cost).ti,ab. (2866)

17 ((energy or oxygen) adj expenditure).ti,ab. (17174)

18 or/15-17 (20039)

19 14 not 18 (763659)

20 editorial.pt. (403756)

21 note.pt. (512055)

22 letter.pt. (780338)

23 or/20-22 (1696149)

24 19 not 23 (686575)

25 (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep).ti,ab,sh. (4589262)

26 exp animal/ (1774414)

27 Nonhuman/ (3812425)

28 or/25-27 (6409052)

29 exp human/ (13448276)

30 exp human experiment/ (299216)

31 29 or 30 (13449711)

32 28 not (28 and 31) (5051153)

33 24 not 32 (638552)

34 3 and 33 (20)

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

Table 95 Quality assessment of included cost-effectiveness studies

	Sharma & Bakal 2002	
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
Study design		
1. Was the research question stated?	Yes	"The purpose of this study is to determine the "value" (defined as the given quality improvement) received from this procedure [PDT] for the resources expended, from the perspective of the patient and the insurer."
2. Was the economic importance of the research question stated?	No	No details provided
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	"The purpose of this study is to determine the "value" (defined as the given quality improvement) received from this procedure [PDT] for the resources expended, <u>from the perspective of the patient and the insurer</u>." "It should also be noted that our model does not factor the costs of blindness into the decision, because it is not relevant from the perspective of a managed care organisation."
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	Comparison was versus no treatment, no rationale provided
5. Were the alternatives being compared clearly described?	No	Comparison was versus no treatment, no details provided
6. Was the form of economic evaluation stated?	Yes	"This study presents… cost-utility analysis"
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	No	No details provided
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	"Therapeutic efficacy data were taken from the VIP Study Report No. 1"
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	No	No details provided

10. Were details of the methods of synthesis or meta-analysis of estimates given (if based on an overview of a number of effectiveness studies)?	NA	Not applicable, based on single study
Study question	**Grade (yes/no/not clear/NA)**	**Comments**
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	"The purpose of this study is to determine the "value" (defined as the given quality improvement) received from this procedure [PDT] for the resources expended, from the perspective of the patient and the insurer."
12. Were the methods used to value health states and other benefits stated?	No	No details provided
13. Were the details of the subjects from whom valuations were obtained given?	No	No details provided
14. Were productivity changes (if included) reported separately?	No	Productivity changes were not mentioned
15. Was the relevance of productivity changes to the study question discussed?	No	Productivity changes were not mentioned
16. Were quantities of resources reported separately from their unit cost?	Yes	"The base-case assumed that the patient received 3.4 treatments" No other quantity data provided
17. Were the methods for the estimation of quantities and unit costs described?	No	No details provided
18. Were currency and price data recorded?	No	No details provided
19. Were details of price adjustments for inflation or currency conversion given?	No	No details provided
20. Were details of any model used given?	Yes	"…a decision analysis was performed followed by a cost-utility analysis"
21. Was there a justification for the choice of model used and the key parameters on which it was based?	No	No details provided
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	"…a cost-utility analysis was performed for a 1-year period"
23. Was the discount rate stated?	Yes	"The 3% annual discount rate has also been factored into our model."
24. Was the choice of rate justified?	Yes	"The rate of discounting is variable, but those with an interest in cost-effectiveness suggest that a 3% rate for health care is probably most appropriate."

25. Was an explanation given if cost or benefits were not discounted?	NA	Not applicable, discounting was used in the model
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	No details provided
27. Was the approach to sensitivity analysis described?	Yes	"One (single variables altered) and two-way sensitivity analyses (two variables altered simultaneously) and a Monte Carlo Simulation were also conducted."
28. Was the choice of variables for sensitivity analysis justified?	No	No details provided
29. Were the ranges over which the parameters were varied stated?	Yes	Number of PDT treatments was varied between 1 and 4.
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	NA	Not applicable, no alternatives were included
31. Was an incremental analysis reported?	Yes	"Relevant incremental costs were obtained from published Medicare Reimbursement data. We assumed that the total incremental cost of photodynamic therapy is $1,998 per treatment."
32. Were major outcomes presented in a disaggregated as well as aggregated form?	No	No details provided
33. Was the answer to the study question given?	Yes	"… photodynamic therapy yields an additional 0.037 QALYs, compared to the no-treatment alternative. This increment represents a 6.4% improvement in the patient's quality of life, and can be considered a large relative improvement." "When the cost of treatment is considered, this treatment would cost an insurer $214,085 per quality of life adjusted year. This falls below the threshold for cost-effectiveness."
34. Did conclusions follow from the data reported?	Yes	"From an outcomes-based perspective, photodynamic therapy… is the preferred course of action (dominant strategy) for patients with subfoveal choroidal neovascularisation secondary to high myopia"
35. Were conclusions accompanied by the appropriate caveats?	No	No details provided
36. Were generalisability issues addressed?	No	No details provided

NA, not applicable; PDT, photodynamic therapy; QALY, quality adjusted life year Adapted from Drummond MF, Jefferson TO (1996) Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party. British Medical Journal 313 (7052): 275–83. Cited in Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

10.12 Appendix 12: Search strategy for section 7.4 (Measurement and valuation of health effects)

The following information should be provided.

10.12.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS Economic Evaluation Database (NHS EED)
- EconLIT.

The systematic literature review was performed in the following databases:

- MEDLINE and MEDLINE In-Process
- EMBASE
- EconLit
- NHS Economic Evaluation Database (NHS EED)
- Health Technology Assessment Database (HTA)
- Health Economic Evaluations Database (HEED)
- CEA Registry
- National Institute for Health and Clinical Excellence (NICE)
- Scottish Medicines Consortium (SMC)
- Clinical Data Repository (CDR)
- Pharmaceutical Benefits Advisory Committee (PBAC)
- Food and Drug Administration (FDA)
- European Medicines Agency (EMA)

10.12.2 The date on which the search was conducted.

Searches were conducted on 30 April 2012 (MEDLINE and MEDLINE In-Process, EMBASE, EconLit, NHS EED, HTA, HEED, CEA Registry) and 1 May 2012 (NICE, SMC, PBAC, FDA, CDR, EMA).

10.12.3 The date span of the search.

The date spans of the various database searches are listed below:

- MEDLINE and MEDLINE In-Process: 1946–2012/Apr week 3
- EMBASE: 1974–2012/week 17
- EconLit: 1961–2012/Apr
- NHS Economic Evaluation Database (NHS EED): 29 April 2012
- Health Technology Assessment Database (HTA): 29 April 2012
- Health Economic Evaluations Database (HEED): 2012/Mar
- CEA Registry: 2012/Mar

No date limits were applied to searches of other sources.

10.12.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

MEDLINE and MEDLINE In-Process (OvidSP)

1 Choroidal Neovascularization/ (3499)
2 ((choroid$ adj3 neovascular$) or CNV or mCNV).ti,ab. (5984)
3 ((subretinal or sub-retinal) adj3 choroid$).ti,ab. (202)
4 Myopia, Degenerative/ (367)
5 (myopi$ adj3 (pathologic$ or degenerative or progressive)).ti,ab. (697)
6 exp Macular Degeneration/ (13473)
7 exp Retinal Degeneration/ (26154)
8 Retinal Neovascularization/ (1898)
9 exp Macula Lutea/ (9257)
10 maculopath$.ti,ab. (2509)
11 ((macul$ or retina$ or choroid$) adj3 degener$).ti,ab. (15309)
12 ((macul$ or retina$ or choroid$) adj3 age related).ti,ab. (8322)
13 ((macul$ or retina$ or choroid$) adj3 senile).ti,ab. (478)
14 ((macul$ or retina$ or choroid$) adj3 dystroph$).ti,ab. (2555)
15 ((macul$ or retina$ or choroid$) adj3 atroph$).ti,ab. (1653)
16 ((macul$ or retina$ or choroid$) adj3 sclerosis).ti,ab. (136)
17 ((macul$ or retina$ or choroid$) adj3 neovasc$).ti,ab. (6143)
18 (macula$ adj2 lutea).ti,ab. (101)
19 (tay$ adj2 choroiditis).ti,ab. (2)
20 (amd or armd).ti,ab. (5697)
21 or/1-20 (47275)
22 "Quality of Life"/ (98071)
23 ((quality adj3 life) or qol).ti,ab. (113697)
24 value of life/ (5209)

25 Quality-Adjusted Life Years/ (5584)
26 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (3727)
27 disability adjusted life.ti,ab. (836)
28 daly$.ti,ab. (854)
29 (index of wellbeing or quality of wellbeing or qwb).ti,ab. (153)
30 (multiattribute$ health or multi attribute$ health).ti,ab. (50)
31 (utility or utilities).ti,ab. (90018)
32 (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab. (9)
33 classification of illness state$.ti,ab. (1)
34 (euro qual or eruo qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab. (2617)
35 (sf36 or sf 36).ti,ab. (10294)
36 (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. (4785)
37 (sf12 or sf 12).ti,ab. (1527)
38 (short form 12 or shortform 12 or sf twelve or short form twelve).ti,ab. (597)
39 (qlq-c30 or fact-c or facit or qli-cp).ti,ab. (1629)
40 (sf 6d or sf6d or short form 6d or shortform 6d or sf six$ or shortform six$ or short form six$).ti,ab. (283)
41 hrqol.ti,ab. (4998)
42 hrql.ti,ab. (1836)
43 (proms or Patient Reported Outcome Measure$).ti,ab. (337)
44 (retinal occlusion adj4 Questionnaire$).ti,ab. (0)
45 best corrected visual acuity score$.ti,ab. (3)
46 (Timetradeoff or time tradeoff or time trade off or tto).ti,ab. (926)
47 (sg or standard gamble or hui or vas or visual analog$).ti,ab. (40050)
48 or/22-47 (282058)
49 21 and 48 (659)
50 animals/ not (animals/ and humans/) (3611730)
51 49 not 50 (645)

EMBASE (OvidSP)

1 subretinal neovascularization/ (5776)
2 ((choroid$ adj3 neovascular$) or CNV or mCNV).ti,ab. (7867)
3 ((subretinal or sub-retinal) adj3 choroid$).ti,ab. (246)
4 degenerative myopia/ (90)
5 (myopi$ adj3 (pathologic$ or degenerative or progressive)).ti,ab. (887)
6 retina macula degeneration/ (7191)
7 retina degeneration/ (7413)
8 retina neovascularization/ (3208)

9 retina macula lutea/ (6791)
10 maculopath$.ti,ab. (3197)
11 ((macul$ or retina$ or choroid$) adj3 degener$).ti,ab. (18947)
12 ((macul$ or retina$ or choroid$) adj3 age related).ti,ab. (10367)
13 ((macul$ or retina$ or choroid$) adj3 senile).ti,ab. (612)
14 ((macul$ or retina$ or choroid$) adj3 dystroph$).ti,ab. (3103)
15 ((macul$ or retina$ or choroid$) adj3 atroph$).ti,ab. (2092)
16 ((macul$ or retina$ or choroid$) adj3 sclerosis).ti,ab. (183)
17 ((macul$ or retina$ or choroid$) adj3 neovasc$).ti,ab. (7606)
18 (macula$ adj2 lutea).ti,ab. (122)
19 (tay$ adj2 choroiditis).ti,ab. (3)
20 (amd or armd).ti,ab. (7621)
21 or/1-20 (47749)
22 "quality of life"/ (192836)
23 ((quality adj3 life) or qol).ti,ab. (170149)
24 quality adjusted life year/ (9020)
25 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (6075)
26 disability adjusted life.ti,ab. (1110)
27 daly$.ti,ab. (1223)
28 (index of wellbeing or quality of wellbeing or qwb).ti,ab. (182)
29 (multiattribute$ health or multi attribute$ health).ti,ab. (60)
30 (utility or utilities).ti,ab. (122497)
31 (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab. (14)
32 classification of illness state$.ti,ab. (1)
33 (euro qual or eruo qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab. (4260)
34 (sf36 or sf 36).ti,ab. (15043)
35 (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. (6126)
36 (sf12 or sf 12).ti,ab. (2393)
37 (short form 12 or shortform 12 or sf twelve or short form twelve).ti,ab. (789)
38 (qlq-c30 or fact-c or facit or qli-cp).ti,ab. (2747)
39 (sf 6d or sf6d or short form 6d or shortform 6d or sf six$ or shortform six$ or short form six$).ti,ab. (456)
40 hrqol.ti,ab. (7463)
41 hrql.ti,ab. (2581)
42 (proms or Patient Reported Outcome Measure$).ti,ab. (538)
43 (retinal occlusion adj4 Questionnaire$).ti,ab. (0)
44 best corrected visual acuity score$.ti,ab. (3)
45 (Timetradeoff or time tradeoff or time trade off or tto).ti,ab. (1242)

46 (sg or standard gamble or hui or vas or visual analog$).ti,ab. (56435)
47 or/22-46 (415045)
48 21 and 47 (881)
49 animal/ (1777286)
50 nonhuman/ (3829165)
51 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. (4948381)
52 or/49-51 (6576605)
53 exp Human/ or Human Experiment/ (13519379)
54 52 not (52 and 53) (5167938)
55 48 not 54 (846)

EconLit (OvidSP)

1 ((choroid$ adj3 neovascular$) or CNV or mCNV).ti,ab. (2)
2 ((subretinal or sub-retinal) adj3 choroid$).ti,ab. (0)
3 (myopi$ adj3 (pathologic$ or degenerative or progressive)).ti,ab. (0)
4 maculopath$.ti,ab. (0)
5 ((macul$ or retina$ or choroid$) adj3 degener$).ti,ab. (2)
6 ((macul$ or retina$ or choroid$) adj3 age related).ti,ab. (2)
7 ((macul$ or retina$ or choroid$) adj3 senile).ti,ab. (0)
8 ((macul$ or retina$ or choroid$) adj3 dystroph$).ti,ab. (0)
9 ((macul$ or retina$ or choroid$) adj3 atroph$).ti,ab. (0)
10 ((macul$ or retina$ or choroid$) adj3 sclerosis).ti,ab. (0)
11 ((macul$ or retina$ or choroid$) adj3 neovasc$).ti,ab. (2)
12 (macula$ adj2 lutea).ti,ab. (0)
13 (tay$ adj2 choroiditis).ti,ab. (0)
14 or/1-13 (3)

NHS EED (CRD interface)

1 MeSH DESCRIPTOR Choroidal Neovascularization EXPLODE ALL TREES (36)
2 ((choroid* NEAR3 neovascular*) OR CNV OR mCNV) (59)
3 ((subretinal NEAR3 chroid*) OR (sub-retinal NEAR3 choroid*)) (0)
4 MeSH DESCRIPTOR Myopia, Degenerative EXPLODE ALL TREES (2)
5 (myopi* NEAR3 pathologic*) OR (myopi* NEAR3 degenerative) OR (myopi* NEAR3 progressive) (2)
6 MeSH DESCRIPTOR Macular Degeneration EXPLODE ALL TREES (130)
7 MeSH DESCRIPTOR Retinal Degeneration EXPLODE ALL TREES (135)
8 MeSH DESCRIPTOR Retinal Neovascularization EXPLODE ALL TREES (2)
9 MeSH DESCRIPTOR Macula Lutea EXPLODE ALL TREES (11)

10 maculopath* (9)

11 (macul* NEAR3 degener*) OR (retina* NEAR3 degener*) OR (choroid* NEAR3 degener*) (145)

12 (macul* NEAR3 age) OR (retina* NEAR3 age) OR (choroid* NEAR3 age) (27)

13 (macul* NEAR3 senile) OR (retina* NEAR3 senile) OR (choroid* NEAR3 senile) (0)

14 (macul* NEAR3 dystroph*) OR (retina* NEAR3 dystroph*) OR (choroid* NEAR3 dystroph*) (0)

15 (macul* NEAR3 atroph*) OR (retina* NEAR3 atroph*) OR (choroid* NEAR3 atroph*) (0)

16 (macul* NEAR3 sclerosis) OR (retina* NEAR3 sclerosis) OR (choroid* NEAR3 sclerosis) (0)

17 (macul* NEAR3 neovasc*) OR (retina* NEAR3 neovasc*) OR (choroid* NEAR3 neovasc*) (60)

18 macula* NEAR2 lutea (4)

19 tay* NEAR2 choroiditis (0)

20 amd OR armd (64)

21 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 (189)

22 * IN NHSEED (12526)

23 #21 AND #22 (45)

HTA (CRD interface)

1 MeSH DESCRIPTOR Choroidal Neovascularization EXPLODE ALL TREES (36)

2 ((choroid* NEAR3 neovascular*) OR CNV OR mCNV) (59)

3 ((subretinal NEAR3 chroid*) OR (sub-retinal NEAR3 choroid*)) (0)

4 MeSH DESCRIPTOR Myopia, Degenerative EXPLODE ALL TREES (2)

5 (myopi* NEAR3 pathologic*) OR (myopi* NEAR3 degenerative) OR (myopi* NEAR3 progressive) (2)

6 MeSH DESCRIPTOR Macular Degeneration EXPLODE ALL TREES (130)

7 MeSH DESCRIPTOR Retinal Degeneration EXPLODE ALL TREES (135)

8 MeSH DESCRIPTOR Retinal Neovascularization EXPLODE ALL TREES (2)

9 MeSH DESCRIPTOR Macula Lutea EXPLODE ALL TREES (11)

10 maculopath* (9)

11 (macul* NEAR3 degener*) OR (retina* NEAR3 degener*) OR (choroid* NEAR3 degener*) (145)

12 (macul* NEAR3 age) OR (retina* NEAR3 age) OR (choroid* NEAR3 age) (27)

13 (macul* NEAR3 senile) OR (retina* NEAR3 senile) OR (choroid* NEAR3 senile) (0)

14 (macul* NEAR3 dystroph*) OR (retina* NEAR3 dystroph*) OR (choroid* NEAR3 dystroph*) (0)

15 (macul* NEAR3 atroph*) OR (retina* NEAR3 atroph*) OR (choroid* NEAR3 atroph*) (0)
16 (macul* NEAR3 sclerosis) OR (retina* NEAR3 sclerosis) OR (choroid* NEAR3 sclerosis) (0)
17 (macul* NEAR3 neovasc*) OR (retina* NEAR3 neovasc*) OR (choroid* NEAR3 neovasc*) (60)
18 macula* NEAR2 lutea (4)
19 tay* NEAR2 choroiditis (0)
20 amd OR armd (64)
21 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 (189)
22 (utility OR utilities) (4212)
23 euroqol OR eq5d OR eq-5d OR sf6d OR sf-6d (641)
24 "standard gamble" OR TTO OR "time trade off" OR "time trade-off" (463)
25 economic* OR cost* (18915)
26 #22 OR #23 OR #24 OR #25 (19165)
27 #21 AND #26 (85)
28 * IN HTA (11112)
29 #27 AND #28 (27)

HEED (Wiley interscience)

AX='choroidal neovascularization' within 3 or 'choroidal neovascularisation' within 3 or CNV or mCNV (19)
AX='subretinal choroidal' within 3 or 'sub-retinal choroidal' within 3 (0)
AX='myopia pathologic' within 3 or 'myopia degenerative' within 3 or 'myopia progressive' within 3 (0)
AX=maculopathy (3)
AX='macular degeneration' within 3 or 'retinal degeneration' within 3 or 'choroidal degeneration' within 3 (77)
AX='macular age related' within 3 or 'retinal age related' within 3 or 'choroidal age related' within 3 (0)
AX='macular senile' within 3 or 'retinal senile' within 3 or 'choroidal senile' within 3 (0)
AX='macular dystrophy' within 3 or 'retinal dystrophy' within 3 or 'choroidal dystrophy' within 3 (0)
AX='macular atrophy' within 3 or 'retinal atrophy' within 3 or 'choroidal atrophy' within 3 (0)
AX='macular sclerosis' within 3 or 'retinal sclerosis' within 3 or 'choroidal sclerosis' within 3 (0)
AX='macular neovascularization' within 3 or 'macular neovascularisation' within 3 or 'retinal neovascularization' within 3 or 'retinal neovascularisation' within 3 or 'choroidal neovascularization' within 3 or 'choroidal neovascularisation' within 3 (20)
AX='macular lutea' within 2 (0)

AX='tay choroiditis' within 2 (0)

AX=(amd or armd) (52)

CS=1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (108)

AX=utility or utilities (4777)

AX=euroqol or eq5d or eq-5d or sf6d or sf-6d (829)

AX=(standard gamble) or TTO or (time trade off) or (time trade-off) (7490)

EE=(Cost Utility Analysis) or (Cost Benefit Analysis) or (Cost Effectiveness Analysis) (9498)

CS=6 and (7 or 8 or 9 or 10) (44)

CEA Registry (www.cearegistry.org)

Each line searched separately

myopia

choroidal neovascularization

CNV

mCNV

maculopathy

macular degeneration

macular neovascularisation

macular lutea

amd

armd

The following regulatory authority websites were browsed and relevant publications were searched for utility data:

- National Institute for Health and Clinical Excellence (NICE) (www.nice.org.uk/)
- Scottish Medicines Consortium (SMC) (www.scottishmedicines.org.uk/)
- Pharmaceutical Benefits Advisory Committee (PBAC) (www.health.gov.au)
- Food and Drug Administration (FDA) (www.fda.gov/)
- Clinical Data Repository (CDR) (http://www.cc.nih.gov/dcri/data_repository.html)
- European Medicines Agency (EMA) (www.ema.europa.eu/)

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.12.6 The inclusion and exclusion criteria.

Participants

Eligible reports included patients with:

- CNV secondary to PM
- PM
- CNV secondary to AMD
- AMD

Study Types

The following types of study were selected:

- Reports of utility elicitation exercises
- Reports of utility validation exercises;
- Reports of economic evaluations using utility measures gathered during the studies

Reviews of utility studies were eligible in order to harvest relevant primary studies. Such reviews could also provide comparative data against which to compare the results of this review. Data from unpublished studies were eligible for inclusion.

In addition, for inclusion a utility report must have included detail on:

- Mean or median utility values at different disease levels (if available)
- The country/perspective
- A standard method of utility assessment (e.g. standard gamble, time trade-off, rating scale)
- A description of the health state valuation instrument (e.g. was a generic preference-based measure such as the EQ-5D used or did they value bespoke health state descriptions)

10.12.7 The data abstraction strategy.

The full text of potentially relevant studies were obtained and assessed for relevance by one reviewer and checked by a second. Discrepancies were resolved through discussion or by consulting a third reviewer.

The following data were extracted from the studies:

- Study details, i.e. first author, journal and year of publication
- Standard error and confidence intervals of utilities
- Disease stage
- Source of perspective of the values (i.e. patients, health care professionals, general population, own health state, hypothetical health state)
- The health state instrument described (i.e. EQ-5D, SF-6D, HUI)
- The scaling method of utility assessment adopted (i.e. standard gamble, time-trade-off, rating scale)

- Number of respondents, response rates
- Study design (clinical decision analyses or outcome studies, in which the derivation of the utilities was the main purpose of the study)
- High anchor of utility (i.e. free of the symptom or full health)
- Country
- Mean or median utility values
- Country perspective

10.13 Appendix 13: Resource identification, measurement and valuation (section 7.5)

The following information should be provided.

10.13.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- NHS EED
- EconLIT.

The systematic review to identify relevant resource use data for the UK was performed alongside the review to identify relevant cost-effectiveness studies and the same methods and search strategy were used, as described in section 10.2.

10.13.2 The date on which the search was conducted.

Search dates are described in detail in section 10.2.2.

10.13.3 The date span of the search.

The date spans of the searches are described in detail in section 10.2.3.

10.13.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete search strategies are described in section 10.2.4.

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional searches were undertaken.

10.13.6 The inclusion and exclusion criteria.

Studies evaluating the costs and benefits of treatment for CNV secondary to PM, including studies of treatment for lesions refractory to other therapies were included

10.13.7 The data abstraction strategy.

Data was to be extracted for any relevant studies identified.

11 Supplementary Appendices (Added by Novartis)

11.1 Appendix 14: Transition probabilities (section 7.3.2)

Tables for mean (SD) transition probabilities by BCVA level (full matrix): ranibizumab

0 to 3m		**Before**							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.000 (0.000)	0.000 (0.000)	0.182 (0.080)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.000 (0.000)	1.000 (0.000)	0.682 (0.097)	0.235 (0.072)	0.125 (0.080)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	75-66	0.000 (0.000)	0.000 (0.000)	0.091 (0.060)	0.588 (0.083)	0.313 (0.112)	0.231 (0.113)	0.000 (0.000)	0.000 (0.000)
	65-56	0.000 (0.000)	0.000 (0.000)	0.045 (0.043)	0.118 (0.054)	0.250 (0.105)	0.308 (0.123)	0.444 (0.157)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.059 (0.040)	0.250 (0.105)	0.308 (0.123)	0.333 (0.149)	0.000 (0.000)
	45-36	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.063 (0.059)	0.154 (0.096)	0.000 (0.000)	0.000 (0.000)
	35-26	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.222 (0.131)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	1.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**0**	**3**	**22**	**34**	**16**	**13**	**9**	**0**

3m to 6m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	0.750 (0.194)	0.107 (0.057)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.250 (0.194)	0.750 (0.080)	0.226 (0.074)	0.059 (0.055)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	75-66	0.000 (0.000)	0.107 (0.057)	0.645 (0.085)	0.294 (0.107)	0.000 (0.000)	0.333 (0.236)	0.000 (0.000)	0.000 (0.000)
	65-56	0.000 (0.000)	0.000 (0.000)	0.129 (0.059)	0.471 (0.118)	0.462 (0.133)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.059 (0.055)	0.538 (0.133)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	45-36	0.000 (0.000)	0.036 (0.034)	0.000 (0.000)	0.118 (0.076)	0.000 (0.000)	0.333 (0.236)	0.000 (0.000)	0.000 (0.000)
	35-26	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.333 (0.236)	1.000 (0.000)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	1.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**4**	**28**	**31**	**17**	**13**	**3**	**2**	**0**

6m to 9m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	0.500 (0.194)	0.000 (0.079)	0.000 (0.084)	0.000 (0.085)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.250 (0.000)	0.741 (0.036)	0.087 (0.069)	0.000 (0.111)	0.000 (0.163)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	75-66	0.250 (0.000)	0.222 (0.000)	0.783 (0.000)	0.133 (0.085)	0.000 (0.163)	0.000 (0.289)	0.000 (0.000)	0.000 (0.000)
	65-56	0.000 (0.000)	0.037 (0.000)	0.130 (0.000)	0.733 (0.000)	0.200 (0.000)	0.000 (0.289)	0.000 (0.236)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.133 (0.000)	0.800 (0.000)	0.500 (0.000)	0.000 (0.236)	0.000 (0.000)
	45-36	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.500 (0.000)	0.333 (0.000)	0.000 (0.000)
	35-26	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.667 (0.000)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	1.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**4**	**27**	**23**	**15**	**5**	**2**	**3**	**0**

9m to 12m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.000 (0.000)	0.063 (0.059)	0.000 (0.123)	0.000 (0.090)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.000 (0.000)	0.875 (0.000)	0.308 (0.000)	0.100 (0.121)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	75-66	0.000 (0.000)	0.063 (0.000)	0.692 (0.000)	0.100 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)

	65-56	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.800 (0.000)	1.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	45-36	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	1.000 (0.000)	0.000 (0.000)
	35-26	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	1.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	1.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**1**	**16**	**13**	**10**	**1**	**1**	**1**	**0**

Tables for transition probabilities by BCVA level (full matrix): vPDT

0 to 3m		**Before**							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.000 (0.000)	0.000 (0.236)	0.125 (0.167)	0.000 (0.104)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.000 (0.000)	0.000 (0.000)	0.125 (0.144)	0.053 (0.098)	0.000 (0.157)	0.000 (0.144)	0.000 (0.000)	0.000 (0.000)
	75-66	0.000 (0.000)	0.667 (0.000)	0.500 (0.000)	0.316 (0.104)	0.000 (0.131)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	65-56	0.000 (0.000)	0.000 (0.000)	0.250 (0.000)	0.263 (0.050)	0.556 (0.099)	0.250 (0.161)	0.000 (0.224)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.236)	0.000 (0.000)	0.316 (0.000)	0.222 (0.099)	0.000 (0.110)	0.000 (0.224)	0.000 (0.000)
	45-36	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.053 (0.000)	0.111 (0.000)	0.625 (0.000)	0.500 (0.000)	0.000 (0.000)
	35-26	0.000 (0.000)	0.333 (0.000)	0.000 (0.000)	0.000 (0.000)	0.111 (0.000)	0.125 (0.000)	0.500 (0.000)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	1.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**0**	**3**	**8**	**19**	**9**	**8**	**4**	**0**

3m to 6m		**Before**							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.000 (0.000)	0.000 (0.236)	0.000 (0.093)	0.000 (0.077)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.000 (0.000)	0.000 (0.000)	0.107 (0.084)	0.043 (0.097)	0.000 (0.063)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	75-66	0.000 (0.000)	0.667 (0.000)	0.536 (0.034)	0.174 (0.069)	0.000 (0.096)	0.000 (0.194)	0.000 (0.000)	0.000 (0.000)
	65-56	0.000 (0.000)	0.000 (0.000)	0.286 (0.034)	0.652 (0.000)	0.095 (0.075)	0.000 (0.194)	0.000 (0.000)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.236)	0.036 (0.000)	0.130 (0.000)	0.714 (0.045)	0.250 (0.194)	0.000 (0.000)	0.000 (0.000)
	45-36	0.000	0.000	0.036	0.000	0.143	0.250	0.000	0.000

		(0.000)	(0.000)	(0.000)	(0.000)	(0.000)	(0.194)	(0.000)	(0.000)
	35-26	0.000 (0.000)	0.333 (0.000)	0.000 (0.000)	0.000 (0.000)	0.048 (0.000)	0.250 (0.000)	1.000 (0.000)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.250 (0.000)	0.000 (0.000)	1.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**0**	**3**	**28**	**23**	**21**	**4**	**0**	**0**

6m to 9m		**Before**							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.000 (0.000)	0.000 (0.194)	0.000 (0.104)	0.000 (0.075)	0.000 (0.048)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.000 (0.000)	0.750 (0.000)	0.143 (0.091)	0.042 (0.099)	0.000 (0.104)	0.000 (0.163)	0.000 (0.000)	0.000 (0.000)
	75-66	0.000 (0.000)	0.250 (0.000)	0.619 (0.000)	0.167 (0.075)	0.050 (0.109)	0.000 (0.163)	0.000 (0.236)	0.000 (0.000)
	65-56	0.000 (0.000)	0.000 (0.000)	0.238 (0.000)	0.583 (0.040)	0.350 (0.065)	0.200 (0.200)	0.000 (0.236)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.167 (0.000)	0.450 (0.000)	0.200 (0.000)	0.333 (0.236)	0.000 (0.000)
	45-36	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.042 (0.000)	0.100 (0.048)	0.600 (0.000)	0.333 (0.000)	1.000 (0.000)
	35-26	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.333 (0.000)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.050 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**0**	**4**	**21**	**24**	**20**	**5**	**3**	**1**

9m to 12m		**Before**							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.000 (0.000)	0.000 (0.160)	0.000 (0.098)	0.000 (0.083)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	85-76	0.000 (0.000)	0.714 (0.000)	0.211 (0.050)	0.000 (0.094)	0.000 (0.111)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)
	75-66	0.000 (0.000)	0.286 (0.000)	0.737 (0.000)	0.259 (0.073)	0.000 (0.125)	0.000 (0.161)	0.000 (0.000)	0.000 (0.000)
	65-56	0.000 (0.000)	0.000 (0.000)	0.053 (0.000)	0.519 (0.000)	0.267 (0.111)	0.000 (0.144)	0.000 (0.000)	0.000 (0.000)
	55-46	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.185 (0.036)	0.467 (0.000)	0.375 (0.110)	0.000 (0.000)	0.000 (0.000)
	45-36	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.267 (0.000)	0.250 (0.144)	1.000 (0.000)	0.000 (0.000)
	35-26	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.037 (0.000)	0.000 (0.000)	0.125 (0.000)	0.000 (0.000)	0.000 (0.000)
	<25	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.000 (0.000)	0.250 (0.000)	0.000 (0.000)	1.000 (0.000)
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**
	n	**0**	**7**	**19**	**27**	**15**	**8**	**1**	**1**

Tables for transition probabilities by BCVA level (split for top two levels): Ranibizumab

0 to 1m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.0000	0.0000	0.3365	-	-	-	-	-
	85-76	0.0000	1.0000	0.4904	0.3365	-	-	-	-
	75-66	0.0000	0.0000	0.1442	0.4904	0.3365	-	-	-
	65-56	-	0.0000	0.0288	0.1442	0.4904	0.3365	-	-
	55-46	-	-	0.0000	0.0288	0.1442	0.4904	0.3365	-
	45-36	-	-	-	0.0000	0.0288	0.1442	0.4904	0.3365
	35-26	-	-	-	-	0.0000	0.0288	0.1442	0.4904
	<25	-	-	-	-	-	0.0000	0.0288	0.1731
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

3m to 6m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	0.7500	0.1034	0.0132	-	-	-	-	-
	85-76	0.2500	0.7241	0.2632	0.0132	-	-	-	-
	75-66	0.0000	0.1379	0.5921	0.2632	0.0132	-	-	-
	65-56	-	0.0345	0.1053	0.5921	0.2632	0.0132	-	-
	55-46	-	-	0.0263	0.1053	0.5921	0.2632	0.0132	-
	45-36	-	-	-	0.0263	0.1053	0.5921	0.2632	0.0132
	35-26	-	-	-	-	0.0263	0.1053	0.5921	0.2632
	<25	-	-	-	-	-	0.0263	0.1316	0.7237
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

6m to 9m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	0.6000	0.0000	0.0141	-	-	-	-	-
	85-76	0.2000	0.7188	0.1831	0.0141	-	-	-	-
	75-66	0.2000	0.2500	0.7042	0.1831	0.0141	-	-	-
	65-56	-	0.0313	0.0986	0.7042	0.1831	0.0141	-	-
	55-46	-	-	0.0000	0.0986	0.7042	0.1831	0.0141	-
	45-36	-	-	-	0.0000	0.0986	0.7042	0.1831	0.0141
	35-26	-	-	-	-	0.0000	0.0986	0.7042	0.1831
	<25	-	-	-	-	-	0.0000	0.0986	0.8028
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

9m to 12m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.0000	0.1333	0.0263	-	-	-	-	-
	85-76	0.0000	0.7667	0.2895	0.0263	-	-	-	-
	75-66	0.0000	0.1000	0.6316	0.2895	0.0263	-	-	-
	65-56	-	0.0000	0.0526	0.6316	0.2895	0.0263	-	-
	55-46	-	-	0.0000	0.0526	0.6316	0.2895	0.0263	-
	45-36	-	-	-	0.0000	0.0526	0.6316	0.2895	0.0263
	35-26	-	-	-	-	0.0000	0.0526	0.6316	0.2895
	<25	-	-	-	-	-	0.0000	0.0526	0.6842
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

Tables for transition probabilities by BCVA level (split for top two levels): vPDT

0 to 1m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.0000	0.0000	0.0769	-	-	-	-	-
	85-76	0.0000	0.0000	0.2885	0.0769	-	-	-	-
	75-66	0.0000	0.6667	0.3846	0.2885	0.0769	-	-	-
	65-56	-	0.3333	0.2115	0.3846	0.2885	0.0769	-	-
	55-46	-	-	0.0385	0.2115	0.3846	0.2885	0.0769	-
	45-36	-	-	-	0.0385	0.2115	0.3846	0.2885	0.0769
	35-26	-	-	-	-	0.0385	0.2115	0.3846	0.2885
	<25	-	-	-	-	-	0.0385	0.2500	0.6346
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

3m to 6m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.0000	0.0000	0.0132	-	-	-	-	-
	85-76	0.0000	0.0000	0.1316	0.0132	-	-	-	-
	75-66	0.0000	0.6667	0.6053	0.1316	0.0132	-	-	-
	65-56	-	0.3333	0.1974	0.6053	0.1316	0.0132	-	-
	55-46	-	-	0.0526	0.1974	0.6053	0.1316	0.0132	-
	45-36	-	-	-	0.0526	0.1974	0.6053	0.1316	0.0132
	35-26	-	-	-	-	0.0526	0.1974	0.6053	0.1316
	<25	-	-	-	-	-	0.0526	0.2500	0.8553
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

6m to 9m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.0000	0.0000	0.0676	-	-	-	-	-
	85-76	0.0000	0.7500	0.2162	0.0676	-	-	-	-
	75-66	0.0000	0.2500	0.5405	0.2162	0.0676	-	-	-
	65-56	-	0.0000	0.1486	0.5405	0.2162	0.0676	-	-
	55-46	-	-	0.0270	0.1486	0.5405	0.2162	0.0676	-
	45-36	-	-	-	0.0270	0.1486	0.5405	0.2162	0.0676
	35-26	-	-	-	-	0.0270	0.1486	0.5405	0.2162
	<25	-	-	-	-	-	0.0270	0.1757	0.7162
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

9m to 12m		Before							
		100-86	85-76	75-66	65-56	55-46	45-36	35-26	<25
After	100-86	1.0000	0.0000	0.0000	-	-	-	-	-
	85-76	0.0000	0.7143	0.2676	0.0000	-	-	-	-
	75-66	0.0000	0.2857	0.5352	0.2676	0.0000	-	-	-
	65-56	-	0.0000	0.1549	0.5352	0.2676	0.0000	-	-
	55-46	-	-	0.0423	0.1549	0.5352	0.2676	0.0000	-
	45-36	-	-	-	0.0423	0.1549	0.5352	0.2676	0.0000
	35-26	-	-	-	-	0.0423	0.1549	0.5352	0.2676
	<25	-	-	-	-	-	0.0423	0.1972	0.7324
	Sum	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**	**1.0000**

11.2 Appendix 15: Summary of utility studies (section 7.4.6)

Table 96 Summary of utility studies for patients with CNV secondary to AMD

Reference (country)	Subjects (n)	Instrument (high anchor)	Results (mean utility with CI)
Bass 2004[112] (USA)	792	Bespoke (full health with perfect vision)	**Better eye** ≥ 20/40: 0.69 (0.56–0.82) 20/50–20/160: 0.58 (0.43–0.76) ≤ 20/200: 0.53 (0.34–0.71) **Worse eye** 20/50–20/160: 0.68 (0.56–0.82) ≤ 20/200: 0.62 (0.50–0.79) **Both eyes** ≥ 20/40 and 20/50–160:0.71 (0.60–0.82) ≥ 20/40 and ≤ 20/200: 0.67 (0.54–0.81) 20/50–20/160 both: 0.56 (0.39–0.75) 20/50–160 and ≤ 20/200:0.59 (0.45–0.78) ≤ 20/200 both: 0.53 (0.34–0.71)
Cruess 2007[110] (Canada)	67	EQ-5D (full health)	0.64 (0.52–0.76). This was not statistically different than the control (no neovascular AMD) value of 0.74, but p-value was 0.06, which suggests the trial was underpowered assuming the difference seen was clinically significant
Lotery 2007[113] (UK)	75	EQ-5D (full health)	> 20/40: 0.52 20/40–20/80: 0.66 20/80–20/200: 0.72 20/200–20/400:0.79 ≤ 20/400: 0.70 Overall: 0.67
Ruiz-Moreno 2008[111] (Spain)	89	EQ-5D (full health)	0.68 (0.62–0.74) adjusted mean from bootstrapping adjusted for age, sex, vision related comorbidity and number of comorbid diseases
Soubrane 2007[90] (France, Germany, Italy, Spain, UK)	401	EQ-5D (full health)	Patients ≥ 70: 0.67 (0.61–0.74) Patients ≥ 75: 0.72 (0.63–0.82) Patients with no comorbidities: 0.68 (0.59–0.78) Overall: 0.65 (0.6–0.69) Found no difference in utilities by level of visual acuity
Bass et al., 2004;[112] Cruess et al., 2007;[110] Lotery et al., 2007;[113] Ruiz-Moreno et al., 2008;[111] Soubrane et al., 2007[90] AMD, age related macular degeneration; CI, confidence interval; CNV, choroidal neovascularisation; EQ-5D, 5-dimension EuroQol questionnaire			

Table 97 Summary of utility studies for patients with AMD

Reference (country)	Subjects (n)	Instrument (high anchor)	Results (Mean with (CI) or [standard deviation])
Aspinall 2007[121] (UK)	122	Bespoke (TTO) (current health with normal sight)	LogMAR 0–0.10: 0.93 (0.86–0.99) LogMAR 0.12–0.40: 0.86 (0.78–0.93) LogMAR 0.42-0.70: 0.74 (0.64–0.83) LogMAR 0.72–1.30: 0.68 (0.57–0.79) LogMAR > 1.30: 0.76 (0.37–1.15)
Au Eong 2012[114] (Singapore)	*Total 338* Dry/normal 35 Dry/dry 178 Wet/normal 64 Wet/dry 31 Wet/wet 30	EQ-5D and Bespoke (TTO and SG) (full health for EQ-5D, perfect binocular vision for TTO, perfect health or perfect binocular vision for standard gamble)	**EQ-5D** Dry/normal: 0.87 [0.12] Dry/dry: 0.91[0.11] Wet/normal: 0.90 [0.11] Wet/dry:0.85 [0.18] Wet/wet: 0.83 [0.19] Overall: 0.89 (0.75–1.03) **TTO** Dry/normal: 0.88 [0.19] Dry/dry: 0.82 [0.23] Wet/normal: 0.77 [0.19] Wet/dry: 0.78 [0.26] Wet/wet: 0.78 [0.26] Overall: 0.81 (0.58–1.04) **SG** (1.0 = perfect health) Dry/normal: 0.97 [0.12] Dry/dry: 0.88 [0.23] Wet/normal: 0.74 [0.31] Wet/dry: 0.80 [0.33] Wet/wet: 0.86 [0.29] Overall:0.86 (0.60–1.12) **SG** (1.0 = perfect binocular vision) Dry/normal: 0.96 [0.12] Dry/dry: 0.92 [0.12] Wet/normal: 0.87 [0.20] Wet/dry: 0.85 [0.27] Wet/wet: 0.94 [0.14] Overall: 0.91 (0.70–1.12)
Bansback 2007[115] (UK)	209	EQ-5D TTO and HUI3 (full health for both TTO and HUI3)	TTO: 0.63 [0.31] HUI3: 0.34 [0.28]
Boland 2011[128] (Netherlands, abstract only)	75	EQ-5D (full health)	Average utility with AMD: 0.792 (0.77–0.81)
Brown (a) 2000[100] (USA)	72	Bespoke (TTO and SG) (full health)	**TTO** 20/20 to 20/25: 0.89 (0.82–0.96) 20/30 to 20/50: 0.81 (0.73–0.89) 20/60 to 20/100: 0.57 (0.47–0.67) 20/200 to 20/400: 0.52 (0.38–0.66)

Reference (country)	Subjects (n)	Instrument (high anchor)	Results (Mean with (CI) or [standard deviation])
			CF to LP: 0.40 (0.29–0.50) Overall: 0.72 (0.66–0.78) **Standard gamble** 20/20 to 20/25: 0.96 (0.92–1.00) 20/30 to 20/50: 0.88 (0.83–0.93) 20/60 to 20/100: 0.69 (0.52–0.86) 20/200 to 20/400: 0.71 (0.57–0.85) CF to LP: 0.55 (0.36–0.74) Overall: 0.81 (0.76–0.86)
Brown (b) 2000[122] (USA)	46	Bespoke (TTO and SG) (full health)	**TTO** 20/20 to 20/25: 0.992 (0.986–0.998) 20/30 to 20/50: 0.97 (0.96–0.98) 20/60 to 20/100: 0.89 (0.86–0.92) 20/200 to 20/400: 0.77 (0.71–0.83) CF to LP: 0.69 (0.64–0.74) Overall: 0.86 (0.84–0.88) **Standard gamble** 20/20 to 20/25: 0.998 (0.993–1.0) 20/30 to 20/50: 0.99 (0.98–1.0) 20/60 to 20/100: 0.96 (0.94–0.98) 20/200 to 20/400: 0.88 (0.84–0.92) CF to LP: 0.77 (0.71–0.83) Overall: 0.93 (0.91–0.95)
Brown 2002[123] (USA)	246	Bespoke (TTO) (full health)	20/20 to 20/25: 0.84 [0.21] (0.82-0.86) 20/30 to 20/40: 0.80 [0.19] (0.75-0.85) 20/50 to 20/100: 0.71 [0.22] (0.65-0.77) ≤20/200: 0.59 [0.22] (0.53-0.65) Overall: 0.74 [0.23] (0.71-0.77)
Czoski-Murray 2009[56] (UK)	108	EQ-5D TTO (full health)	LogMAR ≤ 0.30: 0.706 (0.606-0.805) LogMAR 0.31–0.60: 0.681 (0.623-0.740) LogMAR 0.61–1.30: 0.511 (0.449-0.573) LogMAR ≥ 1.31: 0.314 (0.217–0.410) Overall: 0.550 (0.511–0.589)
Dilokthornsakul 2010[142] (Thailand, abstract only)	510 people across 24 studies	Meta-analysis (not reported)	20/20 to 20/25: 0.91 (0.88–0.94) 20/30 to 20/50: 0.81 (0.78–0.84) 20/60 to 20/100: 0.68 (0.58–0.77) 20/200 to 20/400: 0.62 (0.55–0.68) < 20/400: 0.46 (0.33–0.59)
Espallargues 2005[116] (UK)	209	EQ-5D (health states, VAS and TTO), SF-6D, HUI3 (full health)	EQ-5D (preference based health states) LogMAR ≤ 0.30: 0.75 [0.27] LogMAR 0.31–0.60: 0.70 [0.20] LogMAR 0.61–1.30: 0.75 [0.20] LogMAR 1.31–2.00: 0.71 [0.21] LogMAR > 2.00: 0.63 [0.22]

Reference (country)	Subjects (n)	Instrument (high anchor)	Results (Mean with (CI) or [standard deviation])
			EQ-5D (VAS) LogMAR ≤ 0.30: 71.1 [18.2] LogMAR 0.31–0.60: 62.9 [16.2] LogMAR 0.61–1.30: 66.4 [18.6] LogMAR 1.31–2.00: 62.8 [18.6] LogMAR > 2.00: 59.7 [15.5] **EQ-5D (TTO)** LogMAR ≤0.30: 0.73 [0.30] LogMAR 0.31-0.60: 0.67 [0.31] LogMAR 0.61-1.30: 0.64 [0.30] LogMAR 1.31-2.00: 0.60 [0.33] LogMAR >2.00: 0.47 [0.31] **SF-6D** LogMAR ≤ 0.30: 0.70 [0.18] LogMAR 0.31–0.60: 0.67 [0.14] LogMAR 0.61–1.30: 0.66 [0.14] LogMAR 1.31–2.00: 0.65 [0.11] LogMAR > 2.00: 0.63 [0.10] **HUI3** LogMAR ≤ 0.30: 0.50 [0.35] LogMAR 0.31–0.60: 0.38 [0.25] LogMAR 0.61–1.30: 0.36 [0.25] LogMAR 1.31–2.00: 0.27 [0.24] LogMAR > 2.00: 0.10 [0.18]
Gries 2010[143] (USA, abstract only)	138	NEI VFQ (not reported)	0.68 [0.11]
Kim 2010[125] (Korea)	625	EQ-5D (full health)	0.729 (0.493–0.965) before treatment
Lee 2008[117] (USA)	44	Bespoke (SG) (perfect health or perfect vision)	Perfect health = 1.0 Mild to moderate: 0.89 [0.23] Severe: 0.76 [0.30] Overall: 0.83 [0.27] Adjusted for age and comorbidity Mild to moderate: 0.86 Severe: 0.79 Overall: 0.84 Perfect vision = 1.0 Mild to moderate: 0.86 [0.24] Severe: 0.39 [0.37] Overall: 0.63 [0.38] Adjusted for age and comorbidity

Reference (country)	Subjects (n)	Instrument (high anchor)	Results (Mean with (CI) or [standard deviation])
			Mild to moderate: 0.85 Severe: 0.40 Overall: 0.66
Payakachat 2009[126] (Australia, Netherlands, UK, USA)	151	EQ-5D (full health)	0.77 [0.21]
Sahel 2007[118] (France, Germany, Italy)	360	HUI3 (full health)	≥ 20/40 and ≥ 20/200: 0.62(0.28) ≥ 20/40 and < 20/200: 0.60 < 20/40 and ≥ 20/200: 0.40 < 20/40 and < 20/200: 0.39(0.25) Overall: 0.48 (0.29)
Stein 2003[127] (USA)	115 patients with AMD, 142 healthy volunteers from general public and 62 clinicians	Bespoke (TTO) (states full health but question could be interpreted as current health without AMD)	**Patients with AMD** Mild AMD: 0.832 (0.762–0.901) Moderate AMD: 0.732 (0.669–0.795) Severe AMD: 0.566 (0.487–0.645) **General public** Mild AMD: 0.960 (0.950–0.970) Moderate AMD: 0.918 (0.902–0.934) Severe AMD: 0.857 (0.834–0.879) **Clinicians** Mild AMD: 0.929 (0.904–0.954) Moderate AMD: 0.877 (0.846–0.909) Severe AMD: 0.821 (0.785–0.857)
Williams 1998[119] (USA)	86	Quality of Wellbeing Scale (full health)	Blind one eye: 0.584 [0.08] Blind both eyes: 0.580 [0.07]
Yanagi 2011[120] (Japan)	48	Bespoke (TTO and SG) (current health full visual acuity)	**TTO** LogMAR 0.01–0.15: 0.534 (0.400–0.667) LogMAR 0.2–0.3: 0.574 (0.487–0.660) LogMAR 0.4–0.6: 0.613 (0.523–0.703) LogMAR 0.7–1.0: 0.653 (0.513–0.793) Overall: 0.598 (0.518–0.677) **Standard gamble** LogMAR 0.01–0.15: 0.686 (0.535–0.838) LogMAR 0.2–0.3: 0.695 (0.595–0.794) LogMAR 0.4–0.6: 0.703 (0.601–0.804) LogMAR 0.7–1.0: 0.711 (0.555–0.867)

Reference (country)	Subjects (n)	Instrument (high anchor)	Results (Mean with (CI) or [standard deviation])
			Overall: 0.695 (0.609–0.781)
Aspinall et al., 2007;[121] Au Eong et al., 2012;[114] Bansback et al., 2007;[115] Boland et al., 2011;[128] Brown et al. (a), 2000;[100] Brown et al. (b), 2000;[122] Brown et al., 2002;[123] Czoski-Murray et al., 2009;[56] Dilokthornsakul et al., 2010;[142] Espallargues et al., 2005;[116] Gries et al., 2010;[143] Kim et al., 2010;[125] Lee et al., 2008;[117] Payakachat et al., 2009;[126] Sahel et al., 2007;[118] Stein et al., 2003;[127] Williams et al., 1998;[119] Yanagi et al., 2011;[120] AMD, age related macular degeneration; CF, counting fingers; EQ-5D, 5-dimension EuroQol questionnaire; HUI3, Health Utilities Index Mark 3; logMAR, logarithm of the minimal angle of resolution; LP, light perception; NEI VFQ, National Eye Institute Visual Functioning Questionnaire; SG, standard gamble; SF-6D, short form-6D; TTO, time trade off; VAS, visual analogue scale			

11.3 Appendix 16: Slides presented in clinical expert interviews

An Economic Evaluation of Ranibizumab for the Treatment of Visual Impairment due to CNV Secondary to Pathologic Myopia

Bill Malcolm

19th Feb, 2013

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Objective

- Validate model assumptions:

Population	
Comparators	vPDT Observation – not in current scope
Starting Age	55
Data Source	Trial data
Transition Probabilities	Based on current VA
Natural Progression	From year 2
Convergence	None
Eye Involvement	
Model Based on BSE Only	No
Recurrence	Yes, 6% annually
Bilateral Disease	Yes, 15% at baseline
Results	
Time Horizon	Lifetime
Discounting	3.5% (Costs and outcomes)
Willingness to Pay Threshold	£20,000
Perspective	Health care
Quality of Life	
Utility, BSE	Czosky-Murray, 2009
Utility, WSE	0.1 maximum utility gain – yes (not 0.1 slope as in current model)

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Objective cont.

Unit Costs	
Ranibizumab	£742.17 – we have a UK PAS also
vPDT	£850
Ophthalmologist	£123.62
OCT	£51.27
Injection Visit	£117.26
Cost of Blindness	Year 1: £17,325.94; Year 2+: £17,244.67
Resource Use	
Ranibizumab:	
Treatment Visits	Year 1: 3.5; Year 2: 1; Year 3+: 0
Monitoring Visits	Year 1: 8.5; Year 2: 4 should be 11 as per UK label; Year 3+: 0
vPDT:	
Treatment Visits	Year 1: 3.4; Year 2: 1.7; Year 3+: 0
Monitoring Visits	Year 1: 4; Year 2: 4; Year 3+: 0
Observation:	
Monitoring Visits	Year 1: 4; Year 2: 4; Year 3: 4; Year 4+: 0
Recurrence Treatment and Monitoring Visits	Same as above for each comparator
Adverse Events	
Rates:	
Conjunctival haemorrhage	Ranibizumab: 8.5%
Intraocular pressure increased	Ranibizumab: 4.2%
Visual Disturbance	vPDT: 14.8%; observation: 12.8% - not needed
Injection site AEs (non-ocular)	vPDT: 9.9%; observation: 5.1% - not needed
Costs:	
Conjunctival haemorrhage	£1,234.31
Intraocular pressure increased	£31.67
Visual Disturbance	£0
Injection site AEs (non-ocular)	£100

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Model Structure

- Markov model – patients move between health states
- Health States - This defines the level of visual acuity that the patient experiences during a **fixed** period of time
  - 8 health states = changes of 2 lines clinically significant
- Cycle length - This defines how long a patient stays within a specific "health state" (i.e. how long the patient has a specific level of vision)
  - 3-month cycles
- Transition probabilities – 3 options included
  - Constant across all VA
  - Split for top 2 levels only
  - Based on current VA

4

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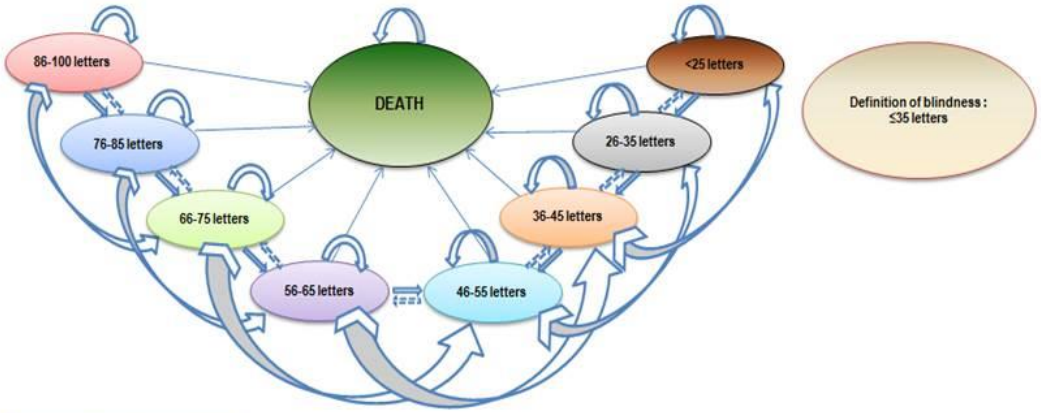
Model Diagram



Note: Approximate Snellen-equivalents
VA: 20/16-20/10=86-100 letters
VA: 20/32-20/20=76-85 letters
VA: 20/64-20/40=66-75 letters
VA: 20/80-20/50=56-65 letters
VA: 20/125-20/80=46-55 letters
VA: 20/200-20/125=36-45 letters
VA: 20/320-20/200=26-35 letters
VA < 20/320=<25 letters

For transition probabilities based on current VA, patients may move between any two states

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Base case assumptions

- Starting age = 55
- Time horizon: Patients are followed over lifetime (as per NICE scope)
- Fellow eye involvement
  - **Bilateral disease = 15% of the baseline patient cohort**
    - Curtin et al. 16.7%; Cohen et al. 14.2%
  - **Recurrence = 6.00% per year over the course of the model**
    - Recurrence is considered when patient stop treatment (from Y3 in our model)
    - Approx. 30% over 5 years as per ACUITY board
- Utility data based on previously accepted NICE submission were used
- Natural progression: options for various data sources
  - Parallel curves over time with an alternative scenario of convergence

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Optional components of model

Various sources for utility data (by BSE and WSE)

Natural history data from multiple sources

Can apply after one year or after three years (if Franqueira data used)

Variable time horizon

Societal perspective included as an option

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Effectiveness Data Sources (up to month 12)

Base case: Trial Data	Cycle 0-3 m	Cycle 3-6 m	Cycle 6-9 m	Cycle 9-12 m
ranibizumab	Radiance	Radiance	Radiance	Radiance
vPDT	Radiance	VIP	VIP	VIP

Alternative option: MTC	Cycle 0-3 m	Cycle 3-6 m	Cycle 6-9 m	Cycle 9-12 m
ranibizumab	Network 1	Network 2	Network 2	Network 2
vPDT	Network 1	Network 2	Network 2	Network 2

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Transition probabilities

- Constant across all levels - patients in the model (regardless of their current VA status) face a consistent probability of gaining and/or losing lines
  - Possibility of the model experiencing a ceiling effect (patients in the highest VA group would be 'unable' to improve)
  - The average VA score over time will gradually fall below the observed value
  - Allows for a larger number of observations to be included in the calculation of each transition probability
- Split for top two levels only - to remove a potential ceiling effect
  - Unique transition probabilities are calculated for patients with a starting VA of >86, a starting VA of 85-76, for the remainder of the states a pooled approach is taken
  - The top two VA groups that are most affected by the ceiling effect
  - Compromise between two other solutions
- Based on current VA - probabilities were based on the exact change between states
  - Patients may move from any one state to any other state
  - There may be a small number of observations for some probabilities

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Base Case Scenario - Number of treatment & monitoring visits

Visits per patient per year

	Year 1		Year 2		Year 3		Year 4+
Treatment	**Treatment visits**	**Monitoring visits**	**Treatment visits**	**Monitoring visits**	**Treatment visits**	**Monitoring visits**	**Annual monitoring visits**
Ranibizumab	3.5	8.5	1.0	4.0	0.0	0.0	0.0
vPDT	3.4	4.0	1.7	4.0	0.0	0.0	0
Observation	0.0	4.0	0.0	4.0	0.0	4.0	0

- Bilateral disease: number of treatment and monitoring visits are just double on the assumption that the eyes are treated independently
- Recurrence is conservatively treated with a mean of 3.5 injections and 8.5 monitoring visits (no efficacy benefit taken in consideration)

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Adverse event rates

- The rates for ranibizumab were selected from the CSR for the Lucentis Phase III trial
- The rates for vPDT and observation were selected from the CSR for the VIP trial
- The model included the events that occurred for at least 5 patients, and the adverse events that are suspected to be related to the study drug and/or ocular injection
- There were no non-ocular adverse events relating to the study drug and/or the ocular injection that occurred for at least 5 patients for ranibizumab

Events per patient (%)	Ranibizumab (N = 106)	vPDT (N = 81)	Observation (N = 39)	Bevacizumab
Conjunctival haemorrhage	8.5% (n = 10)	-	-	
Intraocular pressure increased	4.2% (n = 5)	-	-	
Eye pain	2.5% (n = 3)	-	-	
Injection site (ocular) haemorrhage	2.5% (n = 3)	-	-	
Punctate keratitis	1.7% (n = 2)	-	-	
Conjunctivitis	-	2.5% (n = 2)	0% (n = 0)	
Photophobia	-	2.5% (n = 2	0% (n = 0)	
Visual Disturbance	-	14.8% (n = 12)	12.8% (n = 5)	
Asthenia	-	4.9% (n = 4)	0% (n = 0)	
Headache	-	4.9% (n = 4)	7.8% (n = 3)	
Injection site AEs	-	9.9% (n = 8)	5.1% (n = 2)	
Photosensitivity reaction	-	3.7% (n = 3)	0% (n = 0)	
Pruritus	-	2.5% (n = 2)	2.6% (n = 1)	

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Top AEs of Lucentis

- The top 4 risks are related to the injection procedure itself.
  - endophthalmitis,
  - traumatic cataract,
  - retinal detachment,
  - increased IOP

- Endophthalmitis and traumatic cataract are listed in the physician leaflet
- Retinal detachment is a very important risk, particularly in patients with high (or pathologic) myopia, as they have a much greater inherent risk for retinal detachment than people with an eye of normal length.

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Subgroups Analyses

- Baseline VA
  - VA ≤ 45 letters
  - VA ≤ 60 letters
  - VA ≤ 72 letters
  - VA ≥ 73 letters
- Ethnicity
  - Caucasian vs. Non-caucasian
- Type of lesions
  - Extrafoveal vs. Subfoveal vs. Juxtafoveal
- Age
  - < 45
  - 45-55
  - 55 to 65
  - ≥ 65
- Axial length
  - < 28
  - 28-30
  - ≥ 30

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Cost data

Costs associated with treatment

Treatment	Cost per treatment
Ranibizumab	£742.17
vPDT	£850.00
Observation	£0.00
Bevacizumab	£95.22

Costs per Administration visit	Ranibizumab	vPDT	Observation	Bevacizumab
OCT	£51.27	£51.27	£0.00	£51.27
Ophthalmologist	£0.00	£123.62	£0.00	£0.00
Concomitant drugs	£0.00	£0.00	£0.00	£0.00
Injection visit cost	£117.26	£0.00	£0.00	£117.26
Total for visit (non-drug costs)	**£168.53**	**£174.89**	**£0.00**	**£168.53**

Costs per monitoring visit	Cost
Staffing (ophthalmologist)	£123.62
OCT	£51.27
Total for monitoring visit	**£174.89**

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Cost of blindness

- Cost of blindness applied to those patients whose VA in their study eye falls below 35 letters and only when both eyes are declared blind
  - i.e. when the BSE reaches a VA < 35 letters
  - Calculated using the probability of a patient whose study eye is their BSE
- The cost of blindness is higher during the first year after diagnosis, the *additional* cost of the first year was assigned as an extra cost, during the cycle that the patient becomes blind
- Blindness is not an absorbing state and patients may move in an out of this state. The initial cost of blindness may be applied more than once to a particular patient.

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Quality of life

- Several options for quality of life
- Utility values for the BSE based on Czoski-Murray 2009
- For a given BCVA, higher utility for their worse-seeing eye.
- Utility values for the WSE are proportionate to the utilities for the BSE
  - These could either be anchored at the top of the curve or the bottom
  - Anchoring on the top so that the WSE has higher utilities than BSE (may lead a reduction in QALYs as patients move from the higher curve to the lower curve as they improve)
  - Anchoring at the bottom, patients gain QALYs as their study eye becomes their better-seeing eye.

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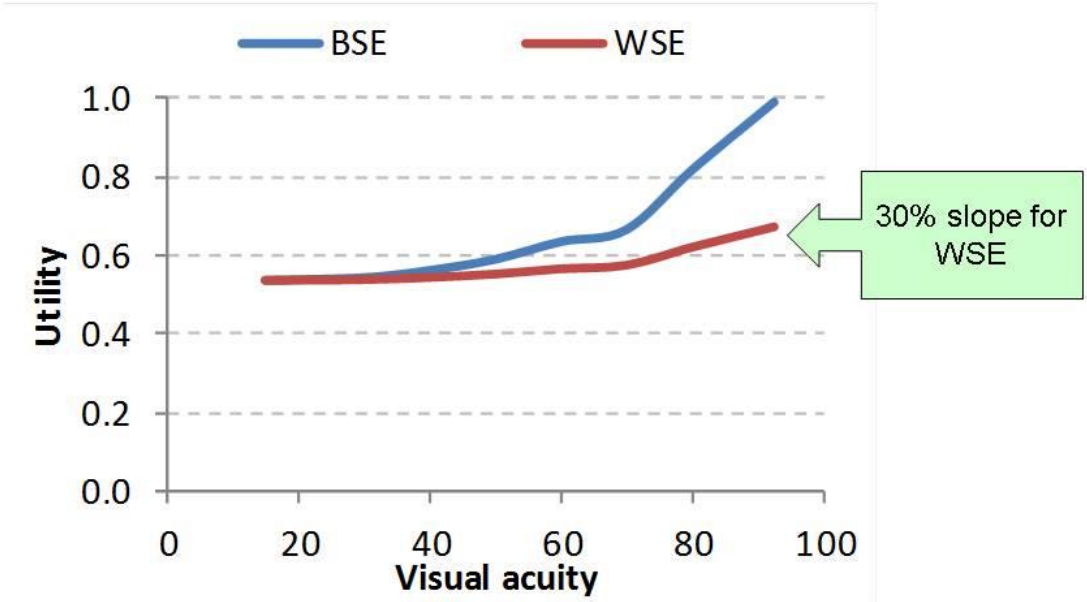
Quality of life



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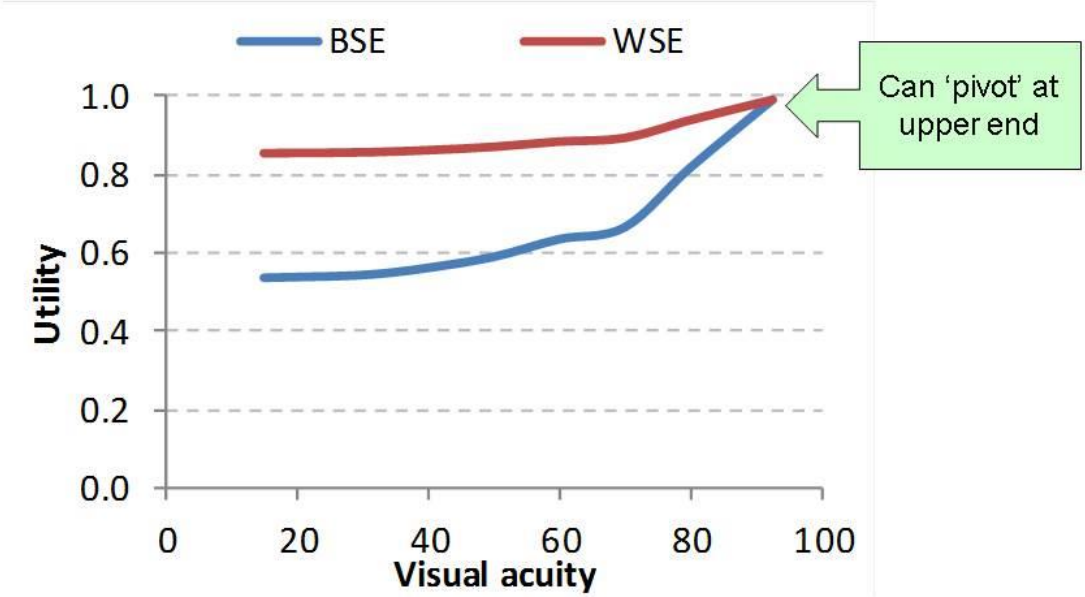
Quality of life



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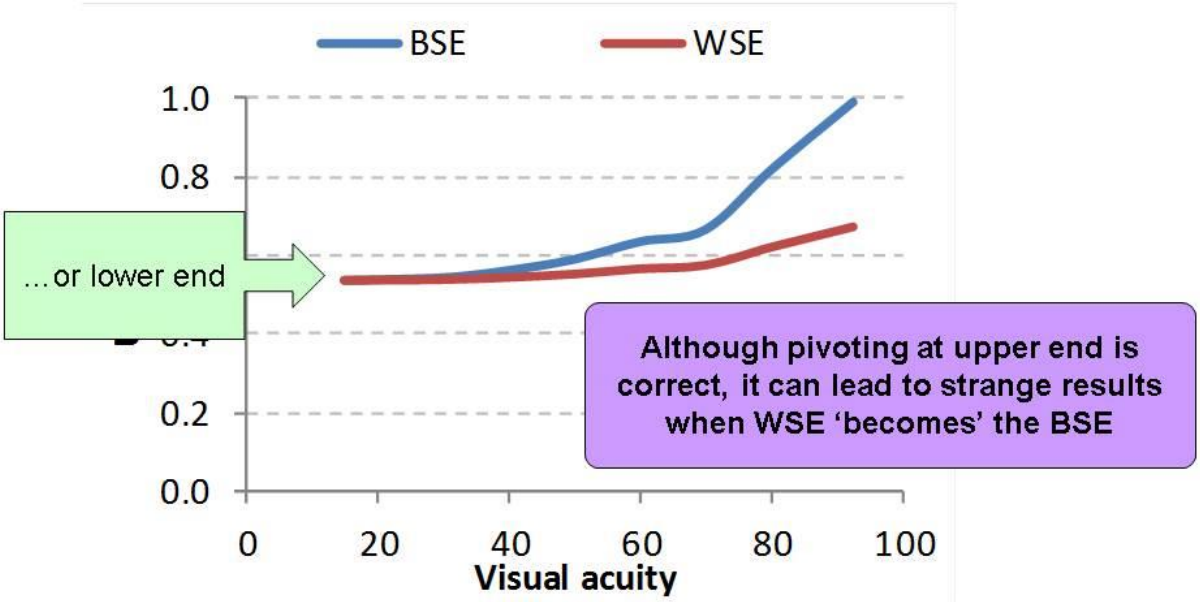
Quality of life



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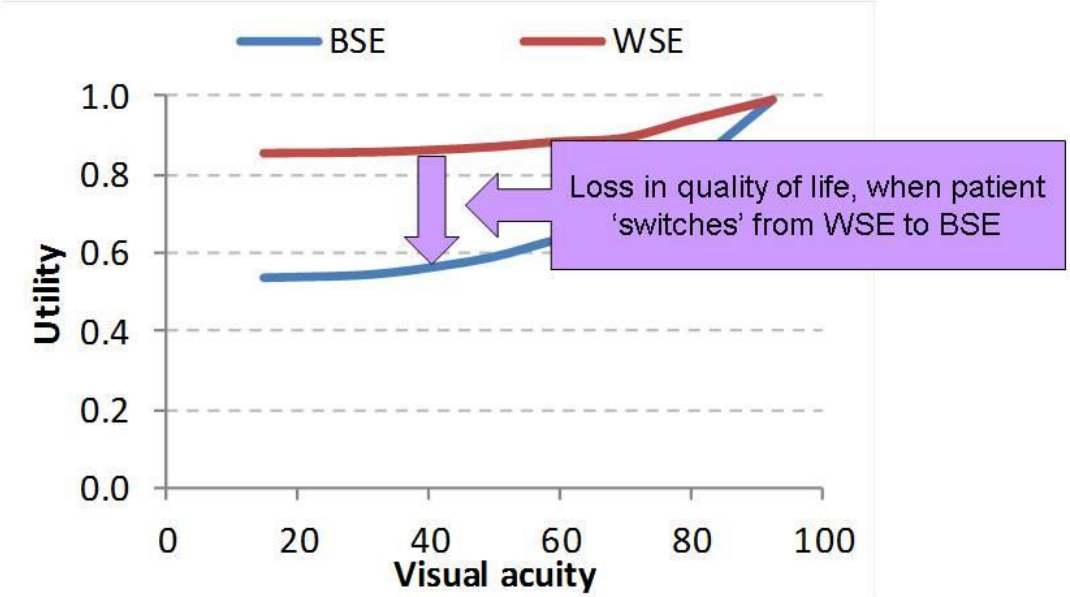
Quality of life (base case approach)



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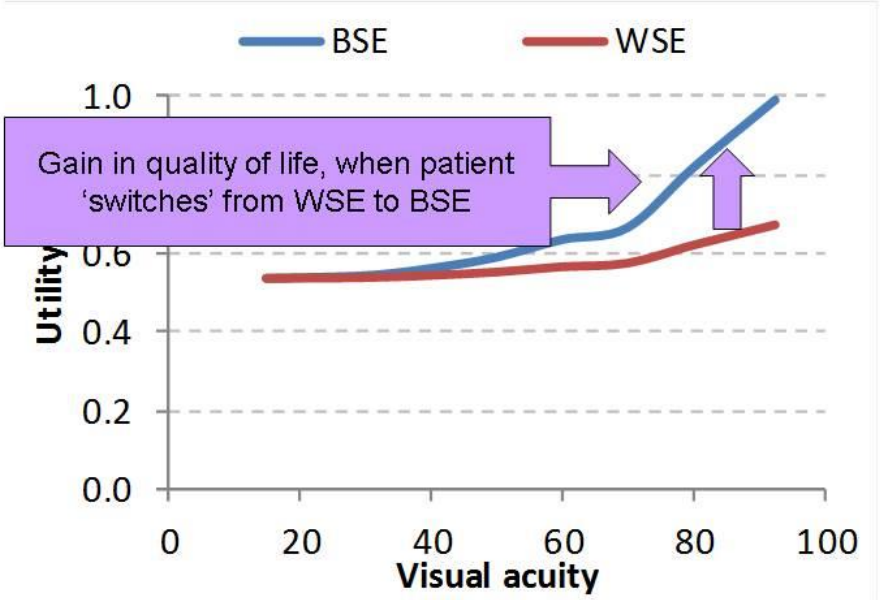
Quality of life



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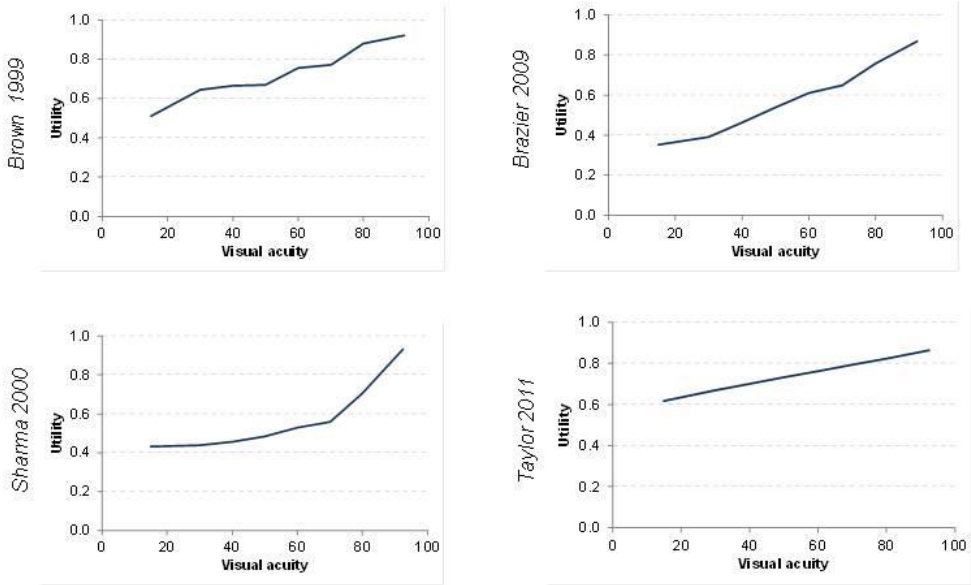
Alternative sources for VA – utility relationship



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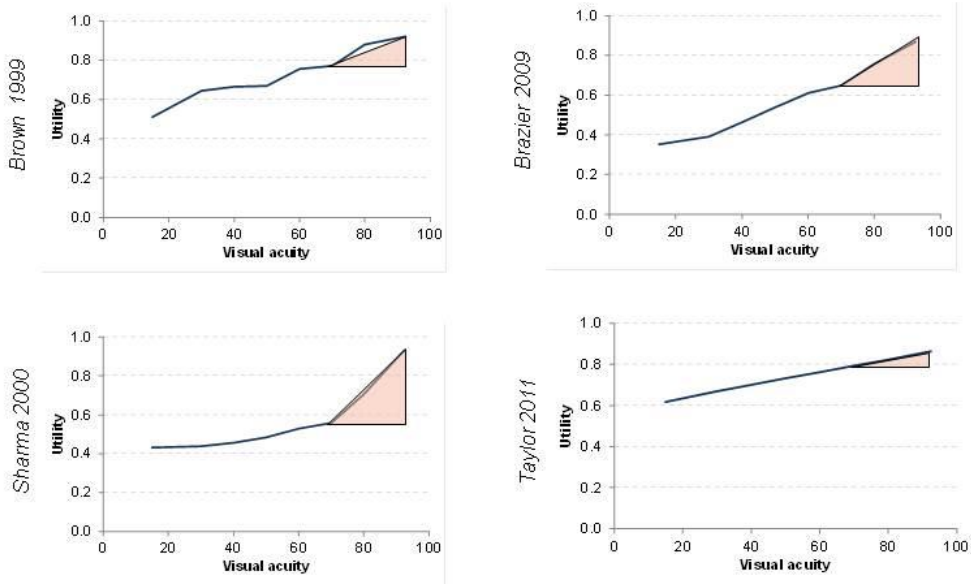
Impact on quality of life (VA increase from 70 to 95)



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Mortality

- All cause mortality based on life tables for England and Wales
- One study demonstrated a relationship between VA and risk of mortality
- Hazard ratio of death based on weighted average of those whose disease was in the WSE and the BSE

BCVA level	HR of mortality (BSE)	HR of mortality (WSE)
86-100	1.00	1.00
76-85	1.00	1.00
66-75	1.00	1.00
56-65	1.00	1.00
46-55	1.23	1.00
36-45	1.23	1.00
26-35	1.54	1.23
<25	1.54	1.23

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Mixed Treatment Comparison

- Networks informed by:
  - Patient level data from two clinical trials (Phase III and VIP)
  - Two studies with bevacizumab as a comparator (Iocono and Parodi)
- A Bayesian fixed effect model was used to describe the probabilities for each arm within trial.
  - The data provides limited information for estimating the between study variance in the random effects model
  - Each edge of the networks is only informed by one piece of direct evidence. For a robust random effects model, data from multiple comparisons of the same pairs of treatments is required
- For Iocono and Parodi, the numbers of patients in each health state in each arm were imputed from the number of patients, and the mean and standard deviation of the change in lines.

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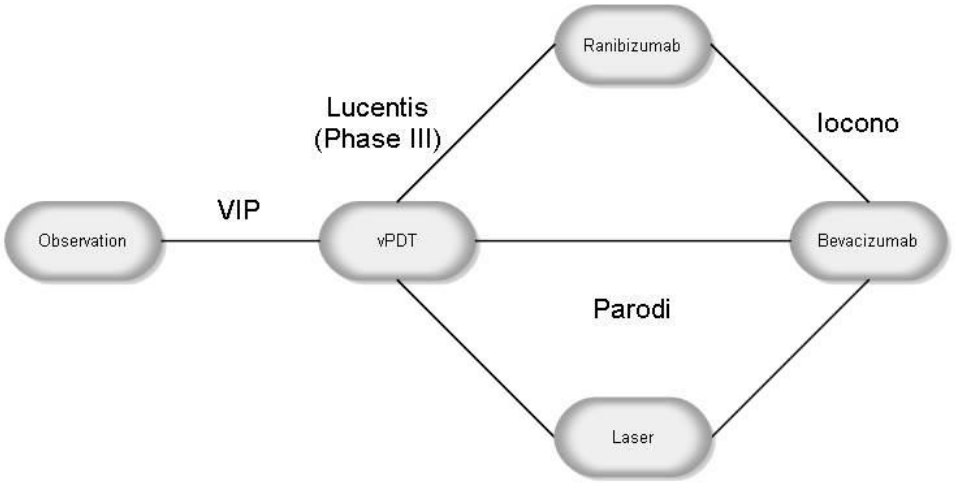
Network 1: Cycle 0-3 months



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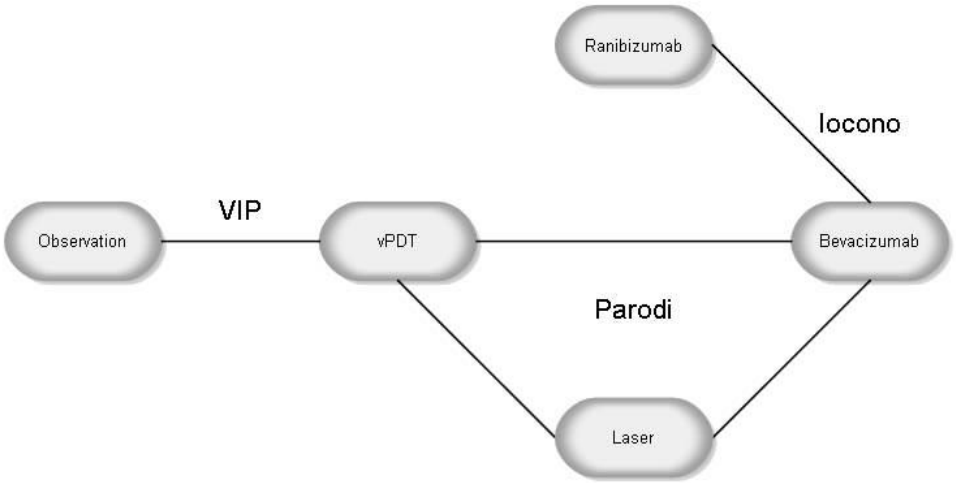
Network 2: Cycles 3-6, 6-9, 9-12 months



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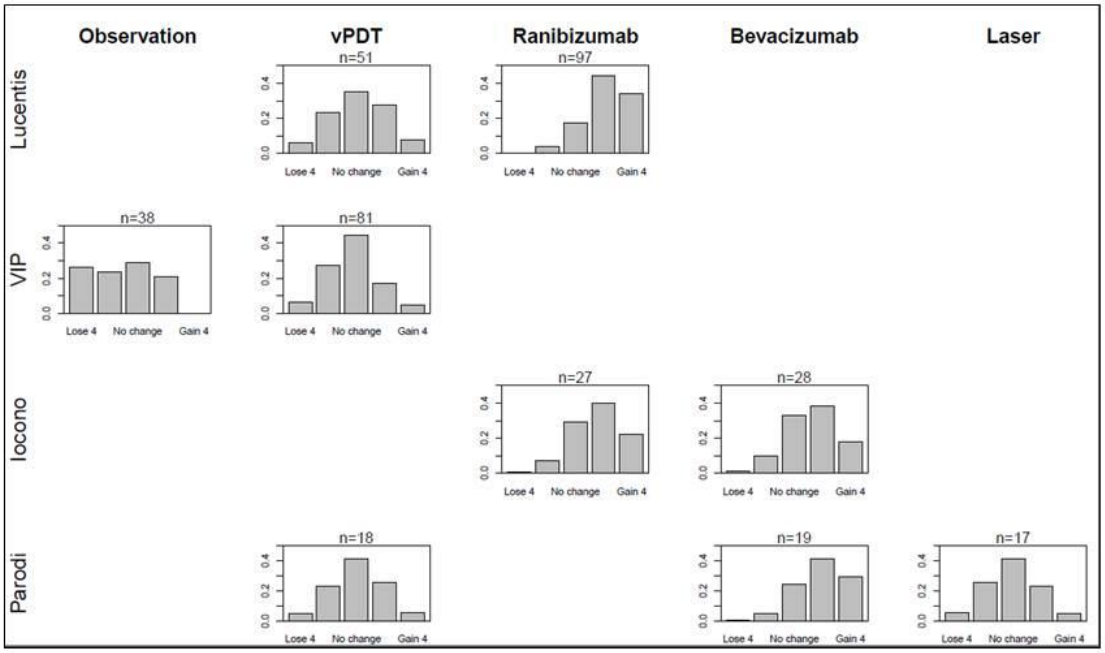
ITC: Months 0 to 3



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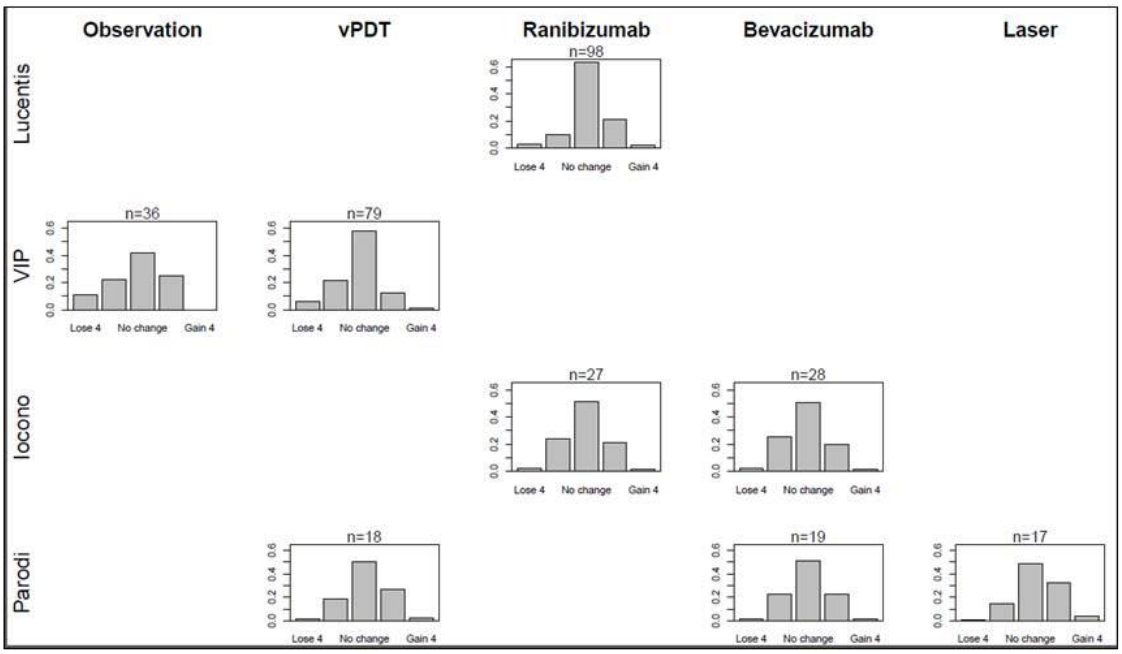
ITC: Months 3 to 6



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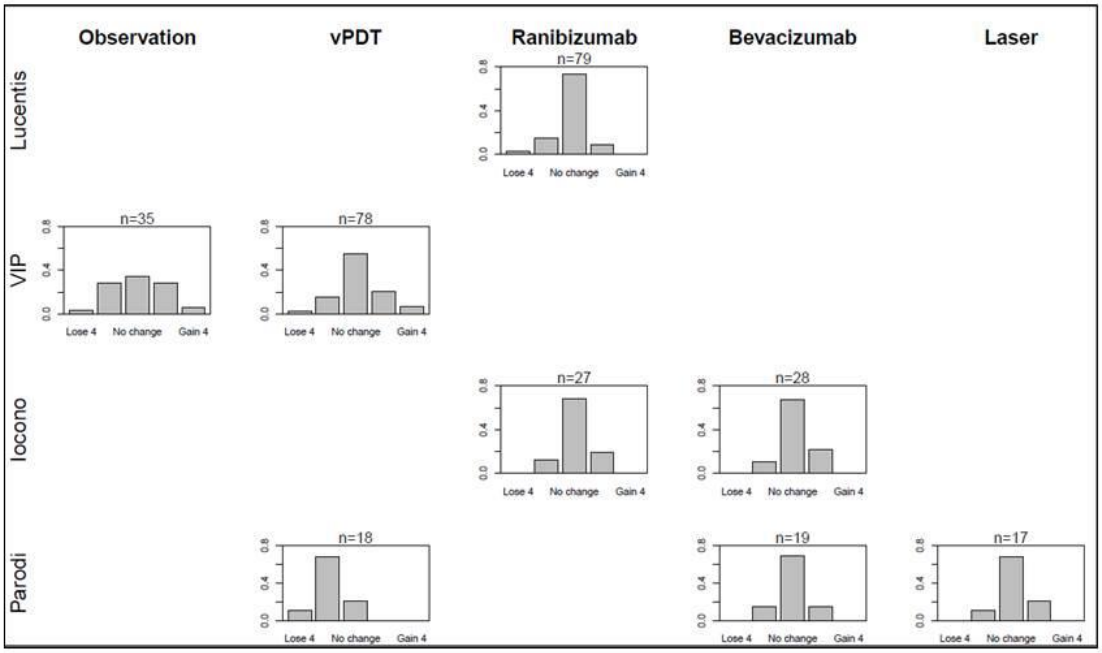
ITC: Months 6 to 9



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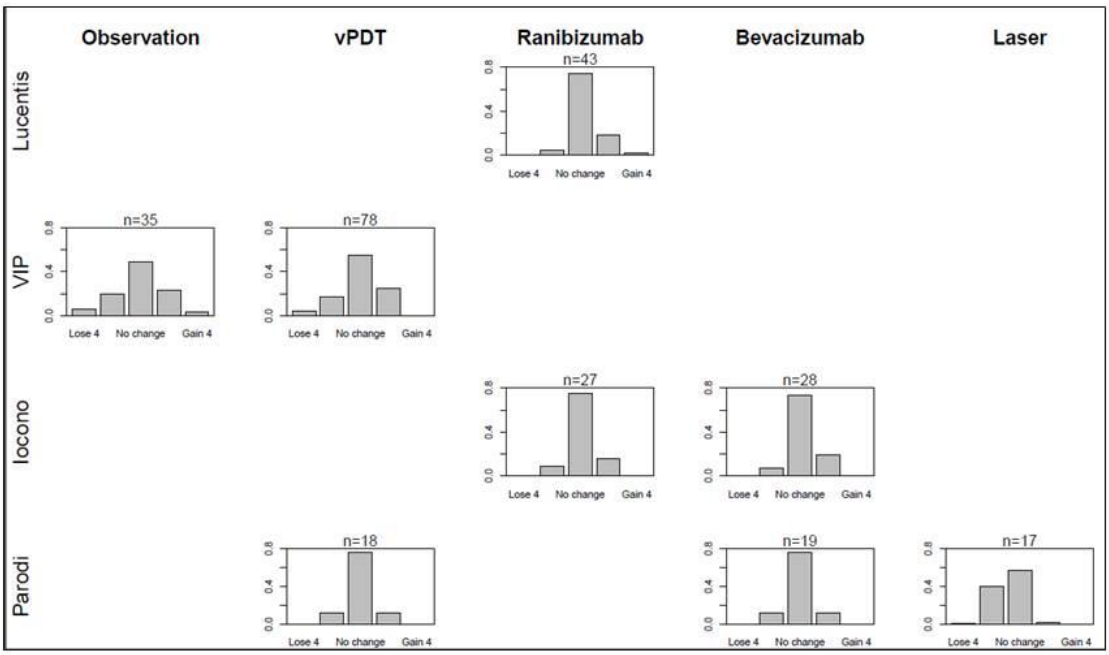
ITC: Months 9 to 12



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Results using base case scenario

Treatment	Ranibizumab
Comparator	vPDT
Time horizon	Lifetime

Willingness to pay	£20'000

	Ranibizumab	vPDT	Incremental
Total costs	£13'644	£21'013	-£7'369
Total QALYs	11.16	10.50	0.67
Life years (undiscounted)	21.42	21.20	0.22
Life years (discounted)	14.36	14.25	0.10
Months free from blindness	258.44	255.56	2.88
Incremental cost per QALY			**Dominant**
Incremental cost per life year			**Dominant**
Incremental cost per month free of blindness			**Dominant**
Net benefit			**£20'682**

Cost breakdown	Ranibizumab	vPDT	Incremental
Treatment costs	£3'222	£4'162	-£939
Admin costs	£732	£856	-£125
Monitoring	£2'100	£1'333	£767
Bilateral costs	£908	£953	-£45
Recurrence costs	£3'509	£3'116	£393
Adverse event costs	£106	£10	£96
Costs of blindness	£3'066	£10'583	-£7'517

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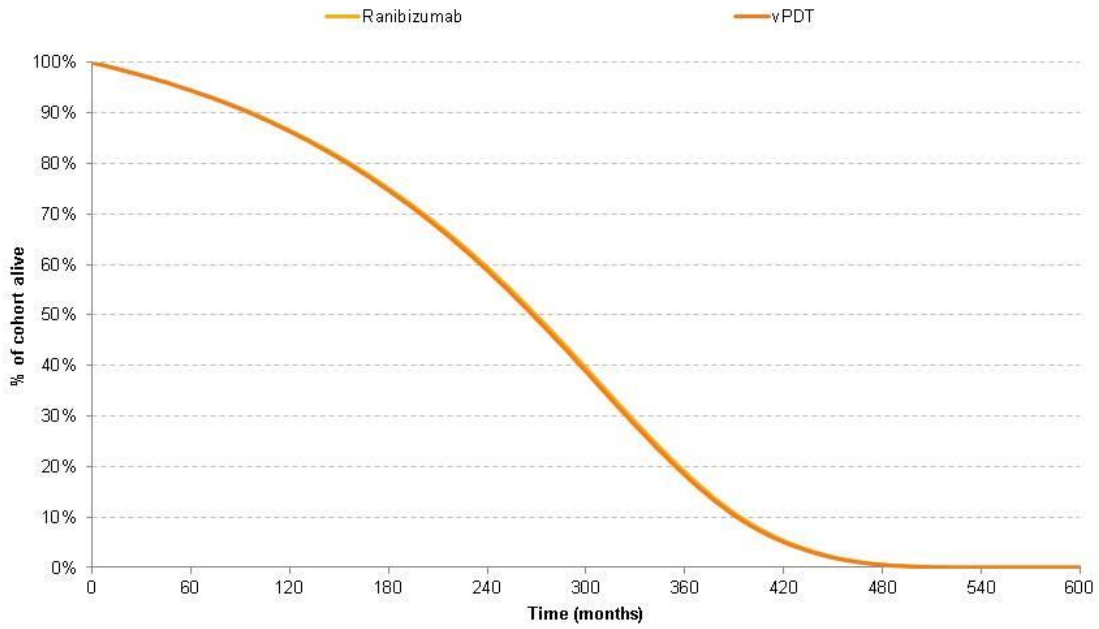
Survival



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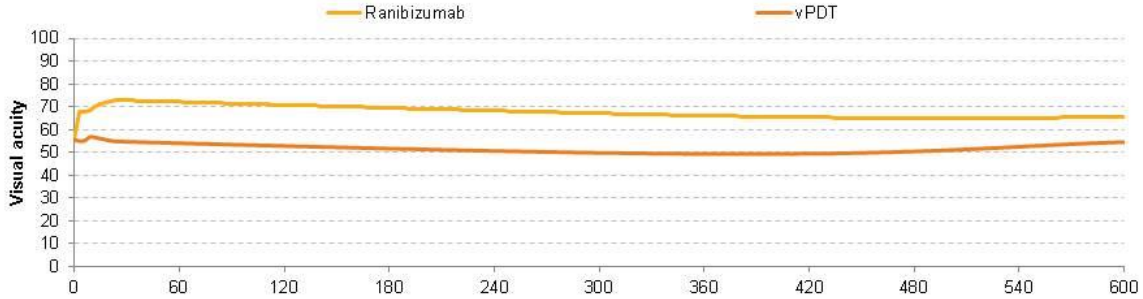
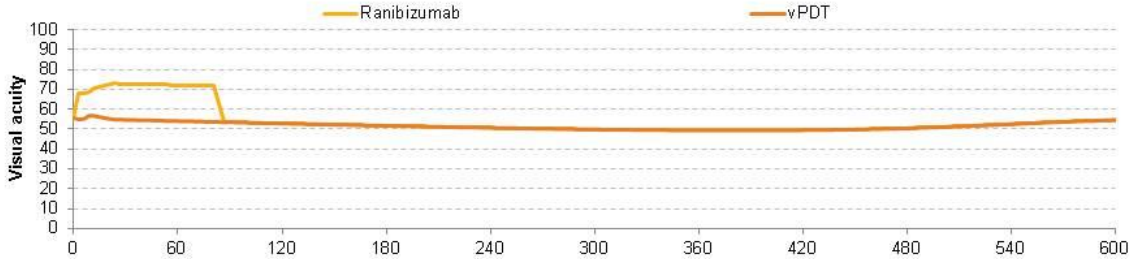
VA Charts: Parallel vs. Convergent Natural History





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Sensitivity Analyses

	Base case value	Range	ICER
Cost of treatment drug	£742.17	$3,750.00	£106,510.24
Cost of comparator drug	£850.00	$250.00	£28,918.50
Frequency of treatment (treatment year 1)	3.5	4	£9,789.29
Frequency of treatment (treatment year 2)	1	2	£12,477.85
Frequency of treatment (comparator year 1)	3.4	2	£16,121.08
Frequency of treatment (comparator year 2)	1.7	2	£4,944.44
Cost of administration visit (treatment)	£168.53	$100.00	£4,574.78
Cost of administration visit (comparator)	£174.89	$300.00	£2,243.04
Cost of monitoring visit	£174.89	$300.00	£10,489.25
Cost of blindness (multiplier)	1	1	£6,845.56
Probability that the study eye is the better seeing eye	1	1	£6,845.56
Starting age	55	70	Dominant
Baseline prevalence of bilateral disease	15%	8%	£6,974.17
Rate of recurrence	6%	3%	£7,076.68
Utility curve for BSE (multiplier)	1	1	£6,845.56
Utility curve for WSE	0.3	0.4	£5,965.85
Treatment transition probabilities (m 0-3)	1	1	£6,845.56
Treatment transition probabilities (m 3-6)	1	1	£6,845.56
Treatment transition probabilities (m 6-9)	1	1	£6,845.56
Treatment transition probabilities (m 9-12)	1	1	£6,845.56
Comparator transition probabilities (m 0-3)	1	1	£6,845.56
Comparator transition probabilities (m 3-6)	1	1	£6,845.56
Comparator transition probabilities (m 6-9)	1	1	£6,845.56
Comparator transition probabilities (m 9-12)	1	1	£6,845.56
Natural progression (multiplier)	1	1	£6,845.56

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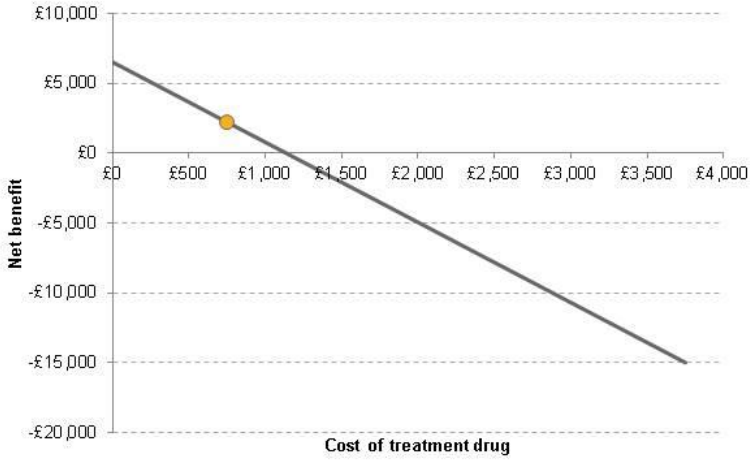
Sensitivity Analyses – cost of ranibizumab



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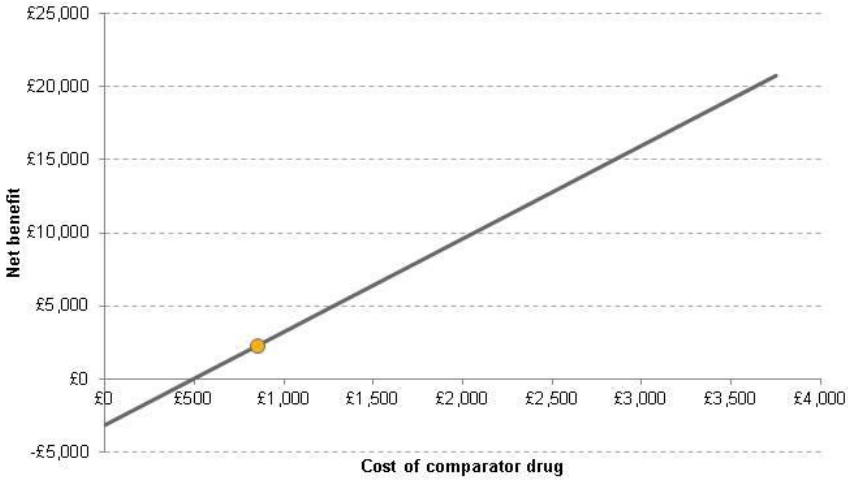
Sensitivity Analyses – cost of vPDT



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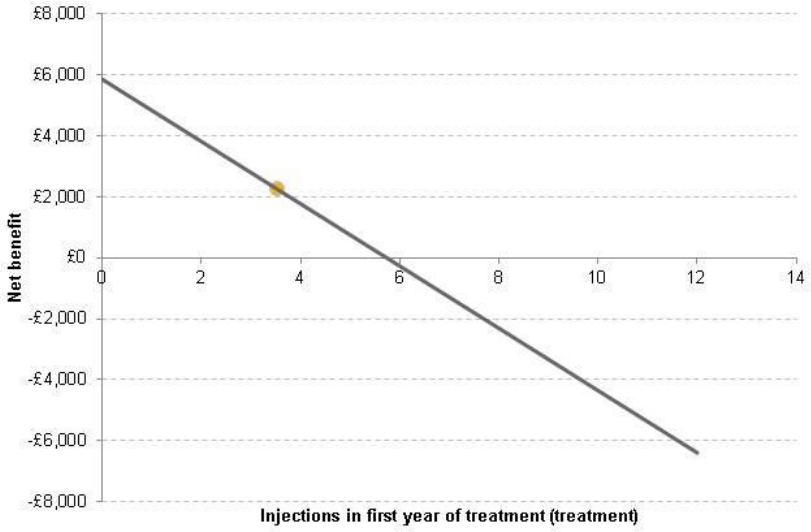
Sensitivity Analyses – ranibizumab injections in first year



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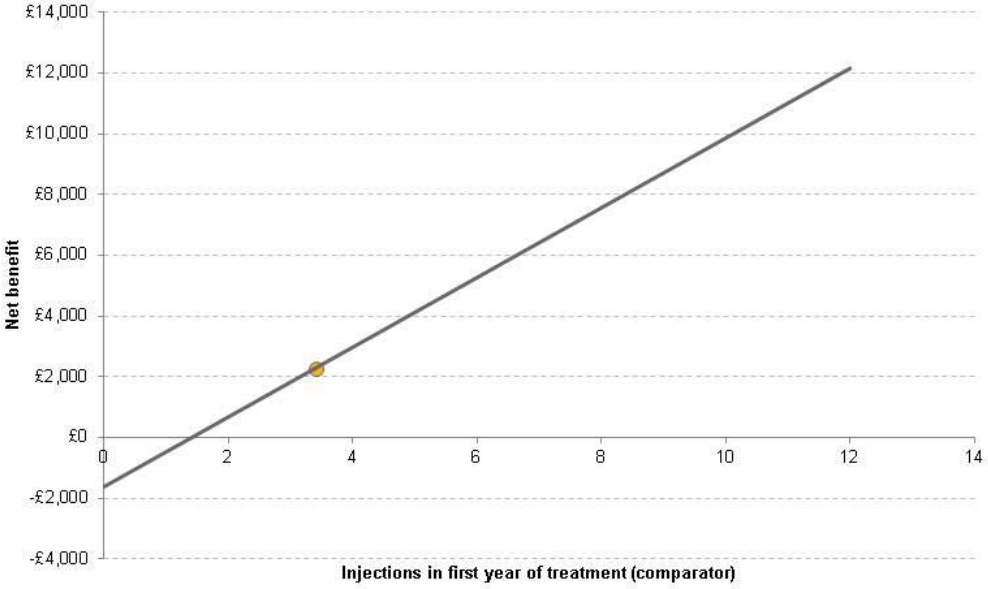
Sensitivity Analyses – vPDT treatments in first year



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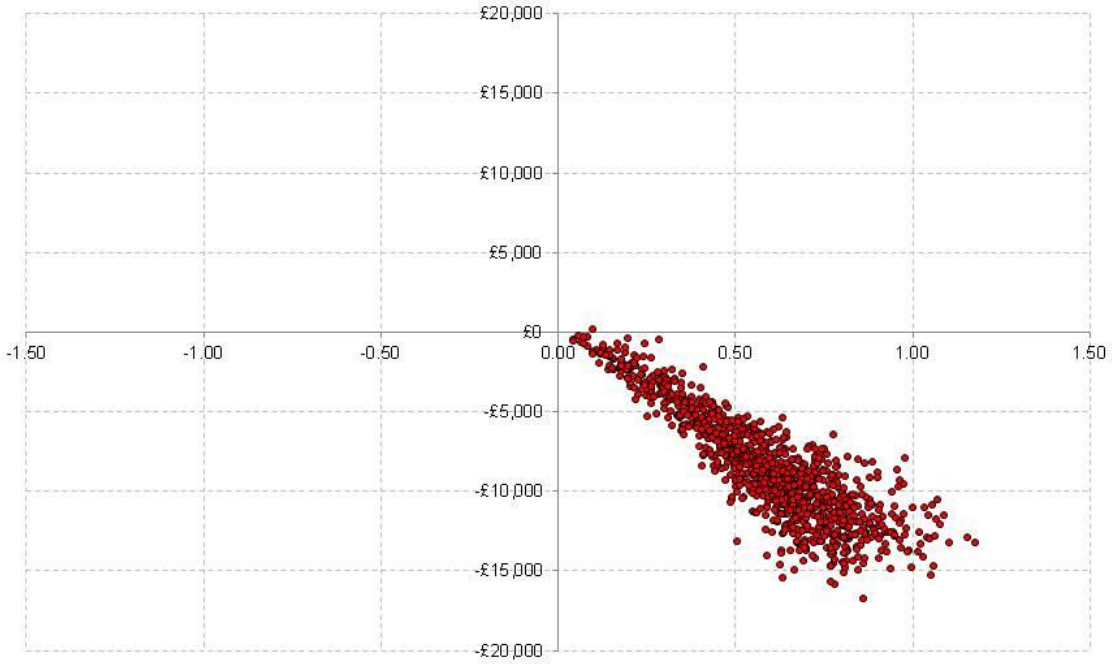
PSA



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Conclusion

- We are dominant versus vPDT over a wide range of assumptions
- Difference in cost
  - vPDT costs GBP 850/vial
  - Lucentis costs GBP 742.17/vial
- Same number of treatments given (3.5 vs. 3.4)
- Clinical trial data demonstrates superior efficacy for Lucentis vs vPDT
  - With Lucentis patients gain a mean of 14.4 letters at month 12 (change from baseline)
  - Patients treated with vPDT experience either a stabilized or deteriorating vision

- The only factor that influences the ICER is the consideration of treatment carry-over (parallel versus converging curves)

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Economically Justifiable Price using base case scenario

- Ranibizumab versus vPDT
  - GBP 3,456.50 to be cost effective at a WTP of GBP 20,000

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Scenario versus avastin (UK PAS applied)

Treatment	Ranibizumab
Comparator	Bevacizumab
Time horizon	Lifetime

Willingness to pay	£20'000

	Ranibizumab	Bevacizumab	Incremental
Total costs	£11'252	£10'801	£452
Total QALYs	11.00	10.97	0.02
Life years (undiscounted)	21.36	21.35	0.00
Life years (discounted)	14.33	14.33	0.00
Months free from blindness	257.66	257.60	0.06
Incremental cost per QALY			**£21'922**
Incremental cost per life year			**£201'159**
Incremental cost per month free of blindness			**£7'417.33**
Net benefit			**-£40**

Cost breakdown	Ranibizumab	Bevacizumab	Incremental
Treatment costs	£1'095	£431	£663
Admin costs	£414	£764	-£349
Monitoring	£2'100	£2'100	£0
Bilateral costs	£541	£494	£47
Recurrence costs	£1'895	£1'734	£162
Adverse event costs	£106	£0	£106
Costs of blindness	£5'100	£5'278	-£177

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Scenario versus Observation

Treatment	Ranibizumab
Comparator	Observation
Time horizon	Lifetime

Willingness to pay	£20'000

	Ranibizumab	Observation	Incremental
Total costs	£15'665	£16'057	-£391
Total QALYs	11.11	10.34	0.77
Life years (undiscounted)	21.37	21.10	0.27
Life years (discounted)	14.33	14.21	0.13
Months free from blindness	257.78	254.39	3.38
Incremental cost per QALY			**Dominant**
Incremental cost per life year			**Dominant**
Incremental cost per month free of blindness			**Dominant**
Net benefit			**£15'762**

Cost breakdown	Ranibizumab	Observation	Incremental
Treatment costs	£3'222	£0	£3'222
Admin costs	£732	£0	£732
Monitoring	£2'100	£1'956	£144
Bilateral costs	£908	£0	£908
Recurrence costs	£3'503	£0	£3'503
Adverse event costs	£106	£5	£101
Costs of blindness	£5'095	£14'096	-£9'001

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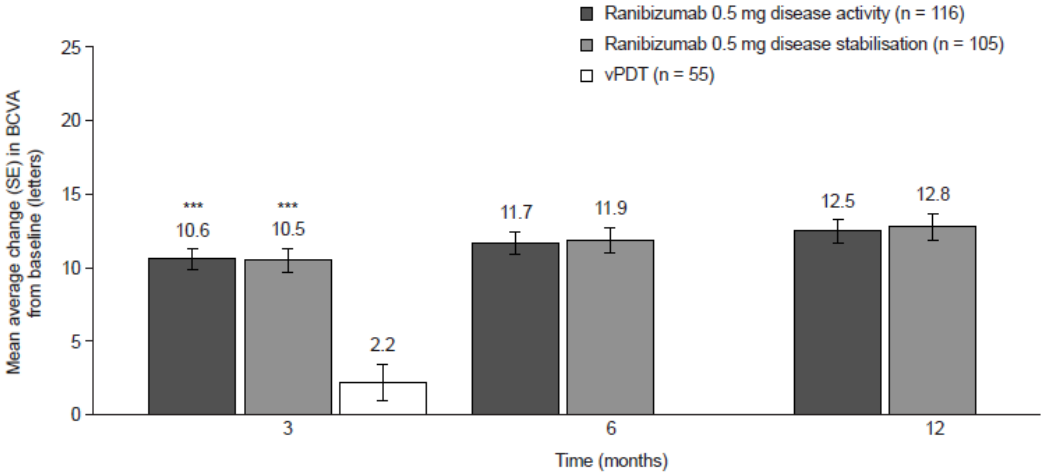
Figure 10 Mean (± SE) average change in BCVA from baseline to months 3, 6 and 12 during treatment with ranibizumab or vPDT



Bandello et al 2013[33,34] and Novartis phase III study 12 month CSR[32]
BCVA, best corrected visual acuity; SD, standard deviation; vPDT, verteporfin photodynamic therapy
***p < 0.001 vs vPDT