NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal (STA)

Specification for manufacturer/sponsor submission of evidence

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Executive summary

The technology

- Aflibercept solution for injection (Eylea) has received a positive opinion from the European Medicines Agency (EMA) to be licensed in the European Union for the treatment of macular oedema (MO) secondary to central retinal vein occlusion (CRVO).
- Aflibercept is a VEGF inhibitor. VEGF (vascular endothelial growth factor) is known to interfere with the growth of new blood vessels that leads to retinal oedema, ischaemia and haemorrhage in diseases of ocular neovascularisation.
- Aflibercept 40 mg/ml solution for injection is available in a vial for intravitreal injection. Each vial provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept. The list price of aflibercept solution for injection is £816, although a confidential simple patient access scheme is available.
- The expected posology for aflibercept solution for injection is to treat monthly, assuming adequate response after three injections, until stable for three consecutive monthly assessments. Thereafter, the need for continued treatment should be reconsidered and, if appropriate, treatment intervals should then be extended.
- Aflibercept does not have a specific requirement for continuous monthly monitoring. It is expected that monitoring will be done at injection visits and then, during treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.

Current treatment pathway

- Ranibizumab is now considered the standard of care for the treatment of MO secondary to CRVO. Ranibizumab was recently recommended for the treatment of CRVO by NICE guidance in May 2013 (TA283). In this appraisal, ranibizumab was found to be a cost effective use of NHS resources compared with best supportive care and, along with best supportive care, dominated dexamethasone. However, for completeness, we have made a comparison with dexamethasone as it is listed in the scope for this appraisal. We also updated the literature searches for bevacizumab to identify any evidence that would alter the Committee's conclusion that there was currently insufficient evidence to make robust comparisons with ranibizumab needed for cost-effectiveness analysis.

- According to its marketing authorisation, ranibizumab is given monthly, assuming adequate response after three injections, and continued until visual acuity has been stable for three consecutive months. Thereafter, visual acuity should be monitored monthly. Treatment should be resumed if monitoring indicates a loss of visual acuity and continued until visual acuity has remained stable for three consecutive months.

Clinical effectiveness

- Two pivotal randomised controlled trials (RCTs), COPERNICUS and GALILEO, compared aflibercept solution for injection to sham injections in patients with MO secondary to CRVO. The results of these studies showed monthly aflibercept injections to have a significant improvement in terms of visual acuity gain at 24 weeks, which was largely maintained through week 52 with dosing as needed.
- A mixed treatment comparison showed aflibercept to be numerically superior to ranibizumab in terms of proportion of patients gaining at least 15 letters from baseline to 24 weeks. Aflibercept was also shown to be numerically better than ranibizumab in terms of proportion of patients losing less than 15 letters and mean change in visual acuity from baseline to 24 weeks.
- Aflibercept was also statistically significantly better than dexamethasone in terms of proportion of patients gaining at least 15 letters and mean change in visual acuity from baseline to 24 weeks, the only two outcomes that were indirectly comparable.

Adverse events

- COPERNICUS and GALILEO demonstrated that aflibercept is well tolerated and had an acceptable safety profile compared to sham over the trial period.
- Although not directly compared in clinical trials for CRVO, the evidence indicates that aflibercept has a similar safety profile to ranibizumab. Both treatments work through VEGF inhibition and are administered via intravitreal injection. The VIEW studies for wet AMD directly compared the treatments and showed aflibercept to have a similar safety profile to that of ranibizumab.
- Dexamethasone, as a steroid, is associated with higher rates of cataract and intraocular pressure. The intravitreal implant also requires a larger needle to administer. However, it is not possible to fully compare safety outcomes for aflibercept with dexamethasone due to differences between studies and, in particular, adverse event reporting.

- There remained insufficient evidence to make a robust comparison with bevacizumab in terms of both efficacy and safety given the small size and modest quality of the studies.

Cost effectiveness

- A de novo Markov state-transition economic model was developed to compare aflibercept to ranibizumab in terms of cost per QALY gained, in line with the NICE reference case.
  - The model assumed that health states were based on the visual acuity in both eyes.
  - Treatment effectiveness was modelled using clinical data from the pivotal clinical trials, COPERNICUS and GALILEO, and the network meta-analysis
  - Utilities were based on EQ5D data from the pivotal trials.
  - Resource use was based on clinical trial data, data systematically obtained from the literature and expert opinion, with unit costs based on NHS reference costs.
- The results of the base-case analysis showed that compared with ranibizumab, aflibercept was associated with marginal gains in life years (LYs) (incremental LYs: 0.001), QALYs (incremental QALYs: 0.054) and costs (incremental costs: £[redacted]). Compared to ranibizumab, aflibercept was deemed cost-effective in the treatment of macular oedema secondary to CRVO (ICER: £[redacted]/QALY).

Base-case results: aflibercept vs. ranibizumab

Technologies	Total costs (£)	Total QALYs	Incremental costs (£)	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	[redacted]	-	-	-
Ranibizumab	[redacted]	[redacted]	[redacted]	0.054	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years					

- Cost effectiveness was sensitive to changes in frequency of injections, monitoring, relative risks and utilities. However, aflibercept remained cost effective versus ranibizumab in all scenario analyses that included changes to assumptions of treatment duration, utility values and adverse events. Compared with dexamethasone, aflibercept was cost effective in terms of the assumed threshold of £20,000 per QALY gained.

- Given that aflibercept was shown to be clinically and cost effective in the entire CRVO population, including ischaemic patients, subgroup analyses were not considered.

Section A – Decision problem

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.

Aflibercept solution for injection (Eylea®) is a vascular endothelial growth factor (VEGF) inhibitor. Aflibercept 40mg/ml solution for injection in a vial is for intravitreal use only. 1ml solution for injection contains 40mg aflibercept.

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

Aflibercept solution for injection treats adults with macula oedema secondary to central retinal vein occlusion (CRVO) through VEGF inhibition. It is a potent specific inhibitor of VEGF that interferes with the growth of new blood vessels that leads to retinal oedema, ischaemia and haemorrhage in diseases of ocular neovascularisation. Aflibercept is a fully human fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1. It binds to all known VEGF-A isoforms and also Placental Growth Factor (PlGF)(1-3).

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).

The Committee for Medicinal Products for Human Use (CHMP) at the European Medicines Agency (EMA) is expected to give its positive opinion to aflibercept solution for injection for the treatment of macula oedema (MO) secondary to CRVO in July 2013. Marketing authorisation is expected to be gained in the UK via the centralised European regulatory procedure in September 2013.

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).

An EPAR and final Summary of Product Characteristics (SmPC) are not yet available. It is not expected that there will be special conditions, exceptional circumstances or conditions attached to the marketing authorisation.

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

It is expected that aflibercept solution for injection will be indicated for the treatment of MO secondary to CRVO. Aflibercept is already licensed in the UK for the treatment of adults with neovascular wet age-related macular degeneration (AMD).

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.

The two pivotal phase III, randomised controlled clinical trials for aflibercept for the treatment of macular oedema secondary to CRVO are the GALILEO and COPERNICUS studies. Both these studies compared aflibercept with sham injections. 6 month and 1 year data have been published for COPERNICUS and 6 month data have been published for the GALILEO study(4-6). Further abstracts and unpublished clinical trial data from 76 week (GALILEO) and 100 week (COPERNICUS) timepoints are available.

There is one other relevant ongoing study of aflibercept solution for injection for CRVO, the NEWTON study (NCT01870427), expected to report in the next 12 months (see www.clinicaltrials.gov). However, no data is yet available for this study.

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

Not applicable

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

The marketing authorisation process for the UK was centralised through the EMA. Eylea received marketing approval from the Food and Drug Administration (FDA) in the USA in September 2012 (http://www.fda.gov/Drugs/default.htm). The recommended dose is 2 milligrams (mg) every 4 weeks (monthly) as this authorisation was based on early data from the pivotal studies which included 6 monthly loading doses of aflibercept. Further data beyond 6 months are available for the European application.

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?

An SMC submission for aflibercept for the treatment of MO secondary to CRVO will be made around the time of marketing authorisation (i.e. September 2013).

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 1. Unit costs of technology being appraised

Pharmaceutical formulation	Eylea 40 mg/ml solution for injection in a vial(5). 1 ml solution for injection contains 40 mg aflibercept(7).
Acquisition cost (excluding VAT)	Each vial contains 100 microlitres, equivalent to 4 mg aflibercept. This provides a usable amount to deliver a single dose of 50 microlitres containing 2 mg aflibercept.
Method of administration	£816 list price. A confidential simple patient access scheme is available.
Doses	Aflibercept solution for injection (Eylea) is for intravitreal injection only
Dosing frequency	The recommended dose for aflibercept is 2 mg aflibercept, equivalent to 50 microlitres. According to the *draft SmPC*, it is expected that after the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended. Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered. If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate. Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections.
Average length of a course of treatment	
Average cost of a course of treatment	
Anticipated average interval between courses of treatments	
Anticipated number of repeat courses of treatments	
Dose adjustments	Not applicable

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 not expected that there will be any additional tests or investigations needed for selection for aflibercept solution for injection compared with current NHS treatment. Ranibizumab, another anti-VEGF, is already recommended by NICE for the treatment of MO secondary to CRVO(8).

Both aflibercept solution for injection and ranibizumab require administration via intravitreal injection only(7;9). As per current practice for treatment with intravitreal injections for other back of the eye conditions, immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available.

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

It is not expected that the need for monitoring with aflibercept solution for injection will be over and above that currently required for the treatment of MO secondary to CRVO in the NHS. The SmPC for ranibizumab(9) specifies that patients should be monitoring monthly for visual acuity following monthly treatment which has been continued until maximum visual acuity is achieved. According to the *draft SmPC*, aflibercept is expected to have a less stringent monitoring requirement compared with ranibizumab. It is expected that monitoring between extended treatment intervals will determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections. Therefore, fewer monitoring visits would be expected overall if treating according to the label.

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?

As with current practice for the treatment of CRVO, aflibercept intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended(7).

2 Context

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.

The presentation of CRVO is usually acute, with the most frequent symptom being an abrupt decrease of central vision that is distressing to many patients. Less frequently, patients may present with a history of transient obscuration of vision, lasting a few seconds to minutes, with complete recovery to normal. There may be a recurrence of these symptoms over a period of days to weeks followed by a decrease in vision. Metamorphopsia (image distortion) and visual field defects have also been described(10).

Clinically, the features of CRVO are characterised by superficial and deep intraretinal haemorrhages in all four quadrants of the retina. This can be accompanied by retinal venous engorgement and tortuosity, optic disc swelling, cotton wool spots, and cystoid macular oedema. The severity of the venous occlusion is reflected by the baseline visual acuity, which is influenced by the degree of macular intraretinal haemorrhage, retinal ischemia (reduced blood supply to the retina), and cystoid macular oedema(11).

In recent years, there has been an increase in the availability of information on the aetiology and pathogenesis of retinal vascular disease in general and its involvement in venous occlusion(12). However, despite the wealth of data available, the pathogenesis of CRVO is not completely understood(11).

Factors underlying the causes of CRVO are clearly multi-factorial in nature. Close associations have been noted between the incidence of CRVO and the presence of cardiovascular risk factors such as increased age, hypertension, diabetes mellitus, and arteriosclerotic vascular disease(13-15). Associations have also been noted with thrombophilia and glaucoma. In contrast, there does not appear to be any association between smoking and CRVO(14;15).

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.

There are currently approximately 12 new patients with MO secondary to CRVO eligible for treatment per 100,000 of the population in England and Wales(16) each year. This equates to 6,720 eligible for treatment overall in a population of 56 million (Office of National Statistics - Mid-1971 to Mid-2011 Population Estimates: England, Wales and regions; estimated resident population, April 2013).

Aflibercept solution for injection in a vial is also indicated for adults for the treatment of neovascular (wet) AMD. There are 39 new patients per 100,000 of the population eligible for treatment each year(17). This equates to 21,840 in the total population of England and Wales.

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.

There is evidence of a link between visual impairment and mortality although the exact nature of this relationship is uncertain.

Thiagarajan et al 2005(18) reported the rate ratio for all-cause mortality for elderly people with binocular visual acuity (VA) <6/18 (20/60 Snellen equivalent) versus people with ≥ 6/6 VA is 1.17 (1.07 – 1.27 95% CI) after adjusting for confounders. Excess mortality for blind patients (both eyes) using the hazard ratio (1.28; 95%CI 1.07-1.53) was also reported by Christ et al 2008(19) in a somewhat younger population. The paper estimated the effects of vision loss on mortality using a structural equation modelling approach.

There is also some evidence of a link between CRVO, vascular risk factors and subsequent mortality. However, as discussed in previous appraisals for retinal vein occlusion (RVO) at NICE(8;20), the exact nature of this relationship is insufficiently clear for inclusion. Tsaloumas et al (2000)(21) addresses this issue in a nine year follow-up study of morbidity and mortality in RVO (including branch retinal vein occlusion) which suggested a relationship between RVO, mortality and increased cardiovascular risk factors (smoking, diabetes and macrovascular disease), and support the possibility of an association between RVO and stroke. However, other studies cited in the NICE appraisal for ranibizumab for RVO(8) have shown that there is no evidence that overall mortality was

lower for RVO patients than the general population (Christofferson 2007 – reference not available)(22) and that low rates have been seen in ranibizumab pivotal clinical trials for RVO (CRUISE, BRAVO).

Please see economic section 7 for further discussion.

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.

TA283 - Ranibizumab for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (May 2013).

TA229 - Macular oedema secondary to retinal vein occlusion – dexamethasone intravitreal implant (July 2011).

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.

Aflibercept solution for injection would be an additional and alternative option to standard of care, ranibizumab, for the treatment of MO secondary to CRVO.

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

The main issue for those involved in the treatment of MO secondary to CRVO in the UK is the burden of treatment with current standard of care and its associated mandatory monthly monitoring in terms of resources required and capacity available in ophthalmology as a whole. With an ageing population, the burden on the NHS is increasing with new patients presenting for back-of the-eye conditions such as wet AMD and diabetic macular oedema (DMO), and existing patients continuing on treatment. This subsequently impacts on resources available to treat CRVO.

Current standard of care, ranibizumab, requires monthly monitoring of visual acuity(9), and usually, anatomical outcomes using optical coherence tomography (OCT). There is still an unmet need for effective treatments without the burden of mandatory monthly monitoring visits.

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

We consider ranibizumab to be the main comparator for this appraisal as it is the treatment which would potentially be displaced by aflibercept. For completeness, we have also made a comparison with dexamethasone as it is listed in the scope for this appraisal.

Ranibizumab is the most recently NICE-recommended option for the treatment of MO secondary to RVO(8), with guidance published in May 2013. In this appraisal, ranibizumab was found to be a cost effective use of NHS resources versus best supportive care (BSC), the comparator used for final decision making. Dexamethasone was extended dominated by both best supportive care and ranibizumab and was, thus, discounted from the decision making process. In this appraisal, the Committee concluded that, with regard to bevacizumab, "…there is currently insufficient evidence to make robust comparisons with ranibizumab needed for a cost-effectiveness analysis."

Dexamethasone intravitreal implant(20) was the first treatment to be recommended by NICE in 2010. Whilst found to be cost effective at that time versus best supportive care, it was subsequently found to be dominated by ranibizumab and BSC in the more recent appraisal of ranibizumab. In addition, steroids are associated with a substantial risk of intraocular pressure, cataracts and have a larger needle for administration. For this reason, according to clinical opinion obtained from a Bayer advisory board in 2013, it is expected that ranibizumab treatment, now licensed and recommended by NICE for CRVO, will become the first choice, standard of care for the treatment for MO secondary to CRVO and that treatment with dexamethasone will now become second-line, and for subgroups of patients such as pseudophakic patients who are at lower risk of cataracts.

The scope for this appraisal also lists bevacizumab and BSC as comparators for CRVO. We have updated the literature searches for bevacizumab to identify any evidence that would alter the Committee's conclusion that there was currently insufficient evidence to make robust comparisons with ranibizumab needed for cost-effectiveness analysis.

These treatments are not recommended by NICE guidance and are no longer considered routine or best practice in the NHS as two NICE recommended treatments are available.

- Prior to 2010, there were no licensed pharmacological treatments in the UK for the treatment of MO secondary to CRVO. Therefore, the options available to clinicians in the NHS were limited to unlicensed treatments, such as bevacizumab, or BSC. Now, with two licensed, NICE-recommended treatments available, according to clinical opinion from a Bayer advisory board in 2013, this situation has since changed and best supportive care and bevacizumab are no longer standard of care in the NHS for the treatment of MO secondary to CRVO. Funding for ranibizumab treatment must be made available within three months of the positive guidance for RVO in May 2013.

- The Decision Support Unit (DSU) report(23) stated that following NICE guidance in favour of the use of ranibizumab in patients with AMD, few clinicians use bevacizumab in this patient group. We assume that this would also be the case for RVO. Given this survey by the DSU was conducted in summer 2012 and, since NICE guidance now exists for ranibizumab, we cannot use this report to evaluate bevacizumab usage as it is now outdated. In addition, at the time, comments made by consultees on the DSU report, question the reliability of the survey methodology and its response rate.

- In addition, as previously mentioned, bevacizumab was excluded from final decision making in the appraisal of ranibizumab for RVO for the following reasons:
  - *"Having noted the available evidence and comments from consultation on the safety, efficacy and quality of intravitreal bevacizumab, the Committee concluded that bevacizumab is an appropriate potential comparator in this appraisal. However, the Committee further concluded that there is currently insufficient evidence to make robust comparisons with ranibizumab needed for a cost-effectiveness analysis"*

In the presence of two NICE recommended treatments, it is unlikely that CRVO patients will go untreated with clinical observation. The occasions where this may occur is when patients are contraindicated to anti-VEGF and steroid treatment or refuse intravitreal injections. These cases would be no more eligible for aflibercept than currently available treatment. Nevertheless, given that the pivotal trials for aflibercept were sham-controlled, we have addressed this as a comparator in terms of clinical effectiveness.

Given its licensed status, positive NICE recommendation, and preferential efficacy and safety profile compared with the previous options available, ranibizumab may now be considered the most relevant comparator for aflibercept. However, for completeness, we have considered the other comparators listed in the scope for this appraisal.

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

The VIEW studies for wet AMD(24) and the subsequent EMA evaluation(7) indicate that aflibercept has a similar safety profile to ranibizumab. Both intervention treat macular oedema secondary to CRVO through VEGF inhibition and both treatments require intravitreal injection using proper aseptic injection techniques. In addition, serious adverse reactions related to the injection procedure have occurred in less than 1 in 1,000 intravitreal injections with aflibercept solution for injection. It is not anticipated that aflibercept will require any additional therapies to manage adverse events than those already used to manage adverse events with current standard of care. As previously described, steroids are generally associated with higher rates of intraocular pressure compared with anti-VEGF injections. As a results, medicines to treat intraocular pressure and cataracts may be required but to a lesser extent than with steroidal treatments. This topic is discussed in more depth in the context of economic modelling in Section 7.

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.

As with current standard of care, treatment with aflibercept takes place in specialist ophthalmologist clinics. Intravitreal injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering intravitreal injections. In general, adequate anaesthesia and asepsis, including topical broad spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface), have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) are recommended(7).

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, sterile equipment for paracentesis should be available(7). Following intravitreal injection patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g. eye pain, redness of the eye, photophobia, blurring of vision) without delay. Each vial should only be used for the treatment of a single eye. After injection any unused product must be discarded(7).

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

No. As with current practice, administration of aflibercept will be via intravitreal injection. As with current practice, monitoring will be of visual acuity and anatomical outcomes using OCT. However, a reduction in monitoring requirements will potentially enable a more efficient use of the infrastructure that is currently in place.

3 Equality

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 identified.

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.

Aflibercept solution for injection is innovative as it has a different mode of action to the other VEGF inhibitors. It addresses a wider range of growth factors and includes Placental Growth Factor (PIGF) binding(1-3).

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.

It is expected that aflibercept solution for injection will provide for reductions in both case load and budget requirements. There would be cost and capacity savings in frequency of monitoring compared with current licensed anti-VEGF treatments in an NHS which is currently under increasing pressure for its ophthalmology services. This impact on service capacity is unlikely to be captured by the QALY calculation.

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.

See response above.

5 Statement of the decision problem

	Final scope issued by NICE	Decision problem addressed in the submission	Rationale if different from the scope
Population	Adults with visual impairment due to macular oedema caused by CRVO	Adults with visual impairment due to macular oedema caused by CRVO	Not applicable.
Intervention	Aflibercept solution for injection	Aflibercept solution for injection	Not applicable
Comparator (s)	Ranibizumab Dexamethasone Bevacizumab Clinical observation	Ranibizumab Dexamethasone Bevacizumab Clinical observation	See Section 2.7
Outcomes	Visual acuity (the affected eye) Visual acuity (the whole person) Need for pan-retinal photocoagulation Adverse effects of treatment Health-related quality of life.	Visual acuity (the affected eye) Visual acuity (the whole person) Need for pan-retinal photocoagulation Adverse effects of treatment Health-related quality of life.	Not applicable
Economic analysis	Incremental cost per quality-adjusted life year. Lifetime horizon Costs will be considered from an NHS and Personal Social Services perspective	Incremental cost per quality-adjusted life year. Lifetime horizon Costs will be considered from an NHS and Personal Social Services perspective	Not applicable
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: •the presence or absence of ischaemia •baseline visual acuity •central macular thickness. Guidance will only be issued in accordance with the marketing authorisation.	If the evidence allows, consideration will be given to subgroups according to: •the presence or absence of ischaemia •baseline visual acuity •central macular thickness. Guidance will only be issued in accordance with the marketing authorisation.	We believe that aflibercept is clinically and cost effective in all patients with macular oedema secondary to CRVO. Therefore, we do not believe such an analysis will be required.
Special considerations	None	None	Not applicable

Section B – Clinical and cost effectiveness

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(s), quality-adjusted life year(s)		

6 Clinical evidence

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 search of the literature was undertaken to identify RCTs investigating the efficacy and safety of aflibercept in the treatment of CRVO. This formed part of a broader search for evidence to support any requirement for indirect comparisons or network meta-analysis (NMA) of clinical studies of ranibizumab, dexamethasone, and bevacizumab, and placebo / sham or BSC for the treatment of patients with MO secondary to CRVO and to identify data for MO secondary to CRVO cost-effectiveness model inputs.

A randomised “controlled” trial was defined as any randomised trial with at least two arms, where the comparator may be a different active ingredient/therapy, placebo or the same active ingredient as the intervention but administered at a different dosage. The RCT publications needed to provide data about efficacy in terms of improved visual acuity and safety for each arm and, if available, on HRQoL.

The search was undertaken on March 11th 2013 using Medline, Medline in process, EMBASE and the Cochrane Library. The databases were searched to identify the relevant studies published over the past 11 years (2002-2013). This period was selected because the start date of the earliest phase III trial identified in the area of CRVO involving at least one of the interventions of interest was 2004. Searches consisting of groups of search strings were developed and run for each database using the platform Ovid.

In addition, various conference proceedings (American Academy of Ophthalmology (AAO), Association for Research in Vision and Ophthalmology (ARVO), European Association for Vision and Eye Research (EVER), Nordic Congress of Ophthalmology (NOK) and the

World Ophthalmology Congress (WOC)), online clinical trial registries (www.clinicaltrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP)), national clinical guidelines and UK HTA reports [in the area of retinal vein occlusion (RVO)] were searched. These additional searches were limited to the past three years.

The explicit methods for systematic review specified by the Cochrane Collaboration and NICE were followed. Full details of the literature search strategy including search terms employed are provided in Section 10.2, Appendix 2.

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.

All references identified through searches were exported to Reference Manager 11 databases. The databases were merged and deduplicated and exported to an Excel spreadsheet. Two reviewers independently screened each reference for relevance and any disagreements were resolved through 'reconciliation' (discussion between the two reviewers) or through 'arbitration' by a third independent reviewer. The 'majority view' determined inclusion or exclusion. Excluded publications were disregarded. Publications that appeared to be potentially relevant were ordered for a full review of the text and assessed for inclusion by two reviewers using the same approach as the initial abstract screening.

Searches were limited to evidence published between 2002-2013 and in the English language.

A flow diagram of the numbers of records included and excluded at each stage is provided in section 6.2.2.

Inclusion and exclusion criteria

Table 2. Eligibility criteria used in search strategy

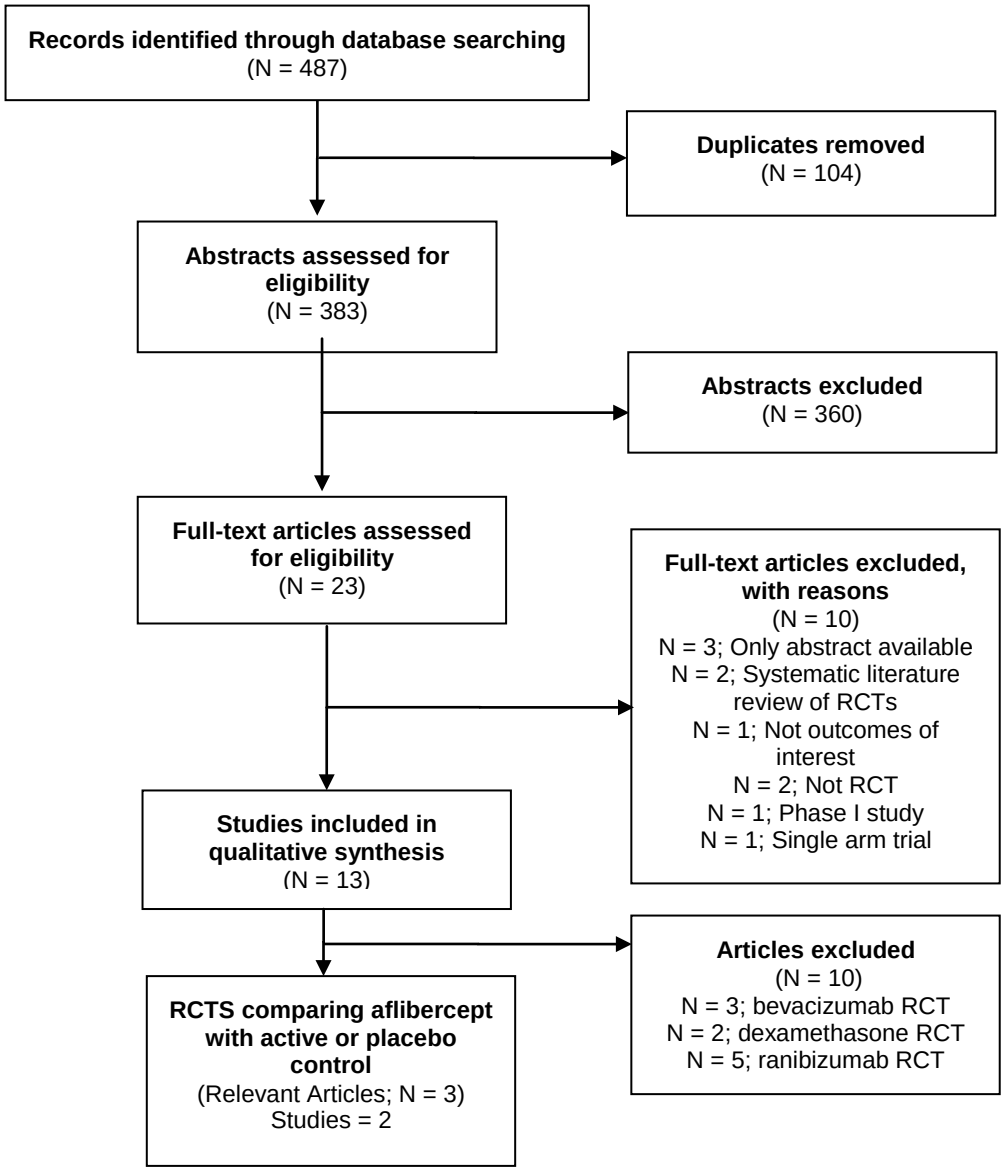
Clinical evidence	Inclusion	Exclusion
Patient population	Adult patients with CRVO (studies	Patients with RVO only*, BRVO,

Clinical evidence	Inclusion	Exclusion
	reporting results for CRVO patients as 'general population' or as RVO subgroup.	DMO and AMD
Interventions	• Aflibercept **OR** • Bevacizumab **OR**** • Dexamethasone **OR**** • Ranibizumab	-
Comparators	• Bevacizumab **OR**** • Dexamethasone **OR**** • Ranibizumab **OR** • Laser[1] **OR** • Placebo/BSC/sham/observation	-
Outcome measures	• Efficacy outomes re visual acuity e.g. percentage of patients gaining 15 letters of BCVA **OR** • Safety outcomes (adverse events) e.g. percentage of patients experiencing intra-ocular pressure • HRQoL	-
Study design	• RCTs • Recent systematic reviews and meta-analyses (past 5 years)	• Editorials **OR** • Notes **OR** • Comments **OR** • Letters **OR** • Observational studies **OR** • Abstracts only*
Restrictions	• Language: English • Published in past 11 years	• Non-English studies • Studies published beyond 11 past years

*Includes RVO patients (no CRVO subgroup) and patients with RVO from which CRVO data cannot be separated
AMD: age-related macular degeneration; BRVO: branch retinal vein occlusion; DMO: diabetic macular oedema; N/A: not applicable; RVO: retinal vein occlusion.
[1]Only studies comparing laser with an active ingredient (with the active ingredient used as a monotherapy or in combination with laser) were included in order to meet the objectives set for the systematic review.
* applies at the full-text review stage only.
Note: Abstracts or conference presentations are eligible for inclusion if adequate data are provided.
** See section 6.1.1

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.

Figure 1. Prisma Flow diagram of the included clinical studies



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.

Multiple publications

The systematic literature review identified two reports of one study (COPERNICUS) comparing aflibercept with sham/BSC treatment:

- Boyer et al. 2012. 'Vascular endothelial growth factor trap-eye for Macular oedema secondary to Central Retinal Vein Occlusion. Six-month results of the phase 3 COPERNICUS study'(4).

- Brown et al 2013. 'Intravitreal aflibercept injection for macular oedema secondary to Central Retinal Vein Occlusion: 1-year results from the phase 3 COPERNICUS study'(5).

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.

Table 3. List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
COPERNICUS (NCT00943072)	n=114 **Year 1** **Week 0-week 24:** Aflibercept 2 mg given intravitreally every 4 weeks (2q4) **Week 24-week 52**: (evaluated monthly) aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria or a sham injection if retreatment not indicated. **Year 2 (extension phase)** aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria (evaluated quarterly).	n=73 **Year 1** **Week 0-week 24:** sham injections every 4 weeks **Week 24-week 52**: (evaluated monthly) aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria or a sham injection if retreatment not indicated. **Year 2 (extension phase)** aflibercept 2mg intravitreally as needed (prn) according to protocol retreatment criteria (evaluated quarterly).	Macular oedema secondary to central retinal vein occlusion (CRVO)	6-month data: Boyer 2012(4) 12 month data: Brown 2013(5)
GALILEO (NCT01012973)	n=103 **Year 1** **Week 0-week 24:** Aflibercept 2 mg given intravitreally every 4 weeks (2q4) **Week 24-week 52**: aflibercept 2mg intravitreally as needed (prn) or a sham treatment according to protocol retreatment criteria (evaluated monthly). **Year 2** **Week 52-week 76:** follow-up visits every 8 weeks. Aflibercept 2mg intravitreally as needed (prn) or a sham treatment according to protocol retreatment criteria.	n=68 **Year 1** **Week 0-week 24:** sham injections every 4 weeks **Week 24-week 52**: sham injection according to protocol retreatment criteria (evaluated monthly). **Year 2** **Week 52-week 76:** follow-up visits every 8 weeks. Aflibercept 2mg intravitreally as needed (prn) or a sham treatment according to protocol retreatment criteria.		6-month data: Holz 2013(6)

prn= pro re nata (as needed)

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.

Selected: Both the COPERNICUS and the GALILEO studies compare aflibercept with a relevant comparator (i.e. placebo / BSC) in a relevant population, applicable to the UK population and the current decision problem in this submission.

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.

With reference to section 6.2.4 and 6.2.5, no studies have been excluded from further discussion.

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.

No non-RCTs are considered relevant to the decision problem given the availability of RCT evidence which is the preferred study design for NICE appraisal.

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.

Two large, randomised, controlled studies were thus designed to evaluate whether aflibercept can achieve long-term control of macular oedema and preservation of vision in CRVO. These were named the COPERNICUS and GALILEO studies(4-6). The primary objective of COPERNICUS and GALILEO was to compare the efficacy of aflibercept with the standard of care in improving best-corrected visual acuity (BCVA) in eyes with macular oedema secondary to CRVO. Key secondary objectives were to assess safety and tolerability and the effects on central retinal thickness (CRT) of aflibercept compared with BSC. The standard of care at the time of study design was observation until progression to anterior segment neovascularisation, and then treatment with panretinal photocoagulation (PRP). Hence the GALILEO and COPERNICUS included a sham control arm to mimic ‘observation’ and all patients could be treated with PRP on progression to anterior segment neovascularisation.

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.

Figure 2. Summary of study design for COPERNICUS and GALILEO studies

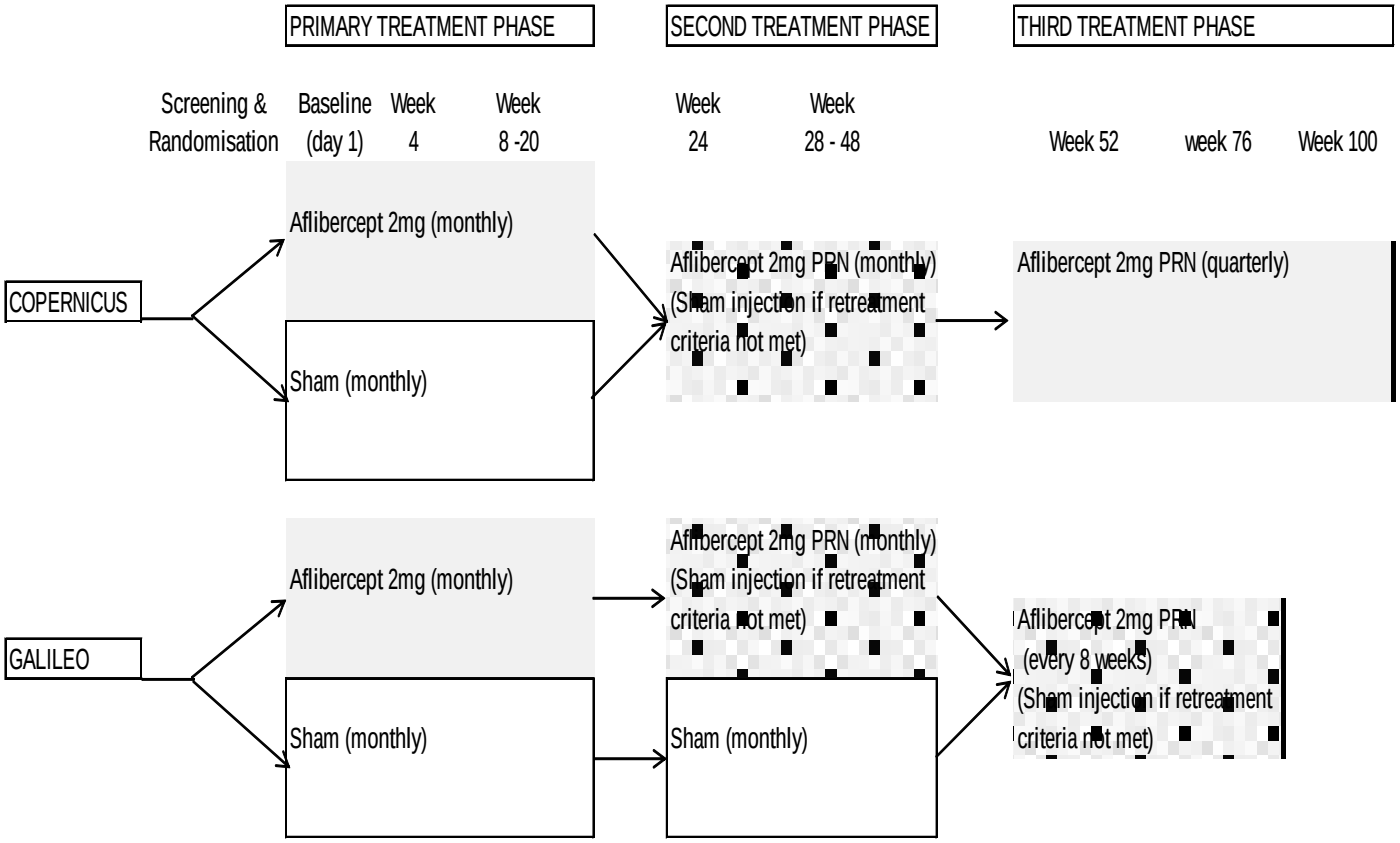


Table 4. Comparative summary of methodology of the RCTs

Trial no. (acronym)	COPERNICUS(4;5;25) (NCT00943072)	GALILEO(6;26) (NCT01012973)
Design	Prospective, phase III, multicentre, randomised, double-masked, sham-controlled study. The study had three phases including • a primary phase (from randomisation to week 24) where treatment was given monthly according to assigned masked treatment group i.e. a total of 6 treatments • a second phase (week 24 – 52) where patients were examined on a monthly basis and active treatment i.e. aflibercept, was given to all patients according to protocol retreatment criteria, on an as needed pro re nata (PRN) basis. Sham injections were given if active treatment was not needed. Masking was maintained throughout this phase. • An extension phase (Year 2) where patients were evaluated quarterly and given active treatment on a PRN basis, according to protocol retreatment criteria. No sham injections were given during this phase.	Prospective, phase III, multicentre, randomised, double-masked, sham-controlled The study had three phases including • a primary phase (from randomisation to week 24) where treatment was given monthly according to assigned masked treatment group i.e. a total of 6 treatments • a second phase (week 24 – 52) where treatment was given according to assigned masked treatment group *except* that aflibercept was given according to protocol retreatment criteria, on an as needed pro re nata (PRN) basis. Sham injections were given to patients in the aflibercept group if active treatment was not needed. The sham procedure group continued to receive sham injections. • An extension phase (week 52 to week 76) where patients were evaluated every 8 weeks and given active treatment on a PRN basis, according to protocol retreatment criteria. Sham injections were given if active treatment was not needed. Masking was maintained throughout the entire study.
Location	70 sites in the United States (US), Canada, India, Israel, Argentina and Columbia.	63 sites across Europe and the Asian-pacific region: Australia 6; Austria 3; France 5; Germany 21; Hungary 5; Italy 7; Japan 6; Latvia 2; Singapore 2; South Korea 6.
Duration of study	Overall: 100 weeks Primary phase: 6 months (data obtained between July 2009 and October 2010) To end of Second phase: At 52 weeks (data obtained between July 2009 and April 2011) To end of Extension phase: At 100 weeks (data obtained between July 2009 and April 2012)	Overall: 76 weeks. Primary phase: 6 months (data obtained between October 2009 and February 2011) To end of Second phase: At 52 weeks (data obtained between October 2009 and July 2011) To end of Extension phase: At 76 weeks (data obtained between October 2009 and February 2012)
Population	Macular oedema (MO) secondary to CRVO 189 patients randomised	Macular oedema (MO) secondary to CRVO 177 patients randomised

Intervention	n=115 (randomised) **Year 1** **Week 0-week 24:** Aflibercept 2 mg given intravitreally every 4 weeks (2q4) **Week 24-week 52**: (evaluated monthly) aflibercept 2mg intravitreally as needed (PRN) according to protocol retreatment criteria or a sham injection if retreatment not indicated. **Year 2 (extension phase) to week 100** aflibercept 2mg intravitreally (evaluated quarterly). Sham injections were not given during the extension phase. Patients could be given more frequent dosing (max every 4 weeks) if the investigator deemed it necessary. Aflibercept was injected in a volume of 50µl.	n=103 **Week 0-week 24:** Aflibercept 2 mg given intravitreally every 4 weeks (2q4) **Week 24-week 52:** Aflibercept 2mg intravitreally as needed (PRN) according to protocol retreatment criteria or a sham injection if retreatment not indicated. **Week 52- week 76:** aflibercept 2mg intravitreally on an as needed (PRN) according to protocol retreatment criteria or a sham injection if retreatment not indicated. Evaluations were every 8 weeks. At week 52 the masked investigator could decide not to administer active treatment if this wasn't in the best interest of the patient. In this situation, the patient received sham treatment.
Comparator	n=74 (randomised) **Year 1** **Week 0 - week 24:** sham injections every 4 weeks **Week 24 - week 52**: (evaluated monthly) aflibercept 2mg intravitreally as needed (PRN) according to protocol retreatment criteria or a sham injection if retreatment not indicated. **Year 2 (extension phase) to week 100** aflibercept 2mg intravitreally as needed (PRN) basis, according to protocol retreatment criteria (evaluated quarterly). Sham injections were not given during the extension phase.	n=68 **Week 0 - week 24:** sham injections every 4 weeks **Week 24 - week 52**: sham injections every 4 weeks (but patients were evaluated according to the protocol retreatment criteria in order to maintain masking). **Week 52- week 76:** aflibercept 2mg intravitreally on an as needed (PRN) basis, according to protocol retreatment criteria or a sham injection if retreatment not indicated. Evaluations were every 8 weeks.
Concomitant & disallowed treatment	All patients were eligible to receive pan retinal photocoagulation at any time during the study, if progress to anterior segment neovascularisation of the disc or elsewhere. No other systemic or local medications for treating CRVO were permitted in the study eye during the study. Cataract surgery was not allowed during the 3 months prior to randomisation. A non-systemic non-investigational therapy could be used to treat CRVO in the fellow eye. [redacted] [redacted]	Pan-retinal photocoagulation (PRP) was allowed at any time for all patients if they progressed to neovascularisation of the anterior segment, optic disc or fundus. Use of PRP meant that a patient was withdrawn from study treatment but could undergo safety follow-up to week 76. No other treatment for treating CRVO was permitted in the study eye until completion of week 76 or an Early Termination of study visit. [redacted] [redacted]

Criteria for Discontinuation of study treatment	Occurred at patient or investigator request, due to intercurrent illness, adverse events, treatment failure, protocol violation, or other reasons. [redacted]	
Method of randomisation	Patients were randomised in a 3:2 ratio using a centralised interactive voice randomisation system (IVRS), and stratified by geographic region (North America vs. rest of the world), and by using a baseline best-corrected visual acuity (BCVA) score (>20/200 [35 to 73 letters] and ≤20/200 [34 to 24 letters]. One eye per patient was randomised.	Patients were randomised in a 3:2 ratio [redacted], and stratified by region (Europe vs. Asia/Pacific) and baseline best -corrected visual acuity (BCVA) (≤20/200 vs. >20/200). One eye per patient was randomised.
Method of blinding (care provider, patient and outcome assessor)	Study drug was prepared by an unmasked individual, and an unmasked physician performed the study drug injections. [redacted] A masked physician assessed adverse events, supervised the assessment of efficacy and decided on the need for retreatment during the PRN phase. Examiners testing visual acuity and site personnel administering National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) were masked to treatment assignment. All aflibercept and sham treatments were packaged in identical treatment kits with identical labelling, except for the kit number (unique to the patient). Sham injections were performed by pressing an empty, needleless syringe barrel to the conjunctival surface to simulate an injection. Retinal characteristics were determined by optical coherence tomography (OCT) scans read at a masked independent central reading centre. Angiographic images were graded by a masked independent central reading centre Masked and unmasked roles were maintained until all enrolled patients at the site had completed the first year of treatment.	Study drug was prepared by an unmasked individual, and an unmasked physician performed the study drug injections. [redacted] All other site personnel were masked to treatment assignment, including the physician assessing adverse events, supervising the assessment of efficacy and deciding on the need for retreatment during the PRN phase. Examiners testing visual acuity and administering National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) were masked to treatment assignment. All aflibercept and sham treatments were packaged in identical treatment kits with identical labelling, except for the kit number (unique to the patient). All Sham procedure was performed by pressing an empty, needleless syringe to the conjunctival surface. OCT, fluoroscein angiography and fundus photography were evaluated centrally by masked reviewers. Electrocardiograms (ECGs) were read by a central reader. Blood and urine samples evaluated centrally. The study remained masked for the entire 76 week study period.
Primary outcomes	Proportion of eyes with a gain of 15 ETDRS (Early Treatment Diabetic Retinopathy Study) letters or more in BCVA from baseline to week 24.	Proportion of eyes with a gain of 15 ETDRS letters or more in BCVA from baseline to week 24.

Secondary outcomes	• Mean change from baseline to week 24 in BCVA, central retinal thickness (CRT), • proportion of patients progressing to ocular neovascularisation by week 24, • and NEI VFQ 25 total score. • safety The tertiary efficacy endpoints were all of the parameters mentioned above measured at 52 weeks.	1) Mean change from baseline to week 24 in BCVA and central retinal thickness (CRT), 2) proportion of patients progressing to neovascularisation of anterior segment, optic disc or elsewhere in the fundus by week 24 3) changes in vision-related and overall health-related quality of life (QoL) as assessed by NEI VFQ-25 and European Quality of Life-5 Dimensions (EQ-5D) Health Questionnaire. 4) Safety The tertiary efficacy endpoints were all of the parameters mentioned above measured at 52 weeks. Time to development of anterior segment neovascularisation or requirement of pan-retinal photocoagulation up to week 52 was also a tertiary endpoint. Selected subscales of NEI VFQ-25 were assessed as tertiary efficacy variables.
Duration of follow-up (& timing of assessments)	Assessments were performed at regular scheduled clinic visits i.e. day 1, week 4 and every 4 weeks thereafter to week 52, and then every 12 weeks to week 100. [redacted] A full ocular examination was conducted at each visit – visual acuity, slit-lamp biomicroscopy, indirect ophthalmoscopy, intraocular pressure (IOP) measurement (pre-injection and 30 minutes after injection), and OCT. Fundus photography and fluorescein angiography were performed at baseline, and weeks 12, 24, 36, 52, 76 and 100. NEIVFQ-25 was administered at baseline, week 24, 52 and 100. Adverse events and concomitant medications were recorded at each visit and vital signs obtained. Laboratory assessments, including measurement of anti-VEGF Trap-eye antibodies, were performed at baseline and weeks 12, 24, [redacted]	Assessments were performed at regular scheduled clinic visits i.e. day 1, week 4 and every 4 weeks thereafter to week 52. From week 52 to week 76, assessments took place every 8 weeks. [redacted] [redacted] Fundus photography and fluorescein angiography performed at baseline, week 12, 24, 36, 52 and week 76. NEIVFQ-25 and EQ-5D were administered at baseline and week 24, 52 and 76. [redacted] [redacted]

Figure 3. Aflibercept retreatment criteria for PRN dosing phases

COPERNICUS (NCT00943072)	GALILEO (NCT01012973)
From week 24 – week 52: all patients; sham injection given if aflibercept not indicated. **From week 52 – week 100:** all patients in study; assessed every 3 months.	**From week 24 – week 52:** patients randomised to aflibercept arm only; sham injection given if aflibercept not indicated; assessed monthly. **From week 52 – week 76:** all patients in study; sham injection given if aflibercept not indicated; assessed every 8 weeks.

Aflibercept 2mg was administered if any of the following criteria were met:

- More than 50-µm increase in CRT on OCT compared to lowest previous measurement
- New or persistent cystic retinal changes of sub-retinal fluid on OCT or persistent diffuse oedema ≥ 250µm in the central subfield on OCT
- A decrease of visual acuity of ≥ 5 letters between the current and most recent visit
- An increase of visual acuity ≥ 5 letters between the current and most recent visit

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 (See Table 5)

COPERNICUS and GALILEO studies included patients with diagnoses of ischaemic or non-ischaemic CRVO, or 'non-perfused' or 'perfused' status.

Ischaemic CRVO is associated with poor visual acuity, relative afferent papillary defect, and fluorescein angiography showing greater than 10 disc areas of retinal capillary non-perfusion, none of which were exclusion factors in the COPERNICUS and GALILEO studies.

Perfusion status is considered a predictor of neovascularisation. When there is less perfusion of the retina, there is a greater chance for neovascularisation, therefore, patients with non-perfused, or ischaemic CRVO generally have the worst prognosis of all RVO patients(27). Baseline perfusion status was determined by FA and classified using the following criteria:

- Non-perfused: ≥10 disc areas (DA) of capillary non-perfusion on FA
- Perfused: < 10 DA of capillary non-perfusion on FA.

Table 5. Eligibility criteria in COPERNICUS and GALILEO studies(4-6;25;26)

Trial: COPERNICUS AND GALILEO	
Inclusion criteria	**Exclusion criteria**
• Signed informed consent • Age ≥ 18 years • Centre-involved macular oedema secondary to CRVO diagnosed within 9 months of study initiation. • Mean central subfield retinal thickness ≥250 um on OCT from Zeiss Stratus OCT (version 4.0 or later; Carl Zeiss Meditec, Jena, Germany) • Early Treatment Diabetic Retinopathy Study (ETDRS) BCVA of 20/40 to 20/320 (73 to 24 letters) in the study eye • Willingness to use adequate contraception in patients of childbearing potential	▪ History of vitreoretinal surgery in the study eye, including radial optic neurotomy or sheathotomy (or anticipated within the next 12 months) ▪ Current bilateral retinal vein occlusion ▪ Previous panretinal or macular laser photocoagulation ▪ Other causes for decreased visual acuity ▪ Ocular conditions with poorer prognosis in the fellow eye ▪ History or presence of AMD, diabetic macular oedema, or diabetic retinopathy ▪ Any use of intraocular or periocular corticosteroids or antiangiogenic treatment in the study eye at any time or in the fellow eye in the preceding 3 months ▪ Iris neovascularisation, vitreous haemorrhage, traction retinal detachment, or preretinal fibrosis involving the macula; vitreomacular traction or epiretinal membrane that significantly affected central vision ▪ Ocular inflammation ▪ Uveitis ▪ Any intraocular surgery in the preceding 3 months ▪ Aphakia ▪ Uncontrolled glaucoma (IOP≥25mmHg) or previous filtration surgery in either eye, ▪ Uncontrolled hypertension, or diabetes ▪ Spherical equivalent of a refractive error of more than 8 diopters ▪ Myopia ▪ Infectious blepharitis, keratitis, scleritis, or conjunctivitis ▪ Cerebral vascular accident or myocardial infarction in the preceding 6 months ▪ Renal failure requiring dialysis or renal transplant ▪ Pregnancy or lactation ▪ History of allergy to fluorescein or povidone iodine ▪ Other conditions that may interfere with interpretation of the results or increase the risk of complications.

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 - patient characteristics(4-6;28;29)

In both studies, the treatment groups were well balanced with regard to demographic and disease characteristics at baseline. The mean baseline total NEI VFQ-25 scores ranged between 77.67±15.96 and 79.80±13.05, which indicates that before the start of the study, patients were experiencing a fair degree of impairment due to vision loss. In both studies, the mean scores for near activities were the lowest of the three sub-scores considered most relevant (i.e. near activities, distance activities and dependency).

Results of baseline characteristics in the per protocol analysis sets (PPS) and safety analysis sets (SAF) were similar to those reported here for the full analysis sets (FAS) of each study.

COPERNICUS – The average age of patients was 66.3 years. Most patients were male (n=107 [57%]), white (n=147 [78.6%]) and originating from North America (n=159 [85%]). The mean BCVA at baseline was 50.0 ETDRS letters (Snellen equivalent, 20/100) and mean CRT was 665 µm. The majority of patients (n=127 [67.9%]) had fewer than 10 disc areas of non-perfusion, and were thus graded as ‘perfused’. [redacted] Most patients had been diagnosed with CRVO within the 2 months prior to starting the study.

GALILEO – The FAS comprised of 55.6% (n=95) males and 44.4% (n=76) females, with an average age of 61.5 years. Most patients were of White race (n=123 [71.9%]). The mean BCVA at baseline was 52.2 ETDRS letters and mean CRT was 665.5 µm. A slight imbalance in mean CRT thickness between groups (683.20 µm [aflibercept group] vs. 638.66 µm [sham]) was observed, however these values are considered to be close to CRT values usually found at baseline in CRVO patients (comparable to those reported in the COPERNICUS study, and in the ranibizumab CRUISE study(30)), thus representative and within the range of contemporary CRVO studies. In addition, the anticipated (and demonstrated) treatment effect between the treated and untreated groups after therapy is

substantially larger, providing good evidence for treatment effect, regardless of small differences in baseline status. Overall, 86.4% of patients in the aflibercept arm of the study and 79.4% of patients in the sham group had 'perfused' retinal occlusion. In both groups, more patients had disease duration of less than 2 months at baseline.

Table 6. Baseline demographic and disease characteristics of patients entering primary treatment phase for COPERNICUS, GALILEO and pooled datasets [FAS]

	Aflibercept 2mg every 4 weeks			Sham treatment every 4 weeks		
	COPERNICUS	GALILEO	Integrated	COPERNICUS	GALILEO	Integrated
	N=114	N=103	N=217	N=73	N=68	N=141
Age, yrs						
Mean (SD)	65.5 (13.6)	59.9 (12.4)	62.9	67.5 (14.3)	63.8 (13.3)	65.7
Median	[redacted]	[redacted]	65.0	[redacted]	[redacted]	67.0
Min-Max	22 - 88	29 - 81	22-88	26 - 89	37 - 88	26-89
Sex n(%)						
Male	69 (61)	58 (56.3)	127 (58.5)	38 (52)	37 (54.4)	75 (53.2)
Female	45 (39)	45 (43.7)	90 (41.5)	35 (48)	31 (45.6)	66 (46.8)
Race n(%)						
White	88 (77.2)	74 (71.8)	162 (74.7)	59 (80.8)	49 (72.1)	108 (76.6)
Black	5 (4.4)	26 (25.2)	5 (2.3)	5 (6.8)	15 (22.1)	5 (3..5)
Asian	7 (6.1)		33 (15.2)	2 (2.7)		17 (12.1)
American Indian / Alaskan native	2 (1.8)		2 (0.9)	0		0
Native Hawaiian/ Pacific Islander	0		0	1 (1.4)		1 (0.7)
Not Reported / multiracial	12 (10.5)	3 (2.9)	16 (6.9)	6 (8.2)	4 (5.9)	10 (7)
Baseline body mass index kg/m2						
Mean (SD)	28.79 (5.995)	26.4 (4.2)	27.67 (5.36)	28.53 (5.989)	26.1 (4.3)	27.38 (5.38)
Median	27.91	26.3	27.10	27.44	25.8	26.50
Min-Max	15.8 – 48.5	17.1 – 41.0	15.8 – 48.5	16.9 – 44.9	18.0 – 38.6	16.9 – 44.9
BCVA n (%)						
>20/200	86 (75.4)	86 (83.5)	180 (82.9)	55 (75.3)	56 (82.4)	115 (81.6)
≤20/200	28 (24.6)	17 (16.5)	37 (17.1)	18 (24.7)	12 (17.6)	26 (18.4)
Mean CRT, µm (SD)	N=112 661.7 (237.4)	N=103 683.2 (234.5)	N=215 672.0 (235.7)	N=69 672.4 (245.3)	N=68 638.7 (224.7)	N=137 655.7 (235.1)
Mean visual acuity (ETDRS)	50.7 (13.9)	53.6 (15.8)	52 (14.9)	48.9 (14.4)	50.9 (15.4)	49.9 (14.9)
Retinal perfusion status n(%)						
Perfused*	77 (67.5)	89 (86.4)	166 (76.5)	50 (68.5)	54 (79.4)	104 (73.8)
Non-perfused	17 (14.9)	7 (6.8)	24 (11.1)	12 (16.4)	7 (10.3)	19 (13.5)
Indeterminate	20 (17.5)	7 (6.8)	27 (12.4)	11 (15.1)	7 (10.3)	18 (12.8)
Mean IOP (mmHg)	15.1 (3.26)	N=102 15.1 (2.8)	N=216 15.1 (3.0)	15.0 (2.81)	N=68 14.4 (2.7)	N=141 14.7 (2.8)
Time since CRVO diagnosis (mths)						
Mean (SD)	2.73 (3.09)	2.56 (2.95)	2.67 (3.03)	1.88 (2.19)	2.88 (2.60)	2.38 (2.46)
≤ 2	64 (56.1)			52 (71.2)		
< 2		55 (53.4)	119 (54.8)		35 (51.5)	87 (61.7)
> 2	49 (43.0)			21 (28.8)		
≥ 2		46 (44.7)	95 (43.8)		33 (48.5)	54 (38.3)
Mean NEI VFQ-25 scores (SD)	N=114	N=103	N=217	N=73	N=67	N=140
Total	77.67 (15.96)	[redacted]	78.68 (14.65)	77.78 (16.25)	[redacted]	78.33 (15.17)
Near activities	69.96 (21.94)			70.72 (20.22)		
Distance activities	75.99 (21.26)	[redacted]		78.08 (21.25)	[redacted]	

	Aflibercept 2mg every 4 weeks			Sham treatment every 4 weeks		
	COPERNICUS	GALILEO	Integrated	COPERNICUS	GALILEO	Integrated
	N=114	N=103	N=217	N=73	N=68	N=141
Vision dependency	83.26 (25.51)	[redacted]		82.76 (27.41)	[redacted]	
Mean EQ-5D score (SD)		[redacted]			[redacted]	

BCVA = best corrected visual acuity; CRVO = central retinal vein occlusion; ETDRS = Early Treatment Diabetic Retinopathy Study; NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire; SD = standard deviation.
* less than 10 disc areas of non-perfusion

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 COPERNICUS and GALILEO studies had similar primary and secondary endpoints (see Table 7), all of which were relevant to the disease and matched the requirements of the decision problem.

Reliability/ validity/ current use in clinical practice - All efficacy and safety parameters assessed in COPERNICUS and GALILEO, and the methods to measure them are standard variables and methods in clinical studies for RVO, and in ophthalmic practice. They are widely used and generally recognised as valid, reliable, accurate and relevant. In addition, all evaluations were in accordance with Good Clinical Practice (GCP) to ensure safety of patients participating in research.

Compliance [redacted]

Table 7. Outcomes of the COPERNICUS and GALILEO RCTs

Endpoint	COPERNICUS	GALILEO	Measure
Primary Endpoint			
BCVA: Proportion of patients with ≥ 15 ETDRS letter gain from baseline to week 24	Assessments performed at day 1, week 4 and every 4 weeks thereafter to week 52, and then: every 12 weeks to week 100.	every 8 weeks to week 76.	The ETDRS protocol (The Early Treatment Diabetic Retinopathy Study Group, 1985) at 4m. Examiners were masked and certified, to ensure consistent measurement of BCVA.
Secondary Endpoints			
Mean change in BCVA from baseline to week 24	As above.	As above.	As above.
Mean change in central retinal thickness (CRT) from baseline to week 24	As above.	As above.	Determined by OCT scans read at a masked independent reading centre (Duke Reading Centre, Durham, USA). CRT was defined as the thickness of the centre subfield (the area of the retina using a 1mm diameter around the centre of the macula).
Proportion of patients progressing to neovascularisation of the anterior segment, optic disc, or elsewhere in the retina from baseline to week 24.	Fundus photography and fluorescein angiography were performed at baseline, and weeks 12, 24, 36, 52, 76 (COPERNICUS only: and 100).		Evaluated by fundus photography and fluorescein angiography. Angiographic images were obtained by certified photographers and transmitted to the independent reading centre (Digital Angiographic Reading Centre, New York, USA) for review by masked graders.
Quality of Life			
Vision-related: Mean changes in NEI VFQ-25 total (and near activities, distance activities and vision dependency subscales) scores from baseline to week 24.	NEIVFQ-25 was administered at baseline, week 24, 52 and (COPERNICUS: week 100; GALILEO week 76).		Assessed with the NEI VFQ-25 in a masked interviewer administered format, before each intravitreal injection. The possible range of the NEI VFQ-25 total score is between 0 (worst) and 100 (best). A change in NEI VFQ-25 total score of 4-6 points corresponds to a 15-letter gain in BCVA and is considered clinically meaningful in published studies. Near activities: difficulty reading ordinary print in newspapers, performing work or hobbies requiring near vision, or finding something on a crowded shelf. Distance activities: reading street signs or names on stores, and going down stairs, steps or curbs. Vision dependency: the need to stay at home, reliance on others, and need of help.
Overall Health-related: changes in European Quality of Life-5 Dimensions (EQ-5D) Health Questionnaire from baseline to week 24.	Not performed.	Administered at baseline, week 24, 52 and week 76).	Provides feedback on patient's overall state of health (from the patient's perspective). It consists of five dimensions: Mobility, Self-care, Usual activities, Pain / discomfort, Anxiety /depression, with each dimension reflecting 'no health problems'(level 1), 'moderate health problems' and 'extreme health problems'(level 3).

Endpoint	COPERNICUS	GALILEO	Measure
Safety: Ocular and non-ocular adverse events (AEs), and serious adverse events (SAEs), vital signs, laboratory measures, and serum analysis for anti-VEGF Trap-Eye antibodies. [redacted]	AEs, vital signs and concomitant medications were recorded at each visit. Ocular SAEs included any AE that caused a decrease in VA of >30 letters or a decrease in VA to the level of light perception or worse that lasted >1 hour; or required medical or surgical intervention; or was associated with severe intraocular inflammation. [redacted]		Adverse events were summarised using the Medical Dictionary for Regulatory Activities (MedRA) preferred term within primary organ class.
Tertiary endpoints			
All primary and secondary endpoints measured at 52 weeks	Plus endpoints at 100 weeks (descriptive only)		Plus Time to development of anterior segment neovascularisation or need for pan-retinal photocoagulation up to week 52; and endpoints at 76 weeks (descriptive only)

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.

Analysis populations

The following populations were used for statistical analyses:

Table 8. Definition of Analysis populations in COPERNICUS and GALILEO studies(4-6;25;26)

Analysis	Population	COPERNICUS	GALILEO
Primary Efficacy	**Full Analysis set (FAS)**	All randomised patients who received any study medication and had a baseline assessment and at least 1 efficacy assessment after baseline. Analysed as randomised.	
Sensitivity	**Per Protocol (PP)**	All patients in the FAS who received at least five injections of study medication and did not have any major protocol violations or deviations. Analysed as treated.	
Safety	**Safety (SAF)**	All randomised patients who received any study medication. Analysed as treated.	

Table 9. Summary of statistical analyses in COPERNICUS and GALILEO

	COPERNICUS	GALILEO
Primary Hypotheses or hypothesis objective	• The primary hypothesis is that the proportion of patients who gain at least 15 letters in best-corrected ETDRS visual acuity (BCVA) is higher in the group who receive aflibercept (pt) than those who receive standard of care (observation [sham]) (pc), thus demonstrating superiority. H0: pt = pc versus H1: pt ≠ pc	
Statistical Analysis	• Primary efficacy analyses were conducted using the full analysis set (FAS) and was a statistical evaluation of superiority (achieved if treatment was better than sham and 2-sided p-value was less than or equal to 0.05). Patients who discontinued prematurely (prior to week 24) and had less than 5 injections of study drug or sham were evaluated as non-responders. Otherwise, missing values were imputed using last observation carried forward (LOCF) analyses. • Proportions of 15-letter gainers were compared with a 2-sided Cochran-Mantel-Haenszel (CMH) test, stratified for region and baseline BCVA. • Additional analyses of the primary efficacy variable were also performed on the PPS to support the FAS analysis. • The secondary analyses (endpoints) were conducted on the FAS and PPS analysis populations to test for the superiority of aflibercept over sham treatment. • The hypothesis was tested only if all the previous null hypotheses in the sequence could be rejected. The sequence of analysis was as follows: • change from baseline in BCVA score at week 24; • change from baseline in CRT at week 24; • proportion of subjects progressing to anterior segment neovascularisation, neovascularisation of the optic disc, or neovascularisation of the retina elsewhere at week 24; and • change from baseline in the NEI VFQ-25 total score week 24. • Secondary end point analyses were performed sequentially according to the order in which the variables were defined to preserve an α of 0.05. • Proportions were analysed with the Cochran-Mantel-Haenszel test, and continuous variables were analysed with an analysis of covariance main effects model with treatment	• Primary efficacy analyses were conducted using the full analysis set (FAS) and was a statistical evaluation of superiority (achieved if treatment was better than sham and 2-sided p-value was less than or equal to 0.05). Patients who discontinued prematurely (prior to week 24) were evaluated as non-responders. Otherwise, missing values were imputed using last observation carried forward (LOCF) analyses. • Proportions of 15-letter gainers were compared with a 2-sided Cochran-Mantel-Haenszel (CMH) test, stratified for regions and baseline BCVA. • The secondary analyses (endpoints) were conducted on the FAS to test for the superiority of aflibercept over sham treatment, using a LOCF analyses (except for the progression to neovascularisation variable). • Secondary end point analyses were performed sequentially according to the order in which the variables were defined to preserve an α of 0.05. The sequence of analysis was as follows in order to control for multiplicity: • change from baseline in BCVA score at week 24; • change from baseline in CRT at week 24; • proportion of subjects progressing to anterior segment neovascularisation, neovascularisation of the optic disc, or neovascularisation of the retina elsewhere at week 24; and • change from baseline in the NEI VFQ-25 total score at week 24; • change from baseline in the EQ-5D total score at week 24 • Proportions were analysed with the CMH test, and continuous variables were analysed by analysis of variance main effects model with treatment group, region, and baseline BCVA as fixed factors.

	COPERNICUS	GALILEO
	group, region, and baseline BCVA as fixed factors and the respective baseline variable as a covariate (using last observation carried forward). Time to first injection was analysed using Kaplan-Meier methodology. Cox proportional hazards model was used to quantify differences in rates of time to first injection between treatment groups. • Week 52 and week 100 data were evaluated descriptively. Sensitivity analyses included: 'LOCF', 'observed case', 'pure LOCF' and 'dropouts counted as non-responders' analyses, in both the FAS and PPS populations for the primary endpoint; and observed case analyses in the FAS and PPS populations for the secondary endpoints of change from baseline in BCVA score, CRT and NEI VFQ-25 total score at week 24, 52 and 100.	• A descriptive post-hoc analysis using a double-sided Fisher test was conducted to evaluate the between-group differences in the proportion of patients losing ≥1 and ≥10 letters. • Sensitivity analyses included: 'LOCF', 'observed case', 'discontinued patients before week 24 with < 5 injections as failures', 'discontinued patients before Week 52 as failures', 'discontinued patients before week 24 as failures' (week 52 and week 76 results) analyses, in both the FAS and PPS populations for the primary endpoint; and observed case analyses in the FAS and PPS populations for the secondary endpoints of change from baseline in BCVA score, CRT and NEI VFQ-25 total score at week 24, 52 and 76
Power calculation / Sample size	• The study was designed to have 90% power to detect a difference of 25% in the proportion of eyes gaining at least 15 letters of vision at week 24 at the 5% significance level using a 2-sided Fisher exact test or a Cochran-Mantel-Haenszel test. Estimated proportions of eyes meeting the primary endpoint were 15% in the sham group and 40% in the aflibercept group). • The planned sample size of 165 eyes (99 in the aflibercept group and 66 in the sham group) was based on a dropout rate of 9%.	• The study was designed to have 90% power to detect a difference of 25% in the proportion of eyes gaining at least 15 letters of vision at week 24 using a 2-sided Fisher exact test. • The planned sample size of 165 eyes (99 in the aflibercept group and 66 in the sham group) was based on a dropout rate of 10%.
Data management / Patient withdrawals / censoring methods	• In the primary efficacy analysis, patients who discontinued prematurely (before week 24) and had fewer than 5 injections of aflibercept or sham were evaluated as non-responders; otherwise, missing values were imputed using last observation carried forward (LOCF) analyses. • Pure last observation carried forward analyses were also performed as a sensitivity analysis, as were 'observed case' analyses. • The number of patients lost to randomisation at the end of the 6 month study was 5 (4.3%) and 14 (18.9%) in the aflibercept and sham arms respectively.	• In the primary efficacy analysis, patients who discontinued prematurely (before week 24) were evaluated as non-responders; otherwise, missing values were imputed using last observation carried forward (LOCF) analyses.

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.

In both studies, subgroup analyses by gender, age, race, renal function, hepatic impairment, were performed on the following variables at week 24, 52, and 76 (GALILEO only) and 100 (COPERNICUS only):

- Efficacy (plus additional subgroups of baseline BCVA, geographic region, baseline retinal perfusion status, and time since CRVO diagnosis)
- Primary endpoint: proportion of patients who gain at least 15 letters (FAS and PPS)
- Change from baseline in BCVA score (FAS, [and PPS at week 52])
- Change from baseline in CRT as assessed by OCT (FAS, [and PPS at week 52])
- Proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina (FAS, [and PPS at week 52])
- Change from baseline in the NEI VFQ-25 in total score (FAS, [and PPS at week 52])

[redacted]

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.

See Figure 4 and Figure 5.

Figure 4. Patient disposition for COPERNICUS

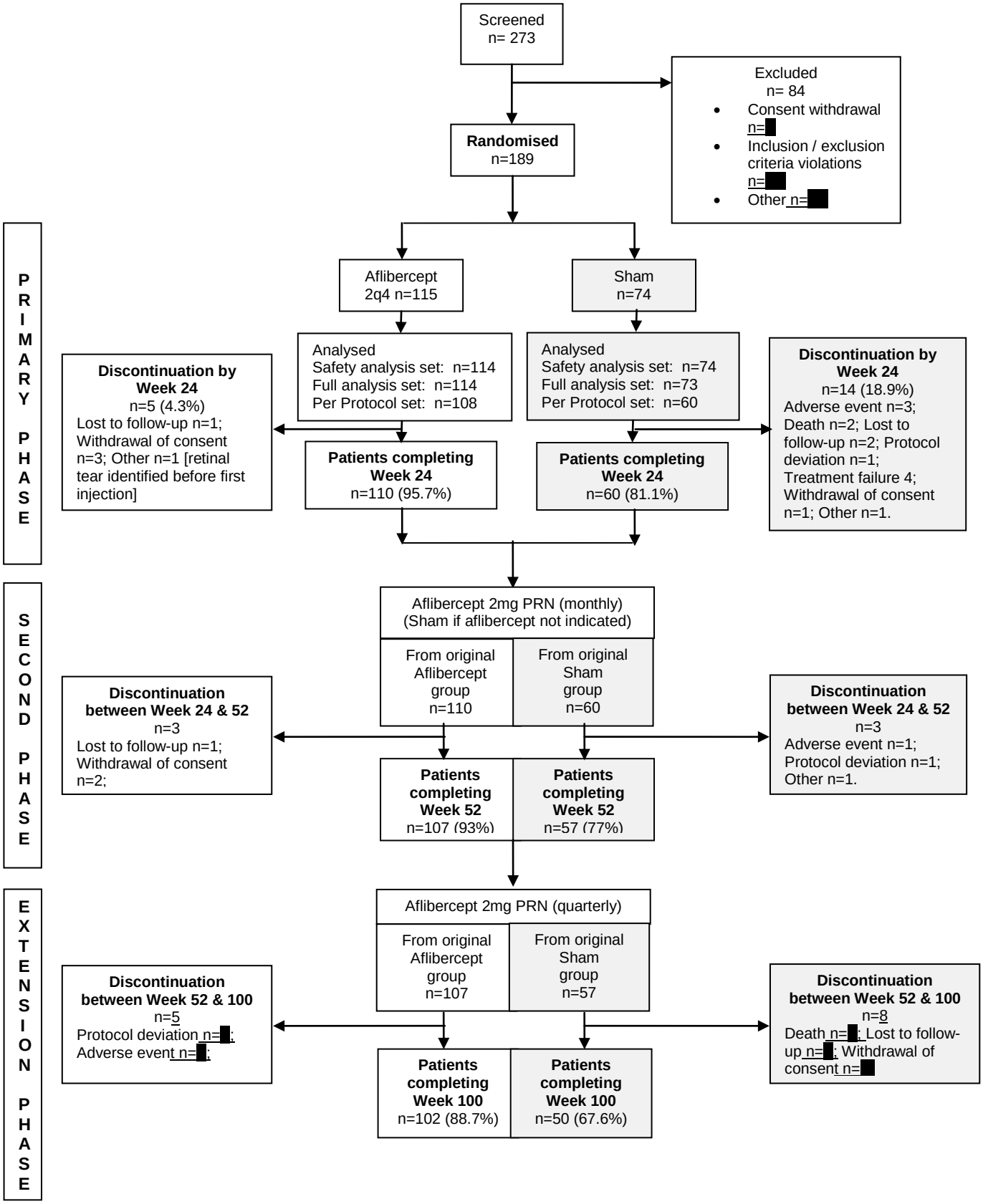
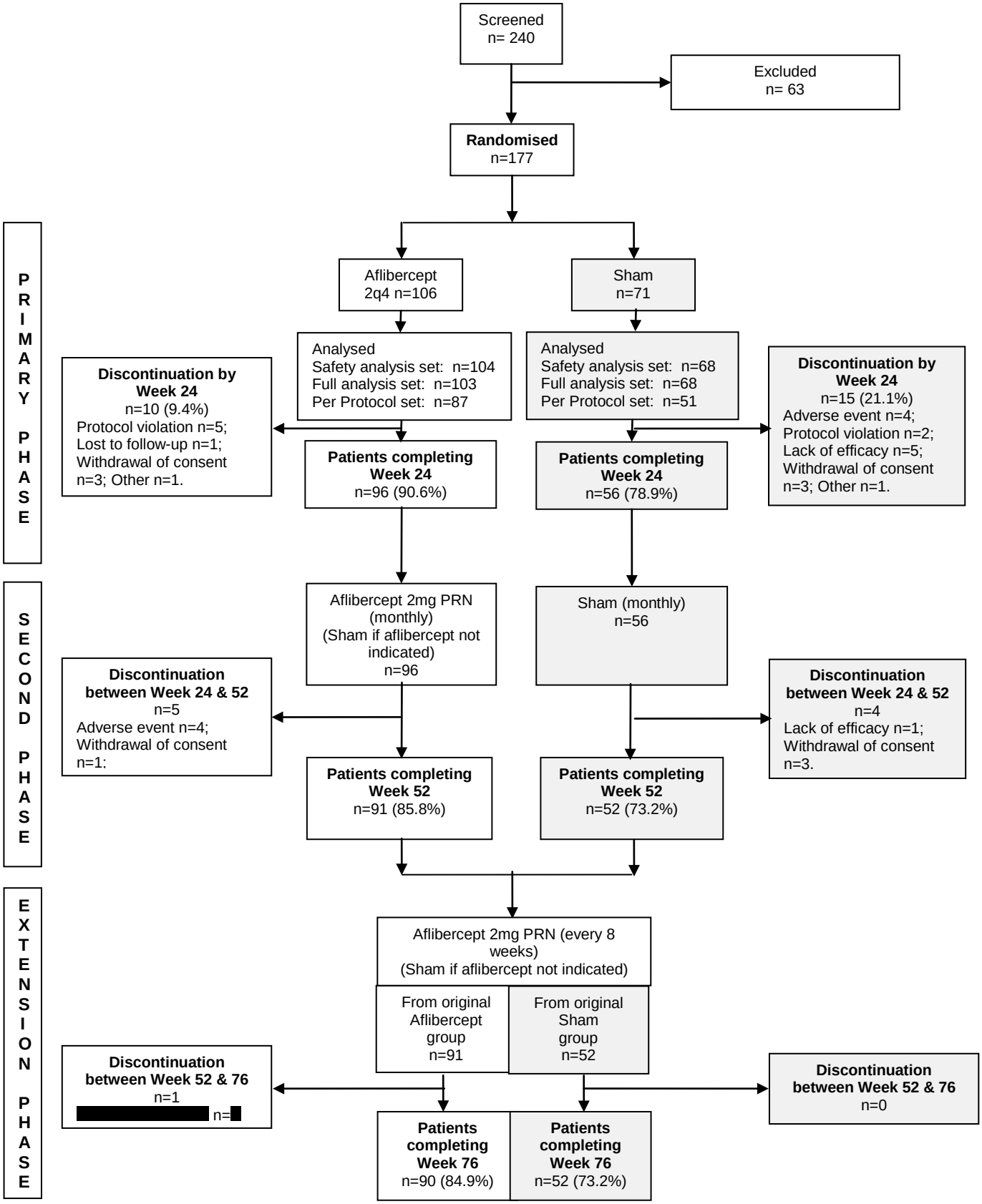


Figure 5. Patient disposition for GALILEO



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.

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.

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.

Table 10. Quality assessment results for RCTs

Trial no. (acronym)	COPERNICUS	GALILEO
Was randomisation carried out appropriately?	Yes	Yes
Was the concealment of treatment allocation adequate?	Yes	Yes
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes	Yes
Were there any unexpected imbalances in drop-outs between groups?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	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?	No. Full analysis sets were reported (includes all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment). Sensitivity analyses included FAS observed values.	

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.

Primary efficacy endpoint

Proportion of patients with ≥ 15 ETDRS letter gain from baseline to week 24(4;6;28;29)

At Week 24

In both studies, monthly intravitreal injection of aflibercept (2mg) in eyes with MO resulting in CRVO, demonstrated improved visual acuity, and the primary endpoint was met (see

Table 11, Table 12, Figure 6 and Figure 7). Improvement in visual acuity was evident as early as 4 weeks after the first injection in both studies.

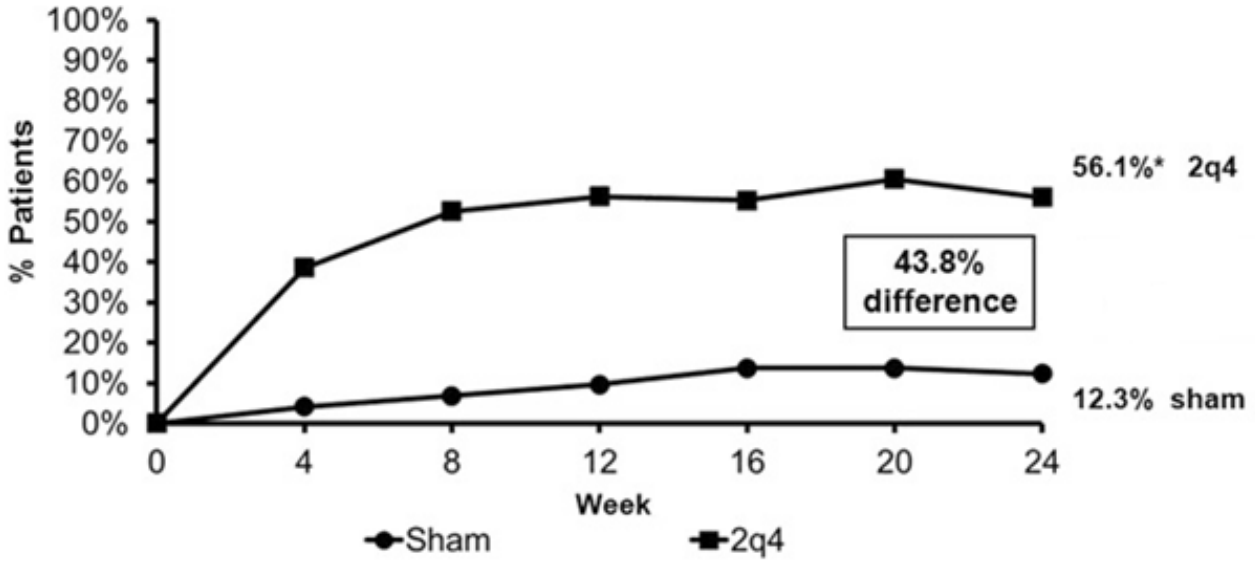
COPERNICUS – At week 24, 56.1% of eyes treated with aflibercept gained 15 ETDRS letters or more from baseline compared with 12.3% of sham-treated eyes (P<0.001)[FAS with patients discontinued before week 24 with <5 injections judged as failures]. The difference adjusted for region and baseline BCVA was 44.8%, 95% confidence interval (CI), 33.0%-56.6%; P<0.001.

GALILEO – Similar to the COPERNICUS study, significantly more patients in GALILEO receiving monthly aflibercept injections up to week 24, gained ≥15 letters (60.2%) compared with those receiving sham injections (22.1%) (p<0.0001), with a CMH-adjusted difference of 38.3% (95% CI = 24.4 TO 52.1%)) [FAS with patients discontinued before week 24 judged as failures].

INTEGRATED – These findings were confirmed in an integrated analysis using the FAS last observation carried forward (LOCF) dataset (see Table 12).

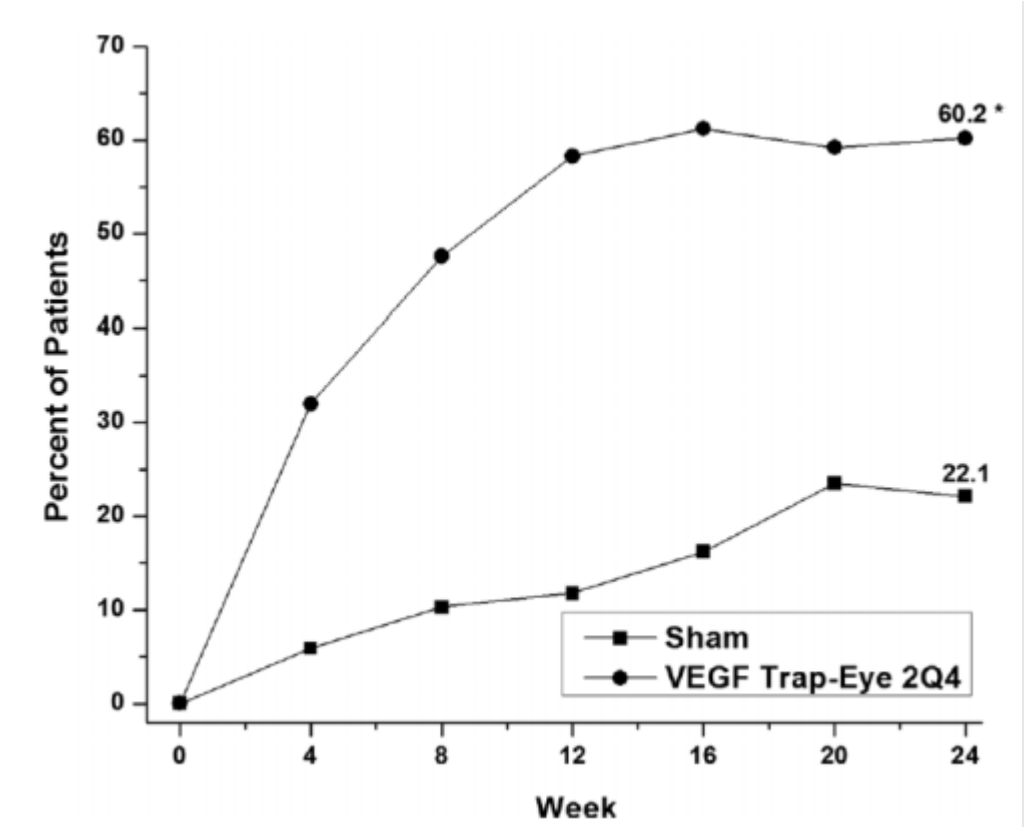
Figure 6. Percentage of patients who gained ≥15 letters over the course of 24 weeks in the COPERNICUS study

A)



*p<0.0001 vs sham

Figure 7. Percentage of patients who gained ≥15 letters over the course of 24 weeks in the GALILEO study



*p<0.0001 vs sham. VEGF Trap-Eye 2Q4 = aflibercept group

Table 11. Summary of results for the primary endpoint (proportion of patients gaining ≥15 ETDRS letters) (FAS LOCF*)

Patients gaining ≥ 15 ETDRS letters	**Aflibercept**		**Sham**	
	COPERNICUS	**GALILEO**	**COPERNICUS**	**GALILEO**
Week 24 (FAS LOCF*) n (%)	**2mg Q4**		**Sham Q4**	
	N=114	**N=103**	**N=73**	**N=68**
	64 (56.1%)	62 (60.2%)	9 (12.3%)	15 (22.1%)
Difference	43.8%	38.1%		
Adjusted Difference (%) (95% CI) [1]	44.8 (33.0, 56.6)	38,3 (24,4, 52.1)		
P-value [2]	<0.001	<0.0001		
Week 52 (FAS LOCF*) n (%)	**PRN (Q4)**	**PRN (Q4)**	**(Aflibercept) PRN (Q4)**	**Sham Q4**
	N=114	**N=103**	**N=73**	**N=68**
	63 (55.3%)	62 (60.2%)	22 (30.1%)	22 (32.4%)
Difference	25.1%	27.8%		
Adjusted Difference (%) (95% CI) [1]	25.9 (11.8, 40.1)	27.9 (13.0, 43.7)		
P-value [2]	<0.001	0.0004		
Week 76 (FAS LOCF*) n (%)		**PRN (Q8)**		**(Aflibercept) PRN (Q8)**
		N=103		**N=68**
		59 (57.3)		20 (29.4%)
Difference		27.9%		
Adjusted Difference (%)		28.0 (13.3, 42.6)		

(95% CI) [1]			
P-value [2]		0.0004	
Week 100 (FAS LOCF*) n (%)	**PRN (Q12)** **N=114** 56 (49.1%)		**(Aflibercept) PRN (Q12)** **N=73** 17 (23.3%)
Difference	25.8%		
Adjusted Difference (%) (95% CI) [1]	26.7 (13.1, 40.3)		
P-value [2]	0.0003		

* LOCF (Last observation carried forward). The COPERNICUS study primary efficacy analysis set was the FAS with patients discontinued before week 24 with <5 injections judged as failures for the analysis at week 24, 52 and 100. The GALILEO study primary efficacy analysis set was the FAS with patients discontinued before week 24 judged as failures for the week 24 analysis. Analysis was performed in the FAS LOCF set for week 52 and 76 of the primary endpoint.
[1] Adjusted difference (%), aflibercept minus sham and associated 95% CI were calculated using the Cochran-Mantel-Haenszel weighting scheme adjusted by regions (COPERNICUS: North America versus Rest of World; GALILEO: Europe vs. Asia / Pacific) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200).
[2] P-value for the primary endpoint was calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by regions (COPERNICUS: North America versus Rest of World; GALILEO: Europe vs. Asia / Pacific) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200).

Table 12. INTEGRATED Analysis - Summary of results for the primary endpoint (proportion of patients gaining ≥15 ETDRS letters) at week 24(FAS LOCF*)

Patients gaining ≥ 15 ETDRS letters	**Aflibercept**			**Sham**		
	COPERNICUS	**GALILEO**	**Integrated**	**COPERNICUS**	**GALILEO**	**Integrated**
	2mg Q4			**Sham Q4**		
Week 24 (FAS LOCF*) n (%)	**N=114**	**N=103**	**N=217**	**N=73**	**N=68**	**N=114**
	66 (57.9%)	65 (63.1%)	131 (60.4%)	9 (12.3%)	15 (22.1%)	24 (17.0%)
Difference	45.6%	41%				
Adjusted Difference (%) (95% CI) [1]	47.3 (35.7, 58.8)	41.1 (27,4, 54.9)	43.6 (34.6, 52.6)			
P-value [2]	<0.0001	<0.0001	<0.0001			

* LOCF (Last observation carried forward). In order to integrate the COPERNICUS and GALILEO data results are reported here as FAS LOCF. For integrated data, all subjects who discontinued prematurely prior to Week 24 have been evaluated with their last post-baseline value.
[1] Adjusted difference (%), aflibercept minus sham and associated 95% CI were calculated using the Cochran-Mantel-Haenszel weighting scheme adjusted by regions (COPERNICUS: North America versus Rest of World; GALILEO: Europe vs. Asia / Pacific) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200).
[2] P-value for the primary endpoint was calculated using 2-sided Cochran-Mantel-Haenszel test adjusted by regions (COPERNICUS: North America versus Rest of World; GALILEO: Europe vs. Asia / Pacific) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200).

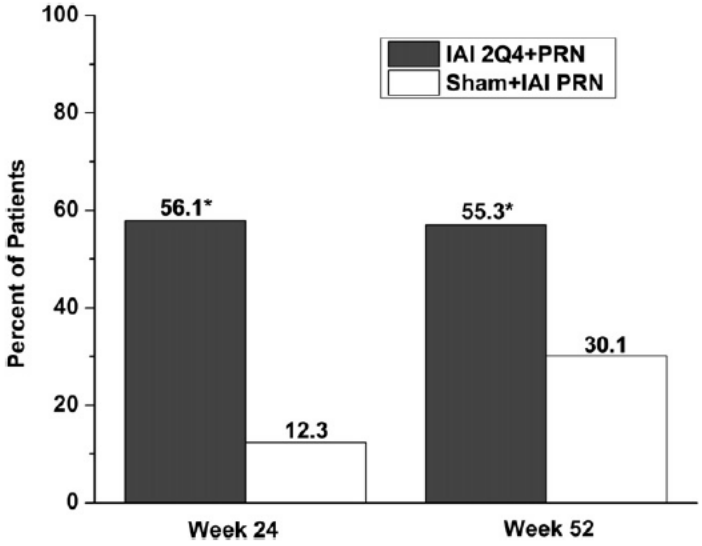
At Week 52 (a tertiary efficacy endpoint)(5;31)

In both studies, in the group of patients receiving aflibercept since the beginning of the study, the proportion of patients gaining ≥15 letters at 52 weeks was similar to that at 24 weeks, demonstrating that aflibercept treatment continued to be superior at week 52, and that efficacy could be maintained over a year-long period.

COPERNICUS – From week 24 to week 52, all patients were assessed monthly using retreatment criteria. If treatment was necessary, 2mg aflibercept was given by intravitreal injection, otherwise a sham injection was administered.

At week 52, 55.3% of patients originally randomised to the aflibercept group had gained ≥ 15 letters compared with 30.1% of sham patients (P<0.001))[FAS with patients discontinued before week 24 with <5 injections judged as failures], demonstrating that aflibercept 2Q4+*pro re nata* (PRN) continued to be superior to the sham+PRN group. Patients in the sham group, who had crossed over to receive aflibercept PRN after week 24, showed improvement in BCVA at week 52 vs. week 24. Patients in the aflibercept group who received aflibercept from the beginning of the study maintained the improvements in BCVA achieved during the first 24 weeks, and continued to do better than those in the sham group, who only received aflibercept after week 24 on a PRN basis (see Figure 8). These data indicate that earlier treatment with aflibercept may be more beneficial compared to delayed treatment.

Figure 8. Proportion of patients with BCVA improvement ≥15 letters at week 24 and 52



*P<0.001; IAI = intravitreal aflibercept injection; PRN = as needed *(pro re nata);*

GALILEO – From week 24 to week 52, patients in the aflibercept group received aflibercept PRN i.e. they were assessed monthly using retreatment criteria and if treatment was necessary, 2mg aflibercept was given by intravitreal injection, otherwise a sham injection was administered. Patients in the sham treatment group continued to receive monthly sham injections.

The proportion of patients experiencing an increase in BCVA letter score of at least 15 letters from baseline at Week 52 was 32.4% in the sham group and 60.2% in the aflibercept group (FAS LOCF). In the primary analysis dataset i.e. 'FAS with patients discontinued before week 24 judged as failures' superiority of aflibercept over sham treatment were also confirmed (58.3% aflibercept group vs.32.4% sham group). The increase in the sham patients achieving a gain of 15 letters or more is likely a reflection of the discontinuation of sham patients who experienced a deterioration of symptoms over the course of the study such that the sham patients who remained in the study and contributed to the calculation were those who did well without active treatment. At 24 and 52 weeks, however, a clear and clinically meaningful difference between sham and aflibercept treatment was evident.

At Week 76(32)

GALILEO - From week 52 to week 76, all patients were assessed every 8 weeks using retreatment criteria. If treatment was necessary, 2mg aflibercept was given by intravitreal injection, otherwise a sham injection was administered.

The proportion of patients experiencing a gain of at least 15 letters from baseline at week 76 was 29.4% in the sham plus (now) intravitreal aflibercept PRN and 57.3% in the original aflibercept group (FAS LOCF). In the primary analysis dataset i.e. 'FAS with patients discontinued before week 24 judged as failures' superiority of aflibercept over sham treatment were also confirmed (55.3% aflibercept group vs.29.4% sham group).

At Week 100(33)

COPERNICUS – From week 52 to week 100, all patients were assessed every 12 weeks using retreatment criteria. If treatment was necessary, 2mg aflibercept was given by intravitreal injection. No sham injections were administered if treatment was not indicated.

The proportion of patients experiencing a gain of at least 15 letters from baseline at week 100 continued to be better in the aflibercept group (49.1%) than in the sham group (23.3%))[FAS with patients discontinued before week 24 with <5 injections judged as failures]. It is noteworthy that 56.1% and 55.3% of patients gained at least 15 letters in BCVA at week 24 and week 52 in the aflibercept group, while only 49.1% of patients gained at least 15 letters in BCVA at week 100. The treatment effect is largely maintained, but does appear to have slight tendency towards deterioration over this time period where

the visit interval was extended to every 12 weeks. Overall, patients in the aflibercept group who received monthly treatment during the first 24 weeks, prior to switching to PRN dosing, had a better outcome than those in the sham + PRN group who began treatment with aflibercept on a PRN basis at week 24. The difference in outcome between the two groups supports the clinical benefit of initiating treatment with a monthly dosing compared to a PRN regimen, and the importance of not delaying treatment.

Sensitivity analyses

The proportion of patients gaining ≥15 letters in vision was similar (for both studies) among treatment groups in all of the sensitivity analyses in both the FAS and PPS populations at week 24, 52, 76 (GALILEO only) and 100 (COPERNICUS only) (i.e. COPERNICUS: LOCF, observed values, pure LOCF, dropouts counted as non-responders; GALILEO: LOCF (for results at 24 weeks), observed values, discontinued patients before week 24 with < 5 injections as failures, analysis considering discontinued patients before Week 52 as failures, analysis considering discontinued patients before week 24 as failures (week 52 and week 76 results), thus supporting the primary analysis results in demonstrating the superiority of aflibercept over sham treatment.

Subgroup analyses of the primary endpoint (see Table 13 and Table 14**)**

The results of the subgroup analyses (e.g. age, gender, race, ethnicity, BCVA, geographic location, baseline perfusion status [presence or absence of ischaemia], time since CRVO diagnosis) in each study and in the combined analysis were consistent with the results seen in the overall populations at 24, 52, 76 (GALILEO only) and 100 (COPERNICUS only) weeks and supported the superiority of aflibercept treatment, although some subgroups have too few patients to draw meaningful conclusions.

In general, within the aflibercept group, the proportion of patients who gained at least 15 letters at week 24 was higher for those with a baseline BCVA of ≤20/200 letters, and those beginning treatment within ≤ 2 months of CRVO diagnosis. Baseline perfusion status did not appear to have any significant effect on response rates, indicating that aflibercept treatment will benefit both non-ischaemic and ischaemic CRVO types.

COPERNICUS – Note: As the numbers in the ‘Rest of World’ (n=28) and BCVA ≤20/200 (n=46) subgroups are small, any conclusions drawn from these analyses of these strata are limited.

GALILEO – Note: As the numbers in the ‘Asia/Pacific’ (n=50) and BCVA ≤20/200 (n=29) subgroups are relatively small, any conclusions drawn from these analyses of these strata are limited.

Table 13. Subgroup analyses of primary efficacy endpoint (COPERNICUS study) (FAS LOCF*)(4;5;28;33;34)

	Week 24			Week 52			Week 100		
	Aflibercept (2Q4) N=114	Sham N=73	Difference (%) (95% CI) [1]	Aflibercept PRN Q4 N=114	Sham (Aflibercept PRN Q4) N=73	Difference (%) (95% CI) [1]	Aflibercept PRN Q12 N=114	Sham (Aflibercept PRN Q12) N=73	Difference (%) (95% CI) [1]
Geographic Region									
North America n (%)	59/95 (62.1)	8/64 (12.5)	49.6 (36.92, 62.29)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Rest of World n (%)	5/19 (26.3)	1/9 (11.1)	15.2 (-13.32, 43.73)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Baseline BCVA									
BCVA ≤ 20/200 n (%)	19/28 (67.9)	3/18 (16.7)	51.2 (26. 8, 75.6)	[redacted] (60.7)	[redacted] (22.2)	[redacted]	[redacted]	[redacted]	[redacted]
BCVA >20/200 n (%)	45/86 (52.3)	6/55 (10.9)	41.4 (28.0, 54.8)	[redacted] (53.5)	[redacted] (32.7)	[redacted]	[redacted]	[redacted]	[redacted]
Baseline Perfusion status [2]									
Nonperfused n (%)	19/37 (51.4)	1/23 (4.3)	47.0 (28.9, 65.1)	[redacted] (48.6)	[redacted] (30.4)	[redacted]	NR	NR	NR
Perfused n(%)	45/77 (58.4)	8/50 (16.0)	42.4 (27.5, 57.4)	[redacted] (58.4)	[redacted] (30.0)	[redacted]	NR	NR	NR
CRVO diagnosis time									
≤ 2 months n (%)	44/64 (68.8)	8/52 (15.4)	53.4 (38.36, 68.37)	[redacted] (64.1)	[redacted] (34.6)	29.4 [redacted]	NR	NR	NR
> 2 months n (%)	19/49 (38.8)	1/21 (4.8)	34.0 (17.61, 50.42)	[redacted] (42.9)	[redacted] (19.0)	23.8 [redacted]	NR	NR	NR

* Full analysis set, Last observation carried forward

[1] Mantel-Haenszel estimate for difference is aflibercept minus sham. C.I. for primary endpoint is calculated using Cochran-Mantel-Haenszel, confidence interval without adjustment.

[2] [redacted]

[3] Mantel-Haenszel estimate for difference is aflibercept minus Sham. Difference and 95% CI were calculated using the Cochran-Mantel-Haenszel, CI without adjustment by regions (North America versus Rest of World) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200) because there was only one record for Rest of World with BCVA ≤20/200.

Table 14. Subgroup analyses of primary efficacy endpoint (GALILEO study) (FAS LOCF*)(29;31;32)

	Week 24			Week 52			Week 76		
	Aflibercept (2Q4) N=103	Sham N=68	Difference (%) (95% CI) [1]	Aflibercept PRN Q4 N=103	Sham N=68	Difference (%) (95% CI) [1]	Aflibercept PRN Q8 N=103	Sham (Aflibercept PRN Q8) N=68	Difference (%) (95% CI) [1]
Geographic Region									
Europe n (%)	44/73 (60.3)	12/48 (25.0)	35.3 (18.4, 52.2)	[redacted]					
Asia/Pacific n (%)	18/30 (60.0)	3/20 (15.0)	45.5 (21.9, 69.0)						
Baseline BCVA									
BCVA ≤ 20/200 n (%)	11/17 (64.7)	3/12 (25.0)	40.0 (6.2, 73.8)						
BCVA >20/200 n (%)	51/86 (59.3)	12/56 (21.4)	37.9 (22.8, 53.0)						
Baseline Perfusion status [2]									
Nonperfused n (%)	10/14 (71.4)	1/14 (7.1)	64.3 [redacted]						
Perfused n(%)	52/89 (58.4)	14/54 (25.9)	32.5 [redacted]						
CRVO diagnosis time									
< 2 months n (%)	39/55 (70.9)	7/35 (20.0)	50.9 (33.0, 68.8)						
≥ 2 months n (%)	23/46 (50.0)	8/33 (24.2)	25.8 (5.2, 46.3)						

* Full analysis set, Last observation carried forward

[1] Mantel-Haenszel estimate for difference is aflibercept minus sham. C.I. for primary endpoint is calculated using Cochran-Mantel-Haenszel, confidence interval adjusted for by regions (Europe vs. Asia/Pacific) and baseline BCVA (BCVA >20/200 and BCVA ≤20/200)

[2] [redacted]

Secondary & Tertiary endpoints(4-6;28;29;31-34)

The phase 3 COPERNICUS study met all of the secondary efficacy end points, including BCVA and improvement in CRT. The conditional sequence of statistical hypothesis for GALILEO, on the other hand, was stopped after the testing of the proportion of patients progressing to neovascularisation (test 3), as this proved statistically non-significant.

Although the hierarchical testing of secondary efficacy variables stopped in the GALILEO study after the testing of the proportion of patients progressing to any neovascularisation, statistical tests were still performed for the changes in NEI VFQ-25 and EQ-5D scores (tests 4 and 5) at Week 24 and any p-values provided for these analyses were considered to be for descriptive purposes only.

Sensitivity analyses of secondary endpoint FAS LOCF results.

In both studies, the results of the secondary endpoints at weeks 24[redacted](GALILEO onl[redacted] (COPERNICUS only) in the PPS were similar to those in the FAS[redacted]

Mean change in BCVA from baseline

At Week 24

In both studies and in the combined analysis of the two studies, monthly intravitreal injection of aflibercept 2 mg improved visual acuity and was statistically significantly superior to sham in the increase in BCVA at week 24 (see Table 15, and Figure 10).

COPERNICUS – Aflibercept-treated eyes gained a mean of 17.3 letters versus sham-treated eyes, which lost 4.0 letters (P<0.001).

GALILEO – Aflibercept patients gained a mean of 18.0 letters compared with 3.3 letters with sham injections (p<0.0001).

At Week 52

COPERNICUS – At week 52, patients in the aflibercept PRN group had gained a mean of 16.2 letters of vision (from baseline), maintaining the gains achieved in the initial 24 weeks

of treatment. In comparison, the sham group, who were now eligible to receive aflibercept PRN, also improved and now had a mean change in BCVA letters from baseline of 3.8 letters (P<0.001) – a gain of 7.8 letters from week 24, demonstrating that even with delayed treatment, some improvements in BCVA can be achieved.

GALILEO – Patients treated with aflibercept had a superior outcome, to those treated with sham, in mean BCVA letter score at week 52 (mean BCVA letter change from baseline: Aflibercept group = +16.9 letters; sham group = +3.8 letters; p<0.0001). The switch from a fixed monthly dosing regimen to PRN dosing (with monthly assessments) in the aflibercept group did not lead to any significant vision loss.

At Week 76

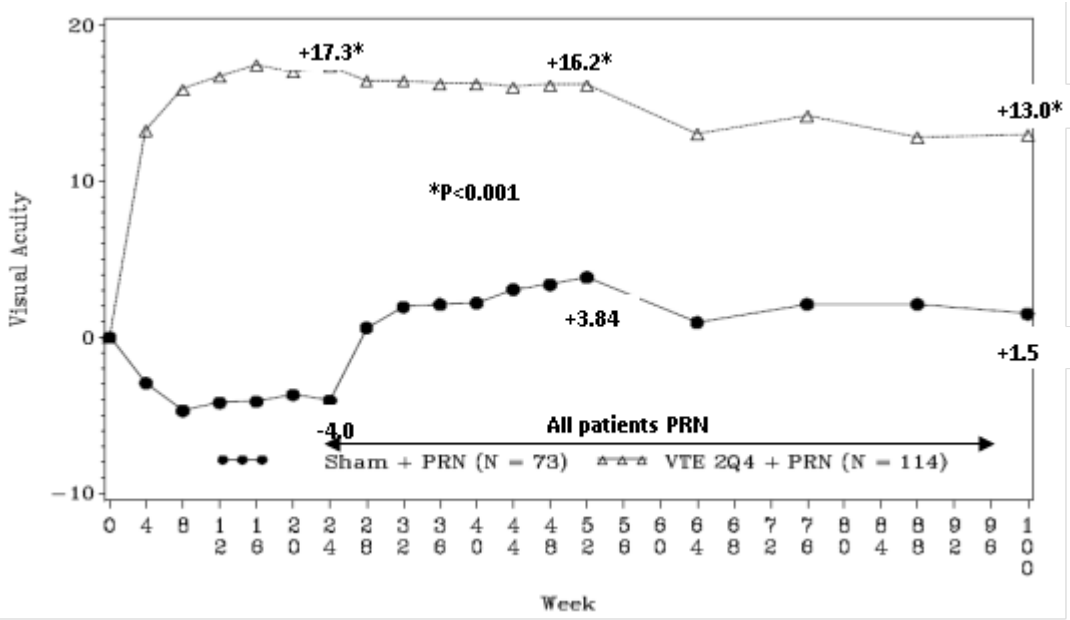
GALILEO – At week 76, the aflibercept group had a mean change of approximately +14 letters above baseline, representing a loss of approximately 3 letters from week 52, and an overall decrease of almost a full line of vision (4 letters) over a year [i.e. week 24 to week 76]. These data may suggest that a reactive PRN regimen is less able to control the disease, especially with extended monitoring intervals. The sham group, who waited a full year before receiving active treatment, had a mean change (6.2 letters) in BCVA letters of from baseline to week 76, suggesting that a delayed start to treatment, with fewer and less frequent injections under a PRN regimen might not provide the best efficacy results.

At Week 100

COPERNICUS - The mean ETDRS letter score was increased from baseline in the aflibercept group (+13 letters) but had decreased by approximately one line of BCVA from week 24. By week 100, BCVA had returned to around baseline level in the sham+PRN group (-0.2 letters). These data strongly suggest the additional benefit of treating CRVO with at least an initial proactive, fixed dosing compared to a reactive PRN regimen, as well as the benefit of prompt treatment. Deterioration of mean change of ETDRS letter score was faster after extending the monitoring interval to 12 weeks (week 52 to week 100), indicating that PRN dosing may require a more rigorous monitoring schedule than every 12 weeks for CRVO.

Figure 9. Mean change from baseline in BCVA (FAS LOCF)

A) COPERNICUS study



B) GALILEO study

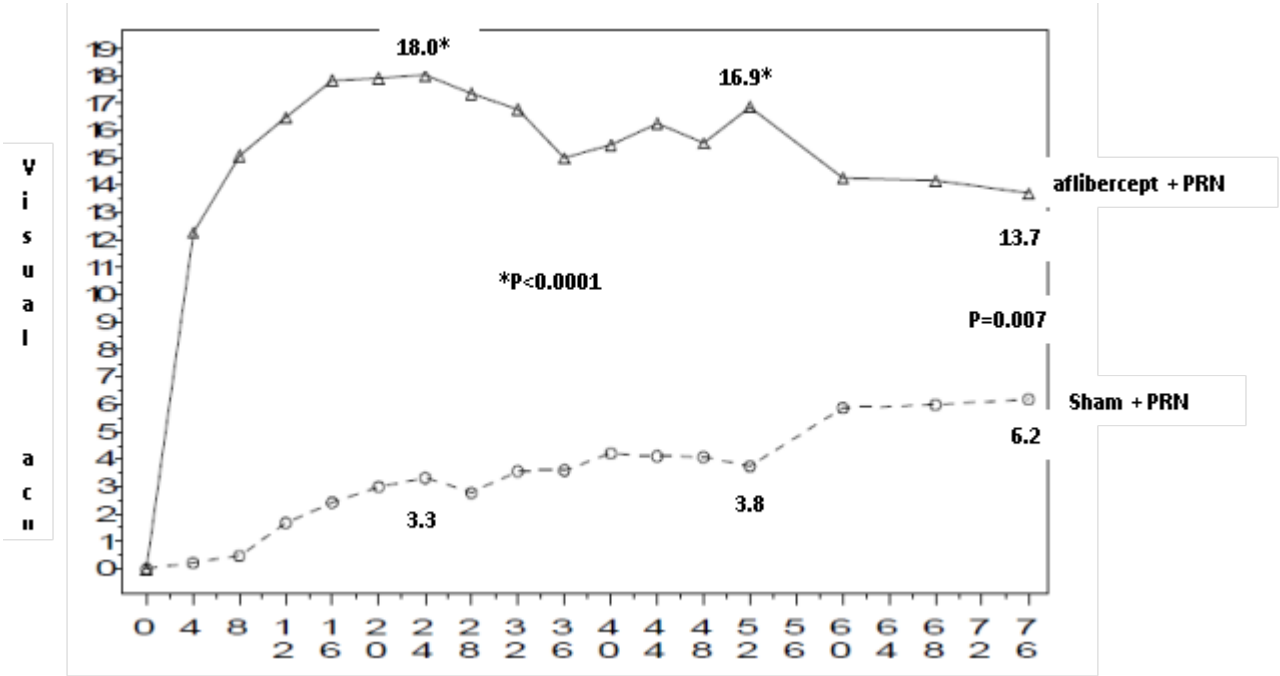


Figure 10. Integrated analysis: Mean change from baseline in BCVA at 24 weeks (FAS LOCF);

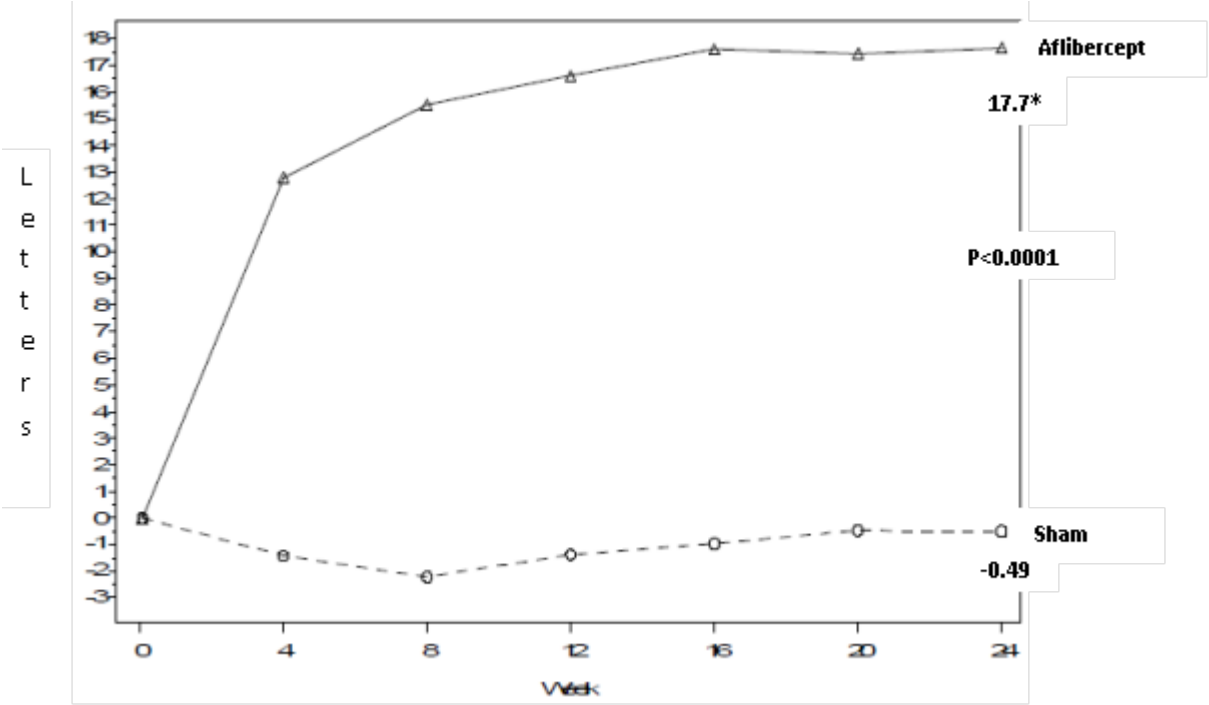


Table 15. Mean change in ETDRS letter score in the study eye from baseline to Week 24, 52, 76 (GALILEO only) and Week 100 (COPERNICUS only) (FAS LOCF)

	Aflibercept			Sham		
	COPERNICUS N=114	GALILEO N=103		COPERNICUS N=73	GALILEO N=68	
Baseline						
Mean (SD)	50.7 (13.9)	53.6 (15.8)		48.9 (14.4)	50.9 (15.4)	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
Week 24						
Mean	[redacted]	[redacted]		[redacted]	[redacted]	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
Week 24 (change from baseline)						
Mean	17.3 (12.8)	18.0 (12.2)		-4.0 (18.0)	3.3 (14.1)	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
LS Mean change	[redacted]	[redacted]		[redacted]	[redacted]	
LS means difference[1] 95.1% CI for difference	21.70 (17.36, 26.04)	14.70 (10.8, 18.7)				
P-value vs sham	<0.001	<0.0001				
Week 52						
Mean (SD)	[redacted]	[redacted]		[redacted]	[redacted]	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
Week 52 (change from baseline)						
Mean (SD)	16.2	16.9 (14.8)		3.8	3.8 (18.1)	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
LS Mean change	14.01	18.1		1.30	4.9	
LS means difference[1] 95.1% CI for difference	12.71 (7.69, 17.74)	13.2 (8.2; -18.2)			-	

P-value vs sham	<0.001	<0.0001			
Week 100/76	**Week 100**	**Week 76**		**Week 100**	**Week 76**
Mean (SD)	[redacted]	67.3 (21.4)		[redacted]	57.1 (21.3)
Median	NR	72.0		NR	59.5
Min: Max	NR	[0; 95]		NR	[0; 94]
Week 100/76 (change from baseline)					
Mean (SD)	13.0	13.7 (17.8)		1.5	6.2 (17.7)
Median	NR	17.0		NR	8.5
Min: Max	NR	[-56; 53]		NR	[-30; 40]
LS Mean change	11.6	15.0		-0.20	7.4
LS means difference[1] 95.1% CI for difference	11.81 (6.65, 16.79)	7.6 (2.1; 13.1)			
P-value vs sham	<0.0001	0.0070			

[1] Point estimate and 95% CI and p-value based on treatment difference (aflibercept minus sham) of LS mean changes using ANCOVA model with treatment group, region and baseline BCVA as fixed factors; CI = confidence interval.

Subgroup analyses of the 'Mean change in BCVA from baseline'

In general, the results of the subgroup analyses of the change from baseline to week 24, [redacted] (GALILEO only) and [redacted](COPERNICUS only) in BCVA were consistent with those seen in the overall population for COPERNICUS and GALILEO. As per the primary endpoint, baseline perfusion status did not affect response to aflibercept (see Figure 11). In COPERNICUS (at 24 weeks) Improvements in visual acuity were quantitatively larger when the time from diagnosis was 2 months or less compared with more than 2 months.

[redacted]

Baseline perfusion status

Perfusion status is known to play an important role in the natural course of the disease in untreated CRVO patients (i.e. patients have a much worse prognosis if they have ischaemic (non-perfused) CRVO. Treatment with aflibercept seems to eliminate the progression of deterioration of visual function in ischaemic patients. In both the COPERNICUS and GALILEO studies, both perfused and non-perfused patients experienced a very similar beneficial effect when treated with aflibercept, such that the

time-course curves of BCVA improvement are very similar to each other (see Figure 11 and Figure 12). In contrast, the sham groups show different behavior if divided by perfusion status at baseline.

Figure 11. COPERNICUS study: Change in BCVA based on perfusion status at baseline (by weeks)

[redacted]

Figure 12. GALILEO study: Change in BCVA based on perfusion status at baseline (by weeks)

[redacted]

Mean change in central retinal thickness (CRT) from baseline

At Week 24

In both studies, and the integrated analysis, at 24 weeks, monthly intravitreal injection of aflibercept 2 mg in eyes with macular oedema resulting from CRVO improved CRT (see Figure 13, and Table 16).

COPERNICUS – By week 24, CRT decreased by 457.2µm in eyes treated with aflibercept versus 144.8µm in sham-treated eyes (P<0.001). The reduction in CRT was rapid and could be seen at week 4, continuing through week 24.

GALILEO – Mean CRT had decreased in the GALILEO study at week 24, by 448.6 and 169.3 µm in the aflibercept and sham groups, respectively (p<0.0001).

At Week 52

COPERNICUS **–** The rapid reduction in CRT observed in the aflibercept group through week 24 was largely maintained through week 52. After week 24, when patients in the sham group were eligible to receive aflibercept PRN, the mean CRT reduction in the sham group was similar to that seen in the aflibercept group (-381.8 µm [sham+PRN] vs. -413µm [aflibercept+PRN]).

GALILEO – At week 52, mean change from baseline in CRT was greater in the aflibercept+PRN group (-423.53 µm) compared to the sham group (-219.26 µm), the difference being highly significant (p<0.0001) and supportive of the superiority of aflibercept over sham. With the switch from fixed monthly treatment to a PRN regimen, CRT values had increased slightly in the aflibercept group, compared to measurements at week 24.

At Week 76

GALILEO – The superiority of aflibercept over sham was still apparent at week 76, however, as noted at week 52, PRN dosing was associated with an erosion of the reductions achieved in the aflibercept group from baseline to week 24, and the difference between treatment groups was smaller (than at weeks 24 and 52). At week 76, the mean change from baseline in CRT was -389.35 µm [aflibercept+PRN]) vs. -306.37 µm [sham+PRN] (p=0.11). The sham+PRN group did not achieve the level of CRT improvement as achieved by patients in the aflibercept group, supporting the conclusion that better efficacy is achieved with a proactive dosing regimen compared with a reactive PRN dosing regimen based on deterioration in morphologic endpoints.

At Week 100

COPERNICUS – At week 100, reductions in CRT were similar in the aflibercept+PRN and sham+PRN groups (-431.4 µm and -386.8 µm respectively). While patients who had

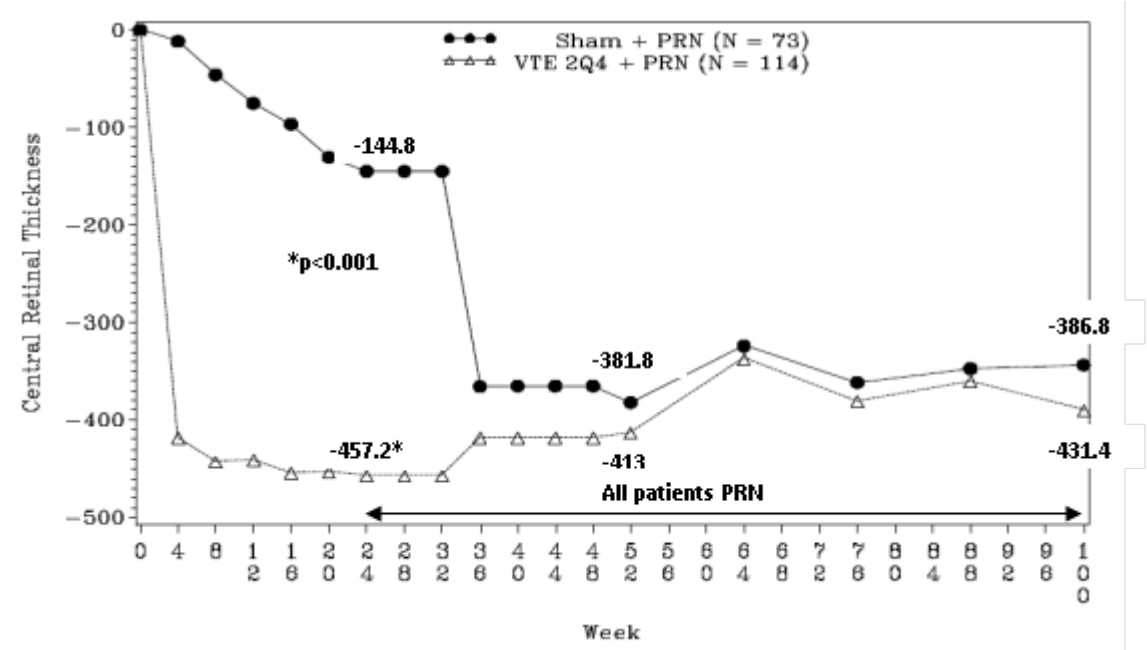
delayed treatment i.e. the sham group, were able to obtain robust reductions in CRT, this anatomic improvement did not translate to improved visual function.

Subgroup analyses of the 'Mean change in CRT from baseline'

In general, the results of the subgroup analyses of the change from baseline to week 24, 52, 76 (GALILEO only) and 100 (COPERNICUS only) in CRT were [redacted] with those seen in the overall population for COPERNICUS and GALILEO. Baseline perfusion status did not affect response to aflibercept.

Figure 13. Mean change from baseline in CRT (FAS LOCF)

A) COPERNICUS study (by weeks)



B) GALILEO study (by weeks)

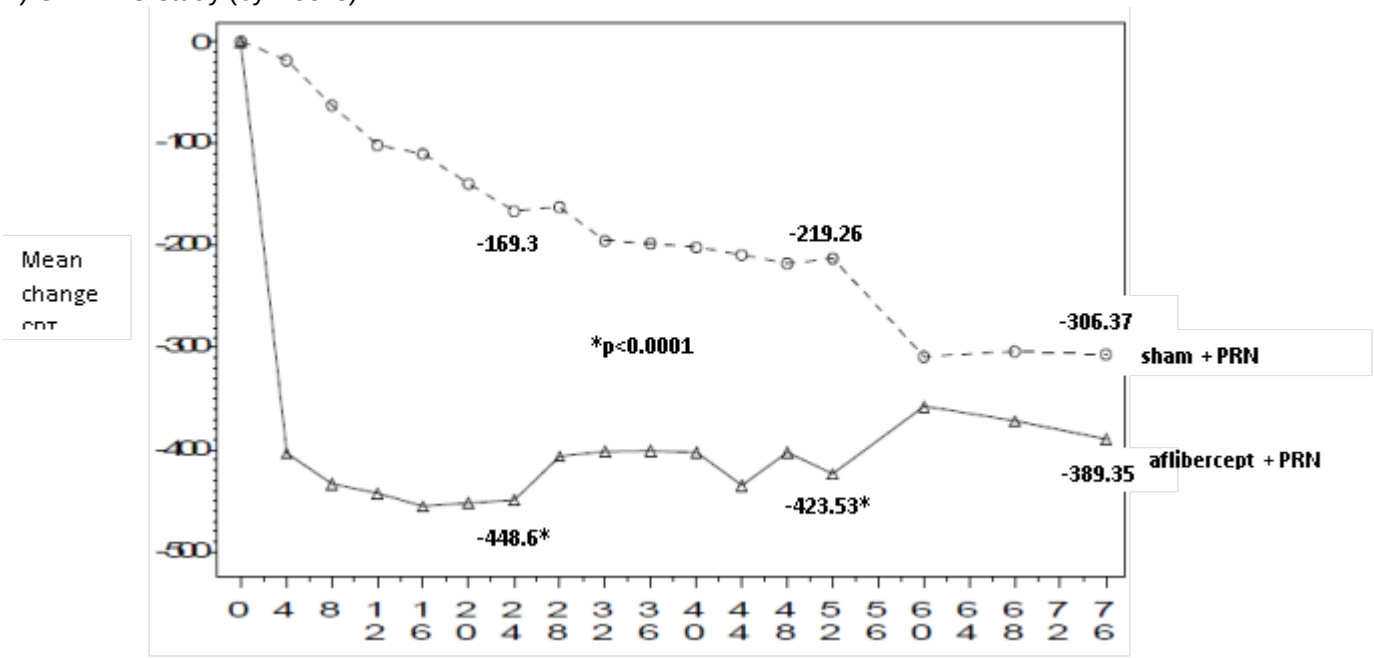


Table 16. Mean change from baseline to Week 24, 52, 76 (GALILEO only) and Week 100 (COPERNICUS only) in CRT (FAS LOCF)

	Aflibercept			Sham		
	COPERNICUS N=112	GALILEO N=103		COPERNICUS N=65	GALILEO N=68	
Baseline						
Mean (SD)	661.7 (237.4)	683.2 (234.5)		664.0 (245.3)	638.7 (224.7)	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
Week 24						
Mean	[redacted]	[redacted]		[redacted]	[redacted]	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
Week 24 (change from baseline)						
Mean	-457.2	-448.6[redacted]		-144.8	-169.3[redacted]	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
LS Mean change	[redacted]	-447.97		[redacted]	-208.55	
LS means difference[1] 95.1% CI for difference P-value vs sham	-311.9 (-389.4, -234.4) <0.001	-239.42 (-286.31, -192.53) <0.0001				
Week 52						
Mean (SD)	[redacted]	[redacted]		[redacted]	[redacted]	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
Week 52 (change from baseline)						
Mean (SD)	-413.0	-423.53 (250.29)		-381.8	-219.26 (233.85)	
Median	NR	[redacted]		NR	[redacted]	
Min: Max	NR	[redacted]		NR	[redacted]	
LS Mean change	-455.1	-441.62		-426.7	-274.15	
LS means difference[1] 95.1% CI for difference P-value vs sham	-28.44 (-121.2, 64.34) 0.546	-167.47 (-216.62; -118.33) <0.0001			-	
Week 100/76	**Week 100**	**Week 76**		**Week 100**	**Week 76**	

Mean (SD)	[redacted]	293.85 (173.01)		[redacted]	327.79 (191.58)
Median	NR	225.0		NR	248.0
Min: Max	NR	[89.6; 1054.4]		NR	[117.4; 941.1]
Week 100/76 (change from baseline)					
Mean (SD)	[redacted]	-389.35 (273.71)		[redacted]	-306.37 (246.85)
Median	NR	-398.8		NR	-319.0
Min: Max	NR	[-1028.7; 451.0]		NR	[-930.5; -277.6]
LS Mean change	-390.0	-408.85		-343.3	-364.69
LS means difference[1] 95.1% CI for difference P-value vs sham	-44.63 (-141.8, 52.58) 0.3661	-44.16 (-98.76; 10.44) 0.1122			

[1] Point estimate and 95% CI and p-value based on treatment difference (aflibercept minus sham) of LS mean changes using ANCOVA model with treatment group, region and baseline BCVA as fixed factors; CI = confidence interval.

Proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina from baseline

Overall, the development of any neovascularisation was infrequent in both studies with, ultimately, no meaningful differences between the two treatment groups in either study (see Table 17). In COPERNICUS, aflibercept initially appeared to eliminate the risk of developing neovascularisation, during the first 6 months of treatment, with no reported cases of neovascularisation in the aflibercept group during this period.

At Week 24

COPERNICUS – Progression to any neovascularisation was eliminated in the aflibercept group between baseline and week 24, occurring in 0 and 5 (6.8%) of patients treated with aflibercept and sham, respectively (P=0.006). By week 24, panretinal photocoagulation (PRP) had been performed on 4 of the sham-treated patients.

GALILEO – Between baseline and 24 weeks, neovascularisation developed in 3 aflibercept-treated patients (2.9%) and 3 sham-treated patients (4.4%). All three of the sham-treated patients with neovascularisation received panretinal photocoagulation, along with one aflibercept patient (iris neovascularisation). All patients developing neovascularisation had [redacted] at baseline. [redacted] of the patients developing neovascularisation had a baseline perfusion status of [redacted] while [redacted] had a baseline perfusion status of [redacted]

[redacted]

(P=0.5947).

At Week 52

In COPERNICUS, there were no new cases of neovascularisation reported from weeks 24 to 52. In GALILEO, a further 3 patients in each treatment group developed neovascularisation. One aflibercept-treated patient underwent PRP.

At Week 76, in GALILEO, there were two new cases of neovascularisation during the week 52 to week 76 period. Both were from the aflibercept-treated group and neither of which underwent PRP. At Week 100, in COPERNICUS, between week 52 and week 100, six aflibercept patients and 3 sham patients developed neovascularisation.

Table 17. Incidence of neovascularisation during the COPERNICUS and GALILEO studies

COPERNICUS study								
	Aflibercept				**Sham**			
	N=114				**N=73**			
	Week 24	**Week 52**	**Week 100**	**Total**	**Week 24**	**Week 52**	**Week 100**	**Total**
Any neovascularisation n (%)	0	0	6 (5.3)	6 (5.3)	5 (6.8)	0	3 (4.1)	8 (11.0)
Anterior segment	0	0	1 (0.9)^	1 (0.9)^	5 (6.8)	0	0	5 (6.8)
Optic disc	0	0	6 (5.3)^	6 (5.3)^	0	0	3 (4.1)	3 (4.1)
Retina elsewhere	0	0	0	0	0	0	0	0
Adjusted difference (%) 95% C.I. [1] CMH test P-value	-6.8 (-12.4, -1.2) P=0.006	-						
Panretinal photocoagulation performed	0	0	0	0	4 (5.5)	0	0	4 (5.5)
GALILEO study								
	Aflibercept				**Sham**			
	N=103				**N=68**			
	Week 24	**Week 52**	**Week 76**	**Total**	**Week 24**	**Week 52**	**Week 76**	**Total**
Any neovascularisation n (%)	3 (2.9)	3 (2.9)	2 (1.9)	8 (7.8)	3 (4.4)	3 (4.4)	0	6 (8.8)
Anterior segment	2 (1.9)	3 (2.9)#	2 (1.9)^	7 (6.8)	1 (1.5)	0	0	1 (1.5)
Optic disc	0	0	1 (1.0)^	1 (1.0)	0	1 (1.5)	?1 (1.5)	2 (2.9)
Retina elsewhere	1 (1.0)	1 (1.0)#	0	2 (1.9)	2 (2.9)	2 (2.9)	0	4 (5.9)
Adjusted difference (%) 95% C.I. [1] CMH test P-value	-1.5 (-7.4, 4.4) 0.5947							
Panretinal photocoagulation performed	1 (1.0)	1 (1.0)	0	2 (1.9)	3 (4.4)	0	0	3 (4.4)

[1] calculated using Cochran-Mantel-Haenszel weighting scheme adjusted by region and baseline BCVA
^ one patient developed both anterior segment neovascularisation and neovascularisation of the optic disc
# one patient developed both anterior segment neovascularisation and neovascularisation of retina or elsewhere

Subgroup analyses of the 'Proportion of patients progressing to neovascularisation of the anterior segment, optic disc or elsewhere in the retina from baseline'

In general, the results of the subgroup analyses of the development from baseline to week 24, 52, 76 (GALILEO only) and 100 (COPERNICUS only) of neovascularisation were [redacted] with those seen in the overall population for COPERNICUS and GALILEO

Vision-related Quality of Life

Mean changes in NEI VFQ-25 total (and near activities, distance activities and vision dependency subscale) scores from baseline

At Week 24

COPERNICUS – By week 24 patients treated with aflibercept showed a clinically relevant improvement of 7.2 points in NEI VFQ-25 total score compared with an improvement of 0.8 points in the sham group (P<0.001). Clinically relevant improvements (i.e. an increase in score of at least 4 to 6 points) in the subscale scores (near activities, distance activities and vision dependency) were also observed (see Table 18).

GALILEO – The mean change from baseline to week 24 in total NEI-VFQ-25 scores was 7.5 for the aflibercept group and 3.5 for the sham group. The between-group difference in both the total NEI-VFQ score and the near-activities subscore was significant at week 24 (p=0.0013 and p=0.0003, respectively). A trend was observed between groups in favour of aflibercept for the distance-activities and dependency subscores (p=0.0689 and p=0.2552, respectively). SeeTable 19.

[redacted]

INTEGRATED – Similarly to the individual studies, the integrated analysis produced significant differences for the NEI VFQ-25 total score and near activities subscale score at 24 weeks.

At Week 52

COPERNICUS – Both treatment groups experienced a clinically relevant improvement in the mean NEI VFQ-25 total, near-activities, distance-activities and vision dependency subscale scores at week 52. Although the improvement was numerically larger for the aflibercept group, a significant difference between treatment arms was not seen, likely due to the crossover of sham patients at week 24 to receive aflibercept PRN. As observed with other parameters of visual function, those patients treated from the beginning of the study with aflibercept obtained and maintained greater improvements.

GALILEO – At week 52, continued treatment with aflibercept PRN maintained clinically meaningful improvements in total NEI VFQ-25 scores and the near activities and distance activities subscores. Neither treatment group experienced clinically meaningful change in 'vision dependency' subscale score at week 52, likely because the scores were already high at baseline.

At Week 76

GALILEO – For all defined NEI VFQ-25 endpoint scores (i.e. total, near-activities, distance-activities, vision dependency), the aflibercept group demonstrated a greater change from baseline to week 76 than the sham group, however these differences did not reach significance.

At Week 100

COPERNICUS – A clinically relevant improvement in the mean NEI VFQ-25 total score was seen in both aflibercept and sham treatment groups; however, the improvement was numerically larger in the aflibercept group than in the sham group. It was thus demonstrated that the clinically relevant improvements achieved in the aflibercept group during the first 6 months of monthly dosing, were largely maintained in the subsequent 18 months of less frequent PRN dosing. Clinically relevant improvements also seen in the sham group indicate that delayed treatment can still provide benefit, though patients treated early still obtained and maintained greater improvements than those treated later. Changes from baseline in NEI VFQ-25 subscales (near-activities, distance-activities, and vision dependency) at week 100 generally reflected that of the change from baseline in NEI VFQ-25 in total score.

Table 18. Mean change in NEI VFQ-25 subscale scores from baseline to Week 24, 52, and Week 100 in the COPERNICUS study (FAS LOCF)

COPERNICUS study							
Week 24	**Aflibercept**			**Sham**			**Difference in LSmean change 95% CI [1] p-value**
NEI VFQ-25 score (SD)	**Baseline**	**Week 24**	**Mean Change from baseline**	**Baseline**	**Week 24**	**Mean Change from baseline**	
	N=114	**N=104**	**N=104**	**N=73**	**N=59**	**N=59**	
Total	77.7 (16.0)	84.9 (12.9)	7.2 (12.1)	77.8 (16.3)	78.8 (16.5)	0.8 (9.8)	6.26 (2.61, 9.91) =0.001
Near-activities	70.0 (21.9)	77.9 (20.5)	8.3 (22.0)	70.7 (20.2)	72.7 (21.7)	1.84 (19.75)	[redacted]
Distance-activities	76.0 (21.3)	82.5 (20.3)	6.1 (20.0)	78.1 (21.3)	77.5 (21.1)	-0.64 (15.2)	
Vision dependency	83.3 (25.5)	90.7 (18.3)	7.1 (20.5)	82.8 (27.4)	84.5 (27.1)	1.1 (20.5)	
Week 52	**Baseline**	**Week 52**	**Mean Change from baseline**	**Baseline**	**Week 52**	**Mean Change from baseline**	**Difference in LSmean change 95% CI [1] p-value**
	N=114	**N=109**	**N=109**	**N=73**	**N=59**	**N=59**	
Total	[redacted]		7.5	[redacted]		5.1	2.37 (-1.40, 6.1) 0.2164
Near-activities			11.35			8.26	2.95 (-3.11, 9.00) 0.3379
Distance-activities			8.52			3.81	4.67 (-0.65, 10.00) 0.0850
Vision dependency			5.96			3.39	2.48 (-3.50, 8.46) 0.4148
Week 100	**Baseline**	**Week 100**	**Mean Change from baseline**	**Baseline**	**Week 100**	**Mean Change from baseline**	**Difference in LSmean change 95% CI [1] p-value**
	N=114	**N=110**	**N=110**	**N=73**	**N=69**	**N=69**	
Total	[redacted]						
Near-activities							
Distance-activities							
Vision dependency							

NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire SD= standard deviation
[1] Point estimate, 95% CI and p-value are based on treatment differences (aflibercept minus sham) of the LS mean changes using an ANCOVA model with treatment group, region and baseline BCVA as fixed factors

Table 19. Mean change in NEI VFQ-25 subscale scores from baseline to Week 24, 52, and 76 in the GALILEO study (FAS LOCF)

GALILEO study							
Week 24	**Aflibercept**			**Sham**			**Difference in LSmean change 95% CI [1] p-value**
NEI VFQ-25 score (SD)	**Baseline**	**Week 24**	**Mean Change from baseline**	**Baseline**	**Week 24**	**Mean Change from baseline**	
	N=103	**N=96**	**N=96**	**N=68**	**N=65**	**N=65**	
Total	[redacted]	[redacted]	7.5	[redacted]	[redacted]	3.5	4.2 (1.7, 6.8) 0.0013
Near-activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distance-activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision dependency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Week 52	**Baseline**	**Week 52**	**Mean Change from baseline**	**Baseline**	**Week 52**	**Mean Change from baseline**	**Difference in LSmean change 95% CI [1] p-value**
	N=103	**N=98**	**N=98**	**N=68**	**N=67**	**N=67**	
Total	[redacted]	[redacted]	7.8	[redacted]	[redacted]	4.5	3.6 (1.1, 6.0) 0.0049
Near-activities	[redacted]	[redacted]	12.2	[redacted]	[redacted]	5.0	6.9 (3.1, 10.8) 0.0005
Distance-activities	[redacted]	[redacted]	8.4	[redacted]	[redacted]	3.9	4.2 (0.4, 7.9) 0.0283
Vision dependency	[redacted]	[redacted]	3.8	[redacted]	[redacted]	3.1	1.6 (-1.7, 4.8) 0.3423
Week 76	**Baseline**	**Week 76**	**Mean Change from baseline**	**Baseline**	**Week 76**	**Mean Change from baseline**	**Difference in LSmean change 95% CI [1] p-value**
	N=103	**N=98**	**N=98**	**N=68**	**N=67**	**N=67**	
Total	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Near-activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Distance-activities	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Vision dependency	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

NEI VFQ-25 = National Eye Institute 25-item Visual Function Questionnaire SD= standard deviation
[1] Point estimate, 95% CI and p-value are based on treatment differences (aflibercept minus sham) of the LS mean changes using an ANCOVA model with treatment group, region and baseline BCVA as fixed factors

Table 20. INTEGRATED analysis - Mean change NEI VFQ-25 subscale scores from baseline to Week 24 in (FAS LOCF)

Integrated analysis							
Week 24	**Aflibercept**			**Sham**			**Difference in LSmean change 95% CI [1] p-value**
NEI VFQ-25 score (SD)	**Baseline**	**Week 24**	**Mean Change from baseline**	**Baseline**	**Week 24**	**Mean Change from baseline**	
	N=217	**N=200**	**N=200**	**N=140**	**N=125**	**N=124**	
Total	[redacted]						
Near-activities							
Distance-activities							
Vision dependency							

Subgroup analyses of the 'Mean changes in NEI VFQ-25 total (and near activities, distance activities and vision dependency subscale) scores from baseline'

[redacted]

[redacted]

[redacted]

[redacted]

Mean changes in European Quality of Life-5 Dimensions (EQ-5D) Health Questionnaire from baseline

At Week 24

A trend was observed between groups in favour of aflibercept for the overall mean EQ-5D score at week 24 (p=0.0627; 0.044 [-0.002, 0.090] adjusted difference between treatment groups [95% CI]).

At Week 52

Mean EQ-5D scores were similar between treatment groups at baseline and week 52. The sham-group mean EQ-5D score had the biggest improvement between week 24 and week 52[redacted]

At Week 76

There was little change of note in mean EQ-5D score from baseline to week 76, for either treatment group.

Additional endpoints efficacy analysis

Time to development of anterior segment neovascularisation or need for pan-retinal photocoagulation up to week 52 (GALILEO only)

[redacted]

Summary of extent of vision gain and loss (using ETDRS letter score)

Several additional analyses referred to certain categories of vision gain and vision loss from baseline as measured by the ETDRS letter score. A summary of these results can be found in Table 21 and Table 22.

COPERNICUS – At 24 weeks**,** most eyes (93.9%) in the aflibercept group gained ≥0 letters or more compared with 52.1% of eyes in the sham group. Over half (56.1%) of patients receiving aflibercept gained ≥ 15 letters of vision compared to 12.3% of patients in the sham group. More patients in the sham group than in the aflibercept group lost 15 letters or more (27.4% versus 1.8%, respectively). At 52 weeks, visual function was

maintained in the aflibercept group, with 92.1% patients gaining > 0 letters of vision from baseline, and 55.3% patients gaining ≥ 15 letters from baseline. Patients in the sham group showed improvements during week 24 and 52, as they were now receiving aflibercept PRN (68.5% gained >0 letters of vision at week 52). [redacted] however this was an improvement (for the sham group) compared to the extent of losses at week 24 (47.9%) and demonstrates that delayed treatment can lead to modest vision gains.

GALILEO – The aflibercept treatment arm showed higher proportions of vision gains at week 24. In all, 11 patients (10.7%) in the aflibercept experienced a loss of 1 or more letters during the course of the 24 weeks compared with 27 (39.7%) patients in the sham arm (p<0.0001). In the aflibercept treatment group, vision continued to be maintained for the primary endpoint at week 52 (60.2% gained ≥ 15 letters at week 52) although, during the second phase of treatment (week 24 to 52), when patients were receiving treatment in a PRN regimen, the aflibercept group showed slight decreases in most categories of vision gain compared to week 24 and some increases of vision loss. This pattern of decreases in vision gain for the aflibercept group and increases in vision loss continued to week 76, while in the sham group (who received aflibercept PRN weeks 52 to 76) slight increases in vision gain and decreases in proportions of patients with visual loss were observed.

Table 21. COPERNICUS STUDY: Summary of vision gains and losses compared with baseline using the ETDRS letter score (FAS LOCF)

	Week 24	Week 52	Week 100
Letter gains: n (%)			
≥ 15 letters			
Sham group	9 (12.3)	22 (30.1)	17 (23.3)
Aflibercept group	66 (57.9)	65 (57.0)	58 (50.9)
≥ 10 letters			
Sham group	16 (21.9)	34 (46.6)	[redacted]
Aflibercept group	87 (76.3)	88 (77.2)	
≥ 5 letters			
Sham group	29 (39.7)	43 (58.9)	
Aflibercept group	97 (85.1)	93 (81.6)	
≥ 0 letters			
Sham group	38 (52.1)	50 (68.5)	
Aflibercept group	107 (93.9)	105 (92.1)	
Loss of letters: n (%)			
> 0 letter			
Sham group	35 (47.9)	23 (31.5)	[redacted]
Aflibercept group	7 (6.1)	9 (7.9)	
≥ 5 letters			
Sham group	29 (39.7)	17 (23.3)	
Aflibercept group	5 (4.4)	8 (7.0)	
≥ 10 letters			
Sham group	22 (30.1)	13 (17.8)	
Aflibercept group	2 (1.8)	6 (5.3)	
≥ 15 letters			
Sham group	20 (27.4)	11 (15.1)	

Aflibercept group	2 (1.8)	6 (5.3)	[redacted]

Table 22. GALILEO STUDY: Summary of vision gains and losses compared with baseline using the ETDRS letter score (FAS LOCF)

	Week 24	Week 52	Week 76
Letter gains: n (%)			
≥ 30 letters			
Sham group	2 (2.9)	5 (7.4)	5 (7.4)
Aflibercept group	17 (16.5)	15 (14.6)	12 (11.7)
≥ 15 letters			
Sham group	15 (22.1)	22 (32.4)	20 (29.4)
Aflibercept group	65 (63.1)	62 (60.2)	59 (57.3)
≥ 10 letters			
Sham group	21 (30.9)	26 (38.2)	32 (47.1)
Aflibercept group	78 (75.7)	74 (71.8)	70 (68.0)
Loss of letters: n (%)			
< 0 letters			
Sham group	44 (64.7)	38 (55.9)	43 (63.2)
Aflibercept group	98 (95.1)	92 (89.3)	87 (84.5)
< 10 letters			
Sham group	59 (86.8)	52 (76.5)	56 (82.4)
Aflibercept group	102 (99.0)	102 (99.0)	97 (94.2)
< 15 letters			
Sham group	63 (92.6)	58 (85.3)	61 (89.7)
Aflibercept group	102 (99.0)	102 (99.0)	98 (95.1)

Table 23. INTEGRATED analysis: Summary of vision gains and losses compared with baseline using the ETDRS letter score (FAS LOCF)

	Week 24
Letter gains: n (%)	
≥ 30 letters	
Sham group	[redacted]
Aflibercept group	
≥ 15 letters	
Sham group	24 (17.0)
Aflibercept group	131 (60.4)
≥ 10 letters	
Sham group	37 (26.2)
Aflibercept group	165 (76.0)
> 0 letters	
Sham group	[redacted]
Aflibercept group	
Loss of letters: n (%)	
≥ 15 letters	
Sham group	26 (18.4)
Aflibercept group	3 (1.4)
≥ 30 letters	
Sham group	[redacted]
Aflibercept group	

Treatment compliance

COPERNICUS - Compliance was excellent in both groups (mean compliance: 98.5%, 96.4% (aflibercept group); 97.7%, 96.4% (sham group) at Week 24, and 52 respectively.

GALILEO - Compliance was excellent in both groups (mean compliance: 96.5%, 93.9%, 93.4% (aflibercept group); 90.1%, 87.8%, 87.5% (sham group) at Week 24, 52 and 76 respectively.

Injection frequency

COPERNICUS – During the first 24 weeks of treatment, the planned exposure to aflibercept was 2mg administered monthly (i.e. 6 injections, 12 mg in total). Even though week 88 was the last scheduled mandatory study visit when a PRN injection could be administered, investigators were allowed to bring patients in as often as monthly for PRN injections so the last possible PRN injection was at week 96. Beginning at week 24, patients in the sham group began receiving active PRN doses of aflibercept with sham injections given when retreatment criteria were not met. A total of 57/60 patients in the sham group who completed week 24, crossed over to receive aflibercept PRN for the rest of the study [redacted]

From baseline to week 100, the mean number of 'active' injections was higher in the aflibercept group (as expected) (11.8 injections) than in the sham group (6.4 injections) (see Table 24).

GALILEO – During the 76 weeks of treatment, the total exposure to aflibercept in the aflibercept group was 18.3 mg over a mean duration of 450 days, whereas in the sham group, who didn't start receiving aflibercept PRN until week 52, total exposure to aflibercept was 2.5 mg over a mean duration of 400 days.

The mean number of active injections in the aflibercept group from week 24 to week 52 was 2.5 injections. During this time the sham group was still receiving sham injections. Between week 52 and week 76, the mean number of 'active' injections was higher in the sham+PRN group (1.7 injections) than in the aflibercept group (1.7 injections) (see Table 24). [redacted]

Table 24. Exposure to study drug (excluding sham injections) from baseline to week 100 (COPERNICUS) [Week 24 completers within the safety analysis set]

	COPERNICUS			GALILEO	
	Aflibercept + PRN	Sham + PRN		Aflibercept + PRN	Sham + PRN
	N=110	N=60		N=91	N=52
Total number of aflibercept	1293	384		[redacted]	

injections				[redacted]	
Number (%) of patients with aflibercept injections					
0	[redacted]			[redacted]	
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
13					
14					
15					
16					
17					
18					
19					
21					
Frequency count					
n	110	60		91	52
Mean (SD)	11,8 (3.35)	6.4 (3.72)		1.3 (1.1)	1.7 (1.1)
Median	[redacted]				
Min-Max					
Duration of treatment [1]					
n	110	57		104	68
Mean (SD)	[redacted]				
Median					
Min-Max					

[1] COPERNICUS: Duration of study drug = [last active injection date] – [first active injection date] + 28
GALILEO: Duration of study treatment = [last (active or sham) injection date] – [first (active or sham) injection] +28

Time to first PRN injection (COPERNICUS: week 24 to week 100)

COPERNICUS -

[redacted]

GALILEO – Such information was not reported.

Time intervals between PRN injections

COPERNICUS: The mean time between aflibercept PRN injections was shorter in the sham+PRN group (61.40 days) than in the aflibercept+PRN group (87.41 days).

The proportion of patients receiving re-treatment always at intervals of ≥ 12 weeks was 1.7% in the sham+PRN group and 14.5% in the aflibercept+PRN group (see Table 25).

[redacted]

GALILEO - Such information was not reported

Table 25. COPERNICUS - Proportion of patients receiving retreatment at intervals of 4, 8, and at least 12 weeks [Week 24 completers within the safety analysis set]

	COPERNICUS	
	Aflibercept + PRN	**Sham + PRN**
	N=110	**N=60**
Proportion of patients receiving retreatment:		
Always ≥ 12 weeks	16 (14.5%)	1 (1.7%)
Always ≥ 8 weeks	28 (25.5%)	6 (10.0)
At least once in a 4 week interval	[redacted]	
No aflibercept PRN injection		

Efficacy summary

- In COPERNICUS and GALILEO, monthly intravitreal injection of aflibercept (2mg) for 24 weeks demonstrated improved visual acuity in eyes with MO secondary to CRVO.
- Improvements in visual acuity were rapid and were evident as early as 4 weeks after the first injection in both studies.
- The primary endpoint of ‘the proportion of patients with a gain of 15 ETDRS letters or more from baseline to week 24’ was met in both studies, where aflibercept treatment was significantly superior to sham treatment (COPERNICUS $p<0.001$; GALILEO $p<0.0001$).
- The superiority of aflibercept treatment compared to sham-treatment was also demonstrated in the secondary end points of mean change in BCVA - as assessed by ETDRS letter score, and the morphological endpoint of CRT at 24 weeks.
- Aflibercept-treated patients continued to maintain superior efficacy for the primary endpoint and for the secondary endpoint of 'mean change in BCVA from baseline' over the duration of the studies (COPERNICUS: at 52 and100 weeks; GALILEO: at 52 weeks [NB at 76 weeks mean change in BCVA $p=0.007$]). A slight deterioration in VA was observed as patients switched from monthly to PRN dosing, which became more accentuated as the evaluation intervals extended (COPERNICUS: from monthly to 12-weekly; GALILEO: monthly to 8-weekly). For sham-treated patients crossing over to aflibercept PRN treatment (COPERNICUS: from 24 weeks; GALILEO: from 52 weeks) improvements in BCVA were also shown, however this was less robust than those achieved in the patients in the aflibercept group, who had received monthly treatment during the first 24 weeks, prior to switching to PRN dosing.
- These data suggest that a delayed start to treatment with fewer and less frequent injections under a PRN regimen might not provide the best efficacy results for the treatment of CRVO and that initiating treatment with monthly dosing compared to a PRN regimen may be more beneficial. However, even if treatment is delayed for 6 months (COPERNICUS) or 12 months, small benefits in BCVA, CRT, and even vision-related quality of life endpoints are possible. The deterioration in visual acuity observed after the shift of evaluation for PRN dosing from 4 weeks to 8 weeks (in GALILEO) or 12 weeks (in COPERNICUS) suggests that PRN dosing may require a more rigorous monitoring schedule than, for example, every 12 weeks (COPERNICUS study) for CRVO.

- CRT reductions were maintained in the aflibercept group at week 52 in both studies. Crossover to aflibercept PRN for the original sham-treated patients in COPERNICUS enabled patients to achieve similar CRT reductions to those of the aflibercept group. In GALILEO, patients did not achieve the level of CRT improvement as achieved by patients in the aflibercept group. As seen in VA outcomes, the results in the aflibercept group for CRT suggest that the morphological endpoint is also sensitive to changes in the dosing frequency and that reductions in CRT are better maintained with a fixed regimen than a PRN dosing scheme.
- In addition, at all timepoints post-baseline, the proportion of patients with dry status in retinal fluid, as assessed by OCT, was greater in the aflibercept group than the sham group (only measured in COPERNICUS).
- The superiority of aflibercept to sham in the overall population was confirmed in a series of subgroup analyses (including those with baseline BCVA >20/200, baseline BCVA ≤ 20/200, perfused or non-perfused status) and supported by sensitivity analyses in both FAS and PPS populations, including observed values. At all timepoints, subgroup and sensitivity analyses were generally consistent with those in the overall population.
- The development of neovascularisation was infrequent in both studies with, ultimately, no meaningful differences between the two treatment groups in either study. In GALILEO (not measured in COPERNICUS), five percent of patients in the sham group developed neovascularisation by day 85, while 5% of patients in the aflibercept group had developed neovascularisation by day 240.
- In COPERNICUS and GALILEO, monthly aflibercept treatment (for 24 weeks) produced statistically significant clinically relevant improvements in vision-related quality of life, as measured by total score on NEI VFQ-25. Clinically relevant improvements were also demonstrated for sub scale scores of near-activities (GALILEO: p=0.0003), distance-activities and vision dependency. Improvements from baseline continued to be observed throughout the studies, even in the sham patients crossing over to receive aflibercept PRN (COPERNICUS: from 24 weeks; GALILEO: from 52 weeks), however patients treated with aflibercept from the beginning of the study, obtained and maintained greater improvements.
- Mean EQ-5D scores were relatively high and similar between groups at baseline and remained relatively unchanged throughout the GALILEO study (not measured in COPERNICUS). It is suggested that the EQ-5D, as a generic instrument, is not sensitive enough to detect changes in vision-related quality of life in CRVO.

6.6 Meta-analysis

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 individuall and combined results (such as through the use of forest plots).

See responses below

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.

COPERNICUS(4;5) and GALILEO(6) were similarly designed studies, in order that their data could be pooled for integrated or ‘meta-analysis’. The integrated data and analyses of the studies have been presented alongside the individual study data throughout sections 6.3 to 6.5.

For the purposes of indirect comparison, meta-analyses on the three outcomes were conducted on the aflibercept trials at 6 months. The pooled estimate was then used in the indirect comparison with ranibizumab. The results are as follows:

Table 26. Meta-Analysis - Patients gaining ≥15 letters of BCVA from baseline to 6 months

Study	OR	[95% Conf. Interval]		% Weight
COPERNICUS	9.10	4.13	20.05	40.09
GALILEO	5.34	2.66	10.72	59.91
M-H pooled OR	6.85	4.08	11.51	100
Heterogeneity chi-squared = 0.99 (d.f. = 1) p = 0.320				
I-squared (variation in OR attributable to heterogeneity) = 0.0%				

Study	RR	[95% Conf. Interval]		% Weight
COPERNICUS	4.55	2.42	8.58	35.89
GALILEO	2.73	1.70	4.38	64.11
M-H pooled RR	3.28	2.25	4.79	100
Heterogeneity chi-squared = 1.61 (d.f. = 1) p = 0.204				
I-squared (variation in OR attributable to heterogeneity) = 38.0%				

RR – relative risk; M-H - Mantel–Haenszel

Table 27. Meta-Analysis - Patients losing ≥15 letters of BCVA from baseline to 6 months

Study	OR	[95% Conf. Interval]		% Weight
COPERNICUS	0.05	0.01	0.21	58.97
GALILEO	0.30	0.12	0.75	41.03
M-H pooled OR	0.15	0.07	0.31	100
Heterogeneity chi-squared = 4.43 (d.f. = 1) p = 0.035				
I-squared (variation in OR attributable to heterogeneity) = 77.4%				

Study	RR	[95% Conf. Interval]		% Weight
CRUISE	2.82	1.85	4.30	100
M-H pooled RR	2.82	1.85	4.30	100
Heterogeneity chi-squared = 0.00 (d.f. = 0) p = .				
I-squared (variation in OR attributable to heterogeneity) = .%				

RR – relative risk; M-H - Mantel–Haenszel

Table 28. Meta-Analysis - Change in BCVA/number of letters read from baseline to 6 months

Study	WMD	[95% Conf. Interval]		% Weight
COPERNICUS	21.30	16.55	26.05	42.65
GALILEO	14.70	10.60	18.80	57.35
I-V pooled WMD	17.52	14.41	20.62	100
Heterogeneity chi-squared = 4.25 (d.f. = 1) p = 0.039				
I-squared (variation in WMD attributable to heterogeneity) = 76.5%				

Study	RR	[95% Conf. Interval]		% Weight
GENEVA 008 & 009	1.44	0.82	2.54	100
M-H pooled RR	1.44	0.82	2.54	100
Heterogeneity chi-squared = 0.00 (d.f. = 0) p = .				
I-squared (variation in OR attributable to heterogeneity) = .%				

RR – relative risk; M-H - Mantel–Haenszel

The pooled estimates indicate that:

- a higher proportion of patients treated with aflibercept achieve a gain of ≥15 letters, from baseline to 6 months, when compared with sham;
- a lower proportion of patients treated with aflibercept lose ≥15 letters, from baseline to 6 months, when compared with sham;
- patients treated with aflibercept achieve a higher change in BCVA/number of letters read from baseline.
- all the results are statistically significant.

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.

Not applicable

6.7 Indirect and mixed treatment comparisons

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.

Data on the relative efficacy and safety of aflibercept in comparison to the main comaparator, ranibizumab, is not available from active-controlled trials. A network meta-analysis (NMA) was therefore carried out to assess the effects on visual acuity outcomes of aflibercept 2mg compared with 0.5mg ranibizumab in a ‘reactive dosing’ (or treatment as needed) regimen.

As discussed in Section 2.7, for completeness, we have also considered the data available for dexamethasone and bevacizumab from the systematic review described in Section 6.1.1 to include these treatments in the NMA, as these treatments were also listed in the scope as comparators. Best supportive care has already been considered in the context of the COPERNICUS and GALILEO studies where a direct comparison is available.

The search undertaken to identify relevant clinical data on ranibizumab given in a PRN or ‘reactive dosing’ regimen, was the main part of the broader systematic review described in section 6.1, 6.2 and appendix 10.2.

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.

Please refer to section 6.1, section 6.2 and appendix 10.2 for details of the search strategy, inclusion and exclusion criteria used in the search strategy and the Prisma flow diagram of the numbers of studies included and excluded at each stage.

The systematic review identified 8 relevant trials that explored the efficacy and safety of aflibercept, ranibizumab, dexamethasone and bevacizumab. Two studies (CRUISE(30;35) and ROCC(36)) investigated ranibizumab and 2 trials (COPERNICUS and GALILEO)

investigated aflibercept. All 4 of these trials included either ranibizumab or aflibercept versus a sham regimen. No trials investigated both ranibizumab and aflibercept. The review additionally identified 2 studies (the GENEVA 008 and GENEVA 009 studies)(37) involving dexamethasone intravitreal implant versus sham injection. CRUISE, GALILEO, COPERNICUS and GENEVA were the only phase III pivotal trials of regulatory standard. The search further identified 2 small studies evaluating bevacizumab in CRVO by Epstein et al. and Wittstrom et al. (38-40). Two abstracts (Habibabadi 2007 and 2008) previously identified by the DSU in a review of the evidence(23), were not included. These abstracts did not report detailed data such as patient characteristics at baseline. There was also insufficient information in the abstracts to be able to make any assessment of quality.

Methodology of included studies

Key study characteristics of the ranibizumab studies are summarised below. Details of the aflibercept trials have already been described in Section 6.3.

CRUISE, was a phase III, randomised, double-blind, sham-controlled trial of ranibizumab (0.3 mg and 0.5 mg) in patients with MO secondary to CRVO(30;35). Eligible patients were randomized 1:1:1 to receive monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections for the first 6 months and during the observation period (months 6-11) all patients could receive monthly intraocular ranibizumab according to retreatment criteria (cross-over design). The 0.3 mg arm was excluded from the analyses as this formulation is not licensed for the treatment of patients with reduced visual acuity due to MO following CRVO.

Please note that the HORIZON study(41), the open-label extension trial of the 12-month BRAVO (in patients with BRVO) and CRUISE trials was captured in the systematic literature review. However this study is excluded from this analysis on the basis of trial design as this is a single arm trial with no sham control.

ROCC was a prospective, multicenter, randomized, double-masked, 6 month placebo-controlled trial(36) where 32 patients with MO secondary to CRVO were randomized to receive monthly intravitreal ranibizumab 0.5 mg or sham injections for 3 consecutive months. This trial will be considered as a sensitivity analyses only given its exploratory nature and respective low number of patients included (29 patients completed the study: 15 and 14 patients to ranibizumab and sham, respectively).

Dexamethasone has been investigated in patients with MO secondary to RVO in two identical, prospective, multicenter, phase III clinical trials (GENEVA 008 and GENEVA 009)(37). Randomization was stratified by the underlying cause of RVO (BRVO or CRVO). Each trial consisted of a 6-month, randomized, sham-controlled, parallel-group, double-masked phase followed by a 6-month open-label extension. Both trials presented the 6-month pooled results for both BRVO and CRVO patients (for each indication separately) and the 12-month results were reported by Haller *et al.* 2011. Patients could receive dexamethasone 0.7mg, 0.35mg or sham at day 0 and could be retreated at day 180 according to pre-specified retreatment criteria. A total of 1,267 patients (dexamethasone implant 0.7 mg: n=427; dexamethasone implant 0.35 mg: n=414; sham: n =426) were enrolled across the two trials.

Bevacizumab has been evaluated in two small randomised studies (N=60 and N=19) published by Epstein et al., 2012 and Wittstrom et al., 2012(38-40). Epstein compared bevacizumab with sham and Wittstrom with PRP, although PRP was also included in the bevacizumab arm which may confound any results. As described by the DSU in their report, caution should be taken in interpreting Epstein due to its small size.

Table 29. Eligibility criteria in included RCTs

	CRUISE (NCT00485856)	ROCC (NCT00567697)
Inclusion criteria	• Foveal center-involved macular oedema secondary to CRVO• BCVA using ETDRS charts of 20/40 to 20/320 (Snellen equivalent) • Mean central subfield thickness ≥ 250 µm on two optical coherence tomography (OCT) measurements (at screening [confirmed by the central reading center] and Day 0 [confirmed by the evaluating physician]) • Media clarity, pupillary dilation, and participant cooperation sufficient to obtain adequate fundus photographs	Patients with MO secondary to CRVO in one eye, previously untreated
Exclusion criteria	• Prior episode of retinal vein occlusion (RVO) • Brisk afferent pupillary defect • History of radial optic neurotomy or sheathotomy • History or presence of age-related macular degeneration (AMD; dry or wet form) • History of any anti-VEGF treatment in the study eye within 3 months prior to Day 0 • History of laser photocoagulation for macular oedema within 4 months prior to Day 0 • History of panretinal scatter photocoagulation or sector laser photocoagulation within 3 months prior to randomization or anticipated within the next 4 months following randomization • History of intraocular corticosteroid use within 3 months prior to Day 0 • History of pars plana vitrectomy	Concomitant ocular disease, prior MO treatment, history of glaucoma, filtration surgery, prior corneal transplant, cataract surgery 3 months before study, aphakia, cataract or diabetic retinopathy in rapid progression, vitreous haemmorhage, previous rhegmatogenous retinal detachment

	GENEVA 008 and 009 studies
Inclusion criteria	Patients who were at least 18 years of age and had decreased visual acuity as a result of clinically detectable MO associated with either CRVO or BRVO were recruited into both studies. Duration of MO (defined as the time since initial diagnosis of MO) was required to be between 6 weeks and 9 months in patients with CRVO and between 6 weeks and 12 months in patients with BRVO. The investigator selected 1 eye per patient to be the study eye. If both eyes were eligible, then the eye with the shorter duration of MO was selected. Eligible patients had to have best-corrected visual acuity (BCVA) of between 34 letters (20/200) and 68 letters (20/50) in the study eye and better than 34 letters in the non-study eye. Retinal thickness in the central subfield (as measured by optical coherence tomography; OCT2 or OCT3) had to be 300 m in the study eye. Retreatment criteria at day 180 (6 months): BCVA was < 84 letters or the retinal thickness by OCT was > 250 µm in the central 1 mm macular subfield and, in the investigator's opinion, the procedure would not put the patient at significant risk.
Exclusion criteria	Key exclusion criteria included the presence of a clinically significant epiretinal membrane, active retinal or optic disc neovascularization, active or history of choroidal neovascularization, presence of rubeosis iridis, any active infection, aphakia or anterior-chamber intraocular lens, clinically significant media opacity, glaucoma or current ocular hypertension requiring more than 1 medication to control IOP in the study eye, or a history of steroid-induced IOP increase in either eye. Patients were also excluded if they had diabetic retinopathy in either eye, had any uncontrolled systemic disease, were currently using or anticipating the use of systemic steroids or anticoagulants during the study, or had any ocular condition in the study eye that, in the opinion of the investigator, would prevent a 15-letter improvement in visual acuity.

	Epstein et al. 2012	Wittstrom et al. 2012
Inclusion criteria	• CRVO with a duration of 6 months or less • Best corrected visual acuity (BCVA) between 15–65 ETDRS letters (Snellen equivalent approximately 20/50 to 20/500) • Mean central subfield thickness ≥ 300µm as measured by optical coherence tomography (Cirrus OCT)	Patients with iris or anterior chamber neovascularization and IOP > 22 mmHg
Exclusion criteria	• CRVO with neovascularisation • Any previous treatment for CRVO • Intraocular surgery during the previous 3 months • Vascular retinopathy of other causes • Glaucoma with advanced visual field defect or uncontrolled ocular hypertension ≥25mmHg despite full therapy • Myocardial infarction or stroke during the last 12 months	Patients with visual acuity less than light perception, diabetes, ocular inflammation, cloudy media due to cataract, keratopathy, vitreous haemhorrage. Patients with history of thromboembolic disorders.

Table 30. Characteristics of participants in included RCTs (by treatment arm)

	CRUISE (NCT00485856)			ROCC (NCT00567697)	
Baseline characteristic	Ranibizumab 0.3mg	Ranibizumab 0.5mg	Sham	Ranibizumab 0.5 mg	Sham
Sample size (n, patients)	132	130	130	15	14
Patient demographics					
Age in years (SD)	69.7 (11.6)	67.6 (12.4)	65.4 (13.1)	72 years (52-88 range)	72 years (52-88 range)
Proportion or number of males	71 (53.8%)	80 (61.5%)	72 (55.4%)	55.17%	55.17%
Baseline ocular characteristics in study eye					
BCVA at baseline (SD)	47.4 (14.8)	48.1 (14.6)	49.2 (14.7)	45 (23)	41 (22)
Number (%) patients with IOP-lowering medication at baseline	13 (10%)	22 (16.9%)	13 (10%)	-	-
Duration of MO from diagnosis to screening (SD)	-	-	-	-	-
Baseline central retinal thickness/central foveal thickness, µm (SD)	679 (242.4)	688 (253.1)	687 (237.6)	661 (161)	587 (154)
Baseline perfusion status distribution	-	-	-	-	-
Time from CRVO diagnosis to treatment (SD)	3.6 months (3.2)	3.3 months (3.7)	2.9 months (2.9)	78 days	78 days
Fellow eye vision compared with study eye	better:123 (93.2%); worse:3 (2.3%); same:6 (4.5%)	better:120 (92.3%); worse:7 (5.4%); same:3 (2.3%)	better:117 (90%); worse:8 (6.2%); same:5 (3.8%)	-	-

	GENEVA 008 and 009 (BRVO and CRVO)	
Baseline characteristic	Sham	Dexamethasone (0.7 mg)
Sample size (n eyes)	426	427
Age in years (SD)	63.9 (31-91)	64.7 (33-90)
Proportion or number of males	240 (56.3%)	217 (50.8%)
BCVA at baseline (SD)	54.8 (9.86)	54.3 (9.93)
Number (%) patients with IOP-lowering medication at baseline	38 (9%)	27 (6%)
Duration of MO from diagnosis to screening (SD)	156.1 (19-374)	157.6 (19-374)
Baseline central retinal thickness/central foveal thickness, µm (SD)	539 (186)	562 (188)
Baseline perfusion status distribution	-	-
Time from CRVO diagnosis to treatment (SD)		-
Fellow eye vision compared with study eye		-

	Epstein et al. 2012a & Epstein et al. 2012b		Wittstrom et al. 2012	
Baseline characteristic	Bevacizumab 1.25 mg	Sham	Bevacizumab + PRP	PRP
Sample size (n, patients)	30	30	10	9
Patient demographics				
Age in years (SD)	70.6 (12.6)	70.4 (10.4)	78.4 (7.8)	78.0 (8.7)
Proportion or number of males	19 (63%)	17 (57%)	20.0%	55.6%
Baseline ocular characteristics in study eye				
BCVA at baseline (SD)	44.4 (15.3)	43.9 (16.0)	1.8 (0.61) logMAR	2.0 (0.43) logMAR
Number (%) patients with IOP-lowering medication at baseline	-	-	-	-
Duration of MO from diagnosis to screening (SD)	9.4 weeks	8.3 weeks	-	-
Baseline central retinal thickness/central foveal thickness, µm (SD)	712 (330)	729 (195)	-	-
Baseline perfusion status distribution	-	-	-	-
Time from CRVO diagnosis to treatment (SD)	8.3 (4.8) weeks	9.4 (6.5) weeks	-	-
Fellow eye vision compared with study eye	-	-	-	-

Results of the included studies

The results of CRUISE(30;35) demonstrated that ranibizumab improved BCVA levels from baseline to month 6 and month 12. The percentage of patients who gained 15 letters from baseline to 6 months was 46.2%, 47.7%, 16.9% for the 0.3 mg, 0.5 mg and sham, respectively.

The mean change from baseline BCVA letter score at months 6 was 12.7 CI:(9.9 to 15.4) and 14.9 CI:(12.6 to 17.2) in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, and 0.8 CI:(-2.0 to 3.6) in the sham group (P<0.0001 for each ranibizumab group vs. sham).The benefits were sustained at month 12, as reported by Campociaro et al., 2011 where 47%, 50.8%, 33.1% in the respective 0.3 mg, 0.7 mg and sham groups achieved at least a gain of 15 letters.

In the ROCC study(36) at 6 months, the mean change (SD) in BCVA was 12 (20) ETDRS letters in the ranibizumab group compared with -1 (17) ETDRS letters in the sham group (P = .067).

In the GENEVA studies(37), after a single administration, the percentage of eyes with at least 15-letter improvement in BCVA was significantly higher in both dexamethasone groups compared with sham at days 30 (29% for 0.7 mg, 33% for 0.35mg, 9% for sham) to 90 (18% for 0.7 mg, 24% for 0.35mg, 10% for sham). At day 180, the % of patients gaining ≥15 letters was 18%, 17%, 12% for the 0.7 mg, 0.35 mg and sham respectively. It should be noted that in the GENEVA trials, the disease duration was longer compared to the aforementioned trials which may explain the low improvement in the BCVA. Note that, in these analyses, it was necessary to consider the pooled results of the GENEVA 008 and GENEVA 009 trials as no separate results are available.

No information about patient attrition was reported by Epstein *et al.* 2012 for the first 6 months of the phase III trial. Four patients discontinued the study during the open-label extension phase (3 patients in the bevacizumab/ bevacizumab group and 1 patient in the sham/ bevacizumab group). At month 6, eighteen of 30 patients (60.0%) in the study group gained at least 15 letters compared with 6 of 30 patients (20.0%) in the control group (p<0.003). The mean change in BCVA from baseline to 6 months was 14.1 letters, and -2.0 letters in the control group (p< 0.003). At month 12, patients on bevacizumab/ bevacizumab group, improved their visual acuity by 16.1 letters. In the sham/bevacizumab group, visual acuity improved by 4.6 letters at 12 months. Notably, neither treatment-

related adverse events nor non-ocular adverse events were reported during the whole treatment period. However, given the low sample size, *the authors noted that in order to detect unexpected severe adverse events that occur at a 1% rate, the study would have required approximately 300 subjects exposed to drug treatment*. To detect an increase in incidence of serious adverse events (e.g., myocardial infarction or stroke of 1% from 2% to 3%) would require a study with thousands of subjects.

The only relevant outcome reported in the study by Wittstrom et al. 2012 was the mean change from baseline in the logMar scale, which indicated that there were no significant differences across groups. The paper also reported that 2 patients from the bevacizumab/PRP arm experienced a stroke.

Quality assessment of RCTs

Quality assessments of the ranibizumab studies are presented in Appendix 0. Overall, CRUISE, GENEVA and ROCC could be considered studies of high quality, with most of the checklist items covered, indicating two well conducted phase III trials. Due to the cross over design of CRUISE after the first 6 months, quality assessment is only presented for the first 6 months. However, given the small sample size (n=29) in the ROCC study, caution should be applied when interpreting the results. Epstein was small (n=60) of moderate quality and Wittstrom was a very small study (n=18) that was poorly reported, and included PRP in the intervention arm. These studies are not considered sufficient evidence to assess the efficacy and safety of bevacizumab in the absence of adequately powered, high quality, regulatory studies and regulatory assessment. As discussed in Section 2.7 and the following Section 6.7.3, no such comparison with bevacizumab was conducted in the technology appraisal (TA283) of ranibizumab despite these studies then being available.

6.7.3 Provide a summary of the trials used to conduct the indirect comparison. A suggested format is presented below. Network diagrams may be an additional valuable form of presentation.

The NMA was conducted on 6 Phase 3 trials exploring the efficacy and safety of aflibercept (COPERNICUS and GALILEO) and two active treatments, ranibizumab (CRUISE and ROCC) and dexamethasone (GENEVA 008 and 009) against sham (see Table 31 below).

Bevacizumab has not been included in the NMA. As discussed in Section 5, we do not consider that bevacizumab is the standard of care for CRVO. As discussed in the previous section, Epstein and Wittstrom were the only studies relevant to the decision problem. Wittstrom was a small study (n=19), included laser treatment and was poorly reported. Epstein was also a small study (n=60) of moderate quality that is insufficiently robust for evaluating clinical and cost effectiveness. In particular, *according to the authors*, the Epstein study alone was insufficiently powered to report on all adverse events for bevacizumab in CRVO as this would have required 300 rather than 60 participants.

In the appraisal of ranibizumab (TA283), a mixed treatment comparison including this study was therefore not conducted:

- *4.8…..However, the Committee further concluded that there is currently insufficient evidence to make robust comparisons with ranibizumab needed for a cost-effectiveness analysis (TA283).*

This follows on from the appraisal of ranibizumab in DMO (TA274) where it stated:

- *"…Also, the Committee heard conflicting evidence about the extent to which bevacizumab is currently used to treat diabetic macular oedema in England and Wales. It concluded that bevacizumab is adopted by some clinicians and funded by some NHS trusts, but is not in use throughout the NHS. The Committee was aware that some consultees and commentators supported a comparison with bevacizumab and others opposed it. The Committee discussed whether a cost-effectiveness analysis of ranibizumab compared with bevacizumab was possible. The Committee recognised that a formal comparison of the 2 drugs would need evidence not only of all aspects of clinical effectiveness and safety, but also of the costs associated with preparing and administering bevacizumab, including the dose and number of injections needed. The Committee agreed that such evidence, in particular about the balance of harms and benefits associated with bevacizumab, was not readily available for people with diabetic macular oedema. The Committee also noted that it was unaware of any evidence of the effectiveness of intravitreal bevacizumab compared with ranibizumab in the subgroup of patients with thicker retinas. The Committee agreed that, taking into account all these uncertainties, it could not consider a comparison of ranibizumab with bevacizumab…"*

Table 31. Summary of the trials used to conduct the indirect comparison

No. trials	References of trials	Intervention	Comparator
1	COPERNICUS	Aflibercept	Sham
2	GALILEO	Aflibercept	Sham
3	CRUISE	Ranibizumab	Sham
4	ROCC	Ranibizumab	Sham
5	GENEVA 008	Dexamethasone	Sham
6	GENEVA 009	Dexamethasone	Sham
Adapted from Caldwell et al.(2005) Simultaneous comparison of multiple treatments combining direct and indirect evidence. BMJ 331: 897–900			

The SR identified a total of 8 publications reporting the results of these trials at 6 and 12 months(4-6;30;35-37). Note that only pooled results of GENEVEA 008 and GENEVA 009 are published (37). Given the cross over design of the COPERNICUS, CRUISE and GENEVA trials at 6 months (24 weeks), and therefore the lack of common comparator, the NMA was conducted on 6-month trial data only. As a result, only the 5 publications reporting the 6-month results of the trials of interest were included in the NMA. The trials used to conduct the NMA are presented in the Network of evidence diagram below:

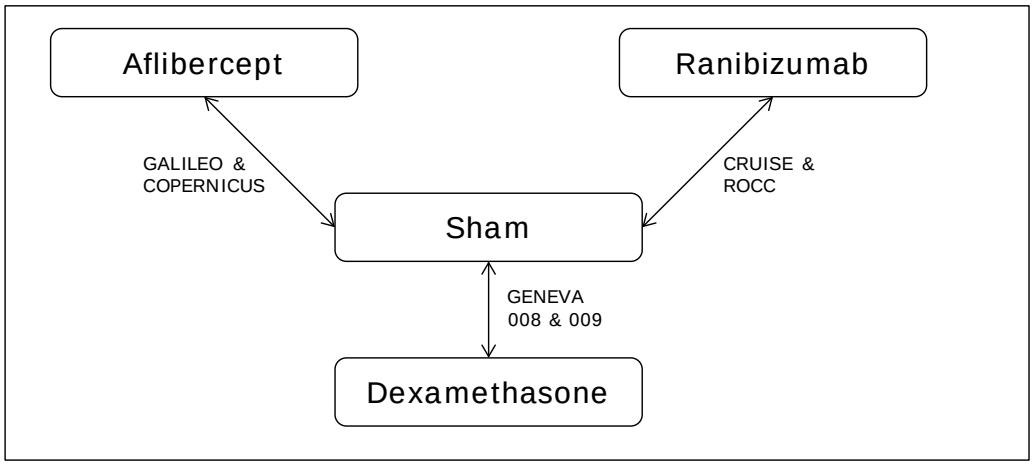


Figure 16. Network of Evidence - 6 months

These 5 publications reported results for the three key common trial efficacy endpoints:

- Proportion of patients gaining ≥15 letters of BCVA from baseline at 6 months
- Proportion of patients losing >15 letters of BCVA from baseline at 6 months
- Mean Change in BCVA/number of letters read from baseline at 6 months

Trial results for these 3 endpoints were therefore used as inputs for the NMA.

Note that the ROCC study only reported endpoint for the mean change in BCVA from baseline. Consequently, the sensitivity analyses presented below in Section 6.7.8, where the ROCC study is excluded, are only comprised of analyses for the mean change in BCVA.

The base-case NMA was conducted on efficacy endpoints only. The number of patients experiencing adverse events was overall too low (and sometimes null) to conduct a robust NMA on safety endpoints. Populating evidence synthesis models with such little (or no) data would make the results very uncertain, i.e., with very wide credible intervals around the mean estimates. While no analyses on safety endpoints were conducted in the base-case NMA, an NMA on safety endpoints was conducted as part of a sensitivity analysis (see Section 6.7.8). Any conclusions drawn from these results must be interpreted with a high degree of caution.

6.7.4 For the selected trials, provide a summary of the data used in the analysis.

The NMA used efficacy data from each of the 6 individual trials. Table 32 below provides a summary of the efficacy data used in the NMA:

Table 32. Summary of efficacy data used in the NMA

	COPERNICUS		GALILEO		CRUISE		ROCC		GENEVA 008 & 009	
	Aflibercept 2mg	Sham	Aflibercept 2mg	Sham	Ranibizumab 0.5mg	Sham	Ranibizumab 0.5mg	Sham	Dexamethasone 0.7mg	Sham
Number of patients in each arm (n)	114	73	103	68	130	130	15	14	136	147
Number (%) of patients gaining ≥ 15 letters of BCVA from baseline	64 (56.1)	9 (12.3)	62 (60.2)	15 (22.1)	62 (47.7)	22(16.9)	NR	NR	24 (18)	18 (12)
Number (%) of patients losing≥ 15 letters of BCVA from baseline	2 (1.8)	20 (27.4)	8 (7.8)	15 (22.1)	2 (1.5)	20 (15.4)	NR	NR	NR	NR
Change in BCVA/number of letters read from baseline (SD)	17.3 (12.8)	-4 (18)	18.0 (12.2)	3.3 (14.1)	14.9 (13.2)	0.8 (16.2)	12 (20)	-1 (17)	0.1 (NR)	-1.8 (NR)

BCVA: best-corrected visual acuity; NR: not reported; SD: standard deviation

6.7.5 lease provide a clear description of the indirect/mixed treatment comparison methodology. Supply any programming language in a separate appendix.

The NMA were conducted using the Bayesian approach. Odds ratios are the natural outputs of a Bayesian NMA. The NMA was performed using WinBUGS version 1.4.3 following the methodology promoted by the DSU of NICE[1]. WinBUGS is Bayesian analysis software that, through the use of Monte Carlo Markov chains, calculates posterior distributions for the parameters of interest, given likelihood functions derived from data and prior probabilities. The Monte Carlo Markov Chain simulation begins with an approximate

[1] Evidence Synthesis TSD (Technical Support Document) Series. NICE Decision Support Unit (DSU). http://www.nicedsu.org.uk/Evidence-Synthesis-TSD-series(2391675).htm

distribution and, if the model is a good fit to the data, the distribution converges to the true distribution(42).

Both fixed and random effects models were conducted with the latter being preferred in the presence of heterogeneity. Further, a comparison was made by observing the Deviance Information Criterion (DIC) statistics and the total residual deviance, to ensure that the selected model's overall fit is adequate. The DIC provides a measure of model fit that penalizes model complexity – lower values of the DIC suggest a more parsimonious model; however, differences of less than 3 are not considered to be important(43).

To check formally whether a model's fit is satisfactory we consider an absolute measure of fit: the overall residual deviance. We compared the value of the overall residual deviance to the number of independent data points to check if the model fit can be improved. As the rule of the thumb each data point should contribute about 1 to the posterior mean deviance, hence these two values should be very close in the presence a model that is a good predictor.

Convergence was assessed by using the Brooks-Gelman-Rubin diagnostic in WinBUGS. In all cases a burn-in of at least 20,000 simulations were discarded. And all results are presented based on a further sample of at least 50,000 simulations.

Lastly, the Monte Carlo error, which reflects both the number of simulations and the degree of autocorrelation, was observed. This should be no more than 5% of the posterior standard deviation of the parameters of interest.

All baseline and intervention effect parameters were given flat (uninformative) Normal (0, 10000) priors and the between-study standard deviation flat Uniform distributions with an appropriately large range given the scale of measurement.

While ORs are the natural outcomes of an NMA using a Bayesian approach, odds ratios (ORs) can be converted to relative risks (RRs) providing that a baseline treatment effects for the reference treatment (sham) is available. This baseline treatment effects can be obtained via different ways such as cohort studies, a single trial or set of trials considered to reflect contemporary outcomes under treatment, expert opinion, etc. In order to generate RRs, we have "modelled" the sham baseline treatment effects across the 6 clinical trials included.

6.7.6 Please present the results of the analysis.

The Bayesian methods allowed conducting both fixed effects and random effects models on the data set. The results of the NMA are presented below for binary outcomes, i.e. proportion of patients gaining/losing 15 letters in terms of ORs and RRs for binary outcomes; for continuous outcomes the difference in means is reported.

Patients gaining ≥15 letters of BCVA from baseline

Table 33 and Table 34 below present the OR and RR generated by the NMA for the proportion of patients gaining 15 letters.

Table 33. Odds Ratios - Patients gaining ≥15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Odds Ratio	lCr.Int.	uCr.Int.	Odds Ratio	lCr.Int.	uCr.Int.
Dexamethasone 0.7mg vs. Aflibercept 2mg	[redacted]					
Ranibizumab 0.5mg vs. aflibercept 2mg						
sd	n.a.			0.67	0.03	1.90
totresdev	7.38	2.69	17.10	7.26	2.22	17.30
Data Points	8					
DIC	52.996			53.607		

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

Both fixed and random effects models converged well and the overall fit appears to be similar (similar DIC and overall residual deviance). The fixed effects model will be used to make inference given that it presents a lower DIC and a total residual deviance that is closer to the number of data points.

Table 34. Relative risks - Patients gaining ≥15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Relative Risk	lCr.Int.	uCr.Int.	Relative Risk	lCr.Int.	uCr.Int.
Dexamethasone 0.7mg vs. Aflibercept 2mg	[redacted]					
Ranibizumab 0.5mg vs. aflibercept 2mg						
sd	n.a.			0.67	0.03	1.90
totresdev	7.38	2.69	17.10	7.26	2.22	17.30
Data Points	8					
DIC	52.996			53.607		

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

Note that the RRs of patients gaining ≥15 letters presented above (fixed effect) in Table 34 were used as inputs in the de novo cost-effectiveness analyses (see Section 7.2).

Patients losing >15 letters of BCVA from baseline

Table 35 and Table 36 below present the OR and RR generated by the NMA for the proportion of patients losing 15 letters.

Table 35. Odds Ratios - Patients losing >15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Odds Ratio	lCr.Int.	uCr.Int.	Odds Ratio	lCr.Int.	uCr.Int.
Ranibizumab 0.5mg vs. aflibercept 2mg						
sd				1.18	0.15	1.96
totresdev	9.50	5.87	18.20	5.79	1.35	15.20
Data Points	6					
DIC	37.66			34.94		

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

The random effects model should be chosen to make inference given the lower DIC and the fact that the total residual deviance is closer to the number of data points.

Table 36. Relative risks - Patients losing >15 letters of BCVA from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Odds Ratio	lCr.Int.	uCr.Int.	Odds Ratio	lCr.Int.	uCr.Int.
Ranibizumab 0.5mg vs. aflibercept 2mg						
sd				1.18	0.15	1.96
totresdev	9.50	5.87	18.20	5.79	1.35	15.20
Data Points	6					
DIC	37.66			34.94		

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

Note that since Haller *et al.* 2010(37) did not report trial results for the outcome of losing 15 letters of BCVA, the GENEVA trials were not included in this analysis and therefore ORs and RRs were estimated for ranibizumab compared to aflibercept only. Data for ranibizumab were taken from CRUISE only as ROCC did not explore patients losing 15 letters BCVA as an endpoint.

Change in BCVA/number of letters read from baseline

Results for the change in BCVA from baseline are presented in Table 37 below. The random effects model should be chosen to make inference given that it has a lower DIC

and the total residual deviance is closer to the number of data points, reflecting the high levels of heterogeneity.

Table 37. Mean Change in BCVA/number of letters read from baseline at 6 months

Treatments	Fixed Effects			Random Effects		
	Mean Change	lCr.Int.	uCr.Int.	Mean Change	lCr.Int.	uCr.Int.
Aflibercept 2mg vs. dexamethasone 0.7mg						
Aflibercept 2mg vs. ranibizumab 0.5mg						
sd	n.a.			2.86	0.23	4.88
totresdev	11.64	6.45	21.66	9.31	3.25	19.89
Data Points	10					
DIC	50.38			49.22		

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

6.7.7 Please provide the statistical assessment of **heterogeneity** undertaken. The degree of, and the reasons for, heterogeneity should be explored as fully as possible.

Tests for heterogeneity in effects across the studies were conducted using the Q and I^2 statistics. All the analyses were performed using Stata/SE™ 11.2 (StataCorp, College Station, Texas, USA). A meta-analysis of all the included studies' individual estimates of effect using a fixed effects model (Mantel–Haenszel method for binary outcomes and Inverse Variance for continuous outcomes) was conducted and resulting Q and I^2 statistics were observed.

Although there can be no absolute rule for when heterogeneity becomes important, Higgins et al. (2003) suggest adjectives of low for I^2 values between 25%–50%, moderate for 50%–75%, and high for ≥75%.

Low levels of heterogeneity were observed (I2 of 3.1%, p=0.356) for the proportion of patients gaining 15 letters of BCVA from baseline; for the proportion of patients gaining 15 letters of BCVA from baseline heterogeneity is considered to be moderate (p = 0.075) and for change in BCVA from baseline, heterogeneity is deemed high.

Table 38. Analysis of heterogeneity - Patients gaining 15 letters of BCVA from baseline

Study	OR	[95% Conf. Interval]		% Weight
COPERNICUS	9.10	4.13	20.05	20.47
GALILEO	5.34	2.66	10.72	30.59
CRUISE	4.48	2.52	7.94	48.94
GENEVA	1.54	0.79	2.98	25.4

M-H pooled OR	5.69	3.88	8.35	100
Heterogeneity chi-squared = 2.06 (d.f. = 2) p = 0.356				
I-squared (variation in OR attributable to heterogeneity) = 3.1%				

Table 39. Analysis of heterogeneity - Patients losing 15 letters of BCVA from baseline

Study	OR	[95% Conf. Interval]		% Weight
COPERNICUS	0.05	0.01	0.21	39.72
GALILEO	0.3	0.12	0.75	27.63
CRUISE	0.09	0.02	0.38	32.65
M-H pooled OR	0.13	0.07	0.25	100
Heterogeneity chi-squared = 5.19 (d.f. = 2) p = 0.075				
I-squared (variation in OR attributable to heterogeneity) = 61.5%				

Table 40. Analysis of heterogeneity - Change in BCVA/number of letters read from baseline

Study	WMD	[95% Conf. Interval]		% Weight
COPERNICUS	21.30	16.55	26.05	16.92
GALILEO	14.70	10.60	18.80	22.75
CRUISE	14.10	10.51	17.69	29.59
GENEVA	1.90	-1.75	5.55	28.64
ROCC	13.00	-0.48	26.48	2.10
I-V pooled WMD	11.94	9.98	13.89	100.00
Heterogeneity chi-squared = 47.12 (d.f. = 4) p = 0.000				
I-squared (variation in WMD attributable to heterogeneity) = 91.5%				

6.7.8 If there is doubt about the relevance of a particular trial, please present separate sensitivity analyses in which these trials are excluded.

Exclusion of ROCC trial

The ROCC trial was included in the base-case NMA analyses, despite its small sample size. A sensitivity analysis (SA) was therefore conducted in which ROCC was excluded. The SA was performed on the mean change in BCVA only since no data from ROCC were reported in the publication for the 2 other outcomes explored in the base-case NMA.

As expected, the exclusion of the ROCC trial had no impact in the results (Table 41 below) given that this is a clinical trial with a small sample size – the contribution of this trial for the pooled mean change from baseline it is approximately 2% (see Section 6.7.8 above).

Table 41. Mean Change in BCVA/number of letters read from baseline at 6 months (ROCC excluded)

Treatments	Fixed Effects			Random Effects		
	Mean Change	lCr.Int.	uCr.Int.	Mean Change	lCr.Int.	uCr.Int.
Aflibercept 2mg vs. dexamethasone 0.7mg						
Aflibercept 2mg vs. ranibizumab 0.5mg						
sd	n.a.			3.00	0.25	4.90
totresdev	10.60	5.93	20.20	8.08	2.45	18.30
Data Points	8					
DIC	38.29			36.58		

lCr.Int – lower credible interval; uCr.Int – upper credible interval; sd – between study standard deviation; totresdev – total residual deviance; DIC – deviance information criterion

6.7.9 Please discuss any heterogeneity between results of pairwise comparisons and inconsistencies between the direct and indirect evidence on the technologies.

In the absence of head-to-head data a NMA was conducted in order to compute the relative treatment effects between aflibercept, ranibizumab and dexamethasone.

A full Bayesian analyses was conducted. This allows fitting random effects models to the data set so that heterogeneity is taken into account. Note that random effects models do not explain the reasons for heterogeneity between studies. Meta-regression techniques would have to be applied but the low number of studies, and consequently of data points, hinders any attempt of adjusting for possible covariates.

Tests for heterogeneity revealed that heterogeneity is considered to be low when the outcome is the proportion of patients gaining 15 letters of BCVA from baseline; results suggest that a higher proportion of patients treated with aflibercept achieve a gain of 15 letters, from baseline to 6 months, when compared with ranibizumab but the difference between agents is not statistically significant. For the comparison of aflibercept versus dexamethasone, the higher proportion of patients achieving 15 letters gain with aflibercept is statistically significant.

For the remaining two outcomes tests for heterogeneity indicate that random effects models should be applied to the data set, producing therefore more conservative estimates (widen credible intervals). Nevertheless, the directionality and the significance of the results remain the same regardless of the method used.

Under the limitations above, although numerically in favour of aflibercept for all three outcomes, this analysis did not detect any significant difference (on efficacy and safety) between aflibercept and ranibizumab regarding the outcomes synthesised.

Summary of the network meta-analysis results:

- The mixed treatment comparison showed aflibercept to be numerically superior to ranibizumab in terms of proportion of patients gaining at least 15 letters from baseline to 24 weeks.
- Aflibercept was also shown to be numerically better than ranibizumab in terms of proportion of patients losing less than 15 letters and mean change in visual acuity from baseline to 24 weeks.
- Aflibercept was also statistically significantly better than dexamethasone in terms of proportion of patients gaining at least 15 letters and mean change in visual acuity from baseline to 24 weeks, the only two outcomes that were indirectly comparable.

6.8 Adverse events

6.8.1 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.

Neither COPERNICUS nor GALILEO included safety outcomes as a basis for primary analysis.

6.8.2 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.

Evidence of the safety and tolerability profile of aflibercept in the treatment of macular oedema secondary to CRVO, is provided by safety analyses and adverse event (AE) reporting from the two international, multicentre, double-masked, phase III RCTs (COPERNICUS and GALILEO)(4-6;28;29;31-34). The design, methodology, descriptions of all endpoints, and efficacy results from these studies are detailed in Section 6.1 to 6.5.

The safety and tolerability of repeated intravitreal administration of aflibercept, when compared with BSC for a period of up to 76 weeks (GALILEO) and 100 weeks (COPERNICUS) was included as a secondary objective in the COPERNICUS and GALILEO studies.

Safety was monitored with the recording of ocular (in the study and fellow eye) and non-ocular AEs at each study visit. The term AE refers here to treatment-emergent AEs, (TEAEs) i.e. AEs which occurred or worsened after the first administration of study drug.

Adverse events were summarised using the Medical Dictionary for Regulatory activities (MedRA) (version 13.1) and were assessed for seriousness, intensity, pattern, causal relationship to study drug, and causal relationship to the injection procedure. Other safety procedures included the documentation of pregnancy (in a female patient or female partner of a male study patient), laboratory evaluations including determination of antibodies to aflibercept, electrocardiography, measurement of vital signs, and intraocular pressure (IOP) measurements,

The safety analysis population (SAF) included all randomised patients who had received any study medication (see Table 42).

Table 42. Safety analysis population – COPERNICUS, GALILEO and Integrated (to week 24)

	Aflibercept (n)	Sham (n)
COPERNICUS	114	74
GALILEO	104	68
INTEGRATED (to week 24 only)	218	142

From baseline to week 24, the design of the studies was identical (i.e. monthly aflibercept 2mg vs. sham injection), hence an integrated analysis of safety components was also performed to 24 weeks. After 24 weeks, all patients in COPERNICUS were assessed using retreatment criteria (monthly 24 to 52 weeks, then 12-weekly from week 52 to week 100) and received 2mg aflibercept, as necessary, otherwise a sham injection was administered (week 24 to 52 only). Safety data for COPERNICUS are thus presented as 0-24 weeks, 24 to 52 weeks, and 24 to 100 weeks study periods. In GALILEO, from week 24 to 52, patients continued to receive either aflibercept or sham treatments, as randomised, *except* that the aflibercept group received aflibercept on a PRN basis. From week 52 to 76, all patients were assessed every 8 weeks using retreatment criteria and received 2mg aflibercept, as necessary, otherwise a sham injection was administered. Safety data for GALILEO are presented as 0-24 weeks, 0 to 52 weeks, and 52 to 76 weeks study periods.

Overall, in the COPERNICUS and GALILEO studies, aflibercept treatment was well tolerated, with an acceptable safety profile over both study durations, without notable differences compared to sham (plus PRN) in ocular (study eye and fellow eye) or non-ocular TEAEs (see Table 43). Drug-related ocular TEAEs were reported infrequently and numbers were similar between treatment groups. More patients in the sham group

experienced ocular SAEs in the study eye compared to the aflibercept group in COPERNICUS, while ocular SAEs were similar between treatment groups in GALILEO. The most commonly reported non-ocular TEAEs were hypertension and nasopharyingitis. The overall incidence of non-ocular SAEs was low and similar between treatment groups. TEAEs that led patients to discontinue study drug were higher in the sham groups than in the aflibercept groups. The integrated analysis at 24 weeks generally reflected the findings of the individual studies as noted above, with no area of concern highlighted from the analysis. Safety outcomes were consistent with those reported in aflibercept studies in wet AMD.

Ocular TEAEs and Serious Adverse Events (SAEs)

Ocular TEAEs occurred in similar proportions of patients in each treatment group in each study, with the exception of the first 6 months of the GALILEO study, where more sham patients than aflibercept patients reported ocular TEAEs in the study eye [redacted] Ocular TEAEs were consistent with what might be expected with the nature of underlying disease, disease progression, or attributable to the injection procedure (see Table 44).

The most common ocular TEAEs in both groups included ‘conjunctival haemorrhage’,’ reduced VA’, ‘retinal haemorrhage’ and ‘intraocular pressure increased’– all consistent with complications of CRVO, or injection procedure. Eye pain occurred more frequently in the aflibercept groups than the sham groups and is attributed to the injection procedure. Vitreous haemorrhage, also consistent with complications of CRVO, occurred more frequently in the sham group as did retinal pigment epitheliopathy. Other complications of CRVO, including macular oedema, cystoid macular oedema, and retinal exudates, occurred more frequently with aflibercept treatment. Most events of macular oedema in the aflibercept groups occurred following the switch to PRN dosing, suggesting a destabilisation of the disease with PRN dosing. This likely reflects the losses observed in BCVA in the aflibercept groups as they switched from monthly to PRN treatment, and the gains in BCVA observed in patients in the sham groups after crossing over to aflibercept PRN. In both studies, and both treatment groups, most of these TEAEs were judged to be mild.

During COPERNICUS, more patients in the sham group experienced ocular SAEs in the study eye compared to the aflibercept group [redacted] In GALILEO,

the incidence of ocular SAEs was similar in the two treatment groups [redacted] Most SAEs appear to be related to the disease state or injection procedure.

The most common SAEs were vitreous haemorrhage [redacted] macular oedema [redacted] cataract [redacted] glaucoma [redacted] iris neovascularization [redacted] visual acuity reduced [redacted] cystoid macular oedema [redacted] and retinal haemorrhage and retinal tear [redacted] All other SAEs occurred in no more than 1 patient in both groups. There was one case of endophthalmitis - occurring in the aflibercept group before week 24 in COPERNICUS - considered by the investigator to be related to intravitreal injection.

The proportion of patients experiencing at least one drug-related TEAE was low in both COPERNICUS [redacted] and GALILEO [redacted]

In COPERNICUS, drug-related TEAEs included [redacted] of cataract, eye irritation, macular oedema, macular hole, vision blurred (sham) and macular fibrosis, ocular discomfort and retinal artery occlusion (aflibercept); of which the cataract and retinal artery occlusion were reported as drug-related SAEs. In GALILEO, there were [redacted] eye irritation in each treatment group. Other drug-related TEAEs in GALILEO included increased intraocular pressure [redacted] abnormal sensation in eye, retinal haemorrhage, retinal ischaemia, retinal pigment epitheliopathy, visual acuity reduced in the sham group and cataract, eye pain, macular ischaemia [reported as an ocular SAE], macular oedema, ocular hyperaemia and ocular hypertension in the aflibercept group.

Table 43. Summary of safety data TEAEs during the COPERNICUS and GALILEO studies (and INTEGRATED 24 week analysis)(SAF)

NB. The hatched areas indicate when the sham group has crossed over to receive aflibercept PRN

	COPERNICUS						GALILEO						Integrated	
	Aflibercept			Sham			Aflibercept			Sham			Aflibercept	Sham
	0-24 weeks	24-52 weeks[a]	24-100 weeks[a]	0-24 weeks	24-52 weeks[a]	24-100 weeks[a]	*0-24 weeks*	0-52 weeks	52-76 weeks	*0-24 weeks*	0-52 weeks	52-76 weeks	0-24 weeks	
	N=114 n (%)	*N=110 n (%)*	N=110 n (%)	N=74 n (%)	*N=60 n (%)*	N=60 n (%)	*N=104 n (%)*	N=104 n (%)	n (%)	*N=68 n (%)*	N=68 n (%)	n (%)	N=218 n (%)	N=142 n (%)
Any TEAE													**164 (75.2)**	**115 (81)**
Non-ocular (systemic)													105 (48.2)	
Ocular (study eye)													129 (59.2)	
Any study drug-related TEAE														
Ocular (study eye)														7 (4.9)
Non-ocular														
Any injection-related TEAE														
Any TEAE causing treatment discontinuation														
Any death														
Any TEAE SAE														
Non-ocular (systemic)	6 (5.3)	*7 (6.4)*		6 (8.1)									12 (5.5)	11 (7.7)
Ocular (study eye)	4 (3.5)	*3 (2.7)*		10 (13.5)										
Any study drug-related TEAE SAE														
Any injection-related TEAE SAE (study eye)														

[a] week 24 completers within safety analysis set

Table 44: Ocular TEAEs in the study eye occurring in ≥3.0% of patients at preferred term level in any treatment group in the COPERNICUS and GALILEO studies (and integrated 24 week analysis)(SAF) NB. The hatched areas indicate when the sham group has crossed over to receive aflibercept PRN

MedDRA preferred term	COPERNICUS						GALILEO						Integrated	
	Aflibercept			Sham			Aflibercept			Sham			Aflibercept	Sham
	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	0-24 weeks	*24-52 weeks*[a]	*24-100 weeks*[a]	*0-24 weeks*	0-52 weeks	52-76 weeks	*0-24 weeks*	0-52 weeks	*52-76 weeks*	0-24 weeks	
	N=114 n (%)	*N=110 n (%)*	N=110 n (%)	N=74 n (%)	*N=60 n (%)*	*N=60 n (%)*	*N=104 n (%)*	N=104 n (%)	N=91 n (%)	*N=68 n (%)*	N=68 n (%)	*N=52 n (%)*	N=218 n (%)	*N=142 n (%)*
Any ocular TEAE (study eye)		*62 (56.4)*			*33 (55.0)*								129 (59.2)	
Patients with at least 1 preferred term ≥3% in any group					*29 (48.3)*								NR	
Conjunctival haemorrhage					*8 (13.3)*								26 (11.9)	
Visual acuity reduced					*3 (5.0)*									
Eye pain					*3 (5.0)*								28 (12.8)	7 (4.9)
Intraocular pressure increased					*5 (8.3)*								17 (7.8)	
Cystoid macular oedema					*2 (3.3)*									
Macular oedema														
Maculopathy					*4 (6.7)*								13 (6.0)	
Retinal pigment epitheliopathy					*5 (8.3)*									
Retinal haemorrhage					*3 (5.0)*									
Retinal vascular disorder													12 (5.5)	
Cataract														

MedDRA preferred term	COPERNICUS						GALILEO						Integrated	
	Aflibercept			Sham			Aflibercept			Sham			Aflibercept	Sham
	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	*0-24 weeks*	0-52 weeks	52-76 weeks	*0-24 weeks*	0-52 weeks	52-76 weeks	0-24 weeks	
	N=114 n (%)	*N=110 n (%)*	N=110 n (%)	N=74 n (%)	*N=60 n (%)*	N=60 n (%)	*N=104 n (%)*	N=104 n (%)	N=91 n (%)	*N=68 n (%)*	N=68 n (%)	N=52 n (%)	N=218 n (%)	*N=142 n (%)*
Vitreous detachment														
Eye irritation					*2 (3.3)*									
Cataract nuclear					*9*									
Dry eye					*1 (1.7)*									
Optic disc vascular disorder					*2 (3.3)*								12 (5.5)	
Macular fibrosis														
Lacrimation increased					*3 (5.0%)*									
Vitreous floaters													11 (5.0)	
Vitreous haemorrhage					*2 (3.3)*									
Retinal exudates					*4 (6.7)*								14 (6.4)	
Iris neovascularisation					*2 (3.3)*									
Ocular discomfort					*2 (3.3)*									
Punctate keratitis														
Ocular hyperaemia														
Foreign body sensation in eyes					*2 (3.3)*									
Visual acuity tests abnormal														
Retinal aneurysm														
Retinal degeneration														
Drug hypersensitivity														
Macular ischaemia														
Papilloedema														
Retinal ischaemia														
Injection site pain														
Retinal neovascularisation														
Retinal vein occlusion														
Ocular hypertension														
Visual impairment														

	COPERNICUS						GALILEO						Integrated	
	Aflibercept			Sham			Aflibercept			Sham			Aflibercept	Sham
	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	*0-24 weeks*	0-52 weeks	52-76 weeks	*0-24 weeks*	0-52 weeks	52-76 weeks	0-24 weeks	
MedDRA preferred term	N=114 n (%)	*N=110 n (%)*	N=110 n (%)	N=74 n (%)	*N=60 n (%)*	N=60 n (%)	*N=104 n (%)*	N=104 n (%)	N=91 n (%)	*N=68 n (%)*	N=68 n (%)	N=62 n (%)	N=218 n (%)	*N=142 n (%)*
Macular degeneration	[redacted]													
Retinal oedema														
Eyelid oedema														
Injection site haemorrhage														

[a] week 24 completers within safety analysis set

Fellow eye

The overall incidence of ocular TEAEs in the fellow eye was [redacted] The most frequently occurring ocular TEAES in the fellow eye (in ≥3% of patients)were [redacted] During the studies, the fellow eye was not eligible to receive treatment with aflibercept, but could receive treatment for wet AMD with ranibizumab.

[redacted] report of an ocular TEAE in the fellow eye in COPERNICUS was considered to be injection related [redacted] In GALILEO, there was [redacted] hence it was unclear why the fellow eye would experience an injection-related TEAE. It is not known if this patient may have received ranibizumab for wet AMD in the fellow eye, which was permitted under study protocol.

In COPERNICUS, ocular SAEs in the fellow eye were experienced by [redacted] No other ocular SAEs, or drug- or injection-related TEAEs or SAEs were reported in the fellow eye in either study.

Injection-related TEAEs and SAEs

As may be expected, a higher number of injection-related TEAEs were reported in the aflibercept groups than the sham groups, in particular when the sham groups were receiving only sham treatment (COPERNICUS 0-24 weeks; GALILEO 0-52 weeks). The most common injection-related TEAEs (occurring in ≥10% of all patients) were conjunctival haemorrhage, eye pain, and eye irritation. [redacted] No non-ocular TEAEs were considered related to injection procedure. Injection-related SAEs in the

study eye were extremely low. Two of the ocular SAEs reported in COPERNICUS were considered injection-related (the endophthalmitis case mentioned previously [see ‘ocular TEAEs and SAEs’] and one report of cataract). In GALILEO, one SAE of vitreous haemorrhage and one of vitreous detachment were considered by the investigator as related to the injection-procedure.

Non-ocular TEAEs and SAEs

Non-ocular AEs reported over the entire study period covered a broad range of medical conditions (see Table 45). The proportion of patients experiencing ≥ 1 non-ocular TEAE over the entire duration of the studies was slightly higher in the sham groups in both studies[redacted]

In general, non-ocular TEAEs were mild or moderate, and individual non-ocular TEAEs occurred in only a small number of patients. Hypertension and nasopharyngitis were reported most commonly across both studies. In addition, ‘upper respiratory tract infection’, ‘influenza’, [redacted]

The incidence of study drug-related non-ocular TEAEs was extremely low in both studies i.e. one drug-related TEAE in each treatment group in each study, and the type of events consistent with events expected within this older patient population.[redacted]

Both of the drug-related non-ocular TEAEs reported in the sham patients occurred within the first study phase of COPERNICUS and GALILEO, where sham patients were only receiving ‘sham injections’ and no active treatment.

The incidence of non-ocular SAEs was low overall and similar between treatment groups in both studies. Non-ocular SAEs reported more than once in any treatment group for each study were[redacted]

[redacted]

Deaths

There were [redacted] deaths across both studies, [redacted] occurring in the sham group within the first 24 weeks in the COPERNICUS study (Arrhythmia/AMI) and the others, also in the sham group in COPERNICUS, occurring between week 52 and 100 (oesophageal adenocarcinoma stage IV, pneumonia).

Additional Adverse Events of interest: Arterial Thromboembolic Events Based on Anti-Platelet Triallists' Collaboration (APTC) endpoint

ATEs, as defined by APTC criteria, include non-fatal myocardial infarction, non-fatal stroke, or vascular death (including deaths of unknown cause). APTC events were adjudicated in [redacted] patients in COPERNICUS, two vascular deaths (in the sham treatment group), as discussed already (see 'Deaths'), and one 'non-fatal myocardial infarction' and [redacted] both occurring in the aflibercept group. No APTC events were adjudicated in GALILEO.

Table 45. Non-ocular TEAEs in the study eye occurring in ≥3.0% of patients in any treatment group in the COPERNICUS and GALILEO studies (and integrated 24 week analysis) by system organ class (SOC) and preferred term (SAF) NB. The hatched areas indicate when the sham group has crossed over to receive aflibercept PRN

	COPERNICUS						GALILEO						Integrated	
	Aflibercept			Sham			Aflibercept			Sham			Aflibercept	Sham
Primary System Organ Class	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	*0-24 weeks*	0-52 weeks	52-76 weeks	*0-24 weeks*	0-52 weeks	52-76 weeks	0-24 weeks	
MedDRA preferred term	N=114 n (%)	*N=110 n (%)*	N=110 n (%)	N=74 n (%)	N=60 n (%)	N=60 n (%)	*N=104 n (%)*	N=104 n (%)	N=91 n (%)	*N=68 n (%)*	N=68 n (%)	N=52 n (%)	N=218 n (%)	N=142 n (%)
Non-ocular (systemic) TEAEs										*37 (54.4)*			105 (48.2)	
Patients with at least 1 preferred term ≥3% in any group										*NR*			NR	
Infections and Infestations														
Nasopharyngitis										*6 (8.8)*				
Sinusitis														
Upper respiratory tract infection														
Bronchitis										*1 (1.5)*				
Influenza										*0*				
Urinary tract infection														
Pneumonia														
Herpes Zoster														
Vascular disorders														
Hypertension										*3 (4.4)*				
Investigations														
Urine protein/creatinine ratio increased														
Protein urine present														
Blood glucose increased														
Blood pressure systolic increased														
Blood urine present														
Glucose urine present														

	COPERNICUS						GALILEO						Integrated	
	Aflibercept			Sham			Aflibercept			Sham			Aflibercept	Sham
Primary System Organ Class	**0-24 weeks**	***24-52 weeks[a]***	**24-100 weeks[a]**	**0-24 weeks**	***24-52 weeks[a]***	**24-100 weeks[a]**	***0-24 weeks***	**0-52 weeks**	**52-76 weeks**	***0-24 weeks***	**0-52 weeks**	**52-76 weeks**	**0-24 weeks**	
MedDRA preferred term	**N=114 n (%)**	***N=110 n (%)***	**N=110 n (%)**	**N=74 n (%)**	***N=60 n (%)***	**N=60 n (%)**	***N=104 n (%)***	**N=104 n (%)**	**N=91 n (%)**	***N=68 n (%)***	**N=68 n (%)**	***N=52 n (%)***	**N=218 n (%)**	**N=142 n (%)**
Blood pressure increased	[redacted]													
Blood creatinine increased														
Lymphocyte count decreased														
Gastrointestinal disorders														
Nausea														
Vomiting														
Diarrhoea														
Constipation														
Dyspepsia														
Abdominal pain														
Dysphagia														
Gastritis														
Metabolism and nutrition disorders														
Hypercholesterolaemia														
Hypokalaemia														
Injury, poisoning and procedural complications														
Fall														
Accident														
Musculoskeletal and connective tissue disorders														
Osteoarthritis														
Arthralgia														
Arthritis														
Back pain														
Bursitis														
Pain in extremity														
Respiratory, thoracic and														

Primary System Organ Class MedDRA preferred term	COPERNICUS						GALILEO						Integrated	
	Aflibercept			Sham			Aflibercept			Sham			Aflibercept	Sham
	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	0-24 weeks	*24-52 weeks*[a]	24-100 weeks[a]	*0-24 weeks*	0-52 weeks	52-76 weeks	*0-24 weeks*	0-52 weeks	52-76 weeks	0-24 weeks	
	N=114 n (%)	*N=110* *n (%)*	N=110 n (%)	N=74 n (%)	*N=60* *n (%)*	N=60 n (%)	*N=104* *n (%)*	N=104 n (%)	N=91 n (%)	*N=68* *n (%)*	N=68 n (%)	N=52 n (%)	N=218 n (%)	N=142 n (%)
mediastinal disorders Cough Dyspnoea Hypoxia	[redacted]													
Nervous system disorders Headache Syncope	[redacted]													
General disorders and administration site conditions Pyrexia	[redacted]													
Cardiac disorders Cardiac failure congestive	[redacted]													
Blood and lymphatic system disorders Anaemia	[redacted]													
Psychiatric disorders Depression Anxiety	[redacted]													
Renal and urinary disorders Renal failure acute	[redacted]													
Immune system disorders Seasonal allergy Drug hypersensitivity	[redacted]													

[a] week 24 completers within safety analysis set

Intraocular pressure (IOP)

Generally, the analyses of IOP measurements in the study eye yielded consistent results across the treatment groups and the two studies. All treatment groups showed only a slight increase in mean IOP post-injection compared with pre-injection throughout the course of both studies and aflibercept injections did not appear to be accompanied by sustained increases in IOP.

Immunogenicity

During both studies, very low levels of treatment-emergent immunogenicity to aflibercept were exhibited, and no neutralising antibody activity was detected.

A total of 8 patients (3 sham, 5 aflibercept) in COPERNICUS and 9 patients (5 sham, 4 aflibercept) in GALILEO tested positive in the anti-drug antibody assay (ADA). No additional patients tested positive in either study after week 52.

In COPERNICUS, all 3 positive sham assays and one aflibercept assay were positive at baseline and in subsequent samples (with no titres >30). One of the aflibercept patients only had a positive assay at baseline. The other 3 positive patients in COPERNICUS from the aflibercept group were all negative at baseline and positive at week 52. Again titers were low, with no titre exceeding the minimum of 30. In GALILEO, of the 5 sham patients, one was positive in the baseline sample, one was considered to be transiently positive, and three had persistently positive results. Of the 4 aflibercept positive ADA cases, one was positive in the baseline sample, two were considered to be transiently positive, and one had persistently positive results

The positive results exhibited in baseline samples, and also in the sham patients who had never been exposed to aflibercept, suggest the positive results are most likely due to high serum background levels and not a drug-induced response. The finding that after week 52, no additional positive results were seen is in line with this suggestion. Furthermore, a positive ADA assay did not interfere with primary efficacy outcome, as aflibercept patients with positive ADA tests were within the group of patients gaining at least 15 letters from baseline. No patterns in TEAEs in patients with positive ADA tests were suggestive of immunological reactions either.

Other investigations

No clinically meaningful change in laboratory values or vital signs was seen in either treatment group of either study.

Adverse events leading to withdrawal

In both studies, the incidence of ocular and non-ocular TEAEs leading to withdrawal from the study drug was low but was higher in the sham groups (see Table 46).

Table 46. TEAEs leading to discontinuation of study medication

Study period n (%)	COPERNICUS		GALILEO	
	Aflibercept	Sham	Aflibercept	Sham
	N=114	N=74	N=104	N=68
TOTAL during study	**4 (3.5)**	**5 (6.8)**	**7 (5.8)**	**7 (10.3)**
0-24 weeks	**2**	**5**	**2**	**6**
24-52 weeks	**0**	**0**	**4**	**1**
52-76 weeks			**1**	**0**
52-100 weeks	**2**	**0**		

Subgroup analyses

Results of the subgroup analyses of patients with any TEAEs, any ocular TEAE/SAE (study or fellow eye), non-ocular TEAEs/SAEs, and TEAEs leading to withdrawal, were generally similar to those seen in the overall population throughout both studies. Some analyses had too few patients to make any meaningful comparisons. There were no clinically relevant imbalances or trends seen between treatment groups. Overall, no differences that would suggest a safety trend or concern were observed between aflibercept-treated patients in different sub-groups.

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

In summary, aflibercept 2mg intravitreal injection for the treatment of macular oedema secondary to CRVO is demonstrated to be well tolerated, with an acceptable safety profile and no notable differences compared to sham injections. The longer term safety of aflibercept in CRVO was also confirmed in COPERNICUS (to 100 weeks) and GALILEO (76 weeks).

Ocular TEAEs were consistent with those expected with the nature of underlying disease, disease progression, or attributable to the injection procedure. There was a low incidence of drug-related ocular TEAEs and numbers were similar between treatment groups. One case of endophthalmitis was reported (COPERNICUS). Non-ocular AEs covered a broad

range of medical conditions, with hypertension and nasopharyngitis, the most commonly reported across both studies. No clinically meaningful imbalances were noted in SAEs. Arterial thromboembolic events, based on APTC criteria were adjudicated in [redacted]

patients only, two of which occurred in patients allocated to sham treatment, prior to receiving any aflibercept treatment.

The slight transient increases in mean intraocular pressure post-injection associated with aflibercept injection was in line with experience in wet AMD, for aflibercept, and also another anti-VEGF agent, ranibizumab.

Safety outcomes were consistent with those reported in aflibercept studies in wet age-related macular degeneration (AMD), confirming the validity of the safety results for aflibercept across larger cohorts.

No direct comparison with other active agents used to treat CRVO in clinical practice was included in COPERNICUS or GALILEO for safety and an indirect comparison with ranibizumab could not be performed due to differences in reporting and populations reported (see section 6.7). Of the 3 adverse events (vitreous haemorrhage, neovascular glaucoma and iris neovascularisation) reported across the studies, results indicated a non-statistical trend in favour of aflibercept patients experiencing less vitreous haemorrhage and neovascular glaucoma events compared with ranibizumab. Patients treated with aflibercept appeared to experience more iris neovascularisation events when compared with ranibizumab (also not-statistically significant). However, this type of cross-study comparison should be treated with caution.

A comparable safety profile between aflibercept and ranibizumab has already been demonstrated in wet AMD. Based on the safety profile of aflibercept demonstrated in COPERNICUS and GALILEO, it is anticipated that aflibercept will also have a comparable safety profile to ranibizumab - recently approved by NICE in RVO (TA283) - in the treatment of macular oedema secondary to CRVO in patients of England and Wales.

6.9 Interpretation of clinical evidence

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

Clinical evidence in this submission is derived from two, phase III, multicentre, double-masked, randomised controlled trials – COPERNICUS and GALILEO. Results from both RCTs demonstrate the effectiveness and safety of aflibercept as a new treatment for macular oedema secondary to CRVO.

Monthly intravitreal injections of aflibercept for a period of 6 months achieved rapid improvements of visual acuity, as measured by the primary endpoint: the proportion of patients gaining at least 15 ETDRS letters from baseline to week 24. In both studies, aflibercept was significantly superior to sham treatment with 56.1% and 60.2% of aflibercept-treated patients gaining at least 15 ETDRS letters within 24 weeks (COPERNICUS $p<0.001$; GALILEO $p<0.0001$, respectively). During this initial phase of treatment, mean change in BCVA, as assessed by ETDRS letter score, was statistically superior for aflibercept-treated patients (COPERNICUS: +17.3 letters vs. -4.0 letters [sham], $p<0.001$; GALILEO: +18.0 letters vs. +3.3 letters [sham], $p<0.0001$), as was reduction in central retinal thickness (CRT). The benefits seen in vision and eye morphology translated into clinically relevant improvements in vision-related quality of life (NEI VFQ-25 total score, subscale near activities, distance activities and vision dependency scores) – potentially making the difference as to whether a patient with CRVO can perform activities requiring near vision, move around safely in or outside the home, or even live independently.

The longer-term effectiveness of aflibercept (studied for up to 2 years) was also demonstrated in COPERNICUS and GALILEO, during which time the improvements in visual acuity (i.e. ≥15 ETDRS letter gains, mean change in BCVA from baseline), CRT, and vision-related quality of life were largely maintained, despite a switch at 24 weeks to PRN dosing.

Delays in starting aflibercept treatment (by up to 6 months [COPERNICUS] or a year [GALILEO]), and initiating therapy only as a PRN regimen, as reflected in the design of the sham treatment arms of the studies, still appears to provide improvements in BCVA, CRT and even vision-related quality of life endpoints, however these are not as marked or

robust as the clinical effects observed in patients receiving prompt, and fixed monthly doses of aflibercept at the start of the studies.

The beneficial clinical profile of aflibercept was accompanied by an acceptable safety profile. In both RCTs, aflibercept was well tolerated throughout the 76- and 100-week study durations, without notable differences compared to sham (plus PRN) in ocular (study eye and fellow eye) or non-ocular TEAEs. Ocular TEAEs were consistent with those expected with the nature of underlying disease, disease progression, or attributable to the injection procedure. Slight increases in intraocular pressure post-injection were transient. AEs potentially, or theoretically, related to systemic VEGF inhibition (i.e. non-infectious inflammatory eye or systemic reactions due to immunogenicity, arterial thromboembolic events [ATE], hypertension, erosions and ulcerations of the nasal mucosa, retinal pigment tears, and embryo-fetotoxicity) were generally infrequent and similar between treatment groups, with the exception of hypertension (the sum of all MedDRA descriptions of increased blood pressure) which occurred in >10% of all patients. In both studies, further investigations revealed a similar distribution between treatment groups, despite the greater level of exposure to aflibercept in the aflibercept group. Also, hypertension was present in both studies in over 50% of patients at baseline, and is a predominant risk factor in the onset of CRVO(27). A significant clinical systemic effect was therefore not apparent. Similarly no association was observed between ATE and treatment.

The development of neovascularisation was infrequent in both studies, with no meaningful numerical difference between the aflibercept and sham arms, although, in GALILEO (not measured in COPERNICUS), it took 240 days for 5% of patients in the aflibercept group to have developed neovascularisation whereas it took only 85 days in the sham group.

The safety and efficacy of aflibercept in the overall populations (at all timepoints) of the COPERNICUS and GALILEO studies was confirmed in a series of subgroup analyses and supported by sensitivity analyses in both FAS and PPS populations, including observed values. Both studies included patients with non-ischaemic (perfused) or ischaemic (non-perfused) CRVO. A diagnosis of ischaemic CRVO typically has a worse prognosis than non-ischaemic CRVO and it is harder to treat. Confirmation of efficacy and safety in these subgroups, plus the broad range of other subgroups analysed, indicates that aflibercept can achieve clinically meaningful treatment effects and is well tolerated in a broad population irrespective of CRVO-type.

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

A key strength of the evidence base is that the efficacy and safety of aflibercept in treating MO secondary to CRVO was corroborated in two independent, international RCTs, and across all subgroup and sensitivity analyses conducted, indicating the robustness of the results in a broad spectrum of patients. This is particularly important for patients with ischaemic CRVO, since efficacy in this subgroup has not been specifically explored for other available CRVO treatments e.g. ranibizumab. Subgroup analyses included all those specified in the decision problem, with the exception of central macular thickness.

All efficacy and safety assessments in COPERNICUS and GALILEO are standard variables and methods in clinical studies for RVO, and in ophthalmic practice(27). They are widely recognised as valid, reliable, accurate and relevant.

The incorporation of PRN dosing into the design of both studies was also a strength as it enabled the assessment of efficacy and safety in a dosing regimen more in line with current longer-term management of CRVO patients in clinical practice, whereby a period of fixed monthly dosing is followed by PRN dosing and regular monitoring. In both studies, the rapid effect on visual outcomes and vision-related quality of life were largely maintained over a period of up to 2 years, by PRN dosing.

The range of PRN monitoring and dosing intervals studied i.e. monthly / 8-weekly / 12-weekly also provides information on the viability of a ‘treat and extend’ regimen in CRVO, consistent with the use of aflibercept in wet AMD. The burden of treatment and monitoring, in terms of resources required and capacity available within Ophthalmology departments is an ongoing issue in the UK, and with an ageing population the number of patients presenting with back-of –the-eye conditions is increasing. Current standard of care, ranibizumab, requires monthly monitoring of VA, and usually, anatomical outcomes using OCT. Hence, an opportunity to extend the injection interval without the burden of monthly monitoring would be a key benefit in the introduction of aflibercept for the treatment of CRVO.

It was also demonstrated that CRVO patients (by crossover to active treatment in the studies) can achieve some clinical benefit, even if aflibercept treatment is not initiated

promptly - although this management strategy was less effective than prompt treatment and an initial period of fixed monthly dosing, and would not be recommended as an optimal treatment approach for CRVO.

A perceived limitation could be that there was no ‘active’ comparator in either study i.e. one of the currently approved therapies in CRVO. At the time of study design, although several treatment modalities were under investigation, there was no approved treatment for CRVO and the standard of care was observation until progression to anterior segment neovascularisation, for which PRP was then administered. Hence the sham-treatment design in COPERNICUS and GALILEO, where patients in the sham group were ‘observed’ and PRP was administered (to any patient) as deemed necessary, was representative of BSC.

An indirect comparison with ranibizumab (0.5mg in a reactive dosing regimen), another intravitreal anti-VEGF treatment, has been included in this submission (see section 6.7), in order to put the results of COPERNICUS and GALILEO into a more up-to-date context. Visual acuity improvement outcomes of patients gaining ≥ 15 letters of BCVA from baseline at 6 months, patients losing ≥ 15 letters of BCVA from baseline at 6 months, and mean change in BCVA/number of letters read from baseline to 6 months were evaluated in a mixed treatment comparison and results suggest non-significant differences that were numerically in favour of aflibercept, despite the aflibercept studies including the harder to treat ischaemic patients. These results were significantly in favour of aflibercept versus dexamethasone for the two comparable outcomes (proportion of patients gaining at least 15 letters and mean change in visual acuity from baseline to 24 weeks).

6.9.3 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.

Evidence to support the use of aflibercept for the treatment of macular oedema secondary to CRVO is provided by results from well-designed trials i.e. large, prospective, randomised, double-masked, placebo-controlled, multicentre, adequately powered, demonstrating the superiority of aflibercept when compared with BSC. These characteristics, in addition to those described below, demonstrate the credibility and relevance of the evidence base to the decision problem.

Population

Adults with ’macular oedema secondary to CRVO’ was the key inclusion criterion for COPERNICUS and GALILEO study entry. All patients had visual impairment (BCVA of 20/40 to 20/320) and a mean CRT ≥ 250µm on OCT. Therefore the population included within the clinical studies is reflective of the population considered within this appraisal.

The demographic and baseline characteristics were representative of a population of patients with CRVO. Typically over 50% of patients diagnosed with CRVO are 65 years of age or older. The combined pool of patients in the integrated analysis, showed that 53.9% of patients recruited across COPERNICUS and GALILEO were 65 years of age or older.

Benefits of aflibercept were consistent across subgroups including age, gender, race, renal function, hepatic impairment, baseline BCVA, and baseline retinal perfusion demonstrating that a wide range of patients with CRVO, typical of those presenting in clinical practice in England and Wales, can benefit from aflibercept. These analyses also confirmed the experience in wet AMD with regard to safety and the lack of restrictions needed in relation to organ function such as renal impairment, liver function or diabetes status.

Comparators

In COPERNICUS and GALILEO, aflibercept treatment was compared with the best standard of care at the time of study design i.e. observation until progression to anterior segment neovascularisation, and then treatment with PRP. This was one of the comparators stated in the decision problem. Since then, as discussed in Section 2.7, new treatments have been introduced and approved by NICE: dexamethasone intravitreal implant (July 2011, NICE TA229) and most recently, ranibizumab (May 2013, TA283)(8;20).

As discussed in Section 2.7, during the NICE appraisal of ranibizumab for RVO, dexamethasone was found to be extended dominated by both best supportive care and ranibizumab; hence ranibizumab appears to have superseded dexamethasone implants as the first choice standard of care for CRVO treatment in the UK. On this basis, ranibizumab is included as the most appropriate comparator and a mixed treatment comparison between aflibercept, ranibizumab and BSC (observation and PRP) was conducted. As discussed in section 6.7 and 6.10.2, results of this comparison were numerically in favour of aflibercept, despite the aflibercept studies also including the harder to treat ischaemic

patients, but differences were not statistically significant. For completeness, an indirect comparison with dexamethasone was statistically significantly in favour of aflibercept.

The evidence base in this submission does not address a comparison between bevacizumab and aflibercept. As discussed in Section 5 and 6.7, our findings when reviewing the literature, found no evidence to change the conclusions reached during the NICE appraisal of ranibizumab for the treatment of macular oedema secondary to RVO i.e. that there was insufficient information to compare bevacizumab to ranibizumab for decision making given the small size of the studies, limited reporting and modest quality.

Intervention

Dose per injection in COPERNICUS and GALILEO studies was 2mg intravitreally. This is the same dose per injection utilised in aflibercept treatment of wet AMD and in the *draft SmPC*. The dosing regimen, following initial monthly injections during the first 24 weeks, followed a PRN regimen based on monthly monitoring. However, in practice, the draft SmPC indicates a treat to stability then extend regimen which may allow less frequent injection and monitoring frequency than that seen in the trial.

Outcomes

All efficacy and safety assessments in COPERNICUS and GALILEO, are standard variables and methods in clinical studies for RVO, and in ophthalmic practice(27) and are thus highly relevant to the decision problem.

The main impact of the disease is the rapid loss or change in vision due to macular oedema(44). With this in mind, outcome measures in COPERNICUS and GALILEO, were based around assessment of treatment effects on vision and also aflibercept's ability to halt or slow disease progression – of direct relevance to the CRVO patient.

The primary efficacy endpoint in COPERNICUS and GALILEO was an assessment on the ability of aflibercept to improve visual function i.e. *the proportion of patients who gained at least* 15 letters in the *ETDRS letter score at 6 months compared to baseline*. During assessment, letters are read from standard eye-charts, commonplace worldwide and used routinely in 'eye tests' in clinical practice in the UK.

The primary endpoint was met in both studies - aflibercept treatment was found to be significantly superior to sham treatment (COPERNICUS $p<0.001$; GALILEO $p<0.0001$).

Improvements in visual acuity were rapid and were evident as early as 4 weeks after the first injection in both studies.

Secondary endpoints included mean change in BCVA as measured by ETDRS letter score, which further assessed the effects of aflibercept on vision, and an anatomical endpoint of mean change in CRT provided information on the morphological effects of aflibercept. Superiority of aflibercept treatment compared to sham-treatment was demonstrated for both of these endpoints.

The decision problem also stated the ‘need for PRP’ as an outcome. This is relevant as it indicates the onset of significant progression of CRVO to anterior segment neovascularisation. Such disease progression signals a worsened prognosis for the patient, hence, the importance of exploring whether new treatments are able to halt or slow this process. The development of neovascularisation was infrequent in both studies with, ultimately, no meaningful differences between the two treatment groups in either study at 76 and 100 weeks. In GALILEO, five percent of patients in the sham group developed neovascularisation by day 85, while 5% of patients in the aflibercept group had developed neovascularisation by day 240. Time to neovascularisation was not measured in COPERNICUS), Across the two studies, within the first 24 weeks of treatment, only 1 patient required PRP from the aflibercept-treated groups whereas 7 patients underwent PRP in the sham-treated groups. One further patient in the original aflibercept treated group required PRP between week 24 and week 52 in GALILEO. No other patients in either study or treatment arm required PRP.

As acknowledged in the ‘Interim guidelines for the management of RVO’ produced by the Royal College of Ophthalmologists, sudden onset of visual loss results in significant distress and CRVO is associated with a decreased vision-related quality of life(27). Patient reported outcomes were therefore included in COPERNICUS and GALILEO. These assessments are important as they are reported and/or scored directly by the patient, free of interpretation by a clinician. It is an account of how the patient functions or feels relative to a health condition or therapy and a useful indicator as to how patients might experience the treatment in clinical practice and how the therapy impacts on aspects of daily living and health related quality of life. ‘Change in total NEI VFQ-25 (National Eye Institute 25-item Visual Function Questionnaire) score from baseline’ was a secondary endpoint. Total score and subscales (i.e. near activities, distance activities, and vision dependency) of the questionnaire were assessed. Monthly aflibercept treatment (for 24 weeks) produced

statistically significant clinically relevant improvements in vision-related quality of life, as measured by total score on NEI VFQ-25 Clinically relevant improvements were also demonstrated for sub scale scores of near-activities (GALILEO: p=0.0003), distance-activities and vision dependency.

Improvements in vision, leading to an improved vision-related quality of life, can mean the difference between independent and dependent living, improved wellbeing or depression, and also mean patients are less at risk of falls or accidents due to visual problems(45-47). Although impact on societal costs were not quantified in this study, it is anticipated that the improvements in vision and vision-related quality of life achieved with aflibercept injections will have some positive effect on the degree of additional medical (e.g. the cost of falls) and non-medical care (e.g. carers) required by patients with CRVO.

The safety profile and patient tolerability of aflibercept were also evaluated at every study visit throughout COPERNICUS and GALILEO – important features before being accepted for use in a broader population, and integrated into standard clinical practice. All AEs were assessed for seriousness, intensity, pattern, study drug action, drug treatment, causal relationship to study drug, and causal relationship to the injection procedure. Aflibercept was well tolerated throughout the 76- and 100-week study durations, without notable differences compared to sham (plus PRN) in ocular (study eye and fellow eye) or non-ocular TEAEs. Due to differences in study populations and reporting, it was not feasible to include adverse events in the indirect comparison.

Importantly, the positive effects of aflibercept on all measured efficacy and safety outcomes were shown to be durable throughout the studies (measured for up to 2 years). This is a relevant feature of study considering treatment requirements for patients in practice are likely to extend beyond 6 months or a year.

6.9.4 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 results of the COPERNICUS and GALILEO trials are directly applicable to the population of CRVO patients in England and Wales who are eligible for anti-VEGF treatment. The broad inclusion criteria for study, including ischaemic CRVO, and also the extensive subgroup analyses within efficacy and safety outcomes support this view. Baseline demographics were also similar to that expected in clinical practice in England and Wales e.g. median age 63-69 years, slightly more males than females, and approximately three-quarters of patients described as of 'White race'.

Aflibercept solution for injection is an additional and alternative option to currently available treatments, ranibizumab and dexamethasone implant, for the treatment of MO secondary to CRVO. Recent NICE guidance on ranibizumab appears to supersede any recommendations for use of dexamethasone implant in CRVO, so it is likely the choice for clinicians will be between ranibizumab and aflibercept. A direct comparison with ranibizumab is not available for CRVO, however, evidence suggests a similar efficacy and safety profile i.e. indirect comparison of efficacy outcomes with ranibizumab in CRVO showed non-significant differences that were numerically in favour of aflibercept, despite the aflibercept studies including the harder to treat ischaemic CRVO patients; and aflibercept and ranibizumab have previously been shown to have a similar safety profile in the VIEW studies in wet AMD. Outcomes from the indirect comparison versus dexamethasone were statistically significant in favour of aflibercept.

Patient selection – use of aflibercept in CRVO in clinical practice

Patients included in the CRVO trials had not received any prior therapy, which may not be the case in clinical practice. According to the draft SmPC, treatment in patients who have discontinued other CRVO therapies is not a specific contraindication to use of aflibercept in CRVO.

There are also no additional tests or investigations required for selection of patients appropriate for aflibercept, over and above the current routine assessments in CRVO.

In addition, although no studies in patients with hepatic and/or renal impairment have been conducted with aflibercept, available data from subgroup analyses of COPERNICUS and GALILEO (CRVO) and previous studies in wet AMD do not suggest a need for any dose adjustment with aflibercept in these patients.

What proportion of the evidence base is for the dose(s) given in the SPC?

The entire evidence base relates to the dose of aflibercept to be licensed for use in the treatment of CRVO (i.e. 2mg).

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.

A systematic literature review was conducted to identify economic evaluations (EE), including cost-effectiveness, cost-benefit, cost-utility and cost-minimisation studies, published in the area of CRVO and RVO in the English language between January the 1st, 2001 and March the 11th, 2013. The EE review was also tailored to identify resource use and costing papers (e.g. burden-of-illness analyses) reporting resource use for the targeted population as required in Section 7.5.3 of this submission. The scope of the systematic literature review was widened to include the broader RVO indication – of which CRVO represents a population subgroup - as exploratory searches demonstrated that no EE had been published for CRVO alone. The review was limited to the following products: aflibercept, bevacizumab, dexamethasone, ranibizumab, laser treatment, and BSC. The searches were conducted on Embase, Medline (including Medline (R) in process), EconLit and NHS EED using the OVID platform[2]. For each database, a search was developed combining disease terms (CRVO, RVO) with interventions and comparators terms (aflibercept, bevacizumab, ranibizumab, laser, dexamethasone, BSC), study design terms (CEA, CUA, CBA, CMA) and specified limits (time horizon and English language). The relevance of references identified by the search across the four databases was assessed against eligibility criteria that were defined following enhanced PICO (Patients, Intervention, Comparator and Outcomes) criteria. The search strings can be found in Section 10.10, Appendix 10.

[2] Ovid is a platform that provides standardised access to a wide range of economic and clinical literature databases

All references captured by the combined search were double reviewed based on their abstracts and titles against the eligibility criteria presented in Table 47 below:

Table 47. Eligibility criteria for economic evaluation (and resource use) search

Economic evidence	Inclusion	Exclusion
Patient population	Adult patients with CRVO or BRVO or RVO	Patients with AMD and DMO
Interventions**	• Aflibercept **OR** • Bevacizumab **OR** • Dexamethasone **OR** • Ranibizumab **OR** • Laser	-
Comparators**	• Bevacizumab **OR** • Dexamethasone **OR** • Ranibizumab **OR** • Laser **OR** • Placebo/BSC/sham/observation	-
Outcome measures	Resource use & costs	-
Study design	• Cost-benefit analysis **OR** • Cost-effectiveness analysis **OR** • Cost-minimisation analysis **OR** • Cost-utility analysis **OR** • Costing analysis **OR** • Resource use study	• Editorials **OR** • Notes **OR** • Comments **OR** • Letters **OR** • Systematic reviews of EE **OR** • Abstracts only*
Restrictions	• Language: English • Published in past 11 years	• Non-English studies • Studies published beyond past 11 years

AMD: age-related macular degeneration; BRVO: branch retinal vein occlusion; DMO: diabetic macular oedema; N/A: not applicable; RVO: retinal vein occlusion.
* applies at the full-text review stage only.
**applies only to cost-benefit, cost-effectiveness, cost-utility and cost-minimisation studies.

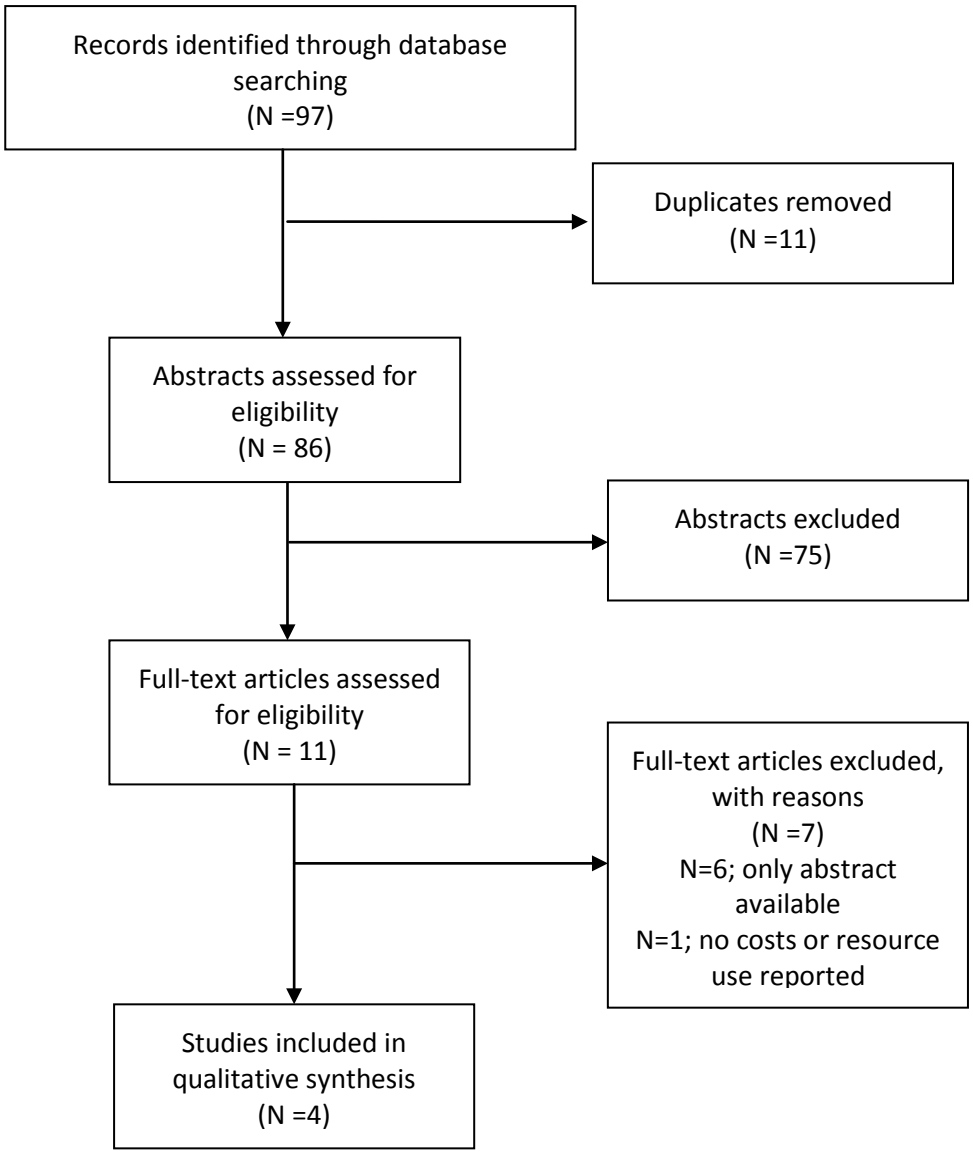
All publications where there was disagreement about inclusion at this stage were resolved either through “reconciliation” (discussion between the two reviewers) or through “arbitration” by a third independent reviewer. The “majority view” determined inclusion or exclusion. Included publications were retained for full text review; excluded publications were disregarded. The full texts of the publications retained after the abstracts review were judged once more by the two reviewers against the eligibility criteria presented. The approach to resolve any disagreement was the same as for the abstracts review process. All papers included after the full text review were retained for data extraction.

Overall, the EE and resource use (RU) search yielded a total of 97 hits, of which 11 were duplicates, leaving 86 records to be reviewed against the eligibility criteria. After screening

86 titles and abstracts, 11 studies were selected for full-text review. Of these, only four were retained for data extraction.

The process of study selection and the final results of the search are illustrated below in Figure 17 using the PRISMA Flow diagram.

Figure 17. Study flow diagram for systematic review of economic evaluations



This systematic literature review was complemented by a search of abstracts presented at the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) conferences. The search was limited to conference proceedings presented at the ISPOR

North American and European conferences held over the past two years (2011-2012). All searches were performed using disease area (CRVO) and interventions (aflibercept, ranibizumab, bevacizumab, dexamethasone, placebo, best supportive care and laser) search terms.

The abstracts captured for each congress were then reviewed using the eligibility criteria developed for the systematic literature review (see Table 47 above). Five relevant abstracts were identified (Table 48). Details of the congress search strategies and the studies selected can be found in Section 10.10.5, Appendix 10. Neither the systematic literature review nor the ISPOR congress abstracts search identified EE that included aflibercept.

In addition, a search for technology appraisals (TAs) published on NICE's website for the treatment of CRVO and RVO was conducted to identify earlier models developed for these indications. Two TAs were identified for the treatment of RVO with dexamethasone and ranibizumab respectively:

- Dexamethasone intravitreal implant (Ozurdex®) was approved by NICE for the treatment of MO secondary to RVO (TA229)(20) in 2011;
- Ranibizumab (Lucentis®) for the treatment of visual impairment due to MO secondary to CRVO or BRVO (TA283)(8) in 2013.

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.

Of the 11 papers initially identified for full text review (see Figure 17 above), seven papers were excluded, bringing down the number of included studies to four. The list of excluded studies as well as the primary reason for exclusion is presented below in Table 48 for each study.

Table 48. EE and resource use search - Summary of excluded studies

#	Author & Year	Type of Study	Reason for exclusion
1	Almond *et al.* 2011(48)	Cost-utility analysis	Abstract only
2	Duff *et al.* 2012(49)	Cost-utility analysis	Abstract only
3	Fish *et al. 2008(50)*	Retrospective chart review	No costs or resource use reported
4	Haig *et al.* 2012(51)	Cost-utility analysis	Abstract only
5	Hayward *et al*. 2011(52)	Cost-effectiveness analysis	Abstract only
6	Kowalski *et al.* 2011(53)	Cost-utility analysis	Abstract only
7	Taylor *et al.* 2012(54)	Cost-utility analysis	Abstract only

The four studies identified by the EE search included two cost-utility analyses (CUA) (Brown *et al.* 2002 and Smiddy *et al.* 2011(55;56), and two costing studies reporting resource use data (Fekrat *et al.* 2010 and Augustin *et al.* 2012(57;58).The two studies identified for resource use data are discussed in Section 7.5.37.5.3. For each CUA, a narrative summary is provided below. A study summary is provided in Table 49.

Brown *et al.* 2002(59) reports the results of a cost-utility analysis comparing laser photocoagulation with observation (natural history) in BRVO patients from the United States (US) payer perspective. The main outcomes were medical costs, quality adjusted life years (QALYs) and quality of life due to treatment and associated vision improvement. A Markov model was developed to account for recurrent risk of developing RVO in the fellow eye over a patient's lifetime; the model comprised two states: "one eye treated" and "two eyes treated". No adverse events were modelled. Clinical data were taken from the Branch Vein Occlusion Study Group. Medical costs included cost of laser therapy and of fluorescein angiogram. Utility values were derived from Brown *et al.* 1999(60) and assigned based on BCVA level in the best-seeing eye (BSE). The disutility of laser therapy with regards to pain or lost time from the activities of normal living was considered to be negligible. Two way sensitivity analyses were performed. Laser therapy was estimated to be associated with an incremental cost-effectiveness ratio (ICER) of $6,118/QALY (Year $2000).

Smiddy *et al.* 2009(56) presents the results of both cost-effectiveness and cost-utility analyses comparing six treatment therapies (focal laser, intravitreal triamcinolone acetonide (IVTA), dexamethasone, pegaptanib, bevacizumab and ranibizumab) with

observation (natural history) in patients with diabetic macular oedema (DMO) and RVO (BRVO & CRVO) from the US payer perspective. The time horizon was one year. The main outcomes were 1-year treatment cost, vision lines saved, cost/lines saved, cost/line-years saved, cost/QALY. This analysis was not based on a Markov model. Clinical data were taken from the several studies, usually randomised clinical trials (RCTs). Assumptions with regard to resource use frequency (follow-up visits, optical coherence tomography, fluorescein angiogram and injections) were made based on trial data. Discontinuation and adverse events were not modeled. A unique marginal QALY value was ascribed for each line gained, based on Brown *et al*. 2003(61). In CRVO patients, it was estimated that 1.2-3.75 lines were saved across all treatment therapies, that cost per line of saved VA spanned from $704 (corticosteroid) to $21,464 (ranibizumab). Cost per QALY gained spanned from $1,468 (corticosteroid) to $15,867 (ranibizumab).

Table 49. Summary list of published cost-effectiveness evaluations

Reference	**Brown *et al.* 2002(55)**	**Smiddy *et al.* 2011 (56)**
Country(ies) where study was performed	US	US
Patient population		
Study population	MO secondary to BRVO	DMO, BRVO, CRVO
Patient age	66 years	67.5 years
Model characteristics		
Type of evaluation	Cost-utility analysis (Markov model)	Cost-utility and cost-effectiveness analyses (not a Markov model)
Intervention	Laser therapy	IV corticosteroid, dexamethasone implant, pegaptanib, bevacizumab, ranibizumab
Comparator	No treatment	No treatment
Time horizon	Lifetime	1 year
Description of health states	Health states stratified by Snellen BCVA	-
Adverse events modelled	No	-
Perspective	Payer	Payer
Outcomes	Costs, QALYs gained, cost/QALY	Costs, lines saved, cost per line saved, cost per line-year saved, cost per QALY
Discount rates	Costs: 3%; Benefits: 3%	Costs: 0%; Benefits: 0%
Sensitivity analysis	Two-way sensitivity analysis	No
Category of utility reported	BCVA (source: Brown et al. 1999)	Marginal utility based on lines of vision saved (source: Brown *et al.* 2003)
Results		

Total cost (for each intervention)	Laser therapy: $1,057	• Bevacizumab: $4,409 • Dexamethasone: $2,359 • Ranibizumab: $1,536
Total health benefit	-	Number of lines saved: • Bevacizumab: 3.75 • Dexamethasone: 1.2 • Ranibizumab: 2.82 QALY gained: unspecified
Incremental health benefit outcome	0.198 QALYs gained	-
Incremental outcome ratio	$4,439 per QALY gained	Cost per line saved: • Bevacizumab: $1,176 • Dexamethasone: $1,961 • Ranibizumab: $7,611 Cost per QALY gained: • Bevacizumab: $2,613 • Dexamethasone: $5,957 • Ranibizumab: $15,867
BCVA: best corrected visual acuity; BRVO: branch retinal vein occlusion; BSE: best-seeing eye; CRVO: central retinal vein occlusion; DMO: diabetic macular oedema; ICER, incremental cost-effectiveness ratio; QALY: quality-adjusted life year; US: United States.		

These two studies were based on two models that differed significantly in terms of structure and underlying assumptions. Neither explored the impact of BCVA improvement in the study eye relative to fellow eye on quality of life. Both studies were conducted from the US payer perspective and therefore the cost and resource data were not deemed suitable sources for populating a model for a NICE submission. Neither was considered suitable for modeling the decision problem to be explored in the current submission.

In addition to these publications, five economic evaluations were identified that were presented as abstracts at ISPOR conferences over the past two years (Section10.10.5, Appendix 10): two of these were cost-utility analyses presented at two 2011 ISPOR congresses (Baltimore and Madrid) (Kowalski *et al.* 2011 and Hayward *et al*. 2011(52)). They both compared dexamethasone treatment with observation in MO secondary to CRVO and BRVO. Lifetime costs and effects were simulated using patient-level data pooled from two identical phase III studies (GENEVA 008 and GENEVA 009). Results from Kowalski *et al.* 2011 and Hayward *et al*. 2011 were presented from a US and a UK NHS perspective respectively. The remaining three studies (Duff *et al.* 2012, Haig *et al.* 2012 and Taylor *et al.* 2012(54)) were cost-utility analyses of ranibizumab for the treatment of macular oedema secondary to RVO in different country settings. They were presented at the ISPOR conference in Berlin, 2012.

In addition to published studies and conference abstracts, the economic evaluations presented in the two TAs for the treatment of RVO with dexamethasone and ranibizumab (TA229 for dexamethasone intravitreal implant (Ozurdex®)(20) and TA283 for ranibizumab (Lucentis®)(8)) were reviewed. These evaluations (as per manufacturer submission) are described in Table 50 below:

Table 50. Summary list of TA cost-effectiveness evaluations

Reference	**TA229(62)**	**TA283(63)**
Country(ies) where study was performed	United Kingdom	United Kingdom
Patient population		
Study population	MO secondary to RVO	MO secondary to RVO
Patient age	64.5	66.4
Model characteristics		
Type of evaluation	Cost utility analysis	Cost utility analysis
Intervention	Dexamethasone implant	Ranibizumab
Comparator	For CRVO and BRVO: Best supportive care (observation)	CRVO: i. Best supportive care ii. Dexamethasone implant BRVO: i. Dexamethasone implant ii. Grid pattern photocoagulation
Time horizon	Lifetime	15 years (lifetime in revised analyses)
Description of health states	Six BCVA health states (ETDRS scale): • HS0: ≥ 69 • HS1: 59-68 • HS2: 54-58 • HS3: 44-53 • HS4: 39-43 • HS5: ≤ 38 • Death	Nine BCVA health states (ETDRS scale): • HS0: 86-100 • HS1: 76-85 • HS2: 66-75 • HS3: 56-65 • HS4: 46-55 • HS5: 36-45 • HS6: 36-45 • HS7: 26-35 • HS8: ≤25 • Death
Adverse events modelled	IOP, cataract, retinal tears or detachments	Cataracts, IOP increased, stroke
Perspective	NHS and PSS	NHS and PSS
Outcomes	Cost per QALY	Cost per QALY
Discount rates	3.5% for both costs and outcomes	3.5% for both costs and outcomes
Sensitivity analysis	Deterministic and probabilistic sensitivity analyses	Deterministic and probabilistic sensitivity analyses
Category of utility reported	BCVA (utility values were derived from NEI-VFQ-25 mapping exercise)	BCVA (Brown *et al.* 1999)
Results		

Total cost (for each intervention)	CRVO: Dexamethasone: £14,962 Observation: £13,126 BRVO macular haemorrhage: Dexamethasone: £10,943 Observation: £9,434 BRVO with previous laser: Dexamethasone: £14,184 Observation: £12,966	CRVO: Dexamethasone: £14,962 Observation: £13,126 BRVO macular haemorrhage: Dexamethasone: £10,943 Observation: £9,434 BRVO with previous laser: Dexamethasone: £14,184 Observation: £12,966
Total health benefit	CRVO: Dexamethasone: 11.62 QALYs Observation: 11.32 QALYs BRVO macular haemorrhage: Dexamethasone: 11.73 QALYs Observation: 11.54 QALYs BRVO with previous laser: Dexamethasone: 11.56 QALYs Observation: 11.24 QALYs	CRVO: Ranibizumab: £26,327 Observation: £20,727 Dexamethasone: £22,945 BRVO: Ranibizumab: £18,717 Observation: £11,990 Dexamethasone: £18,717
Incremental health benefit outcome	CRVO: 0.31 BRVO macular haemorrhage: 0.19 BRVO with previous laser: 0.31	CRVO: Ranibizumab: 7.551 Observation: 7.061 Dexamethasone: 7.270 BRVO: Ranibizumab: 7.978 Observation: 7.705 Dexamethasone: 7.769
Incremental outcome ratio	CRVO: £6,008 BRVO macular haemorrhage: Dominant	CRVO: Ranibizumab vs. observation: £11,428 Ranibizumab vs. dexamethasone: £12,027 BRVO: Ranibizumab vs. observation: £24,610 Ranibizumab vs. dexamethasone: Extended dominance over dexamethasone
BCVA: best corrected visual acuity; BRVO: branch retinal vein occlusion; BSE: best-seeing eye; CRVO: central retinal vein occlusion; ICER, incremental cost-effectiveness ratio; IOP: intraocular pressure; MO: macular oedema; NEI-VFQ-25: National Eye Institute Visual Function Questionnaire 25-item; NHS: National Health Service; PSS: Personal Social Services; QALY: quality-adjusted life year		

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)[3] or Philips et al. (2004)[4]. For a suggested

[3] 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.

format based on Drummond and Jefferson (1996), please see section 10.11, appendix 11.

Quality assessment of the two full EE studies and of the economic evaluations presented in the previously mentioned RVO TAs is provided in Table 51 below and follows the format of the Drummond and Jefferson studies.

Table 51. Quality assessment for published and TA cost-effectiveness evaluations

Study question	Brown *et al.* 2002	Smiddy *et al.* 2011	TA229	TA283
1. Was the research question stated?	Yes	Yes	Yes	Yes
Study Design				
1 Was the research question stated?	Yes	Yes	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	Yes	Yes	Yes
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Yes	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	Yes	Yes	Yes	Yes
5. Were the alternatives being compared clearly described?	Yes	Yes	Yes	Yes
6. Was the form of economic evaluation stated?	Yes	Yes	Yes	Yes
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	Yes	Yes	Yes
Data collection				
8. Was/were the source(s) of effectiveness estimates used stated?	Yes	Yes	Yes	Yes
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	Yes	No	Yes	Yes
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)?	N/A	N/A	N/A	Yes
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	Yes	Yes	Yes	Yes
13. Were the details of the subjects from whom valuations were obtained given?	No	No	Yes	Yes
14. Were productivity changes (if included) reported separately?	N/A	N/A	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	N/A	N/A	N/A	N/A
16. Were quantities of resources reported separately from their unit cost?	Yes	No	No	No

[4] 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.

17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes	Yes	Yes
18. Were currency and price data recorded?	Yes	Yes	N/A	N/A
19. Were details of price adjustments for inflation or currency conversion given?	No	No	N/A	N/A
20. Were details of any model used given?	No	N/A	N/A	N/A
21. Was there a justification for the choice of model used and the key parameters on which it was based?	Yes	N/A	Yes	Yes
Analysis and interpretation of results				
22. Was the time horizon of cost and benefits stated?	Yes	Yes	Yes	Yes
23. Was the discount rate stated?	Yes	No	Yes	Yes
24. Was the choice of rate justified?	Yes	N/A	Yes	Yes
25. Was an explanation given if cost or benefits were not discounted?	N/A	No	N/A	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	N/A	N/A	Yes	Yes
27. Was the approach to sensitivity analysis described?	Yes	No	Yes	Yes
28. Was the choice of variables for sensitivity analysis justified?	No	N/A	Yes	Yes
29. Were the ranges over which the parameters were varied stated?	Yes	N/A	Yes	Yes
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	Yes	Yes	Yes	Yes
31. Was an incremental analysis reported?	Yes	Not clear	Yes	Yes
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	Yes	Yes	Yes
33. Was the answer to the study question given?	Yes	Yes	Yes	Yes
34. Did conclusions follow from the data reported?	Not clear	Yes	Yes	Yes
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes	Yes	Yes
36. Were generalisability issues addressed?	No	Yes	N/A	N/A
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				

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 population included in the economic model consists of adult patients with MO secondary to CRVO. This patient population reflects the patient population enrolled in the GALILEO and COPERNICUS trials, as described in Section 6.3. The patients included in the economic analyses are also in line with the expected licensed indication for aflibercept, i.e. MO secondary to CRVO, as described in Section 1.5.

The core comparator in the model is ranibizumab in line with the decision problem laid out in Section 2.7 above. This comparator represents the treatment most likely to be displaced through uptake of aflibercept. Please see Section 2.7 for the rationale behind this.

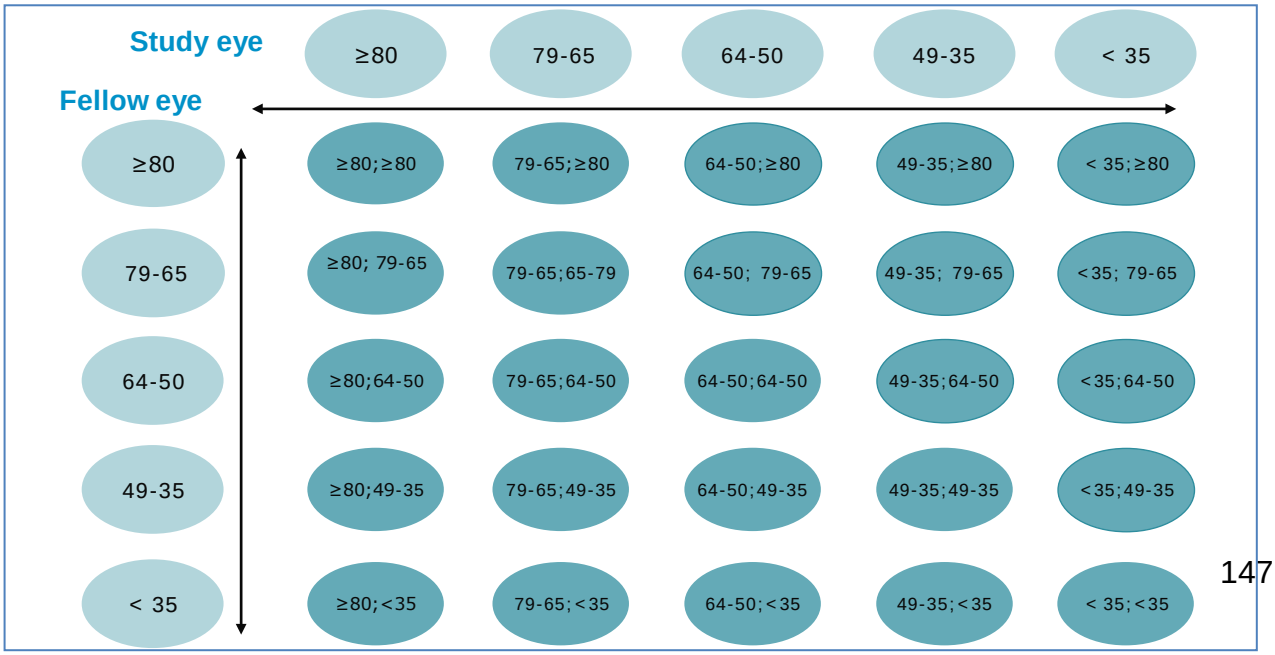
Model structure

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

A de novo economic model was developed to estimate the lifetime outcomes and costs of using aflibercept for the treatment of patients with MO secondary to CRVO. The model was a Markov state-transition model developed in Microsoft Excel®.

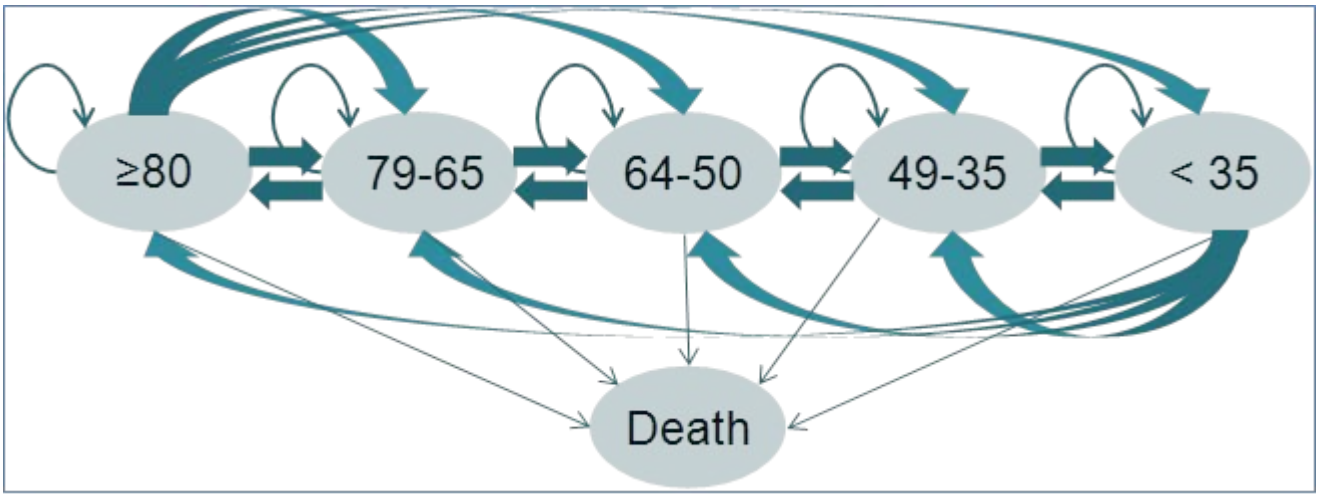
The model encompassed 25 health states (HS) based on BCVA in both the eye receiving investigational treatment, referred to the “study eye” (SE), and the non-treated eye, referred to as the “fellow eye” (FE). In addition, the model includes an absorbing HS for death. A diagrammatical representation of the model is provided in Figure 18 below.

Figure 18. Diagram of the model structure based on the ETDRs scale



Patients entered the model with a baseline vision defined according to a combination of BCVA ranges for the SE and FE. Each model cycle is 4 weeks in duration and in each cycle, patients can transition to any horizontally aligned state i.e. they can improve, remain in the same HS or deteriorate (see Figure 19), although the probability of moving more than one HS in either direction is low to zero depending on the initiating state.

Figure 19. Allowable transitions in the de novo model



Patients FE BCVA is assumed constant over time across all treatment arms i.e. FE involvement is not modelled. Please see Section 7.2.3 for the rationale for this.

Each HS represents a combination of BCVA ranges reflecting BCVA in the SE and the FE respectively. BCVA scores are defined based on the number of letters read by the patient categorised in 15-letter (i.e. 3-line) increments from legal blindness (<35 letters) to no visual impairment (≥80 letters), according to the ETDRS scale(64). As recommended by the evidence review group (ERG) in previous RVO HTA submissions(65), the magnitude of the BCVA change captured in each model HS was aligned with the pre-specified trial primary outcome (i.e. proportion of eyes with a gain of 15 ETDRS letters or more). The ETDRS scale is the primary measure of visual acuity in the model and is also in line with the aflibercept trial protocols and primary outcome measures (see Section 6.3).

The model captures the impact of BCVA on the patient's quality of life through application of HS-specific utility values. This allows utility to be modeled as a function of BCVA in both the SE and FE (presented in the base-case and scenario analysis) or with focus only on the SE (not presented in this submission).

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

The use of aflibercept is not expected to change the current clinical pathway which consists of managing patients with diagnosed MO secondary to CRVO with pharmacological treatment. The use of aflibercept represents an alternative option within the range of pharmacological treatments currently available for this patient population in line with the clinical pathway of care identified in Section 2.5.

The chosen model structure directly captures the main purpose of a pharmacological treatment, which is to improve or stabilise BCVA in the SE, by allowing patients to transit through HS over time according to their expected BCVA. This structure is in line with the modelling approaches used in previous HTA submissions for the treatment of CRVO/RVO.

CRVO is primarily a unilateral disease(8;20). Previous HTA submissions have distinguished between “single-eye” and “two-eye” models, where a single-eye model tracks BCVA changes in one eye only, the trial SE, while a two-eye model tracks BCVA change in the SE *in relation to* BCVA change in the FE. Historically, ophthalmology health economic analyses have primarily been conducted using single-eye models(66) due to lack of data to inform the more complex needs of a fully functioning two-eye model. A further distinction was made between the patient’s best seeing eye (BSE) and worst seeing eye (WSE). Single-eye models typically assumed that the SE was either always the patients’ BSE (100% of SE are BSE) or a constant mix of BSE and WSE.

The current model tracks BCVA change in the SE regardless of whether this is the BSE or WSE, and it assumed that BCVA in the FE remains constant. This approach captures the fact that BCVA in the SE, which is most likely to be the WSE at therapy initiation, may improve during treatment beyond the BCVA score of the FE, at which point the SE will become the BSE (see allowable transitions in Figure 19. It is therefore valuable to evaluate the benefit of treatment in terms of health-related quality of life (HRQoL) affected by the BCVA in both eyes, i.e. to assess the utility impact on the whole person.

The chosen model structure reflects both the expected clinical pathway of care and current availability of data. Please note that the data granularity required to develop a full “two

eye” model, where BCVA is independently tracked over time, is not available. In particular data presenting BCVA change for FE involvement is not available.

The proposed model for aflibercept encompassing utility of both the SE and FE therefore represents an appropriate and pragmatic approach to modelling BCVA over time which is in line with the clinical pathway of care identified in Section 2.5.

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

As shown in Figure 18, five BCVA ranges (in ETDRS letters) were used to define the HS: ≥80; 79-65; 64-50; 49-35; <35. These five BCVA ranges translate into 25 health states, to capture every combination of SE and corresponding FE visual acuity.

Blindness – also referred to as “severe sight impairment” - is defined as a visual acuity of <35 letters NHS(67) and this categorisation is used to capture the worst state possible within the model. Perfect vision, which is defined by patient BCVA ≥80 letters, is used to represent the upper limit HS included in the model.

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.

CRVO is characterised by vision loss – i.e. by a reduction in BCVA -, particularly in patients with associated chronic MO(68;69). In clinical research trials involving patients with MO secondary to CRVO, treatment efficacy is primarily measured by the proportion of patients gaining/losing BCVA (commonly 15 letters of vision) or by the mean number of lines/letters gained/lost from baseline.

The model captures BCVA changes during two sequenced phases: the on-treatment phase and the post-treatment phase. In the base-case analysis, patients were treated for one year. Recommendations on the optimal treatment duration in the UK from the Royal College of Ophthalmologists (RCO) are unclear, reflecting the recent availability of pharmacological treatment for patients with CRVO, and primarily refer to the products’ labels. Given the paucity of evidence regarding optimal treatment duration in CRVO and

the lack of long term trial data (cross ref to clinical section 6.3), it was difficult to assign optimum treatment duration to inform the economic base-case. Available evidence suggests the majority of patients remain on treatment at 6 months but the limited availability of robust efficacy data beyond 6 months of treatment due to trial cross-over design (see below), means that longer treatment durations are by necessity increasingly assumption-led. In this analysis, an assumption of 1-year treatment duration (52 weeks) was used for the base-case analysis. This treatment duration, which is shorter than the treatment duration reported in previous HTA submissions(62;63), was deemed conservative since efficacy assumptions used after the first 6 months of treatment were applied for a shorter period, thereby reducing uncertainty around efficacy for the total treatment duration. Sensitivity analyses assessed the impact of alternate duration assumptions (see Section 7.6.1).

On-treatment disease progression

During the first 24 weeks of treatment, disease progression was modelled using pooled data from the GALILEO and COPERNICUS trials for the aflibercept arm. A relative risk (RR) was applied to these data to estimate efficacy in the ranibizumab arm of the model (see Section 7.3.1for further detail).

Data were pooled only for the first 24-week period. This was due to the design of the COPERNICUS and GALILEO trials (see Section 6.3), whereby COPERNICUS patients were allowed to switch treatment arm at week 24 while GALILEO patients remained on the same arm for the total trial duration. In COPERNICUS, the cross-over option at 24 weeks meant that patients who met treatment or re-treatment criteria either crossed from sham to aflibercept, from aflibercept to sham or remained on aflibercept (depending on the initial treatment they were assigned), making it difficult to assign treatment effect after the first 24-week period. In GALILEO, patients were on active treatment across the course of the trial but only the 0-24 week data could be pooled with the COPERNICUS data.

For the on-treatment period from week 24 to week 52, it was assumed that patient’s vision neither deteriorated nor improved i.e. it was assumed that vision was maintained and patients remained in the same HS. This was a conservative assumption supported by the 52-week results of the GALILEO trial that showed that 60.2% vs. 58.3% of patients treated with aflibercept gained ≥ 15 letters at week 24 vs. at week 52 respectively (see Section

6.3.4, i.e. that the treatment benefit achieved at week 24 was globally maintained when injections were administered on a PRN basis. Note, these data were not used directly in the model.

The same assumption of maintained vision was used to model vision progression over the period week 24-52 in patients treated with ranibizumab due to absence of comparative data for this period. As for the ranibizumab patients, trial outcomes beyond week 24 are less readily assigned to treatment arm due to the option given to sham patients to cross over to the active treatment arm in the CRUISE trial(35). Note that this differs to the approach taken in the recent HTA submission for ranibizumab in the treatment of CRVO(63), where 6-month transition probabilities derived from the 7-12 month trial data were repeatedly applied up to the end of the active treatment duration of 2 years. We believe that the current approach represents a more conservative use of the available data.

Post-treatment disease progression

A systematic literature review by McIntosh *et al.* 2010(70) demonstrated that while spontaneous resolution of ME secondary to CRVO was reported in several studies, this phenomenon is not common, and was primarily observed in non-ischaemic patients. Given that the modelled patient population includes ischaemic patients, it was assumed in the model that post-treatment vision progression would reflect disease natural history. This assumption was further supported by the findings of the ad-hoc physician survey and is aligned with the approach taken in previously submitted models in this disease area(62;63).

The detail of the methods used to model vision progression in the model for both the on- and post-treatment phases is provided as requested in Section 7.3.1 below.

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.

The key features of the model used to conduct the base-case analysis are summarised in Table 52 below:

Table 52. Key features of base-case analysis

Factor	Chosen values	Justification	Reference
Time horizon	30	A lifetime horizon was used to quantify the full impact of costs and outcomes for the different treatments. The time horizon chosen reflects the chronic nature of CRVO and is therefore in line with the NICE reference case	NICE Methods of Technology Appraisal 2013
Cycle length	4 weeks	This is in line with the frequency at which patients were administered aflibercept in the COPERNICUS and GALILEO protocols for the period 0-24 weeks and in line with draft SmPC	GALILEO and COPERNICUS(5;6)
Half-cycle correction	Not applied	Unnecessary when using a short cycle length	Not applicable
Were health effects measured in QALYs; if not, what was used?	QALYs	NICE reference case	NICE Methods of Technology Appraisal 2013
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	NICE Methods of Technology Appraisal 2013
Perspective (NHS/PSS)	NHS/PSS Perspective	NICE reference case	NICE Methods of Technology Appraisal 2013
NHS: National Health Service; NICE: National Institute for Health and Care Excellence; PSS: personal social services; QALYs: quality-adjusted life years; SmPC: Summary of Product Characteristics.			

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?

The economic analysis includes the treatments outlined below, as previously discussed in Section 2.7, for the treatment of adults with MO secondary to CRVO:

- The intervention is 2mg aflibercept solution for injection:
- The comparator is 0.5mg ranibizumab solution for injection:

Both treatments have been incorporated into the economic evaluation based on the data reported in their pivotal clinical trials and in line with their current UK marketing authorisations: ranibizumab is licensed for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (branch RVO or central RVO) and aflibercept for the treatment of MO secondary to CRVO.

The dosing frequency used in the model is in line with that reported in the pivotal clinical trials(5;6;35). Monitoring frequency for both aflibercept and ranibizumab over model time horizon has been estimated based on trial data (base-case) and on a physician survey (scenario analyses) conducted by an independent market research company (see Section 7.5.4. For injection frequency, there are differences between the regimen used in the trials and that specified in the SmPC, although it is uncertain to what extent they will differ in practice. Extended treatment intervals in practice may lead to fewer aflibercept injections than our modeled estimates. For aflibercept, monitoring estimates are conservative as, according to the draft SmPC, they may be less frequent than used in trials. However, for ranibizumab, the monitoring estimates used in the model are less frequent than the mandatory monthly monitoring of visual acuity specified in the SmPC.

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.

The draft summary of products characteristics (SmPC) specifies that, *“the recommended dose for Eylea is 2 mg aflibercept equivalent to 50 microlitres. After the initial injection,*

treatment is given monthly. The interval between two doses should not be shorter than one month. If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended. Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered. If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate. Usually, monitoring should be done at the injection visits. During treatment interval extension through to completion of therapy, the monitoring schedule should be determined by the treating physician based on the individual patient's response and may be more frequent than the schedule of injections."

No treatment continuation rules have been assumed in the model. The SmPCs for both products have similar criteria for discontinuation and it is expected that discontinuation with any anti-VEGF would be the same in practice. Moreover, no treatment discontinuation was modelled in the Novartis RVO submission(63) and this appeared to be accepted.

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 used to model treatment effectiveness over the first 24 weeks were incorporated into the model using:

- For the aflibercept arm: a pooled analyses of results from the GALILEO and COPERNICUS trials;

- For the ranibizumab arm: a network meta-analysis (NMA) of the GALILEO, COPERNICUS and CRUISE results[5].

For the first 24 weeks, efficacy data for the aflibercept arm was incorporated in the model using the results of a pooled analysis of data from the GALILEO and COPERNICUS trials which generated 4-week transition rates across the 24-week active treatment period. The pooled analysis was conducted using observed case data collected at each visit between baseline and week 24 included. In the GALILEO study, some subjects did not have data at baseline and they were therefore not included in the analysis. Confidence intervals were calculated using normal approximation.

Efficacy of ranibizumab for the first 24 weeks was integrated into the model by applying the relative treatment effect of ranibizumab vs. aflibercept to the transition rates generated in the aflibercept arm. The RR of ranibizumab vs. aflibercept was derived from the NMA described in Section 6.3.6 More specifically, the RR [redacted] was obtained by computing a weighted average of the studies' individual estimates of patients gaining at least 15 letters of BCVA from baseline at 6 months using a fixed effects model. The fixed effects model was considered more appropriate for use in the economic model, based on the statistical tests conducted, as described in Section 6.7.

Note that although the NMA was conducted on three efficacy outcomes for ranibizumab vs. aflibercept, more precisely on i) proportion of patients gaining at least 15 letters of BCVA from baseline at 6 months, ii) proportion of patients losing 15 letters of BCVA from baseline at 6 months and iii) mean change of BCVA from baseline to month 6, only the first outcome was used in the economic evaluation. The de novo model is based on 15 letter health states and so the mean BCVA (outcome iii) is not used directly in the model. In addition, the probability matrix contains interrelated probabilities and therefore by applying the RR of improving vision, the risk of deteriorating vision is simultaneously affected. Hence, applying both the RR of improving vision and the RR of worsening vision could have led to overestimating the treatment effect and proportion losing 15 letters (outcome ii) is not applied.

[5] The NMA also included the GENEVA trials to derive outputs for the comparison of aflibercept vs dexamethasone.

For the subsequent 28 weeks, in which patients receive treatment when needed (PRN), it was assumed that patients treated with aflibercept or with ranibizumab maintained the vision gain that was achieved by week 24 and did not continue to improve.

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.

The model distinguishes between the on-treatment and the post-treatment phases. In the base-case analysis, treatment was assumed to continue for one year. Transition probabilities were calculated using trial data according to the following time periods:

- On-treatment 0-24 weeks;
- On-treatment 24-52 weeks;
- Post-treatment.

On-treatment progression

a) Aflibercept arm

During the on-treatment phase, BCVA changes were captured for the SE by the proportion of patients moving between each HS, following transition probabilities derived from trial data, while BCVA in the FE remained constant (according to BCVA distribution at baseline from the pooled trial data).

Baseline

Pooled clinical trial data from the entire (aflibercept and sham) randomised trial population of the GALILEO and COPERNICUS trials were incorporated into the model to define the baseline distribution of the patients across the HS at model start. Baseline distributions were derived for both eyes and patients were assigned to each HS based on their ETDRS score in the SE and FE. Baseline distribution is provided in Table 53 below:

Table 53. Baseline distribution of patients

		Study eye

		≥80	65-79	64-50	49-35	>35
Fellow eye	≥80	[redacted]				
	65-79					
	64-50					
	49-35					
	>35					

0-24 weeks ("routine" treatment)

Following treatment initiation, during week 0 to 24, the probability of patients treated with aflibercept moving across HS was estimated for each 4-week cycle. This probability was derived from pooled GALILEO and COPERNICUS trial results available for 4-week periods. Patients' movement between states was defined according to BCVA in their SE only; BCVA in their FE remained constant over time, reflecting the distribution at baseline from the pooled trial data (see Table 53 above).

Transition probabilities are presented in Table 54 to Table 59 below. Transition probabilities for the SE over a model cycle were calculated by dividing the number of patients moving from HS "x" at the beginning of the cycle to HS "y" at the end of cycle by the total number of subjects in HS "x" at the beginning of the cycle (i.e. total number of patients in HS "x" row). For example, in Table 54, there are 47 subjects in HS "BCVA 65-79" in the aflibercept group at baseline. Among those 47 subjects, 20 shifted to HS "BCVA >=80" at week 4, which represents the transition probability (20/47=[redacted]) of the SE from HS "BCVA 65-79" to HS "BCVA >=80".

Table 54. Transition probabilities at Week 4

N (row)	Baseline	Number of eyes; Probability.(SE)				
	To / From	>=80	65-79	50-64	35-49	<35
0	**>=80**	[redacted]				
47	**65-79**					
81	**50-64**					
40	**35-49**					
33	**<35**					

SE: standard error

Table 55. Transitions and transition probabilities at Week 8

N (row)	Baseline	Number of eyes; Probability.(SE)				
	To / From	>=80	65-79	50-64	35-49	<35
34	>=80					
91	65-79					
54	50-64					
17	35-49					
13	<35					

SE: standard error

Table 56. Transitions and transition probabilities at Week 12

N (row)	Baseline	Number of eyes; Probability.(SE)				
	To / From	>=80	65-79	50-64	35-49	<35
48	>=80					
87	65-79					
42	50-64					
15	35-49					
11	<35					

SE: standard error

Table 57. Transitions and transition probabilities at Week 16

N (row)	Baseline	Number of eyes; Probability.(SE)				
	To / From	>=80	65-79	50-64	35-49	<35
56	>=80					
81	65-79					
45	50-64					
10	35-49					
13	<35					

SE: standard error

Table 58. Transitions and transition probabilities at Week 20

N (row)	Baseline	Number of eyes; Probability.(SE)				
	To / From	>=80	65-79	50-64	35-49	<35
72	>=80	[redacted]				
72	65-79					
40	50-64					
12	35-49					
10	<35					

SE: standard error

Table 59. Transitions and transition probabilities at Week 24

N (row)	Baseline	Number of eyes; Probability.(SE)				
	To / From	>=80	65-79	50-64	35-49	<35
69	>=80	[redacted]				
73	65-79					
39	50-64					
14	35-49					
8	<35					

SE: standard error

As shown in the transition probabilities above, from one cycle to another, patients could:

- stay in the same HS i.e. their vision could remain stable (in the SE, i.e. by extension in the two eyes);
- move from one HS to another reflecting an improvement or a deterioration of their BCVA in the SE.

In the latter case (improvement or deterioration), the magnitude of the change in BCVA was determined by the number of HS by which the patient moved (up to three HS); patients could move to the adjacent HS or to the HS up to three levels higher or lower.

24-52 weeks ("follow-up" treatment period)

During week 24-52, in which patients received treatment when needed (PRN), it was assumed that patients treated with aflibercept maintained the vision gain that was achieved at week 24.This means that for the period of week 24-52, patients remained in the same HS they were in at week 24 . Due to cross-over occurring in the COPERNICUS trial at week 24, pooled transition probabilities from GALILEO and COPERNICUS were not considered appropriate given the lack of common comparator in the trials. Maintenance of vision was considered a conservative approach as we might expect additional BCVA benefits from continued treatment.

b) Ranibizumab arm

0-24 weeks ("routine" treatment)

In each transition matrix for the period 0-24 weeks, the probabilities can be categorized in three groups, depending on whether the patients' SE BCVA improved, remained stable or declined.

For probabilities showing BCVA *improvement*, the RR for improving vision by 15 letters (RR: [redacted]) from the NMA (see Section 6.7 was applied to the aflibercept SE probabilities to derive the probability of improvement in the comparator arm. This RR was applied as a constant to the 0-24 week transition probabilities.

The proportion of patients moving to a *worse* BCVA in the comparator arm was assumed to be the same as in the aflibercept arm, while the proportion of patients *remaining* in the same HS was adjusted to ensure each row of transition probabilities summed up to 1.

For example, in the week 0-4 analysis, for patients with a BCVA of 79-65, the probability of *gaining* 15 letters in the ranibizumab arm was estimated at [redacted], which is equal to the probability of moving from HS "BCVA 79-65" to HS "BCVA ≥80" (i.e.[redacted]) multiplied by the RR (=[redacted]). The likelihood of *losing* vision was assumed to be the same as aflibercept (=[redacted]), and the proportion of patients *staying* in this HS was estimated using the following formula:

1 - (sum of the patients worsening) – (sum of the patients improving) = proportion of patients staying in HS

This amounts to:

[redacted]

Expected ranibizumab transitions were therefore estimated as [redacted] (improved) and [redacted] (maintained) and [redacted] (deteriorated).

24-52 weeks ("follow-up" treatment period)

The same conservative assumption of vision maintenance was considered during week 24-52 for the ranibizumab arm as for the aflibercept arm and it was assumed that patients treated with ranibizumab maintained the vision gain that was achieved at week 24. This was despite aflibercept having a numerical advantage in the NMA outcomes to week 24.

Post-treatment progression

After treatment completion (one year in the base-case analysis), it was assumed that patients' BCVA deteriorated following a natural disease history progression. Post-treatment progression was modelled using data from the Beaver Dam Eye study as reported by Klein *et al.* 1991(68) in line with previous HTA submissions(62;63). According to this publication, it is expected that 7.4% of the patients will experience 2 to 4 lines loss over a period of 20 years. Based on that range, the model assumed that people would lose 3 lines (the midpoint) on average which represents one HS in the model. This progression rate was subsequently converted into a monthly probability for inclusion in the model which was translated into a 0.03% probability of losing 3 lines (15 letters). This probability was assumed to be constant over time and reflects the approach taken in HTA models previously submitted for the treatment of CRVO/RVO(63).

Adverse events

In the base-case analyses, AEs were not included in the economic model. As previously discussed, the VIEW studies for wet AMD showed that the safety profiles between aflibercept and ranibizumab were similar and any differences reflect variation in reporting, differences in trial design or chance. Both treatments are VEGF inhibitors and require intravitreal administration. The draft SmPC for aflibercept discusses systemic effects in the context of anti-VEGF rather than product specific effects. Furthermore, the AE occurrence rates reported were deemed low (see Section 6.8).

The impact of the inclusion of AEs on the model results was explored in a scenario analyses (See Section 7.6.1).

Discontinuation

Discontinuation is not modeled due to a low pooled discontinuation rate, of 6.8% (see Section 6.8 that was deemed not to impact the results of the de novo model. This approach is in line with a previous HTA submission in CRVO/RVO(63), in which the discontinuation rate reported was higher than in the aflibercept trials and which the Appraisal Committee accepted this approach to modeling without discontinuation. It is also assumed that aflibercept and ranibizumab would have similar rates due to their similar mode of VEGF inhibition, mode of administration and subsequent safety profiles.

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.

As described above, transition probabilities for the first 24 weeks were based on patients' transitions in the GALILEO and COPERNICUS trials and varied over time according to the estimated 4-week rates. During the second half of the first year (week 24-52), patients were assumed to stay in the same HS as at week 24, i.e. vision was maintained for the rest of the year. This was considered a conservative assumption given the cross-over design of the COPERNICUS trial (see Section 6.3). The natural disease deterioration in BCVA is integrated from Year 1 onwards in the model as described above.

Age-specific all-cause mortality was obtained from the UK life tables(71) and applied to the model as underlying risk of death to all patients and varied over time according to patient age.

Two separate systematic literature searches (Section 10, Appendix 5) were conducted to identify mortality rates associated with blindness and the vascular nature of RVO in an RVO patient population. A list of publications were identified and further assessed to select

the most suitable study to be used in the economic model. Full details are available upon request.

Regarding mortality associated with vision loss, the economic model utilises an excess mortality hazard ratio (HR) of 1.54 derived from Christ *et al.* 2008(19). This HR was applied in the lowest visual acuity health state (BCVA < 35 letters in both eyes), to reflect increased mortality risk associated with severe vision loss and does not vary over time. This approach is also in line with previous HTA submissions in CRVO/RVO(62;63).

Mortality associated with RVO was not included in the model, due to conflicting results of the studies identified. This approach is in line with previous NICE appraisals in the RVO area(8;20) where the Appraisal Committee accepted there was insufficient and conflicting evidence to conclude on this issue.

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?

The main outcome measure, change in BCVA level from baseline, was directly measured in the trials.

7.3.5 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[6]:

- 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

[6] 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).

Not applicable.

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.

The variables used in the de novo economic model are summarised in Table 60 below:

Table 60. Summary of variables applied in the economic model

Variable	Value	CI (distribution)	Reference to section in submission
Age	64	95%CI: 62.6-54.4 (NA)	Patient characteristics section 6.3
Efficacy parameters			
RR of gaining ≥15 letters, ranibizumab vs. aflibercept	[redacted]	95%CI: [redacted](GAMMA)	NMA section 6.7
Probability of progression (post treatment)	0.0003	± 20% of mean value (BETA)	7.3.1
Mortality rates			
HR of mortality from blindness	1.54	95%CI: 1.28-1.86 (GAMMA)	7.3.1
Mean number of injections (week 0-52)*			
Aflibercept (0-24 weeks)	5.75	± 20% of mean value (N/A)	7.5.1
Aflibercept (24- 52 weeks)	2.55	± 20% of mean value (N/A)	7.5.1
Ranibizumab (0-24 weeks)	5.50	± 20% of mean value (N/A)	7.5.1
Ranibizumab (24- 52 weeks)	3.30	± 20% of mean value (N/A)	7.5.1
Mean number of monitoring visits (week 0-52)*			
Aflibercept (0-24 weeks)	5.75	± 20% of mean value	7.5.1

		(N/A)	
Aflibercept (24- 52 weeks)	3.50	± 20% of mean value (N/A)	7.5.1
Ranibizumab (0-24 weeks)	5.50	± 20% of mean value (N/A)	7.5.1
Ranibizumab (24- 52 weeks)	4.40	± 20% of mean value (N/A)	7.5.1
Utility values			
utility value HS >=80	[redacted]	95%CI: 0.919-0.963 (BETA)	7.4.3
utility value HS 79-65	[redacted]	95%CI: 0.859-0.917 (BETA)	7.4.3
utility value HS 64-50	[redacted]	95%CI: 0.853-0.905 (BETA)	7.4.3
utility value HS 49-35	[redacted]	95%CI: 0.819-0.913 (BETA)	7.4.3
utility value HS <35	[redacted]	95%CI: 0.806-0.906 (BETA)	7.4.3
CI, confidence interval *Note that treatment and monitoring frequency were varied individually for 0-24 weeks and 24-52 weeks for both aflibercept and ranibizumab; total number of injections in year 1 (week 0-52) is 8.3 for aflibercept and 8.8 for ranibizumab and total number of monitoring visits in year 1 (week 0-52) are 10 for both treatments.			

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.

Clinical outcomes were not extrapolated beyond the one-year trial results. Since treatment duration is limited to one year in the base-case analysis, cost outcomes were not projected beyond this period.

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

Table 61 below lists all the assumptions made in the economic model.

Table 61. List of assumptions in the economic model

Parameter	Assumptions	Justification
Time horizon and treatment duration	Treatment duration is 1 year (in base-case); model time horizon is patient's lifetime (30 years).	Given that comparative efficacy data are only available for 24 weeks, extrapolating efficacy beyond 1 year, would introduce more uncertainty in the model. Alternative treatment duration periods are explored in scenario analyses. Lifetime horizon is selected to reflect the chronic nature of the condition.
Baseline distribution	Distribution as in COPERNICUS and GALILEO trials	Baseline health state distribution of the population should reflect the one from the key trials used in the model.
Health states	Defined by 15 letters increments.	A 15-letter improvement was used as a primary endpoint in several trials in ophthalmology, including COPERNICUS and GALILEO.
Treatment efficacy	Patients are assumed to maintain vision after week 24 until end of treatment.	Transition probabilities were derived from pooled COPERNICUS and GALILEO trials. Given the cross-over design of COPERNICUS, comparative data were not available for 24 weeks onwards. This was considered a conservative assumption.
Treated eye	The treated eye, or study eye (SE), is assumed to be the worst-seeing eye (WSE). The fellow eye (FE) BCVA at baseline remains constant over time.	The BCVA treatment benefit in terms of HRQL was captured by applying utility values for the WSE given that >90% of patients' SE at baseline was the WSE.
Mortality	Excess mortality for blindness was applied. Mortality associated with RVO was not modelled.	There is evidence that blindness (≤35 ETDRS letters) is associated with a relative risk of mortality of 1.54 compared to the general population. According to the output of the systematic searches on mortality associated with RVO, evidence on mortality related to RVO was however inconclusive (Appendix 0).
Discontinuation	Patients were assumed to stay on treatment during 1 year; discontinuation was not modeled in the economic model.	Discontinuation rates were low in both aflibercept and ranibizumab trials(5;6)
Adverse events	Adverse event rates were not modeled in the base-case.	Safety profiles between aflibercept and ranibizumab are similar, demonstrated in wet AMD studies. Both products are intravitreally administered and anti-VEGF.
Resource use	A "one-stop" approach was taken to cost resource use.	In each cycle, when the frequency of administration and monitoring visits was the same, the visits were assumed to occur

Parameter	Assumptions	Justification
		simultaneously and the cost of an administration visit only was accounted for. The cost of a monitoring visit was only applied for when additional monitoring visits took place.

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.

MO secondary to CRVO is associated with a rapid decline in vision and therefore affects patients' ability to perform everyday tasks, primarily driving and reading. Consequently, loss of vision also negatively impacts patients' professional and social life and is translated into a significant reduction in HRQoL(72). The literature specifically reports that CRVO is associated with a decline in vision-related QoL scores (as measured by the EQ-5D and NEI VFQ-25 scores) and that this reduction in QoL scores reflects patients' level of BCVA(72).

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

While spontaneous resolution of MO was observed in CRVO patients, untreated MO secondary to CRVO tends to persist and therefore a decline in patients BVCA will be observed(70).In the most severe cases, patients may even experience blindness. Delayed

treatment, and consequently persistent MO, is associated with irreversible vision(73). Vision loss is accompanied by a reduction in HRQL (see Section 7.4.1).

A specificity of CRVO compared with other ophthalmic disease is the rapidity of vision loss. In many cases, visual acuity will decrease suddenly, sometimes overnight, causing anxiety and distress that will affect patients' quality of life. For patients that cannot be treated, additional anxiety and depression is likely to be caused by the prospect of potentially not recovering vision. These relationships were reported in several studies measuring HRQoL in terms of VFQ score in CRVO patients and compared to the general populations(72;74;75).

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.

In the GALILEO trial, HRQL data was collected using the EQ-5D and the NEI VFQ-25 questionnaires. In the COPERNICUS trial, HRQoL data was collected using the NEI VFQ-25 questionnaire only. More detail on HRQL data collected in the trials is available in Section 6.3.

Since the generic EQ-5D measure is the preferred measure in the NICE reference case, the EQ-5D data from GALILEO was used in base-case analysis and the data from COPERNICUS were not used.

Measurements of the EQ-5D in the GALILEO trial were made at baseline, 24, weeks, 52 weeks and 76 weeks (or early termination). The HRQL associated with the BCVA category

of the SE was measured at each of these time points. Because model HS are defined by BCVA category, it is straightforward to derive HS specific utilities from the GALILEO trial data.

Utility values were obtained from the HRQoL measurements by applying the UK population tariff(76); the method for valuing HRQoL was that suggested by the reference case. Details of this are given in Section 7.4.4.

The utility values used in the base-case analysis was based on the European trial population of both treatment arms from the GALILEO clinical trial using an average across all four available time points (see Section 7.4.9 for the methods of the pooled analysis and the values used in the economic model). A pooled data set was chosen in order to obtain the largest possible sample size for each visual acuity group due to the high level of variability that is often observed with HRQL data. This approach is consistent with the NICE reference case.

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.

EQ-5D scores collected throughout the GALILEO clinical trials were mapped to a utility index using an established algorithm.

The EQ-5D health status utility index was derived using the scoring rule developed by Dolan(76) by use of time-trade-off (TTO) responses from a representative sample of 2,997 adults from England, Scotland and Wales. Valuation of the EQ-5D using the UK time-trade-off value set is preferred by the NICE reference case. This tariff reflects the UK population and is recommended by the EuroQol group. Utility values for the 243 health states defined by the EQ-5D classification were calculated via applying an algorithm which used the estimated coefficients in Table 62. The index is calculated by deducting the appropriate weights from 1, the value for full health.

Table 62. Estimated coefficients used to compute the utility weighted EQ-5D values for each health state value

EuroQol dimension	Level 1	Level 2	Level 3
Mobility	0	0.069	0.314
Self-care	0	0.104	0.214
Usual activity	0	0.036	0.094
Pain/ discomfort	0	0.123	0.386
Anxiety/ depression	0	0.071	0.236
Constant for any dysfunctional state of the respective level	-	N2 = 0.081	N3 = 0.269

.

The use of this mapping algorithm is consistent with the NICE reference case.

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 literature review was conducted to identify HRQL studies including health utility elicitation/validation studies, and reports of economic evaluations using utility measures gathered during the studies, published in the area of CRVO/RVO/AMD/DMO in the English language between January the 1st, 2001 and March the 11th, 2013. The purpose of this search was more specifically to identify studies providing:

- utility values that can be used to derive an alternate set of inputs to be used as a scenario analysis and put in perspective the trial-based utility values used in the base-case analysis,

- disutility values for the AEs included in the model scenario analysis (AEs were not included in the base-case).

The scope of the systematic literature review was also widened from the targeted CRVO indication to the other diseases of the retina as exploratory searches demonstrated that no HRQL had been published for CRVO alone. The searches were conducted on Embase, Medline (including Medline (R) in process), EconLit and NHS EED using the OVID platform. For each database, a search was developed using following the structure:

disease terms (CRVO, RVO, AMD or DMO) were combined with quality of life terms and with limits (time horizon and English language). The relevance of references identified by the search across the four databases was assessed against eligibility criteria that were defined following enhanced PICO (Patients, Intervention, Comparator and Outcomes) criteria. Detail about the search strings developed can be found in Appendix 10, Section 10.12.5 During the study selection process, all references captured by the combined search were double reviewed based on their abstracts and titles against the eligibility criteria presented in Table 63 below:

Table 63. Eligibility criteria for HRQL search

Quality of life	Inclusion	Exclusion
Patient population	Adult patients with CRVO, BRVO, RVO, AMD or DMO	Patients with pathologies other than CRVO, BRVO, RVO, AMD or DMO
Interventions	-	-
Comparators	-	-
Outcome measures	• Utility values (visual acuity, treatment adverse events, CRVO complications) stratified by visual acuity or disease severity	Studies that reported utility values not stratified by visual acuity or disease severity of CRVO, BRVO, RVO, AMD or DMO
Study design	• Reports of utility elicitation exercises **OR** • Reports of utility validation exercises **OR** • Reports of economic evaluations using utility measures gathered during the studies.	• Abstracts only*
Restrictions	• Language: English • Published in past 11 years	• Non-English studies • Studies published beyond 11 past years

AMD: age-related macular degeneration; BRVO: branch retinal vein occlusion; DMO: diabetic macular oedema; N/A: not applicable; RVO: retinal vein occlusion.
* applies at the full-text review stage only.

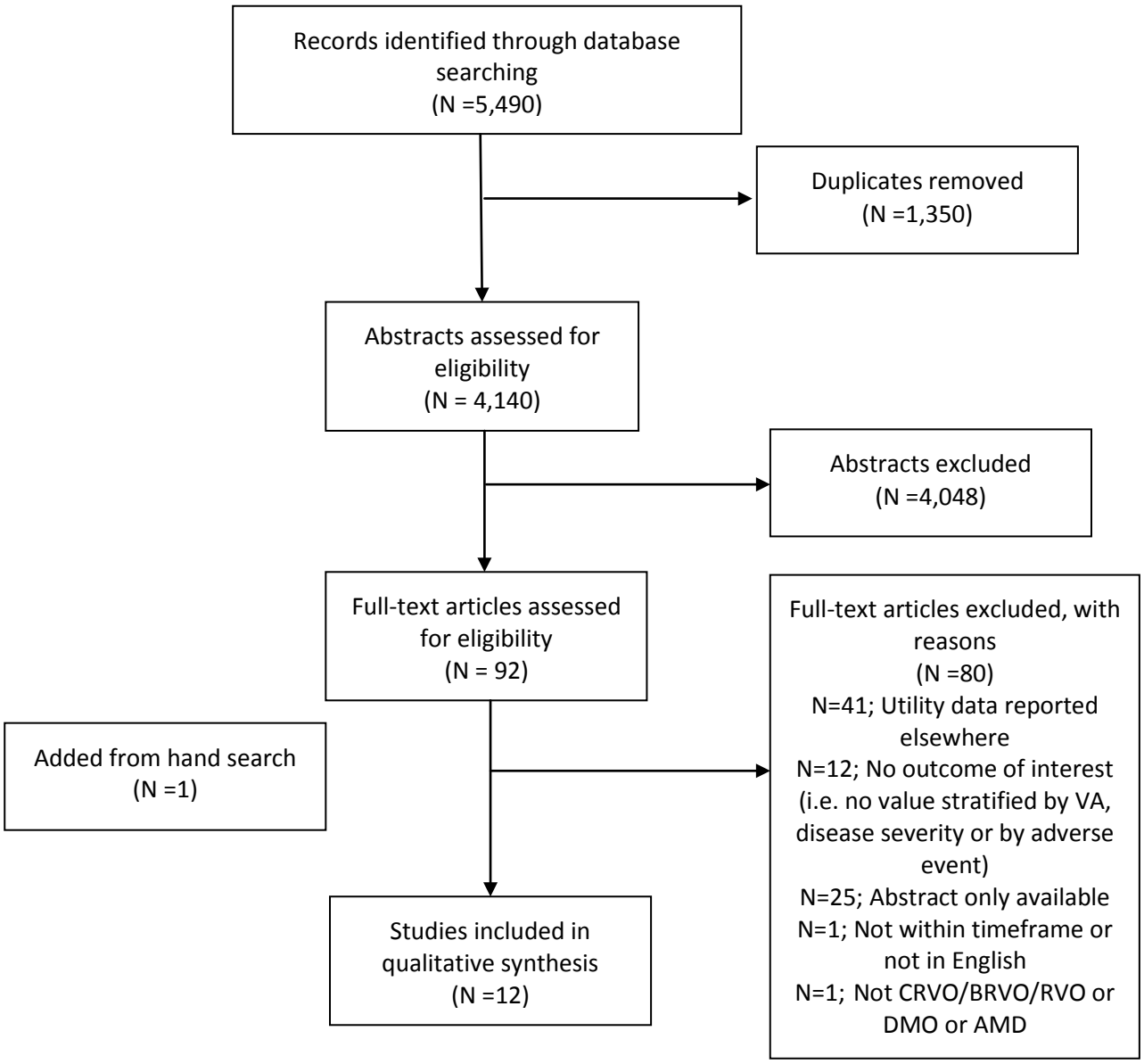
All papers included at the end of this stage were retained for full text review. Papers excluded by the reviewers at this abstract review stage were disregarded. All publications where there was disagreement about inclusion at this stage were resolved either through “reconciliation” or through “arbitration” by a third independent reviewer. The “majority view” determined inclusion or exclusion. Included publications were retained for full text review; excluded publications were disregarded. The full texts of the publications retained after the abstracts review were judged once more by the two reviewers against the eligibility criteria presented. The approach to resolve any disagreement was the same as for the abstracts

review process. All papers included after the full text review were retained for data extraction.

Overall, the HRQL search yielded a total of 5,490 hits, of which 1,350 were duplicates, leaving 4,140 records to be reviewed against the eligibility criteria. A total of 4,048 abstracts were excluded, i.e. 92 studies were selected for full-text review. Of these, 79 were excluded and 12 retained for data extraction. One study was added for data extraction from a hand search.

The process of study selection and the final results of the search are illustrated below in Figure 20 using the PRISMA Flow diagram:

Figure 1. Study flow diagram for systematic review of HRQL studies



This systematic literature review was complemented by a search of abstracts presented during conferences organised by the ISPOR. The search was limited to conference proceedings presented at the ISPOR North American and European conferences held over the past two years (2011-2012). All searches were performed using disease area (CRVO).

The abstracts captured for each congress were then reviewed using the eligibility criteria developed for the systematic literature review (see Table 63 above). Three relevant

abstracts were identified. Details of the congress search strategies and the studies selected can be found in Appendix 10 in Section 10.10.5.

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.

At the stage of full text review, 12 studies were retained for data extraction. As a result of the economic evaluations reference list review, one additional publication was found to be relevant and was included from a hand search (Sharma *et al.* 2002(77)). Consequently, data was extracted from a total of 13 publications. These are presented in alphabetical order in the tables below. A summary of each study is provided in Section 10.12.7, Appendix 10.12.

None of the extracted studies reported disutility estimates associated with the adverse events of interest, or utility estimates associated with each particular intervention.

In line with the CRD guidelines, no formal quality assessment was performed. However each summary identifies any study limitations where possible.

Table 64. Aspinall et al. 2007

Reference	Aspinall *et al.* 2007 (78)
Population	AMD patients with mean age 77.8 (SD±6.7) years; the proportion of males to females in the sample was 0.42.
Information on recruitment	Patients were recruited from the Low Vision and Macular Clinics of the Princess Alexandra Eye Pavilion in Edinburgh, UK.
Interventions and comparators	-
Sample size	122 patients
Response rates	115 patients completed the questionnaire
Description of health states	Patients were separated into 5 logarithm of the minimum angle of resolution (logMAR) ranges: • Group 1: <0.1; • Group 2: 2: 0.12-0.40; • Group 3: 0.42-0.70; • Group 4: 0.72-1.30; • Group 5: >1.30
Adverse events	-
Method of elicitation	The TTO task required respondents to assume that they have either 30, 20 or 10 years to live. The following two-part question was used to generate the percentage of the remaining years of expected life that a respondent was prepared to trade-off for a hypothesised cure to normal vision: 1. How many additional years do you expect to live? Choose from one of three estimates: 30, 20 or 10 years. 2. How many of these years would you be prepared to give up if you could receive a new technology that would restore your sight to a normal level? TTO variable is the percentage of remaining expected life years (P) that the respondent would trade for a cure. The relationship of this variable to utility is: utility= (100–P)/100. A high percentage of years that a person is willing to trade, therefore, represent a low utility associated with a respondent's current state of health. Conjoint analysis also performed.
Method of valuation	NEI-VFQ-25
Mapping	No
Results (mean)	TTO • Group 1: <0.1=0.93 (95% CI, 0.86 - 0.99) • Group 2: 0.12-0.40=0.86 (95% CI, 0.78 - 0.93) • Group 3: 0.42-0.70=0.74 (95% CI, 0.67 - 0.83) • Group 4: 0.72-1.30=0.68 (95% CI, 0.57 - 0.79) • Group 5: >1.30=0.76 (95% CI, 0.37 - 1.15) • All patients=0.805 (95% CI, 0.56-1.05)

Table 65. Au Eong et al. 2012

Reference	Au Eong et al. 2012(79)
Population	AMD patients with mean age of all subjects 68.1 (SD± 9.4) years, range 48-92 years. 207 (61.2%) were male; 303 patients (89.6%) were Chinese.
Information on recruitment	Patients were recruited from outpatient ophthalmology clinics in two Singapore tertiary general hospitals (Alexandra Hospital and Tan Tock Seng Hospital) from April 2006 to December 2007. Eligible patients had dry or wet AMD in one or both eyes, were ≥40 years of age, and could give informed consent. Patients with significant ocular co morbidities in either eye (e.g., significant cataract, uncorrected refractive error, glaucoma, diabetic retinopathy, or myopic macular degeneration), and patients with hearing, psychiatric, or cognitive diseases were excluded.
Interventions and	-

Reference	Au Eong et al. 2012(79)
comparators	
Sample size	Of the 366 eligible patients, 28 patients (8 glaucoma, 12 significant cataracts, 3 diabetic macular oedema, 3 proliferative diabetic retinopathy, 1 dementia, and 1 hearing difficulty) were excluded.
Response rates	338 patients (92.6% participation rate) were included. EQ-5D and SG questions yielded 100% response rates, 44 patients (13.0%) declined to indicate a risk value for the TTO question.
Description of health states	Clinical AMD severity was evaluated by a 5-level categorisation system: • Group 1: Dry/normal (n=35); • Group 2: Dry/dry (n=178); • Group 3: Wet/normal (n=31); • Group 4: Wet/dry (n=64); • Group 5: Wet/wet (n=30)
Adverse events	-
Method of elicitation	A trained interviewer administered the 15-min questionnaire to eligible patients before the outpatient consultation to reduce consultation bias. Where necessary, the questionnaire was verbally translated by the same interviewer into the patient's preferred spoken language, that is, English, Mandarin, or Malay. **TTO:** Assessment of TTO utility used the anchors of 'death' and 'perfect binocular vision'. Participants were asked the number of years they expected to live, and the number of years of their expected remaining life they were willing to trade off for a treatment giving perfect binocular vision. The TTO utility was calculated from the equation: TTO=1.0-(time traded in years/estimated number of years of remaining life). **SG:** SG utilities were assessed in two ways: 1) Policy scale SG (SG(death)) was elicited by asking patients what risk of immediate death they would accept with a hypothetical technology before refusing treatment in return for a state of perfect health. 2) The modified scale SG (SG (blindness)) was assessed by asking patients the risk of immediate binocular blindness they would be able to accept before refusing treatment, in return for a state of perfect vision in both eyes.
Method of valuation	EQ-5D
Mapping	No
Results	**TTO:** • Group 1: Dry/normal: 0.88(SD± 0.19) • Group 2: Dry/dry: 0.82(SD±0.82) • Group 3: Wet/normal:0.77(SD±0.19) • Group 4: Wet/dry:0.78(SD±0.26) • Group 5: Wet/wet:0.78(SD±0.26) **SG (death):** • Group 1: Dry/normal (n=35):0.97(SD±0.12) • Group 2: Dry/dry (n=178):0.88(SD±0.23) • Group 3: Wet/normal (n=31):0.74(SD±0.31) • Group 4: Wet/dry (n=64):0.80(SD±0.33) • Group 5: Wet/wet (n=30):0.86(SD±0.29) **SG (blindness):** • Group 1: Dry/normal (n=35):0.96(SD±0.12) • Group 2: Dry/dry (n=178):0.92(SD±0.12) • Group 3: Wet/normal (n=31):0.87(SD±0.20) • Group 4: Wet/dry (n=64):0.85(SD±0.27) • Group 5: Wet/wet (n=30):0.94(SD±0.12) **EQ-5D:** • Group 1: Dry/normal (n=35):0.87(SD±0.12) • Group 2: Dry/dry (n=178):0.91(SD±0.11) • Group 3: Wet/normal (n=31):0.90(SD±0.11) • Group 4: Wet/dry (n=64):0.85(SD±0.18) • Group 5: Wet/wet (n=30):0.83(SD±0.19)

Table 66. Brown et al. 2002a

Reference	Brown et al. 2002a (59)
Population	Patients with diabetic retinopathy and dry or wet AMD. The mean age of those with diabetic retinopathy was 62.2 (SD±11.8) and of those with AMD 73.2 (SD±9.8) years. In the diabetic retinopathy group there were 187 women and 146 men and in the AMD group there were 163 women and 83 men. 302 white and 31 non-white comprised the diabetic retinopathy group and 245 white patients and 1 non-white patients the AMD group. The mean time of visual acuity loss to the level of visual acuity at the time of examination was 2.5 (SD± 4.0) years in diabetic retinopathy and 2.1 (SD±2.2) years in the AMD group.
Information on recruitment	Patients were recruited from 2 ophthalmologic practices. Five hundred ninety (95%) came from the vitreoretinal practice and 27 (5%) from the comprehensive ophthalmology practice. Patients were considered eligible for the study if they had a diagnosis of diabetic retinopathy or AMD. Only patients who had visual acuity loss occurring primarily secondary to diabetic retinopathy or AMD were included. The lower threshold criteria for the presence of AMD included macular drusen in association with a central macular retinal pigmentepithelial disturbance. Both dry and exudative forms of AMD were included. Only patients who had visual acuity loss were included. Exclusion criteria included the presence of Alzheimer disease or other forms of dementia that were judged to negate the possibility of giving rational answers, visual acuity loss occurring secondary to multiple causes and the inability or unwillingness to answer study questions once they were posed.
Interventions and comparators	-
Sample size	333 patients with diabetic retinopathy and 246 patients with AMD: Among the 617 total patients, 38 (6.1%) were unable or unwilling to completely answer the study questions. 21 (5.9%) of the 354 patients with diabetes were therefore excluded and 17 (6.4%) of the 263 with patients AMD were excluded. The remaining 579 patients included 333 (57%) with diabetic retinopathy and 246 (43%) with AMD.
Response rates	Study questions were administered to a total of 617 patients: 354 with diabetic retinopathy and 263 with AMD.
Description of health states	Patients were stratified in 4 subcategories based on the visual acuity in the better seeing eye (Snellen). • Group 1: 20/20-20/25 (n=60); • Group 2: 20/30-20/40 (n=65); • Group 3: 20/50-20/100 (n=57); • Group 4:≤20/200 (n=65)
Adverse events	-
Method of elicitation	Initially, each person was asked how long he or she expected to live. Patients with abnormal visual acuity (≤20/30 in at least one eye), were asked how much of the remaining time of life he or she would be willing to trade in return for a treatment that would return permanent good vision to each eye. In patients with good bilateral visual acuity (20/20-20/25), the question was modified to ask how much of the remaining time of life he or she would trade in return for a guarantee of retaining good vision in each eye for the remaining years. The TTO utility values was calculated by the formula: 1.0-(number of years traded for good vision)/ (number of years of expected remaining life).
Method of valuation	-
Mapping	No
Results (mean)	TTO (AMD patients): • Group 1:20/20-20/25 (n=60)=0.74 (SD± 0.21); 95% CI: 0.65-0.77 • Group 2:20/30-2040 (n=65)=0.84 (SD± 0.21); 95% CI:0.65-0.77 • Group 3:20/50-20/100 (n=57)=0.71 (SD± 0.22); 95% CI:0.65-0.77 • Group 4: ≤20/200 (n=65)=0.59 (SD± 0.22); 95% CI:0.53-0.65 • All patients (n=246): 0.74 (SD± 0.23); 95% CI:0.71-0.77

Table 67. Czoski-Murray et al. 2009

Reference	Czoski-Murray et al. 2009 (80)
Population	Participants were from the general population with mean age 32 (SD±12.5), being 7 years younger than that for the UK population, with the oldest being 68 years. There were 25 participants (23%) with a long-standing illness. The majority of participants had excellent vision, as best-corrected VA was measured (i.e., corrected with own glasses or contact lenses at baseline).Overall, participants were in good health, with a mean TTO value at baseline of 0.960 (SD± 0.109, range 0.30 to 1) and a mean HUI-3 utility at baseline of 0.934 (SD±0.105, range 0.33 to 1).
Information on recruitment	To recruit a representative sample of the general population of 100 subjects, a random sample of 2000 addresses was selected across six postcode areas around Sheffield. Recruits were sent a letter detailing the study, information sheet, and prequalification questionnaire. After insufficient response (42 subjects were recruited from the random sample), a further 66 subjects were recruited by word of mouth from colleagues and acquaintances of study participants. Recruits were excluded if they had known ocular pathology, high myopia (>5.00 diopters spherical equivalent), recent increase in floaters, or any of a number of high-risk medical complaints.
Interventions and comparators	-
Sample size	108 participants: Of a random sample of 2,000 people, 77 responded and 42 completed the interview, and a further 66 were recruited by word of mouth.
Response rates	104 (4 did not proceed to wearing all three sets of the custom-made contact lenses)
Description of health states	The participants of the general public were wearing contact lenses designed to imitate 3 logMAR scores: • LENS 1 (legal blindness): logMAR = 0.6 (20/80) • LENS 2 (reading limit): logMAR = 1.0 (20/200) • LENS 3 (untreated AMD): logMAR = 1.4 (20/500)
Adverse events	-
Method of elicitation	TTO was used to assess participant's valuation of their own state (before the lens instillation) and the three AMD states simulated by the contact lenses.
Method of valuation	HUI-3, selected items from the VF-14 (at baseline only)
Mapping	No
Results (mean)	TTO values for AMD patients simulated states (VA results presented using LogMAR scale): LENS 1 (reading limit): logMAR = 0.6 (20/80): • Group 1: VA logMAR ≤0.30 (≥20/40)(n=18)= 0.778 (95% CI: 0.706 - 0.851) • Group 2: VA logMAR 0.31 to 0.60 (20/40 to 20/80) (n=40)=0.731 (95% CI: 0.662-0.801) • Group 3: VA logMAR 0.61 to 1.30 (20/80 - 20/400) (n=46)=0.653 (95% CI: 0.563-0.743) • Group 4: VA logMAR ≥1.31 (≤20/400)(n=0) Total (n=104)=0.705 (95% CI: 0.654-0.755) LENS 2 (legal blindness): logMAR = 1.0 (20/200): • Group 1: VA logMAR ≤0.30 (≥20/40)(n=23)= 0.649 (95% CI: 0.531 -0.767) • Group 2: VA logMAR 0.31 to 0.60 (20/40 to 20/80) (n=40)=0.649 (95% CI: 0.561-0.736) • Group 3: VA logMAR 0.61 to 1.30 (20/80 - 20/400) (n=41)=0.486 (95% CI: 0.389 - 0.583) • Group 4: VA logMAR ≥1.31 (≤20/400)(n=0) Total (n=104)=0.585 (95% CI: 0.283-0.433) LENS 3 (untreated AMD): logMAR = 1.4 (20/500):

Reference	Czoski-Murray et al. 2009 (80)
	• Group 1: VA logMAR ≤0.30 (≥20/40)(n=0) • Group 2: VA logMAR 0.31 to 0.60 (20/40 to 20/80)(n=9)=0.603 (95% CI: 0.295 - 0.912) • Group 3: VA logMAR 0.61 to 1.30 (20/80 - 20/400)(n=38)=0.366 (95% CI: 0.246 - 0.912) • Group 4: VA logMAR ≥1.31 (≤20/400)(n=56)=0.314 (95% CI: 0.217- 0.410) Total (n=103)=0.358 (95% CI: 0.283-0.433) Overall: • Group 1: VA logMAR ≤0.30 (≥20/40)(n=41)=0.706 (95% CI: 0.606 - 0.805) • Group 2: VA logMAR 0.31 to 0.60 (20/40 to 20/80)(n=89)=0.681(95% CI: 0.623 - 0.740) • Group 3: VA logMAR 0.61 to 1.30 (20/80 - 20/400)(n=125)=0.511 (95% CI: 0.449 - 0.573) • Group 4: VA logMAR ≥1.31 (≤20/400)(n=56)= 0.314(95% CI: 0.217 - 0.410) Total (n=311)=0.550 (95% CI: 0.511-0.589)

Table 68. Espallargues et al. 2005

Reference	Espallargues et al. 2005 (81)
Population	AMD patient population with mean age 79.6 (SD±7.5) (range: 43-96). The majority (83%) had a long-standing illness or disability unrelated to their vision, and it limited their activities in 71.6% of the cases. On average, AMD was diagnosed 3.7 years ago, and one fifth had dry AMD. Less than 10% had received photodynamic therapy. The mean logMAR VA in the better- and worse-seeing eyes was 1.0 (0.24 in decimal scale) and 1.68 (0.08 decimal), respectively. Mean contrast sensitivity was also low at 0.7 log units, most of the patients being below 1.3.
Information on recruitment	This was a cross-sectional study of patients with unilateral or bilateral AMD from a large Sheffield Teaching Hospital (UK) who attended either the Ophthalmic Clinic or the Low Vision Training Service. All patients diagnosed with AMD were eligible, provided they were able and willing to respond to the interview protocol. Both atrophic (dry), characterised by geographic atrophy, and exudative (wet), characterised by choroidal neovascularisation, AMD were considered. Patients known to have other ocular co morbidities (e.g., glaucoma, uveitis, cataract, amblyopia, corneal scarring, vitreous hemorrhage, optic neuropathy, or other eye conditions that could cause visual impairment) were excluded.
Interventions and comparators	-
Sample size	452 patients who met the criteria were invited to participate; 242 eligible patients declined to participate
Response rates	209 patients completed the visual tests and interviews
Description of health states	Better seeing eye VA (distant logMAR): • Group 1: VA logMAR ≤0.3 • Group 2: VA logMAR 0.31 - 0.60 • Group 3: VA logMAR 0.61 - 1.3 • Group 4: VA logMAR 1.3 - 2.00 • Group 5: VA logMAR >2.00
Adverse events	-
Method of elicitation	TTO, EQ-VAS
Method of valuation	EQ-5D, HUI-3, SF-36, VF-14
Mapping	No
Results (mean)	TTO (n=204):

Reference	Espallargues et al. 2005 (81)
	• Group 1: VA logMAR ≤0.3=0.73 (SD±0.3) • Group 2: VA logMAR 0.31 - 0.60=0.67 (SD±0.31) • Group 3: VA logMAR 0.61 - 1.3=0.64 (SD±0.3) • Group 4: VA logMAR 1.3 - 2.00=0.6 (SD±0.33) • Group 5: VA logMAR >2.00=0.47 (SD±0.31) EQ-VAS (n=209): • Group 1: VA logMAR ≤0.3=71.1 (SD±18.2) • Group 2: VA logMAR 0.31 - 0.60=62.9 (SD±16.2) • Group 3: VA logMAR 0.61 - 1.3=66.4 (SD±18.6) • Group 4: VA logMAR 1.3 - 2.00=62.8 (SD±18.6) • Group 5: VA logMAR >2.00=59.7 (SD±15.5) EQ-5D (n=207): • Group 1: VA logMAR ≤0.3=0.75 (SD±0.27) • Group 2: VA logMAR 0.31 - 0.60=0.7 (SD±0.2) • Group 3: VA logMAR 0.61 - 1.3=0.75 (SD±0.2) • Group 4: VA logMAR 1.3 - 2.00=0.71 (SD±0.21) • Group 5: VA logMAR >2.00=0.63 (SD±0.22) HUI-3 (n=206): • Group 1: VA logMAR ≤0.3=0.5 (SD±0.35) • Group 2: VA logMAR 0.31 - 0.60=0.38 (SD±0.25) • Group 3: VA logMAR 0.61 - 1.3=0.36 (SD±0.25) • Group 4: VA logMAR 1.3 - 2.00=0.27 (SD±0.24) • Group 5: VA logMAR >2.00=0.1 (SD±0.18)

Table 69. Lee 2008 et al. 2008

Reference	Lee et al. 2008(82)
Population	434 patients were included in the study: 58 with diabetic retinopathy, 99 with glaucoma, 44 with AMD (14 with mild, 9 with moderate and 21 with severe AMD), 124 with cataract; 109 with refractive error. All AMD patients were white with mean age 75.4 (SD±6.2) years, 50% of them were men. The mean better eye visual acuity (logMAR) for the AMD patients was 0.40 (SD±0.41), mild AMD patients had mean BEVA 0.09 (SD±0.05), moderate AMD patients had mean BEVA 0.40 (SD±0.15), and severe AMD patients mean BEVA 1.11 (SD±0.16)
Information on recruitment	Participants were recruited from the practices of 18 ophthalmologists affiliated with Washington University School of Medicine using a stratified sampling strategy seeking those with only one of the conditions of interest and a range of disease severity under National Eye Institute Visual Function Questionnaire–25 criteria. 69% of participants came from a single suburban practice, with most in the refractive error or cataract group. Participants were required to have an eye examination on the day they enrolled, be 18 years old, and have sufficient literacy in English to understand the utility assessment instruments. Subjects ≥ 65 years old were excluded if they failed any mental acuity questions on a short form derived from the NEI-VFQ-25.
Interventions and comparators	-
Sample size	From the 434 included patients 44 were AMD patients
Response rates	44 AMD patients
Description of health states	• Group 1: Mild/moderate AMD (≥20/100 better-eye visual acuity) (n=23) • Group 2: Severe AMD(≤20/200 better-eye visual acuity) (n=21)
Adverse events	-
Method of elicitation	SG (computerized, U-Titer-II, large font, or read by interviewer) In the preference assessment, the participant was offered a low-risk SG: “Would

Reference	Lee et al. 2008(82)
	you be willing to undergo a procedure that, if successful, would guarantee you perfect health for the rest of your life if there were no chance that you might immediately die during the procedure?" This was followed by a high-risk scenario (e.g., a 100% chance of death), followed by a series of percentages bisecting the remaining range and asking if the subject would accept the treatment. The computer algorithm reiterated this process until the participants indicated that they had reached a level of success at which they were indifferent between the alternatives. This percentage risk of the negative outcome they were willing to accept was the SG disutility.
Method of valuation	-
Mapping	No
Results (mean)	SG (scale: death=0, perfect health=1): • Group 1: Mild/moderate AMD (n=23): 0.89 (SD±0.23) • Group 2: Severe AMD (n=21): 0.76 (SD±0.30) • All AMD patients (n=44): 0.83 (SD±0.27) SG for perfect vision health state (scale: unilateral blindness=0, perfect vision=1): • Group 1: Mild/moderate AMD (n=23): 0.86 (SD±0.24) • Group 2: Severe AMD (n=21): 0.39 (SD±0.37) • All AMD patients (n=44): 0.63 (SD±0.38) SG for unilateral blindness health state (scale: death=0, perfect vision=1): • Group 1: Mild/moderate AMD (n=23): 0.82 (SD±0.28) • Group 2: Severe AMD (n=21): 0.67 (SD±0.33) • All AMD patients (n=44): 0.75 (SD±0.31) SG for perfect vision health state (scale: death=0, perfect vision=1): • Group 1: Mild/moderate AMD (n=23): 0.24 (SD±0.34) • Group 2: Severe AMD (n=21): 0.32 (SD±0.39) • All AMD patients (n=44): 0.28 (SD±0.36)

Table 70. Lotery et al. 2007

Reference	Lotery et al. 2007(83)
Population	• Patient population NV subfoveal AMD with mean age 79.6 (SD± 6.43) years; 62.7% female • General population (non-AMD controls) with mean age 65.3 years; 49.5% female Significant differences in age (p=0.0001) and race (p=0.0087) existed between the two groups. The presence of co-morbid disease was lower in the patient than in the control group (65.3% vs. 84.6%, respectively; p=0.0038). A higher percentage of NV-AMD patients had vision-related co-morbidities (p=0.0029), while a higher percentage of controls had other co-morbidities including anxiety disorder (p=0.0085), headache (p=0.0393) and asthma (p=0.021).
Information on recruitment	• Patients with bilateral subfoveal NV-AMD were recruited from five retina specialist offices/ clinics, and non-AMD controls were recruited from five general practitioner offices/clinics in the UK. Bilateral subfoveal NV-AMD was required as QOL and functional status impairment have been shown to be correlated with VA in the better seeing eye. • Controls had best-corrected Snellen VA of ≥20/40 in the better eye and were free from serious ocular pathologies. Exclusion criteria included participation in investigational drug studies within 30 days prior to the survey.
Interventions and	-

Reference	Lotery et al. 2007(83)
comparators	
Sample size	• 75 patients • 91 controls
Response rates	• 75 patients • 91 controls
Description of health states	• Group 1: Normal (> 20/40) • Group 2: Mild (20/40 to 20/80) • Group 3: Moderate (20/80 to 20/200) • Group 4: Severe (20/200 to 20/400) • Group 5: Near blind (< 20/400)
Adverse events	-
Method of elicitation	-
Method of valuation	EQ-5D, NEI-VFQ-25, HADS
Mapping	No
Results (mean adjusted for age, race and co-morbidities)	EQ-5D: • Group 1: Normal (> 20/40)= 0.52 • Group 2: Mild (20/40 to 20/80)= 0.66 • Group 3: Moderate (20/80 to 20/200)=0.72 • Group 4: Severe (20/200 to 20/400)=0.79 • Group 5: Near blind (< 20/400)=0.70 • All NV AMD patients (n=75)= 0.67 • Controls (n=91)= 0.77 NEI-VFQ-25: • Group 1: Normal (> 20/40)= 66 • Group 2: Mild (20/40 to 20/80)= 57 • Group 3: Moderate (20/80 to 20/200)=61 • Group 4: Severe (20/200 to 20/400)=50 • Group 5: Near blind (< 20/400)=51 • All NV AMD patients (n=75)= 53 • Controls (n=91)=91

Table 71. Sahel et al. 2007

Reference	Sahel et al. 2007 (84)
Population	AMD patients with mean age was 77 (SD±8.0, range: 51 to 96 years) years; 59.6% were female. The average time elapsing since diagnosis of AMD was 2.3 (SD±3.4) years. The mean best-eye visual acuity (BEVA) at inclusion was 0.49 logMAR; mean worst-eye visual acuity (WEVA) was 1.0 logMAR unit. No significant differences were found between the clinical and sociodemographic data of the 3 countries.
Information on recruitment	Patients were recruited from specialised retinal disease centres in France, Germany and Italy in the period March 15 to July 15, 2004. Patients 50 years or older were included if they visited the centre because of AMD during the enrollment period (for any reason), had a clinical record at the center that contained all of the critical information required by the study, were able to answer and complete the questionnaires personally or with help from a caregiver, and gave their written consent.
Interventions and comparators	-
Sample size	360 patients: from France, 120 (33.3%); from Germany, 126 (35.0%); and from Italy, 114 (31.7%)
Response rates	-

Reference	Sahel et al. 2007 (84)
Description of health states	Patients were classified into 4 groups of severity based on their visual acuity (measured in logarithm of the minimum angle of resolution (log-MAR) units and converted into decimals): • Group 1: BEVA≥20/40, WEVA≥20/200 (n=98); • Group 2: BEVA≥20/40, WEVA<20/200 (n=46); • Group 3: BEVA<20/40, WEVA≥20/200 (n=124); • Group 4: BEVA<20/40, WEVA<20/200 (n=92)
Adverse events	-
Method of elicitation	-
Method of valuation	Patients were asked to complete the self-administered QoL and utility scales (NEI-VFQ-25, HUI-3, MacDQoL), in the official translations for each country.
Mapping	No
Results (mean)	NEI-VFQ-25 France: • Group 1:BEVA≥20/40, WEVA≥20/200=68.5 • Group 2:BEVA≥20/40, WEVA<20/200=70.2 • Group 3:BEVA<20/40, WEVA≥20/200=48.2 • Group 4:BEVA<20/40, WEVA<20/200=37.3 Germany: • Group 1:BEVA≥20/40, WEVA≥20/200=72.4 • Group 2:BEVA≥20/40, WEVA<20/200=68.5 • Group 3:BEVA<20/40, WEVA≥20/200=50.0 • Group 4:BEVA<20/40, WEVA<20/200=44.5 Italy: • Group 1:BEVA≥20/40, WEVA≥20/200=60.6 • Group 2:BEVA≥20/40, WEVA<20/200=56.0 • Group 3:BEVA<20/40, WEVA≥20/200=39.3 • Group 4:BEVA<20/40, WEVA<20/200=35.0 All countries: • Group 1:BEVA≥20/40, WEVA≥20/200=67.0 • Group 2:BEVA≥20/40, WEVA<20/200=66.2 • Group 3:BEVA<20/40, WEVA≥20/200=44.9 • Group 4:BEVA<20/40, WEVA<20/200=40.7 HUI-3 France: • Group 1:BEVA≥20/40, WEVA≥20/200=0.64 • Group 2:BEVA≥20/40, WEVA<20/200=0.59 • Group 3:BEVA<20/40, WEVA≥20/200=0.44 • Group 4:BEVA<20/40, WEVA<20/200=0.35 Germany: • Group 1:BEVA≥20/40, WEVA≥20/200=0.64 • Group 2:BEVA≥20/40, WEVA<20/200=0.58 • Group 3:BEVA<20/40, WEVA≥20/200=0.37 • Group 4:BEVA<20/40, WEVA<20/200=0.38 Italy: • Group 1:BEVA≥20/40, WEVA≥20/200=0.58 • Group 2:BEVA≥20/40, WEVA<20/200=0.64 • Group 3:BEVA<20/40, WEVA≥20/200=0.37 • Group 4:BEVA<20/40, WEVA<20/200=0.47 All countries: • Group 1:BEVA≥20/40, WEVA≥20/200=0.62 • Group 2:BEVA≥20/40, WEVA<20/200=0.60 • Group 3:BEVA<20/40, WEVA≥20/200=0.40 • Group 4:BEVA<20/40, WEVA<20/200=0.39NEI-VFQ

Table 72. Shah et al. 2004

Reference	Shah et al. 2004 (85)
Population	Patient population with AMD (n=48; 35.3%) and diabetic retinopathy (n=88; 64.7%). The mean age of the study population was 67.5 while the median age was 69 (range 25-92) years.
Information on recruitment	Patients seen from November 2001 through January 2003 with previously scheduled appointments in the retina service of a US university-based practice were recruited for the study. Patients with BCVA ≥20/40 in at least one eye were included in the study. Patients were excluded if any other ocular disease was a greater contributor to vision loss than AMD or diabetic retinopathy had a different ophthalmic problem in the second eye, the cause of visual loss was doubtful, or had Alzheimer's disease of other forms of dementia.
Interventions and comparators	-
Sample size	A total of 150 patients were screened from which 14 (9.3%) refused to answer the questions; the number of patients enrolled in the study was 136.
Response rates	136 patients
Description of health states	Data from study participants were divided into 3 groups according to the visual acuity (Snellen) in the better eye: • Group 1: VA 20/20 to 20/40 (n=71); • Group 2: VA 20/50 to 20/100 (n=43); • Group 3: VA 20/200 to NLP (n=22)
Adverse events	-
Method of elicitation	TTO: Participants were asked how long they expected to live, and then how much of that time they would trade-off for a treatment that ensures permanent perfect vision (20/20) bilaterally. Utility was calculated on the basis of the following formula: Utility = 1.0-(time traded/time of remaining life)
Method of valuation	-
Mapping	No
Results (mean)	TTO: • Group 1: VA 20/20 to 20/40 (n=71): 0.88 (SD±0.185); 95% CI: 0.87 - 1.0 • Group 2: VA 20/50 to 20/100 (n=43):0.9 (SD± 0.14); 95% CI:0.853 -1.0 • Group 3: VA 20/200 to NLP (n=22): 0.76 (SD± 0.226); 95% CI:0.73 - 0.87

Table 73. Sharma et al. 2002

Reference	Sharma et al. 2002(77)
Population	170 (33.1%) patients suffered from AMD, 105 (32.5%) from diabetic retinopathy, and 111 (34.4%) from other ocular diseases including cataract, glaucoma, retinal detachment, non-diabetic oedema, amblyopia, vascular obstruction, and corneal disease. The mean age of the sample was 67.5 years(SD± 11.9) years, 63.5% were female, and over 96% were white. Over 60% of the sample had visual loss in the affected eye of 6/60 or worse. The median Snellen acuity in the unaffected eye was 6/12; whereas, the median acuity in the affected eye was 6/90. Patients suffered from their ocular condition for an average of 2.9 years±5.03 years.
Information on recruitment	Patients were eligible for the study if they had 20/40 vision or worse in at least one eye and were deemed competent to answer the required questions. Patients were excluded for communication barriers, developmental disability, and psychiatric illness.
Interventions and comparators	-
Sample size	323 patients
Response rates	All eligible patients (n=323) completed the entire survey.

Reference	Sharma et al. 2002(77)
Description of health states	• Group 1: 6/7.5 or better (n=75); • Group 2: 6/9 to 6/15 (n=136); • Group 3: 6/18 to 6/30 (n=58); • Group 4: 6/60 to 6/120 (n=37); • Group 5: CF to NLP (n=17)
Adverse events	-
Method of elicitation	A standardised interview was performed by an experienced researcher trained in utility valuation. **TTO:** TTO visual utility values were determined by responses to two hypothetical questions. Firstly, patients were asked to estimate their remaining life expectancy. Next, patients were told to consider a hypothetical situation where a technology existed that could permanently return their vision to normal, would always work, but would decrease their survival. Patients were then asked to quantify the maximum number of years out of their expected life expectancy, if any, that they would be willing to trade in return for normal vision. TTO utility was estimated on the basis of the following formula: utility value = (No of years expected life - No of years trade-off)/No of years expected life **SG:** For SG utility, patients were asked to consider a scenario where a new technology for their eye problem exists. When this technology works, they would receive perfect vision in both eyes for the rest of their lives. However, when the procedure fails, they would not survive. Patients were asked to estimate the largest percentage risk of death they would be willing to accept to be relieved of their ocular disease. The SRG utility is this percentage.
Method of valuation	VF-14
Mapping	No
Results (mean)	TTO: • Group 1: 6/7.5 or better (n=75): 0.908 (95% CI:0.875-0.942) • Group 2: 6/9 to 6/15 (n=136): 0.797 (95% CI:0.762-0.833) • Group 3: 6/18 to 6/30 (n=58):0.708 (95% CI:0.653-0.764) • Group 4: 6/60 to 6/120 (n=37):0.621 (95% CI:0.555-0.687) • Group 5: CF to NLP (n=17):0.473 (95% CI:0.323-0.624) • All patients: 0.77 (SD±0.228); 95% CI:0.745-0.795 SG: • Group 1: 6/7.5 or better (n=75): 0.948 (95% CI:0.924-0.972) • Group 2: 6/9 to 6/15 (n=136): 0.897 (95% CI:0.869-0.925) • Group 3: 6/18 to 6/30 (n=58): 0.769 (95% CI:0.696-0.842) • Group 4: 6/60 to 6/120 (n=37): 0.742 (95% CI:0.672-0.812) • Group 5: CF to NLP (n=17): 0.603 (95% CI:0.451-0.754) • All patients: 0.853 (SD± 0.21); 95% CI: 0.829-0.876

Table 74. Soubrane et al. 2007

Reference	Soubrane et al. 2007(86)
Population	Patients with bilateral subfoveal NV-AMD and controls. The patient group was older than the control group (mean age, 78.1 vs. 63.8 years (p=0.001)); had higher percentages of women, white subjects, and subjects living alone; and had a worse mean VA in the better-seeing eye. A higher percentage of patients had vision-related co morbidities (glaucoma and cataract), whereas a higher percentage of controls had other co morbidities, including anxiety disorder and arthritis and rheumatism.
Information on recruitment	Patients were recruited from 31 retina specialist offices and clinics and non-AMD controls were recruited from 30 general practitioner offices and clinics in Canada,

Reference	Soubrane et al. 2007(86)
	France, Germany, Spain, and the United Kingdom. Site study staff identified potential subjects during routine office visits. Data were collected from April 1 through October 28, 2005.
Interventions and comparators	-
Sample size	401 NV-AMD patients and 471 controls
Response rates	-
Description of health states	• Group 1: Normal VA (VA>20/40); • Group 2: Mild VA (VA 20/40 to >20/80); • Group 3: Moderate VA (20/80 to >20/200); • Group 4: Severe VA (20/200 to >20/400); • Group 5: Near blind VA (≤20/400)
Adverse events	-
Method of elicitation	-
Method of valuation	NEI-VFQ-25, EQ-5D, HADS anxiety and HADS depression
Mapping	No
Results (mean)	NEI-VFQ-25: • Group 1: Normal VA (VA>20/40): 62.4 • Group 2: Mild VA (VA 20/40 to >20/80): 57.7 • Group 3: Moderate VA (20/80 to >20/200): 50.0 • Group 4: Severe VA (20/200 to >20/400): 47.7 • Group 5: Near blind VA (≤20/400): 39.4 • Controls: 89.1(95% CI, 86.7-91.6) EQ-5D: • Group 1: Normal VA (VA>20/40): 0.69 • Group 2: Mild VA (VA 20/40 to >20/80): 0.75 • Group 3: Moderate VA (20/80 to >20/200): 0.72 • Group 4: Severe VA (20/200 to >20/400): 0.72 • Group 5: Near blind VA (≤20/400): 0.69 • Controls: 0.75 (95% CI, 0.71-0.79)NEI-VFQ

Table 75. Stein et al. 2003a

Reference	Stein et al. 2003a(87)
Population	• Patients with AMD: mean age 75.1 (SD±7.92) years; from which 35.3% were male • General public: mean age 44.3 (SD±13.32) years; from which 57.9% were male • Care providers: mean age 29 (SD±7.32) years; from which 42.3% were male
Information on recruitment	The clinician group included third and fourth year medical students, house officers, and attending physicians from US medical centres. Ophthalmic clinicians were excluded. Patients with AMD were recruited from two of the authors' (GCB and MMB) clinical practices. Members of the community asked to assume they had each severity of AMD were recruited on a random basis from various public places—such as parks and busy city streets in downtown Philadelphia. Enrolment criteria included an age of 18 years or older and an ability to complete a self-administered questionnaire. Data on respondents from the general public who were employed in the healthcare industry but who did not directly treat patients with ARMD were eliminated from the analysis to prevent potential bias. Other reasons for exclusion were admission by a clinician that he/she has ARMD; failure to report current age or oldest age to which one expects to live (which precludes calculation of a utility score); or expression of the age to which one expects to live to be as "forever" or as a non-specific value, such as "80+ years."
Interventions and	-

Reference	Stein et al. 2003a(87)
comparators	
Sample size	339 participants (15 were excluded from the analysis because of failure to state current age, age to which respondent expected to live, or the number of years traded)
Response rates	324 participants
Description of health states	Patients were stratified into 3 groups on the basis of BCVA and asked to value their own health state: • Group 1: Mild AMD (BCVA 20/30) • Group 2: Moderate AMD (BCVA 20/40 to 20/100) • Group 3: Severe AMD (BCVA ≥20/200) Participants from the general public and care providers valued the three AMD health states - mild, moderate and severe.
Adverse events	-
Method of elicitation	TTO (two part question): (1) How many additional years do you expect to live? (2) For the following question, assume that you are a patient suffering from (mild, moderate or severe age-related macular degeneration). Suppose researchers developed a new technology that could permanently cure you of this condition. The technology always works but decreases your survival. Essentially, the treatment theoretically enhances your quality of life, but decreases the length of time you live. What is the maximum number of years, if any, that you would be willing to give up if you could receive this technology and be cured forever of this condition?
Method of valuation	-
Mapping	No
Results (mean)	**AMD - Patients (valuing their own severity only) valuation:** • Group 1: Mild AMD (BCVA 20/30) (n=34)= 0.832 (95% CI: 0.762 - 0.901) • Group 2: Moderate AMD (BCVA 20/40 to 20/100)(n=47)=0.732 (95% CI: 0.669 - 0.795 • Group 3: Severe AMD (BCVA ≥20/200)(n=37)=0.566 (95% CI: 0.487 - 0.645) **AMD - General public (valuing all AMD health states - mild, moderate and severe) valuation** • Group 1: Mild AMD (BCVA 20/30) (n=142)= 0.96 (95% CI: 0.950 - 0.970) • Group 2: Moderate AMD (BCVA 20/40 to 20/100)(n=142)=0.918 (95% CI: 0.902 - 0.934) • Group 3: Severe AMD (BCVA ≥20/200)(n=142)=0.857 (95% CI: 0.834 - 0.879) **AMD - Care providers (valuing all AMD health states - mild, moderate and severe)** • Group 1: Mild AMD (BCVA 20/30) (n=62)= 0.929 (95% CI: 0.904 - 0.954) • Group 2: Moderate AMD (BCVA 20/40 to 20/100)(n=62)=0.877(95% CI: 0.846 - 0.909) • Group 3: Severe AMD (BCVA ≥20/200)(n=62)=0.821(95% CI: 0.785 - 0.857) **All participants :** • Group 1: Mild AMD (BCVA 20/30) (n=324)= 0.932 (95% CI: 0.919 - 0.947) • Group 2: Moderate AMD (BCVA 20/40 to 20/100)(n=324)=0.873 (95% CI: 0.854 - 0.892) • Group 3: Severe AMD (BCVA ≥20/200)(n=324)=0.806 (95% CI: 0.783 - 0.829**)**

Table 76. Yanagi et al. 2011

Reference	Yanagi et al. 2011(88)
Population	Japanese patients with bilateral exudative AMD with mean age of 75.9 (range: 59–91 years) and sex distribution male: female=85:15.

Reference	Yanagi et al. 2011(88)
Information on recruitment	The participants were consecutive patients who visited the outpatient macular clinic of the University of Tokyo Hospital in July and August 2009. Only those with a definite diagnosis of bilateral exudative AMD, based on fluorescein angiography and indocyanine green angiography were included. Patients attending the clinic for other diseases such as idiopathic choroidal neovascularization (CNV) and myopic CNV were not included. All eligible patients were asked if they were willing to answer questions related to their quality of life, and all provided written informed consent before participating in the study.
Interventions and comparators	-
Sample size	A total of 50 patients were eligible for the study of which 2 were unable to answer the questions.
Response rates	48 patients answered to questions
Description of health states	• Group 1: BCVA 0.01–0.15 in the better seeing-eye (n=11) • Group 2: BCVA 0.2–0.3 in the better seeing-eye (n=15) • Group 3: BCVA 0.4–0.6 in the better seeing-eye (n=11) • Group 4: BCVA 0.7–1.0 in the better seeing-eye (n=11)
Adverse events	-
Method of elicitation	**TTO:** For the TTO method, patients were asked to choose between two alternatives: 10 years in their current health or x years with perfect vision (where x ≤ 10), both followed by immediate death. The value of x was varied until the respondents were indifferent between the alternatives. The utility value was then calculated as x/10. **SG:** For the SG method, patients were asked to select one of two choices: to remain in their current health state for the rest of their lives or to gain perfect vision by choosing a new treatment with a risk of instant death. The interviewer varied the risk of death until the respondents were indifferent between the alternatives. To avoid report bias, the authors used a linear regression model in which obtained values were regressed against age, sex, BCVA categories (0.01–0.15, 0.2–0.3, 0.4–0.6, and 0.7–1.0) in the better eye, order of measurement (TTO or SG), and interviewer's dummy codes.
Method of valuation	-
Mapping	No
Results (mean)	TTO: • Group 1: BCVA 0.01–0.15 in the better seeing-eye: TTO: 0.534 (95% CI: 0.400–0.667) • Group 2:BCVA 0.2–0.3 in the better seeing-eye: TTO: 0.574 (95% CI: 0.487–0.660) • Group 3: BCVA 0.4–0.6 in the better seeing-eye: TTO: 0.613 (95% CI: 0.523–0.703) • Group 4:BCVA 0.7–1.0 in the better seeing-eye: TTO: 0.653 (95% CI: 0.513–0.793) • All patients (n=48): TTO: 0.598 (95% CI: 0.518–0.677) The TTO method utility values correlated with the BCVA in the better-seeing eye. SG: • Group 1: BCVA 0.01–0.15 in the better seeing-eye: SG: 0.68 (95% CI: 0.535–0.838) • Group 2:BCVA 0.2–0.3 in the better seeing-eye: SG: 0.695 (95% CI: 0.595–0.794) • Group 3: BCVA 0.4–0.6 in the better seeing-eye: SG: 0.703 (95% CI: 0.601–0.804) • Group 4:BCVA 0.7–1.0 in the better seeing-eye: SG: 0.711 (95% CI: 0.555–0.867) • All patients (n=48): SG: 0.695 (95% CI: 0.609–0.781) The utility values obtained by the SG method were not significantly correlated with BCVA in the better seeing eye.

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.

In the base-case analysis, trial-based utility values were applied.

The HRQoL systematic literature review is a useful tool to put the trial-based values into perspective. The systematic literature review identified a range of studies that varied in study design and study populations. Among these studies, three were retained to potentially inform an economic model: Czoski-Murray *et al.* 2009(80), Brown *et al.* 2002a(59) and Stein et al. 2003a(87). All studies employed the TTO procedure, a method preferred by NICE for quality of life elicitation. All reported utility values that are consistent with *a priori* expectations of the declining effect a chronic disease has on patients' quality of life. Results were also comparable and supported by relatively narrow 95 percent confidence intervals, suggesting the point estimates are robust. Czoski-Murray *et al.* 2009, also known as the "Brazier study", was deemed the most relevant study to contextualise the trial-based utility values from the GALILEO study, as it is the only study to be UK-based. Furthermore, it has previously been recommended for use by an evidence review group of a HTA in RVO(65).

The Czoski-Murray study was therefore used to derive the utility values used in the de novo model scenario analysis. The utility values presented in Czoski-Murray *et al.* 2009 could not be used directly in the model as these were not reported for the BCVA ranges used to define the model HS. Instead, reported constant and coefficient values obtained from an OLS regression of the relationship between the BCVA score (in BSE) and the collected TTO values (without adjustment for age) were used to generate HS-specific utility values for the de novo model. The methods used to derive these values from the publication are described in detail in Section 7.4.9 and the approach followed to incorporate these values into the model is presented in Section 7.6.1.

Adverse events

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

In the base-case analysis, AEs were not modelled as anti-VEGFs have a similar safety profile (see Section 7.3.2). This is consistent with the disparate evidence base and the approach taken in a previous HTA submission in CRVO/RVO(62). The following adverse

events were modelled in the scenario analysis: IOP, cataract and retinal tear. Blindness, which is treated as a HS rather than an event, does not receive a disutility. Utility decrements were applied for each patient suffering from any of these adverse events in the model. Disutilities for adverse events are allocated during the month (i.e. 4 weeks) of the event.

The disutilities used in the model are summarised in Table 77 below:

Table 77. Disutilities of adverse events

Adverse event	Disutility	Source	Duration (months)	Source
Cataracts	-0.142	Brown 2007(89)	For 1 cycle (4 weeks)	Assumption
IOP	-0.0003	Vaahtoranten-Lehtonen 2007(90)	For 1 cycle (4 weeks)	Assumption
Retinal tear	-0.270	Brown 2007(89)	For 1 cycle (4 weeks)	Assumption

The HRQL systematic literature review did not identify studies that provided values to populate the disutilities associated with AEs.

The disutility associated with retinal tear was taken from Brown *et al.* 2007(89). This study, an economic evaluation in neovascular macular degeneration was captured by the HRQL systematic literature review but was excluded at the abstracts review stage on the basis that the primary source for the utility values could not be identified. However, since this paper was used to derive a disutility for cataracts in a previous HTA submission in CRVO/RVO(8), it was deemed an appropriate source for this input in the de novo model. Note the value used for retinal detachment in the publication was used for retinal tear in the model, as it was the nearest estimate available. The disutility may be overestimated to the detriment of aflibercept, since retinal tears were only observed in the aflibercept trials. For the disutility associated with IOP, the model used the value reported in an economic evaluation in glaucoma by Vaahtoranta-Lehtonen *et al.* 2007(90) in line with a previous HTA submission in CRVO/RVO(63). This study assumed that the utility value for ‘drug-treated ocular hypertension, no glaucoma’ would be the same as that for ‘drug-treated glaucoma’.

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.

Utility values used in the de novo economic model (base-case analysis) were derived from the pooled (aflibercept and sham arm) analysis of the European population of the GALILEO EQ-5D data.

EQ-5D scores collected at each time point in the GALILEO clinical trial were mapped to a utility index using an established algorithm (see Section 7.4.4). The utility values derived from these scores were then analysed based on the WSE of the patients, to reflect that patients enrolled in the aflibercept CRVO trials were predominantly tested in their WSE. A total of 121 patients were included in the analysis, with 440 observations across all time points and across the two arms. Each observation was assigned to one of the five HS BCVA ranges (>=80; 79-65; 64-50; 49-35; or <35) based on the BCVA achieved in the patient's WSE, irrespective of whether the WSE was the SE or the FE. For each BCVA range, the average utility value was then estimated across these observations. This set of trial-based utility values is referred to as the "WSE utilities" dataset in the rest of this submission.

WSE utilities derived from the EQ-5D trial data for each of the 5 BCVA ranges used in the model are presented in Table 78 below:

Table 78. Summary of quality-of-life utility values for base-case analysis

Health states	Utility values (se)
≥80	[redacted]
65-79	
64-50	
49-35	
>35	

se: standard error

These WSE utility values were attributed to the 25 model HS based on BCVA in the WSE, i.e. the utility value was assigned based on the lowest BCVA score achieved in either eye.

For example, patients in HS “BCVA ≥80;79-65” were assigned a utility value of [redacted], given that the lowest BCVA achieved in either eye was BCVA “79-65”, and that the utility value associated with this BVCA range was [redacted]. Similarly, patients in HS “BCVA 79-65; 79-65” or in HS “BCVA 79-65; ≥80” were also assigned a utility of [redacted]. It is acknowledged that these CRVO-specific values are high, especially given the average utility value representative of the UK population. This may be explained by the small size of the sample used to derive these values (n=121), the variety of countries the patients in GALILEO were enrolled in and potential insensitivity of the EQ-5D for eye diseases.

The approach followed to assign the WSE utility values to the model HS is summarised in Table 79 below:

Table 79. Model HS specific WSE utility values derived from trial data

Study Eye, Fellow Eye	**>=80 (1)**	**79-65 (2)**	**64-50 (3)**	**49-35 (4)**	**<35 (5)**
>=80 (1)	[redacted]				
79-65 (2)					
64-50 (3)					
49-35 (4)					
<35 (5)					

In a scenario analysis (see Section 7.6.1 for methods) the impact of using literature-based quality of life values for the BSE derived from Czoski-Murray *et al.* 2009 (80) was tested. This study is a study in age-related macular degeneration (AMD) using the TTO value elicitation method. Three AMD vision states were produced by simulating the visual impairment associated with AMD through the use of custom-made contact lenses. Patients were randomly recruited from the healthy UK population. The TTO was anchored at full health and immediate death. After the insertion of each lens, participants undertook five activities of daily living and completed five VF-14 items, HUI3, and TTO of the new simulated HS.

The TTO-based results presented in Czoski-Murray et al. 2009 were deemed the most relevant results from all papers identified by the HRQoL systematic literature review to contextualise the trial-based quality of life measures (see Section 7.4.5).

Reported constant and coefficient values obtained from an OLS regression of the relationship between best corrected visual acuity (in the best-seeing eye) and the collected TTO values for simulated HS without adjustment for age were used to generate HS specific utility values for the cost-effectiveness model. Firstly, the utility value for each BCVA category was calculated as the constant term plus the coefficient (Table 80) multiplied by the visual acuity score. In order to estimate HS relevant inputs, the visual acuity score recorded in the GALILEO clinical trial (as measured by ETDRS letter scores) was transformed into the logarithm minimal angle of resolution (LogMAR)(91) by using the ETDRS midpoint score for each BCVA category, and used as an input in the utility calculation.

Table 80: Output from a regression of the TTO valuation score for simulated health states on BCVA in the best-seeing eye, as reported by Czoski-Murray et al. 2009(80)

	TTO values for simulated states Regression coefficient (SE)
Constant	0.828 (0.039)
Coefficient (BCVA best-seeing eye)	-0.359 (0.045)

The utility values for the BCVA categories derived from Czoski-Murray *et al*. 2009(80) are presented in Table 81 below:

Table 81. Summary of quality-of-life utility values for scenario analysis

Health states	**Utility values**
≥80	0.828
65-79	0.735
64-50	0.627
49-35	0.519
>35	0.469

Note: standard errors were not provided as these values were not sampled in a probabilistic sensitivity analysis

The utility values were attributed to the 25 model HS based BCVA in the BSE, irrespective of whether the BSE was the SE or the FE, i.e. utility value was assigned based on the highest BCVA score achieved in either eye (see Table 82 below – note numbers in

parentheses represents the HS or BCVA range). Patients in HS “BCVA ≥80;65-79” were assigned a utility value of 0.828, given that the highest BCVA achieved in either eye was BCVA “≥80”, and the utility values associated with this BVCA range was 0.828. Following this approach patients in HS “≥80; ≥80” or in HS “BCVA 65-79; ≥80” would be assigned the same utility of 0.828. .

This approach was consistent with Czoski-Murray *et al.* 2009; in which TTO valuations were collected based on BCVA in the BSE.

Table 82: Model HS specific utility values derived from Czoski-Murray et al. 2009(80)

Study Eye, Fellow Eye	**>=80 (1)**	**79-65 (2)**	**64-50 (3)**	**49-35 (4)**	**<35 (5)**
>=80 (1)	0.828 (1, 1)	0.828 (2.1)	0.828 (3,1)	0.828 (4,1)	0.828 (5,1)
79-65 (2)	0.828 (1,2)	0.735 (2,2)	0.735 (3,2)	0.735 (4,2)	0.735 (5,2)
64-50 (3)	0.828 (1, 3)	0.735 (2,3)	0.627 (3,3)	0.627 (4,3)	0.627 (5,3)
49-35 (4)	0.828 (1,4)	0.735 (2,4)	0.627 (3,4)	0.519 (4,4)	0.519 (5,4)
<35 (5)	0.828 (1,5)	0.735 (2,5)	0.627(3,5)	0.519 (4,5)	0.469 (5,5)

7.4.10 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[7]:

- 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

[7] 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).

Not applicable.

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?

The HS are based on the BCVA category in both eyes. Patients are assumed to have a constant HRQoL during their time in a health state, as such HRQoL is only affected by changes in study eye BCVA and not the duration spent in a particular health state.

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

In the base-case analyses, AEs were not included in the economic model (see Section 7.3.2). As previously discussed, the safety profiles between aflibercept and ranibizumab are assumed to be similar given their anti-VEGF mode of action, intravitreal administration, the results of the VIEW studies and the wording of the SmPC in relation to systemic effects relating to anti-VEGF. Any differences would reflect differences in trial design or chance.

The impact of the inclusion of AEs on the model results was explored in a scenario analysis (see Section 7.6.1). The rationale for inclusion of each AE is determined by the relative prevalence and severity of AEs reported in the clinical trials of aflibercept and ranibizumab and as per previous submissions in the area of CRVO(62;63). In the scenario analysis the three following AEs are considered: IOP, cataract removal and retinal tear. The disutilities associated with these AEs and used in the scenario analysis are presented in Section 7.4.8.

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?

The baseline HRQL was defined according to the baseline distribution of the model cohort across all the model HS (see Section 7.3.2)

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

HRQL was assumed to be constant over time; no adjustment was made for the ageing of the population. HRQL was only dependent on the model HS a patient is in, and changes in HRQL were driven by changes in visual acuity, not ageing. This assumption seemed reasonable as it allowed all patients to have the same HRQL gain from improved vision, regardless of age.

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.

CRVO management broadly encompasses administration of pharmacological treatment and monitoring visits. Management of CRVO patients with anti-VEGF drugs is conducted by ophthalmologists expert in the administration of intravitreal medications. All costs associated with CRVO management and their sources are presented in Section 7.5.5) (Intervention and comparator) 7.5.6 (health-state) and 7.5.7 (adverse events). Cost sources included NHS reference costs, British National Formulary, and published literature.

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

NHS reference costs (2011-12) were preferred to PbR in the base-case and the scenario analyses, as they provide relevant costs and volume that reflect the pattern of care delivered in the NHS. NHS reference Costs represent the cost burden to the NHS rather than internal reimbursement between NHS organisations and allow for a greater level of granularity to be assessed and are more up-to-date.

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 de novo model presented in Section 7.2 included the following main resource use parameters:

- one-year (base-case) as well as two- and four-year (scenario analyses) frequency of injection and drug monitoring,

- the percentage of patients experiencing IOP that receive treatment for IOP, and the percentage of patients suffering from IOP that receive treatment with IOP-lowering drugs as opposed to IOP procedures (scenario analyses),

- the percentage of patients experiencing cataract and retina tear that receive treatment for these side-effects (scenario analyses),

- Key tests used at initial and follow-up visits.

A systematic literature review was conducted to identify sources to populate these resource use model inputs. This systematic literature review was conducted alongside the EE systematic literature review (see methods in Section 7.1.1 and Appendix 10, Section 10.10).

Two publications (Fekrat *et al.* 2010(57) and Augustin *et al.* 2012(58) were identified, none of which was specific to the UK. These studies are summarised in Table 83 below.

Frekrat *et al.* 2010(57) presents the results of a resource use and costing analysis based on a retrospective cohort study of Medicare beneficiaries involving BRVO (n=10 682) and

CRVO (n=6236) patients, as well and control patients with hypertension (n=49 524) and glaucoma patients (n=49 569). Patients were at least 65 years old (CRVO: 78 years old). The study collected data over a five-year period (from 2001 through 2006) and estimated 1- year and 3-year costs for patients in each group by summing Medicare reimbursement amounts as recorded for each inpatient, outpatient, home health, skilled nursing, hospice, durable medical equipment, and professional service claims. CRVO was associated with 22% higher 1-year costs and 15% higher 3-year costs compared with hypertension and 24% higher 1-year costs and 16% higher 3-year costs compared with glaucoma. Use of intravitreal injections increased from less than 1% of patients overall to greater than 13% for BRVO and 16% for CRVO. In CRVO patients, overall direct medical costs (inpatient, outpatients and physician/carrier) were estimated at $11,587 over one year and $31,585 over three years.

Augustin *et al.* 2012(58) used a retrospective chart review to determine resource utilisation and calculate health care costs associated with RVO over a period of one year in France, Italy, and Germany. Patients included in the analyses were over 18 years of age and had a diagnosis of CRVO (n=119) or BRVO (n=109). Country-specific unit costs were assigned to each resource from the perspective of the health care payer. Total costs were higher for patients with CRVO in all countries. Most costs in Italy and France were attributable to outpatient treatment. In Germany, hospitalisation accounted for the largest proportion of costs (80%), although more patients used outpatient services.

Table 83. Summary of resource use studies indentified

Reference	**Fekrat et al. 2010(57)**	**Augustin et al. 2012(58)**
Type of analysis	Costing analysis based on retrospective cohort study	Costing analysis
Study population	CRVO, BRVO, Hypertension, Glaucoma	CRVO, BRVO
Country/setting	US	France, Germany, Italy
Interventions	IV injection, Laser photocoagulation, PRP, Vitrectomy	Not specified
Patient age	BRVO: 76 years, CRVO: 78 years, Hypertension: 77 years, Glaucoma: 79 years	**France:** BRVO: 64.4 (±10.7). CRVO: 61.0 (14.7) **Germany:** BRVO: 69.3 (±11.8). CRVO: 70.6 (12.4) **Italy:** BRVO: 66.6 (±11.8). 61.7 (15.5)
Source of cost data (currency year)	Medicare claims data (2006); USD$	Retrospective chart review; EUR€
Results		

Reference	Fekrat et al. 2010(57)	Augustin et al. 2012(58)
Direct medical costs (1 year)	*Overall direct medical costs over one year: $11,587* • Inpatient direct medical costs over one year: $4,742; • Outpatient direct medical costs over one year: $1,085; • Physician/carrier direct medical costs over one year: $3,585; *Overall direct medical costs over three years: $31,585* • Inpatient direct medical costs over three years: $13,433; • Outpatient direct medical costs over three years: $2,744; • Physician/carrier direct medical costs over three years: $7,455	**France:** • Inpatient direct medical costs over one year: laser/injection €2,075.06; • Outpatient direct medical costs over one year: laser €146.30 or €98.10 and injection €83.60 • Day admission: injection €973.74 **Germany:** • Inpatient direct medical costs over one year: laser/injection €640.80; • Outpatient direct medical costs over one year: laser € 117.67 or €41.22 and injection €5.56 • Day admission: - **Italy:** • Inpatient direct medical costs over one year: laser/injection -; • Outpatient direct medical costs over one year: laser €56.80 and injection €1,081.00 • Day admission: laser €1,032.40 and injection € 1,081.00
Resource use (1 year) (% of CRVO patients)	• Fluorescein angiography:38.9%; • Intravitreal injection: 8.2%; • Laser photocoagulation: 9.6%; • OCT: 16.6%; PRP: 14.8%; • Vitrectomy: 5.5%.	**France:** • Laser: 12 (18%), • Triamcinolone injection: 39 (67%), • Phacoemulsification: 0, • Cryotherapy: 0, • Others: 8 (15%), • Total outpatient treatments: 59, • Total users: 32 (82%) **Germany:** • Laser: 104 (95%), • Triamcinolone injection: 0, • Phacoemulsification: 2 (2%), • Cryotherapy: 3 (3%), • Others: 0, • Total outpatient treatments: 109, • Total users: 32 (66%) **Italy:** • Laser: 14 (35%), • Triamcinolone injection: 20 (50%), • Phacoemulsification: 0, • Cryotherapy: 0, • Others: 6 (15%), • Total outpatient treatments: 40, • Total users: 19 (59%)

Given the description above of the resource use parameters used in the de novo analysis, the studies by Fekrat *et al.* 2010 and Augustin *et al.* 2012 were not deemed to be useful sources. It was concluded that no published data was available to populate these model

inputs and that consequently primary research would be needed (see Section 7.5.4 below).

7.5.4 If clinical experts assessed the applicability of values available or estimated any values, please provide the following details[8]:

- 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).

A physician survey was conducted to provide an estimate for the following resource use model inputs:

- one-year (base-case) as well as two- and four-year (scenario analyses) frequency of injection and drug monitoring;

- the percentage of patients experiencing IOP that receive treatment for IOP and the percentage of patients suffering from IOP that receive treatment with IOP-lowering drugs as opposed to IOP procedures;

- the percentage of patients experiencing cataract and retina tear that receive treatment for these side-effects.

[8] 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.

- Key tests used at initial and follow-up visits,
- The optimal treatment duration with anti-VEGF.

Methods

Five consultant ophthalmologists with experience in treating CRVO patients in the English/Welsh NHS setting were identified by an independent market research company, which conducted phone interviews for each consultant. Physicians were allowed to review the questionnaire for half an hour prior to the interview.

The purpose of the physician survey was to collect data that were not available in the published literature. As expected, physicians had limited to no experience in using aflibercept or ranibizumab for CRVO patients, but had experience with using ranibizumab in other ophthalmic disease such as age-related macular degeneration. Therefore, for inputs related to treatment-specific resource use (i.e. frequency of injection and drug monitoring), physicians were asked to think of a *hypothetical scenario*, in which they could use these treatments for their patients.

Questions

The following questions were asked:

<u>Frequency of injections and monitoring:</u>

- Assuming a maximum treatment period of 5 years, what would the average number of ranibizumab/aflibercept injections per year be for a typical CRVO patient?
    - What is the average number of injections in Year 1 and in subsequent years (Year 2, Year 3, Year 4 and Year 5)?
- What is the average number of monitoring visits per year for a typical CRVO patient?
- How would the annual number of monitoring visits vary across patients treated with ranibizumab as opposed to aflibercept?
- How long would you treat patients with ranibizumab/aflibercept for?

<u>Management of adverse events:</u>

- What is the percentage of patients experiencing IOP that does actually receive IOP treatment?
    - Would this percentage vary between corticosteroids e.g. dexamethasone and anti-VEGF treated patients? If so, please provide details.
- What proportion of patients suffering from IOP is typically:
    - ____treated with medication?
    - ____treated with surgery?
- Would the type of medication or surgery treatment differ greatly between CRVO patients treated with dexamethasone and an anti-VEGF? If so, please provide details.
- What is the percentage of patients experiencing cataract that requires surgery?
- What is the percentage of patients experiencing retinal tear/detachment that requires surgery?

Diagnosis and monitoring tests:

- Is correct to assume that visual acuity tests and OCTs will be performed during most monitoring visits?
- Would fluorescein angiography be performed on a regular basis or only at baseline (irrespective of CRVO treatment used)?

Results

The values for frequency of injection and drug monitoring derived from the physician survey are described below in Table 84 and Table 85 respectively:

Table 84.Physician survey - frequency of drug injection

	Year 1	Year 2	Year 3	Year 4	Year 5
Aflibercept	7.2	4.4	3.0	1.8	1.0
Ranibizumab	7.6	4.0	3.0	2.2	1.6

Table 85.Physician survey - frequency of drug monitoring

	Year 1 (week	Year 2	Year 3	Year 4	Year 5

	24-52)				
Aflibercept	3.5	4.8	3.8	3.2	2.4
Ranibizumab	4.4	5.8	4.4	3.8	2.8

These findings were primarily used for the scenario analyses on treatment duration (see Section 7.6.1). For the base-case analysis, where treatment was assumed to be given for one year, the frequency of injection was derived from trial data, either from data on file (aflibercept) or from a publication (ranibizumab) (see Section 7.5.5). Using trial data as opposed to data from the Physician survey was deemed more conservative for the base-case. The frequency of monitoring for the first six months of treatment (week 0-24) was aligned with the frequency of injections for the same period (six loading doses each given at a 4-week interval). Over the second half of the year (week 24-52), the frequency of monitoring from the physician survey was applied (Table 85). Beyond treatment, it was assumed that patients would still attend monitoring visits but that the frequency would be the same irrespective of the treatment the patients were on. Consequently, post-treatment monitoring was not modelled in the base-case analysis.

In the two- and four-year treatment scenario analyses (see Section 7.6.1), the findings of the physician survey were used to inform the frequency of injections beyond Year 1 of treatment, as no published evidence was available. The frequency of monitoring was also taken from the physician survey. Similarly to the base-case scenario, beyond treatment duration it was assumed that the frequency of monitoring was the same across the two arms.

Non-treatment specific values that were also derived from the physician survey included resource use inputs related to AEs, and key tests at initial follow-up visits. The former inputs were used in the scenario analysis in which AEs were modelled. The values used for this scenario analysis are described in Table 86 below and can also be found in Section 7.6.1.

Table 86.Physician survey - adverse events inputs

Model input	**Value**
Percentage of patients with IOP requiring treatment	43%
Percentage IOP patients treated with IOP-lowering medications	97%
Percentage IOP patients treated with IOP surgery	3%
Percentage of patients with cataracts requiring removal	68%

Percentage of patients with retinal tears requiring treatment	100%

The physicians also reported that while clinical eye examination and OCT were required at all monitoring visits, a fluorescein angiography (FA) was only conducted before treatment initiation.

Furthermore, physicians estimated that the optimal treatment duration for patients receiving anti-VEGF would be 4 years. This output was used to conduct a scenario analysis on treatment duration (see Section 7.6.1).

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.

The cost of each treatment option, aflibercept or ranibizumab, entailed the cost of treatment and the cost of monitoring. The cost of treatment covered the pharmacological cost of the intervention (drug unit cost per injection) and the cost of treatment administration. Treatment and monitoring unit costs were multiplied by a rate reflecting the frequency of occurrence to estimate the expected cost of treatment and monitoring.

Unit costs

Drug unit costs

The unit drugs costs presented in Table 87 and discussed in this section are current British National Formulary (BNF) prices (BNF 65) and do not include nationally agreed patient access scheme (PAS). Information regarding a PAS for aflibercept is detailed in the PAS submission template. Aflibercept is subject to a price discount; however the details of this discount are confidential.

Table 87.Unit costs associated with the technology in the economic model

Cost input	Aflibercept	Ranibizumab	Ref. in submission
Technology cost per dose (per injection)	£816.00	£742.17	BNF 65(92)

Cost of treatment administration

Administration of an anti-VEGF therapy was assumed to consist of an ophthalmologist visit. Whilst intravitreal injections are generally assumed to be an outpatient procedure, it is clear from clinical opinion(93) that the cost of the procedure is higher in practice than a general outpatient visit and this is reflected in NHS activity data that indicates some appointments are charged at day case rates. Based on Hospital Episode Statistics (HES), 52.38% of these visits would take place in the outpatient setting and the remaining in a day-case set(94). Given the cost of an outpatient visit (£79.72) and of a day-case visit (£402.08), a weighted average based in the 52.38%/47.62% split mentioned above was used to derive an average cost of administration of £257.45 per injection (see Table 88 below).

Table 88.Unit costs and assumptions associated with drug administration in the economic model

Cost input	Value	HRG	Reference
Administration visit - outpatient	£79.72	All NHS trusts and NHS foundation trusts - Consultant Led: Follow up Attendance Non-Admitted Face to Face: 130 - ophthalmology.	Department of Health NHS Reference Costs 2011-2012(95)
Administration visit – day case	£402.08	All NHS trusts and NHS foundation trusts - Regular Day / Night Admissions: BZ23Z- Minor Vitreous Retinal Procedures.	Department of Health NHS Reference Costs 2011-2012(95)
Percentage patients treated in outpatient setting	52.38%	NA	HES, 2012(94)
Percentage patients treated in daycase setting	47.62%	NA	HES, 2012(94)
Administration visit – weighted average	£257.45	NA	Estimate

HES: Hospital Episode Statistics; NA: not applicable.

Cost of a monitoring visit

The model differentiates between the cost of a monitoring visit at baseline and at follow-up. These differ in the scope of clinical tests required. Professional guidelines) and expert consultation (see Section 7.5.4) recommend that management should include:

- FA before treatment initiation

- Clinical examination and OCT at all monitoring visits

A clinical examination is assumed to take place during an ophthalmologist outpatient visit and therefore the cost of this visit was applied to capture the cost of clinical examination. This approach was used in a previous HTA submission in wet AMD(93).

Therefore, while all monitoring visits (baseline or follow-up) entailed the cost of a visit to an ophthalmologist and the cost of an OCT, only the baseline visit captured the cost of a FA. All unit costs are summarised in Table 89 below:

Table 89. Unit costs associated with drug monitoring in the economic model

Cost input	Value	HRG	Reference
Ophthalmologist visit	£79.74	All NHS trusts and NHS foundation trusts - Consultant Led: Follow up Attendance Non-Admitted Face to Face: 130 - ophthalmology.	Department of Health NHS Reference Costs 2011-2012(95)
OCT	£117.26	All NHS trusts and NHS foundation trusts - Outpatient Procedures: BZ23Z - Minor Vitreous Retinal Procedures.	Department of Health NHS Reference Costs 2011-2012(95)
Fluorescein angiography	£117.26	All NHS trusts and NHS foundation trusts - Outpatient Procedures: BZ23Z - Minor Vitreous Retinal Procedures.	Department of Health NHS Reference Costs 2011-2012(95)

Frequency of drug administration and monitoring

Treatment duration of one year was assumed in the base-case analysis. Treatment frequency rates were defined for two time periods: week 0-24, which is referred to the “loading dose period”, and the remainder of the year (week 24-52). Note a specific input was created in the model to determine the number of four-week loading doses i.e. the duration of the loading dose period. In the base-case analysis, the number of loading doses was set to six for each treatment option, reflecting the number of loading doses in the COPERNICUS, GALILEO and CRUISE trials, i.e. a loading dose period of 24 weeks was assumed. The number of loading doses cannot exceed six.

Frequency of drug administration

The mean number of injections used for patients treated with aflibercept in the base-case analysis was derived from results of the GALILEO and COPERNICUS trials as follows: the

mean number of injections for the time period 0-24 weeks was taken from pooled exposure data for GALILEO and COPERNICUS (see section 6.5). Drug exposure was 11.5mg (95% CI: 11.32-11.75), i.e. 11.5mg/2mg=5.75 injections over the first 24 weeks i.e. 5.75/6=0.96 injection per 4-week model cycle. For the period 24-52 weeks, due to cross over in the COPERNICUS trial, the estimate was derived from exposure data from GALILEO only (see section 6.5) of 5.1mg (95% CI:4.37-5.77), following the same approach as for the first 6 weeks but with a frequency adjusted for 7 cycles of 4 weeks (28 weeks): 5.1mg/2mg/7=0.36. Note that the product SmPC (see Section 7.2.8 for details) for aflibercept recommends after the initial injection, treatment is given monthly. The interval between two doses should not be shorter than one month. If there is no improvement in visual and anatomic outcomes over the course of the first three injections, continued treatment is not recommended. Monthly treatment continues until visual and anatomic outcomes are stable for three monthly assessments. Thereafter the need for continued treatment should be reconsidered. If necessary, treatment may be continued with gradually increasing treatment intervals to maintain a stable visual and anatomic outcome. If treatment has been discontinued, visual and anatomic outcomes should be monitored and treatment should be resumed if these deteriorate. In total, 8.3 injections as per trial data were applied in the base-case scenario.

The mean number of injections used for patients treated with ranibizumab was derived from one-year results of the CRUISE trial as reported by Campochiaro *et al.* 2011(35), of 5.5 injections during the week 0-24 and 3.3 during the follow-up PRN treatment period (week 24-52), i.e. a total of 8.8 injections. The number of injections was adjusted for each 4-week model cycle using the following formula: 5.5/6=0.92 injection and 3.3/7= 0.47 injections per model cycle for each treatment phase respectively. This estimate of 8.8 injections for Year 1 is deemed conservative given that a Year 1 frequency of 9.0 injections was used in the manufacturer's NICE submission for ranibizumab in CRVO(63).

The rates for the frequency of administration applied in the model are summarised in Table 90 below:

Table 90. Frequency of treatment administration

Intervention	Year 1 (week 0-24)	Year 1 (week 24-52)	Year 1 (week 0-52)	Source
Aflibercept	5.75	2.55	8.30	*GALILEO/COPERNICUS*
Ranibizumab	5.50	3.30	8.80	*Campochiaro et al. 2011*

				(35)

Note that while values for the frequency of injections were derived from trial results, treatment efficacy and frequency of injections were modelled separately. Consequently, varying the frequency of injections does not impact treatment efficacy in the model.

Frequency of monitoring

In the first 6 months (week 0-24) of treatment of the base-case analysis, the frequency of monitoring visits was aligned with the frequency of administration visits i.e. it was assumed that no monitoring visit was required in addition to visits for drug injection. Consequently, no monitoring visit was costed during this period

Over the second half of the year (week 24-52), 3.50 and 4.40 monitoring visits were assumed for aflibercept and ranibizumab respectively based on the findings of the physician survey (see Section 7.5.4).

Beyond the one-year treatment period, the same frequency of monitoring was assumed across the two interventions; consequently, this frequency was not modelled.

The rates for the frequency of monitoring applied in the model are summarised in Table 91 below

Table 91. Frequency of treatment monitoring

Intervention	**Year 1 (week 0-24)**	**Source**	**Year 1 (week 24-52)**	**Source**	**Year 1 (week 0-52)**
Aflibercept	5.75	*GALILEO/COPERNICUS*	3.50	Physician survey	9.25
Ranibizumab	5.50	*Campochiaro et al. 2011* (35)	4.40	Physician survey	9.90

In the loading period (week 0-24), it was assumed that:

- the treatment schedule is fixed, reflecting a total of 5.75 (aflibercept) and of 5.50 (ranibizumab) loadings doses. Note this adjusted to. respectively 0.96 and 0.92 loading doses for each 4-week cycle

- monitoring visits all occur simultaneously with administration visits.

During this period, only the cost of an administration visit was accounted for in the model, as explained above. This approach is in line with the findings of previous HTA submissions in CRVO/RVO(62;63).

After the loading period (week 24-52), the frequency of monitoring visits is independent from the frequency of administration visits, reflecting that in clinical practice, after the loading doses schedule is completed, patients are expected to attend monitoring visits regularly and that based on the clinical assessment made by the ophthalmologist, they may or not be retreated. The number of monitoring visits which will incur a cost was estimated according to the difference in frequency between the per-cycle administration and per-cycle monitoring rates. This reflects the extent of additional costs billed to the NHS for monitoring visits.

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.

Blindness (as a result of CRVO) is the only HS to be associated with additional resource use and costs in the model. The cost of blindness is applied when patient BCVA in the BSE falls below 35 letters in both eyes. The cost of legally defined blindness (also defined as “severe visual impairment”) has been adapted from a study by Colquitt *et al.* 2008(66), in line with previous appraisal of interventions for ocular conditions. It is a composite cost that entails the following components: residential care (30%), depression (39%), hip replacement (5%), low vision aids (33%), low vision rehabilitation (11%), blind registration (95%) and community care (6%). The breakdown of cost is presented in Table 92 below.

Based on the ERG report of the manufacturer’s submission to NICE for the appraisal of ranibizumab in RVO(65), the cost of blindness registration is applied in the first year only and costs of low vision aids and low vision rehabilitation is applied twice a year in Year 1 and Year 2+. Applying costs of low vision aids and low vision rehabilitation twice a year in the Year 1 and the Year 2+ cost is in accordance with the ERG report which states that the Royal National Institute for the Blind (RNIB) reports that these costs would be biannual(65). The Year 1 and Year 2+ costs were adjusted to each model cycle.

All unit costs have been inflated to 2012 prices when needed. Inflation of unit costs has been implemented using the Hospital & Community Health Services (HCHS) Index, as reported by the Personal Social Services Research Unit (PSSRU) inflation indices 2012(96).

Table 92. Cost of blindness

Blindness: item of resource use	Unit cost	Reference for unit cost	% of patients (66)
Residential care	£14,528	PSSRU 2009(96)	30%
Depression	£530	Knapp et al. 1995(97)	39%
Hip replacement	£5,668	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - HA13C non-elective inpatient long stay (95)	5%
Low vision aids	£184	Meads et al. 2001(98)	33%
Low vision rehabilitation	£277	PSSRU 2009(96)	11%
Blind registration	£102	PSSRU 2009(96)	96%
Community care	£7,011	PSSRU 2009(96)	6%
Year 1 total monthly cost	£[redacted].00		
Year 2+ total monthly cost	£[redacted].00		

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.

In the model base-case analysis, no AEs were considered (see Section 7.3.2).

In a scenario analysis, the impact on cost-effectiveness results of three AEs (intraocular pressure, cataract removal and retinal tear) was explored (see Section 7.6.1). These AEs were associated with resource use and costs additional to those incurred by patients for the treatment of CRVO only. These costs have been modelled following the approach used in previous HTA submissions in CRVO/RVO(62;63).

Intraocular pressure

In line with the manufacturer's submission to NICE for the appraisal of ranibizumab in RVO, patients with IOP are assumed to be treated either with IOP drugs or surgery.

For the monthly IOP medication cost, a weighted average of different medication costs was used. For each chemical class (e.g. betablockers, prostaglandins) unit costs from the BNF 65(92) for the most commonly prescribed therapy within the chemical class were used. The medication resource use was based on treatment duration derived from pooled safety data from GENEVA 008 and GENEVA 009 trials(37) and on shelf life of product as detailed in the relevant product SmPC. This approach is in line with previous RVO HTA submissions(62;63). For each class, the cost of the generic molecule was preferred over the cost of the brand product when both were available. Similarly, the monthly IOP surgery cost was derived from a weighted average of different surgery costs (e.g. trabeculoplasty, cryotherapy). For each procedure, a cost was derived from the NHS reference costs that was weighted based on the costs associated with the following care settings: elective inpatient, non-elective inpatient (short stay), non-elective inpatient (long stay) and day case. See Table 93 for detail of the resource use and costing.

Cataract removal

A cost for cataract removal and lens implant was derived from the Department of Health NHS reference costs using the same code for day cases as in the manufacturer's submission for the appraisal by NICE of dexamethasone in RVO(See Table 93 for details of the DRG code and unit cost).

Retinal tear/detachment

A cost for retinal tear was derived from the Department of Health NHS reference costs using the same code as in the manufacturer's submission for the appraisal by NICE of dexamethasone in RVO and was weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay) and day case (See Table 93 for details of the DRG code and unit cost).

Table 93. Cost of adverse events

IOP cost			
		Reference	
% of IOP requiring treatment	43%	Physician Survey	
% IOP patients treated with IOP-lowering medications	97%		

% IOP patients treated with IOP surgery	3%			
Proportion of patients using the following IOP medications				
IOP-lowering medications	100%	Ranibizumab in RVO; NICE manufacturer submission	*Unit cost*	*Reference*
Betablockers	30%		£0.89	BNF 65, March 2013 (92)
Prostaglandins	19%		£8.64	BNF 65, March 2013
CA inhibitors	9%		£3.53	BNF 65, March 2013
Combination therapy	22%		£5.56	BNF 65, March 2013
Brimonidine	20%		£2.32	BNF 65, March 2013
Proportion of patients using the following IOP surgery				
IOP Procedures	100%	Ranibizumab in RVO; NICE manufacturer submission	*Unit cost*	*Reference*
Trabeculoplasty	44%		£95.29	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ19Z glaucoma category 1* (95)
Sclerectomy	10%		£257.92	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ17Z glaucoma category 3* (95)
Aqueous shunt	10%		£257.92	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ17Z glaucoma category 3* (95)
Cryotherapy	10%		£191.99	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ17Z glaucoma category 2* (95)
Iridectomy	16%		£191.99	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ17Z glaucoma category 2* (95)
Scleral reinforcement	10%		£70.60	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ23Z vitreous

				retinal procedures category 1* (95)
Cataract removal cost				
Item	*Unit cost per procedure*	*Reference*		
Cataracts Hospital outpatient fee	£851.00	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ02Z Day Cases HRG data: Phacoemulsification Cataract Extraction and Lens Implant (95)		
Retinal/Vitreous repair cost				
Item	*Unit cost per procedure*	*Reference*		
Pan-retinal photocoagulation	£424.00*	Department of Health NHS Reference Costs 2011-2012. All NHS trusts and NHS foundation trusts - BZ23Z vitreous retinal procedures category 1		

* Weighted cost of the elective inpatient, non elective inpatient short stay, non elective inpatient long stay and day case costs.

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.

Not applicable.

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.

A range of three scenario analyses were undertaken in order to examine the impact of structural assumptions in the model. In addition, whilst ranibizumab is deemed the standard of care for the treatment of MO secondary to CRVO and is the appropriate comparator for this analysis (see Section 2.7), a fourth scenario analysis was conducted for completeness that compared aflibercept with dexamethasone. These analyses are described in greater detail below:

a) <u>Scenario 1: treatment duration</u>

In the base-case analysis, treatment duration of one year was assumed. Given the uncertainty around optimal treatment duration for CRVO patients, a scenario analysis was conducted on two alternative treatment duration of two (Scenario 1a) and four (Scenario 1b) years. These periods reflect respectively the maximum duration for which aflibercept trial data is available and the optimal treatment duration indicated by the Physician survey (see Section 7.5.4).

In these scenarios, efficacy and resource use had to be projected for another one to three year respectively. Note that while Year 1 values for the frequency of injections were derived from trial results treatment efficacy and frequency of injections were modelled separately. Consequently, these inputs are presented separately.

Efficacy

Given the cross-over design in the COPERNICUS and CRUISE trials at week 24, it was conservatively assumed in the base-case analysis that for the remaining of the year (week 24-52), treatment efficacy was maintained as the aim of PRN treatment was to stabilise the vision gain achieved at the end of the loading period (see Section 6.5).

When treatment duration was extended to two and four years, the same conservative assumption was made. Hence, the model assumes that patients on both aflibercept and ranibizumab will remain in the same health state that they are in after 24 weeks, that is patients' VA is maintained after 24 week until end of treatment. This assumption of maintained efficacy is supported by the 100-week and 76-week trial results for COPERNCUS and GALILEO respectively. These showed that 49.1% and 57.3% of patients treated with aflibercept respectively gained at least 15 letters of BCVA. After treatment completion, similarly to the base-case assumptions, all patients follow the same natural disease progression. Efficacy assumptions for these scenario analyses are summarised and put in perspective in Table 94 below:

Table 94. Efficacy assumptions - Scenario analyses 1a and 1b

Efficacy input	Base-case value	Scenario value	Reference (base-case; scenario)
Week 25-52	VA maintained	VA maintained	Assumption
Week 52-Year 2	Natural disease progression; probability of 0.0003	VA maintained	Klein et al. 1991(68); Assumption
Year 2-Year 4	Natural disease	VA maintained	Klein et al.

Efficacy input	Base-case value	Scenario value	Reference (base-case; scenario)
	progression; probability of 0.0003		1991(68); Assumption

Resource use

Patients on treatment in Year 2 (Scenario 1a) and in Year 2 to Year 4 (Scenario 1b) incurred treatment costs following the same approach as in the base-case analysis i.e. based on resource use. Values for frequency of administration and monitoring were derived from trial results (Year 1 – aflibercept and ranibizumab and Year 2 – aflibercept only), previous HTA submission (Year 2 – ranibizumab) and from a physician survey (Year 3 and Year 4, aflibercept and ranibizumab) when no evidence in the published literature was available. The values are described and put in perspective with the base-case values in Table 95 below:

Table 95. Resource use assumptions - Scenario analyses 1a and 1b

Input	Base case value	Scenario value	Reference
Frequency of injections			
Year 1			
aflibercept	8.3	8.3	Pooled GALILEO and COPERNICUS CSR
ranibizumab	8.8	8.8	Campochiaro *et at.* 2011(35)
Year 2			
aflibercept	0	3.5	COPERNICUS Week 100 CSR
ranibizumab	0	3.8	Ranibizumab in RVO, NICE manufacturer submission
Year 3			
aflibercept	0	3.0	Physician survey
ranibizumab	0	3.0	Physician survey
Year 4			
aflibercept	0	1.8	Physician survey
ranibizumab	0	2.2	Physician survey
Frequency of monitoring			
Year 1 (0-6m)			
aflibercept	5.75	5.75	Assumption based on the loading administration visits occurring simultaneously with monitoring
ranibizumab	5.50	5.50	
Year 1 (6m+)			
aflibercept	3.50	3.50	Physician survey

Input	Base case value	Scenario value	Reference
ranibizumab	4.40	4.40	Physician survey
Year 2			
aflibercept	0	4.8	Physician survey
ranibizumab	0	5.8	Physician survey
Year 3			
aflibercept	0	3.8	Physician survey
ranibizumab	0	4.4	Physician survey
Year 4			
aflibercept	0	3.2	Physician survey
ranibizumab	0	3.8	Physician survey

b) Scenario 2: literature-based utility values

Literature-based BSE utility values derived from Czoski-Murray et al. 2009(80), were tested a scenario analysis.

This study is a contact lens stimulation study in AMD using the TTO value elicitation method. Three AMD vision states were produced by simulating the visual impairment associated with AMD through the use of custom-made contact lenses. The method of deriving utility scores for each BCVA category used the regression constant and coefficient terms as reported in Czoski-Murray et al. 2009(80) and was detailed in Section 7.4.9 above.

The utility values were attributed to the 25 model HS based BCVA in the BSE, irrespective of whether the BSE was the SE or the FE, i.e. utility value was assigned based on the highest BCVA score achieved in either eye (see Table 82 above).

While these utility values were derived using TTO elicitation method and reflect general population preferences, they focus on BCVA in the BSE. It was therefore anticipated that using this set of literature-based values would lead to an underestimate of the treatment effect on health-related quality of life in the SE, which is typically the WSE.

c) Scenario 3: inclusion of adverse events

As described in Section 7.3.2, AEs were not modelled in the base-case analysis. The inclusion of selected AEs is explored in a scenario analyses for completeness. Inclusion of AEs was applied for the base-case treatment duration of one year. The following AEs were modelled in the scenario analysis: IOP, cataract and retinal tear. Each AE included in this scenario analysis was selected based on its relative prevalence and severity as reported in

the results of the clinical trials of aflibercept and ranibizumab(5;6;35)) and as per previous HTA submissions in CRVO/RVO(62;63).

The occurrence rates were derived from 0-24 week pooled data of GALILEO and COPERNICUS, while the rates for ranibizumab were taken from the NICE HTA of ranibizumab(8). The frequencies were converted into monthly probabilities in order to be applied in the model for the first 0-24 weeks. For the remaining treatment duration (week 24-52), AE rates were on a per injection basis: the AE rates applied for the period 0-24 weeks were adjusted by the number of injections in each treatment arm for the same period and, these were then multiplied by the number of injections recorded for each treatment arm in week 24-52. AEs rates used in this scenario analysis are presented in Table 96 below (see Section 7.5.7 for more details on resource use and costing and Section 7.4.8 for more details on disutilities).

Table 96. Adverse events parameters used in the scenario analyses

Inputs	Scenario analyses value	Reference
AE rates		
Aflibercept		
Cataracts	0.0%	Pooled 6m COPERNICUS and GALILEO CSR
IOP	7.8%	
Retinal tear	0.5%	
Ranibizumab		
Cataracts	3.3%	Ranibizumab in RVO; NICE manufacturer submission
IOP	5.0%	
Retinal tear	0.0%	
Dexamethasone		
Cataracts	7.3%	Haller *et al*. 2010(37)
IOP	24%	
Retinal tear	0.24%	
Disutility associated with AEs		
Cataracts	-0.142	Brown 2007(89)
IOP	-0.010	Vaahtoranten-Lehtonen 2007(90)
Retinal/tear detachment	-0.270	Brown 2007(89)
Resource use (irrespective of CRVO treatment)		
% of IOP requiring treatment	43%	Physician Survey
% IOP patients treated with IOP-lowering medications	97%	
% IOP patients treated with IOP surgery	3%	
Proportion of patients using the following IOP-lowering medications		
IOP-lowering medications	100%	Ranibizumab in RVO; NICE manufacturer submission
Betablockers	30%	

Prostaglandins	19%	
CA inhibitors	9%	
Combination therapy	22%	
Brimonidine	20%	
Proportion of patients using the following IOP surgery		
IOP Procedures	100%	Ranibizumab in RVO; NICE manufacturer submission
Trabeculoplasty	44%	
Sclerectomy	10%	
Aqueous shunt	10%	
Cryotherapy	10%	
Iridectomy	16%	
Scleral reinforcement	10%	

d) **<u>Scenario 4: aflibercept vs. dexamethasone</u>**

A scenario analysis in which aflibercept is compared with dexamethasone was included only for completeness, as ranibizumab is considered the standard of care for the treatment of MO secondary to CRVO (see Section 2.7)

Relative efficacy of dexamethasone vs. aflibercept

The approach taken for this comparison is consistent with the approach used for the base-case aflibercept vs. ranibizumab comparison. In particular, treatment duration was assumed to be 1 year. During "routine treatment" period (0-24 week), the probabilities showing BCVA improvement, were adjusted by the RR of improving vision by 15 letters (RR: [redacted]) from the NMA (see Section 6.7). This RR was applied to the aflibercept SE probabilities to derive the probability of improvement in the dexamethasone arm. The probabilities showing BCVA deterioration in dexamethasone arm were assumed to have the same proportionality as observed in the aflibercept arm, while the proportion of patients remaining in the same HS was adjusted to ensure each row of transition probabilities summed up to 1. During 24-52 week, the same conservative assumption of vision maintenance was conservatively considered for the dexamethasone arm as for the aflibercept arm. *This is particularly conservative considering that aflibercept was found to be statistically significantly superior to dexamethasone in the NMA in terms of visual acuity outcomes.* After treatment completion, all patients in both arms were assumed to enter natural disease history progression as in the base-case analysis.

Adverse events

Adverse events were included in this scenario analyses due to differences in the safety profiles of aflibercept and dexamethasone. The publication by Haller *et al*. 2010(37) reports the GENEVA trial 6-month rates of patients experiencing AEs. Only pooled rates for the CRVO and BRVO patients were available. The 6-month rates were subsequently converted into monthly probabilities to be applied to the model. For dexamethasone AE rates, the model uses the inputs presented in the scenario 3 above. *These rates are particularly conservative given that the physician survey indicated more frequent administration than that in the trials, which would be expected to increase adverse events.*

Treatment and monitoring frequency

Treatment frequency of dexamethasone was based on assumptions made in a recently published TA on the treatment of MO secondary to RVO with ranibizumab (TA 283)(8). Patients on dexamethasone were allowed to be re-treated every 4 months, which was translated into 4 implants over the 13 cycles of the model for Year 1. The 6 monitoring visits assumed for patients treated with dexamethasone were in line with the assumption made by Novartis in their manufacturer submission for the treatment of MO secondary to CRVO. This assumption was deemed conservative since 7 visits were suggested by Haller *et al.*2011(37). It was assumed that 25%/75% of patients would be administered dexamethasone in an outpatient/day case setting. This is, again, conservative as clinical opinion informs us that some smaller hospitals use more costly theatre facilities for administration. This also excludes any additional cost for additional IOP monitoring which may be expected given the higher rates of IOP with this treatment.

For this scenario analysis, both deterministic and probabilistic analyses were conducted. The inputs were used for this scenario are presented in Table 97 below:

Table 97. Dexamethasone parameters used in the scenario analyses

Inputs	**Scenario analyses value (variation)**	**PSA distribution**	**Reference**
RR of gaining ≥15 letters, dexamethasone vs. aflibercept	[redacted]	LOGNORMAL	NMA Section 6.7
Cataract rate	7.30% (±20% of mean value	BETA	Haller *et al.* 2010 (37) – rates based on re-treatment after 6 months

Inputs	Scenario analyses value (variation)	PSA distribution	Reference
IOP rate	24.00%(±20% of mean value)	BETA	Haller *et al.* 2010 (37) rates based on re-treatment after 6 months
Retinal detachment	0.24% (±20% of mean value)	BETA	Haller *et al.* 2010 (37)
Treatment frequency (1 year)	4.0 (±20% of mean value)	GAMMA	Based on re-treatment frequency of 4 months TA283
Monitoring frequency (1 year)	6.0 (±20% of mean value)	GAMMA	Haller *et al.* 2010(37)
Percentage patients treated with dexamethasone in outpatient setting	25% (±20% of mean value)	BETA	TA 283(8)
Percentage patients treated with dexamethasone in day case setting	75% (100%-25%)	Sampled value is one minus the sampled value of outpatient %	TA 283(8)

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.

Uncertainty around values for key parameters and the implications of using different estimates has been examined through one way sensitivity analyses (OWSA). Parameter ranges used in the OWSA can be found in Table 98. The rationale for including parameters in the OWSA is as follows:

- Discounting: Sensitivity analyses using rates of 1.5% for both costs and health effects (see Section 6.2.19 of the 2013 NICE guide to the methods of technology appraisal
- Efficacy parameters: Relative risks of gaining at least 15 letters of vision with aflibercept against ranibizumab were varied using their associated confidence intervals
- Probability of progression after treatment was varied by ±20%

- Utility values were varied using their associated standard errors
- Costs of administration and monitoring were varied by ±20%
- Number of injections were varied by ±20%
- Monitoring visits were varied by ±20% in the absence of alternative data

Variables included in the OWSA are presented in Table 98.

Table 98. Variables included in the one-way sensitivity analysis (OWSA)

Parameter	Base case value	Lower value	Upper value	Reference
Starting age (years)	64	62.6	65.4	Pooled COPERNICUS and GALILEO CSR
RR of gaining ≥15 letters, ranibizumab vs. aflibercept	[redacted]			NMA Section 6.7
Probability of progression, aflibercept (post treatment)	0.0003	0.0002	0.0004	±20% of mean value
Probability of progression, comparator (post treatment)	0.0003	0.0002	0.0004	±20% of mean value
HR of mortality from blindness	1.54	1.28	1.86	Christ *et al.* 2008 (19)
Utilities				
utility value HS >=80	[redacted]			GALILEO trial
utility value HS 79-65				GALILEO trial
utility value HS 64-50				GALILEO trial
utility value HS 49-35				GALILEO trial
utility value HS <35				GALILEO trial
Administration frequency				
Aflibercept administration frequency (0-24 weeks)	5.75	4.6	6.9	±20% of mean value
Aflibercept administration frequency (24- 52 weeks)	2.55	2.04	3.06	±20% of mean value
Ranibizumab administration frequency (0-24 weeks)	5.50	4.4	6.6	±20% of mean value
Ranibizumab administration frequency (24- 52 weeks)	3.3	2.64	3.96	±20% of mean value
Monitoring frequency				
Aflibercept monitoring frequency (1 year)	9.90	7.92	11.88	±20% of mean value
Ranibizumab monitoring frequency (1 year)	9.25	7.4	11.1	±20% of mean value
Discounting				
Discounting of costs	3.5%	1.5%	6%	NICE reference

Parameter	Base case value	Lower value	Upper value	Reference
				case
Discounting of outcomes	3.5%	1.5%	6%	NICE reference case
Costs				
Cost of an Anti-VEGF injection (£)	233	187	280	±20% of mean value
Cost of vision loss Year 1 (monthly cost) (£)	469	376	563	±20% of mean value
Cost of monitoring visit (£)	197	148	256	±20% of mean value
Proportion of patients treated in the outpatient setting	0.52	0.42	0.63	±20% of mean value
Cost of vision loss Year 2+ (monthly cost)(£)	461	461	553	±20% of mean value
Resource use				
Aflibercept loading dose	6.0	4.8	7.2	±20% of mean value
Ranibizumab loading dose	6.0	4.8	7.2	±20% of mean value

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 order to simultaneously reflect uncertainty associated with parameters in the results of the model. Distributions were assigned to characterise the uncertainty associated with the (precision of) mean parameter values. The distributions chosen for PSA were selected to represent the available evidence on the parameter of interest.

Variables and statistical distributions used in the probabilistic sensitivity analyses are reported in Table 99 below.

Table 99. Probabilistic parameters

Input	Mean	Distribution type	Source
Efficacy			
RR of gaining ≥15 letters, ranibizumab vs. aflibercept	[redacted]	LOGNORMAL	NMA Section 6.7
Transition probabilities (week 0-24)	Section 7.3.2	BETA	Pooled 6m GALILEO and COPERNICUS
Probability of	0.0003	BETA	± 20% of mean value

progression, aflibercept (post treatment)			
Probability of progression, ranibizumab (post treatment)	0.0003	BETA	± 20% of mean value
Mortality			
HR of mortality from blindness	1.54	GAMMA	Section 7.3.1
Utilities			
utility value HS >=80	[redacted]	BETA	Section 7.4.9
utility value HS 79-65		BETA	Section 7.4.9
utility value HS 64-50		BETA	Section 7.4.9
utility value HS 49-35		BETA	Section 7.4.9
utility value HS <35		BETA	Section 7.4.9
Frequency of injections			
Aflibercept (0-24 weeks)	5.75	NORMAL	± 20% of mean value
Aflibercept (24- 52 weeks)	2.55	GAMMA	± 20% of mean value
Ranibizumab (0-24 weeks)	5.50	NORMAL	± 20% of mean value
Ranibizumab (24- 52 weeks)	3.30	GAMMA	± 20% of mean value
Frequency of monitoring			
Aflibercept (0-24 weeks)	5.75	GAMMA	± 20% of mean value
Aflibercept (24- 52 weeks)	3.50	GAMMA	± 20% of mean value
Ranibizumab (0-24 weeks)	5.50	GAMMA	± 20% of mean value
Ranibizumab (24- 52 weeks)	4.40	GAMMA	± 20% of mean value
Costs			
Cost of an administration visit (£)	233	GAMMA	Section 7.5.5 and 7.5.6
Cost of an monitoring visit (£)	197	GAMMA	Section 7.5.5 and 7.5.6
Cost of fluorescein angiography	117	GAMMA	Section 7.5.5 and 7.5.6
Vision loss Year 1 (monthly cost)	469	GAMMA	± 20% of mean value
Vision loss Year 2+ (monthly cost)	461	GAMMA	± 20% of mean value
Aflibercept loading dose	6	GAMMA	± 20% of mean value
Ranibizumab loading dose	6	GAMMA	± 20% of mean value

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.

Outcomes for the SE in the aflibercept arm from both the economic model and the COPERNICUS and GALILEO trials were compared over treatment duration (1 year).

Outcomes were presented in terms of percentage of patients per aggregated HS. In order to interpret these, a reminder of the naming protocol for the 25 individual HS used in the Markov model is presented in Table 100 below:

Table 100. Markov model health states – BCVA ranges (SE, FE)

Study Eye, Fellow Eye	>=80 (1)	79-65 (2)	64-50 (3)	49-35 (4)	<35 (5)
>=80 (1)	>=80,>=80 (1,1)	79-65,>=80 (2,1)	64-50,>=80 (3,1)	49-35,>=80 (4,1)	<35,>=80 (5,1)
79-65 (2)	>=80,79-65 (1,2)	79-65,79-65 (2,2)	64-50,79-65 (3,2)	49-35,79-65 (4,2)	<35,79-65 (5,2)
64-50 (3)	>=80,64-50 (1,3)	79-65,64-50 (2,3)	64-50,64-50 (3,3)	49-35,64-50 (4,3)	<35,64-50 (5,3)
49-35 (4)	>=80,49-35 (1,4)	79-65,49-35 (2,4)	64-50,49-35 (3,4)	49-35,49-35 (4,4)	<35,49-35 (5,4)
<35 (5)	>=80,<35 (1,5)	79-65,<35 (2,5)	64-50,<35 (3,5)	49-35,<35 (4,5)	<35,<35 (5,5)

The BCVA range captured in each HS was also reported as a combination of digits (e.g. “1, 1”) with the lowest digit (“1”) representing a best level of BCVA and highest digit (“5”) representing the poorest level of BCVA.

The health states presented in this table may be compared with the health states and the model structures presented in Section 7.2.2.

Five aggregated HS were derived from the individual HS:

- HS with SE with a BCVA >=80 letters (BCVA range coded as “1”): this aggregated HS includes the following HS: (>=80;>=80), (>=80;79-65), (>=80;64-50), (>=80;49-35), (>=80;<35)

- HS with SE with a BCVA 79-65 letters (BCVA range coded as “2”): this aggregated HS includes the following HS: (79-65;>=80), 79-65;79-65), 79-65;64-50), (79-65;49-35), (79-65;<35)

- HS with SE with a BCVA 64-50 letters (BCVA range coded as “3”): this aggregated HS includes the following HS: (64-50 ;>=80), (64-50 ;79-65), (64-50;64-50), (64-50 ;49-35), (64-50 ;<35)

- HS with SE with a BCVA 49-35 letters (BCVA range coded as “4”): this aggregated HS includes the following HS: (49-35;>=80), (49-35;79-65), (49-35;64-50), (49-35;49-35), (49-35;<35)

- HS with SE with a BCVA <35 letters (BCVA range coded as “5”): this aggregated HS includes the following HS: (<35;>=80), (<35;79-65), (>=80;64-50), (>=80;49-35), (>=80;<35)

Outcomes were reported in Table 101 below for each of the first 6 model cycles – where trial data was applied - and for the remaining cycles of the treatment duration – reflecting the fit of the data for the 7 cycles for which it was assumed that vision achieved at week 24 was maintained (see section 7.3.2). For the period week 0-24, trial data was taken from the integrated COPERNICUS and GALILEO CSR (see Section 7.3.1); for the period week 25-52, trial data was taken from the GALILEO CSR (see Section 6.3.4) due to the cross-over design of COPERNICUS at week 24.

As shown in Table 101 below, during the first 6 cycles (cycles 0-5/ week 0-24), the aflibercept arm distribution of patients across the different levels of VA for the SE closely matches the distribution of patients in the trial (COPERNICUS and GALILEO). The slightly lower proportions of the model cohort relative to the clinical trial data is due to the all-cause background mortality rate applied in the model. Note that for cycle 0, the baseline distribution from the clinical trial was directly applied in the model; the discrepancy observed at cycle 0 between trial and model output resulted from the fact that baseline distribution was calculated from the whole trial population, while transitions from week 0 were taken only from the aflibercept arm.

From cycle 6 until cycle 13 the differences between the model output and the trial data increase slightly. The reason for this is that trial data was derived from the GALILEO trial, while the maintained vision assumption was applied in the model for this time period. Table 101 below shows the distribution of patients across the different HS at the beginning of each cycle compared to the distribution of patients across the different HS in the trial during year 1.

Note, that it was not considered valuable to compare the VA distribution of the ranibizumab arm to clinical trial data as the VA distribution in the ranibizumab arm was calculated applying the relative risk through the NMA to the aflibercept transitions.

Table 101. Year 1 summary of model results compared with clinical data – aflibercept arm

Time period	Source	BCVA HS 1	BCVA HS 2	BCVA HS 3	BCVA HS 4	BCVA HS 5

Cycle 0	Model	0.3%	21.3%	39.9%	21.6%	16.8%
	Trial	0.0%	23.4%	40.3%	19.9%	16.4%
	Difference	0.3%	-2.0%	-0.4%	1.7%	0.4%
Cycle 1	Model	14.8%	43.1%	27.1%	9.3%	5.6%
	Trial	16.9%	45.3%	26.9%	8.5%	6.5%
	Difference	-2.1%	-2.1%	0.2%	0.9%	-0.9%
Cycle 2	Model	23.0%	41.7%	22.3%	8.0%	4.9%
	Trial	23.9%	43.3%	20.9%	7.5%	5.5%
	Difference	-0.9%	-1.6%	1.4%	0.6%	-0.6%
Cycle 3	Model	26.8%	39.4%	23.3%	5.2%	5.1%
	Trial	27.9%	40.3%	22.4%	5.0%	6.5%
	Difference	-1.1%	-0.9%	0.9%	0.2%	-1.3%
Cycle 4	Model	33.6%	35.2%	20.8%	5.9%	4.1%
	Trial	35.8%	35.8%	19.9%	6.0%	5.0%
	Difference	-2.2%	-0.6%	0.9%	0.0%	-0.9%
Cycle 5	Model	31.9%	36.2%	21.0%	7.1%	3.4%
	Trial	34.3%	36.3%	19.4%	7.0%	4.0%
	Difference	-2.4%	-0.1%	1.6%	0.1%	-0.6%
Cycle6	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	39.4%	38.3%	8.5%	6.4%	7.4%
	Difference	-9.6%	3.2%	9.5%	-0.7%	-3.0%
Cycle 7	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	39.4%	38.3%	8.5%	6.4%	7.4%
	Difference	-9.6%	3.2%	9.5%	-0.7%	-3.0%
Cycle 8	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	31.9%	34.0%	17.0%	6.4%	5.3%
	Difference	-2.2%	7.4%	1.0%	-0.8%	-0.8%
Cycle 9	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	33.0%	39.4%	8.5%	7.4%	5.3%
	Difference	-3.3%	2.1%	9.5%	-1.8%	-0.8%
Cycle 10	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	34.0%	29.8%	13.8%	6.4%	5.3%
	Difference	-4.4%	11.6%	4.2%	-0.8%	-0.8%
Cycle 11	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	33.0%	36.2%	11.7%	6.4%	3.2%
	Difference	-3.3%	5.2%	6.3%	-0.8%	1.3%
Cycle 12	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	39.4%	30.9%	16.0%	4.3%	4.3%
	Difference	-9.7%	10.5%	2.0%	1.4%	0.2%
Cycle 13	Model	29.8%	41.5%	18.1%	5.6%	4.5%
	Trial	33.0%	39.4%	11.7%	5.3%	5.3%
	Difference	-3.4%	1.9%	6.2%	0.3%	-0.9%

SE: study eye

The model was additionally validated against the underlying trial data for the mean BCVA of the study eye versus the model's cohort mean BCVA at 6 months and 12 months as shown in Table 102 and Table 103. Both the 24-week and 52-week validations suggest reasonable consistency of results. Taking the 24-week example, the trials suggest an additional treatment effect of aflibercept over ranibizumab of 4.1 letters, while the model estimates an additional treatment effect of 3.1 letters. This suggests a conservative analysis with reasonable integrity.

Table 102. Mean BCVA gain (number of letters) at week 24 – Trial vs. model outputs

	Baseline BCVA	24-week BCVA	Treatment effect	Aflibercept treatment effect	Source
Trial data					
Aflibercept	52.0	69.7	18.2 ((69.7-52)-(49.4-49.9))	4.1	24-week integrated data (see Section 6.3.4)
Sham	49.9	49.4	-	-	24-week integrated data (see Section 6.3.4)
Ranibizumab	48.1	63.0	14.1 ((63-48.1))-(50-49.2))	-	Brown *et al.* 2010
Sham	49.2	50.0	-	-	Brown *et al.* 2010 (30)
Model outputs*					
Aflibercept	53.0	70.7	17.7	3.1	Model output
Ranibizumab	53.0	67.6	14.6	-	Model output

*Mean BCVA estimated assuming a mid-point BCVA for each modeled HS.

Table 103. Mean BCVA gain (number of letters) at week 52 – Trial vs. model outputs

	Baseline BCVA	**52-week BCVA**	**Absolute difference**	**Aflibercept treatment effect**	**Source**
Trial data					
Aflibercept	53.6 *	70.4	13.0 ((70.4-53.6)-(54.7-50.9))	6.4	52-week GALILEO data (see Section 6.5)
Sham	50.9*	54.7	-	-	52-week GALILEO data (see Section 6.5)
Ranibizumab	48.1	62.0	6.6 ((62.0-48.1)-(56.5-49.2))	-	Brown *et al.* 2010(30); Campochiaro *et al.* 2011(35)
Sham	49.2	56.5	-	-	Brown *et al.*

	Baseline BCVA	52-week BCVA	Absolute difference	Aflibercept treatment effect	Source
					2010(30); Campochiaro *et al.* 2011(35)
Model outputs					
Aflibercept	53.0	70.3	17.3	3.1	Model output
Ranibizumab	53.0	67.2	14.2	-	Model output

Note the GALILEO data were used for 52-week validation and therefore baseline data are different from data presented in the table above in which 24-week integrated data were used for baseline.

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 cohort was simulated for a 64 years-old patient over a 30 year lifetime from model entry. The figures and associated tables below provide patient trace outputs for the model. The next two graphs, Figure 21 and Figure 22, and their matching tables, Table 104 and Table 105, provide the detail of the proportion of the model cohort occupying each individual HS over time:

- per cycle (4 weeks each) for treatment duration (i.e. Year 1) and, for purposes of brevity, for the final cycle of each year from Year 2 onwards,
- for the intervention (aflibercept) and the comparator (ranibizumab) arm respectively.

Figure 2. Markov trace: aflibercept arm, 1 year of treatment, aged 64 years at baseline

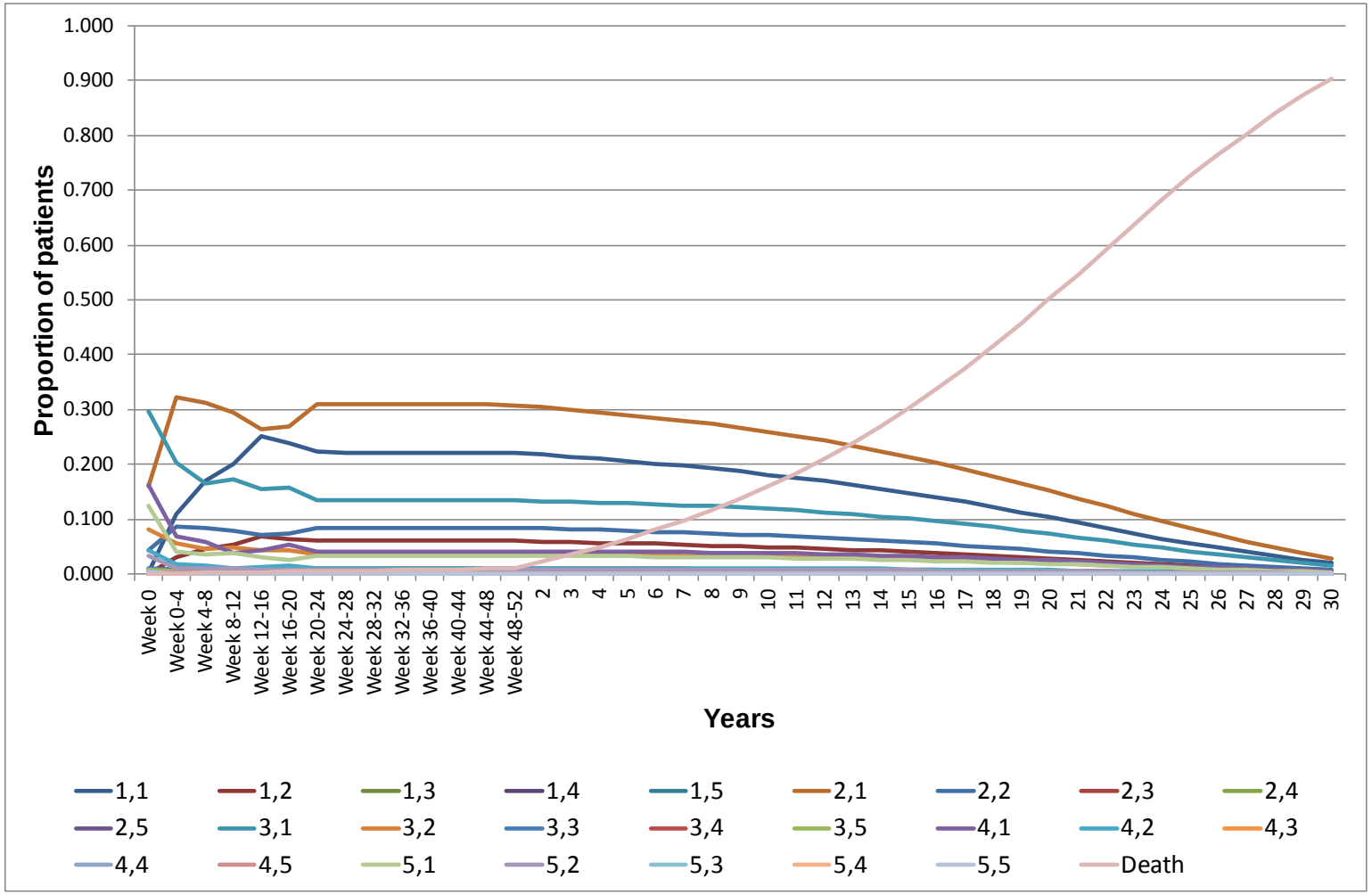


Table 104. Markov trace: aflibercept arm, 1 year of treatment, aged 64 years at baseline

Years	1,1	1,2	1,3	1,4	1,5	2,1	2,2	2,3	2,4	2,5	3,1	3,2	3,3	3,4	3,5	4,1	4,2	4,3	4,4	4,5	5,1	5,2	5,3	5,4	5,5	Death
Week 0	0.002	0.001	0.000	0.000	0.000	0.159	0.043	0.005	0.001	0.004	0.298	0.081	0.010	0.002	0.007	0.162	0.044	0.005	0.001	0.004	0.125	0.034	0.004	0.001	0.003	0.000
Week 0-4	0.111	0.030	0.004	0.001	0.003	0.322	0.088	0.011	0.003	0.008	0.202	0.055	0.007	0.002	0.005	0.070	0.019	0.002	0.001	0.002	0.042	0.011	0.001	0.000	0.001	0.001
Week 4-8	0.171	0.047	0.006	0.001	0.004	0.311	0.085	0.010	0.003	0.008	0.166	0.045	0.006	0.001	0.004	0.060	0.016	0.002	0.001	0.002	0.036	0.010	0.001	0.000	0.001	0.002
Week 8-12	0.200	0.054	0.007	0.002	0.005	0.294	0.080	0.010	0.002	0.007	0.174	0.047	0.006	0.001	0.004	0.039	0.010	0.001	0.000	0.001	0.038	0.010	0.001	0.000	0.001	0.002
Week 12-16	0.251	0.068	0.008	0.002	0.006	0.263	0.071	0.009	0.002	0.007	0.155	0.042	0.005	0.001	0.004	0.044	0.012	0.001	0.000	0.001	0.030	0.008	0.001	0.000	0.001	0.003
Week 16-20	0.238	0.065	0.008	0.002	0.006	0.270	0.073	0.009	0.002	0.007	0.157	0.043	0.005	0.001	0.004	0.053	0.014	0.002	0.000	0.001	0.025	0.007	0.001	0.000	0.001	0.004
Week 20-24	0.222	0.061	0.007	0.002	0.006	0.310	0.084	0.010	0.003	0.008	0.135	0.037	0.005	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.034	0.009	0.001	0.000	0.001	0.005
Week 24-28	0.222	0.060	0.007	0.002	0.006	0.310	0.084	0.010	0.003	0.008	0.135	0.037	0.005	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.006
Week 28-32	0.222	0.060	0.007	0.002	0.006	0.310	0.084	0.010	0.003	0.008	0.135	0.037	0.005	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.007
Week 32-36	0.222	0.060	0.007	0.002	0.006	0.309	0.084	0.010	0.003	0.008	0.135	0.037	0.005	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.007
Week 36-40	0.222	0.060	0.007	0.002	0.006	0.309	0.084	0.010	0.003	0.008	0.134	0.037	0.004	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.008
Week 40-44	0.222	0.060	0.007	0.002	0.006	0.309	0.084	0.010	0.003	0.008	0.134	0.037	0.004	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.009
Week 44-48	0.221	0.060	0.007	0.002	0.006	0.309	0.084	0.010	0.003	0.008	0.134	0.036	0.004	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.010
Week 48-52	0.221	0.060	0.007	0.002	0.006	0.308	0.084	0.010	0.003	0.008	0.134	0.036	0.004	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.011
2	0.218	0.059	0.007	0.002	0.005	0.304	0.083	0.010	0.003	0.008	0.133	0.036	0.004	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.022
3	0.214	0.058	0.007	0.002	0.005	0.300	0.082	0.010	0.003	0.008	0.132	0.036	0.004	0.001	0.003	0.041	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.035
4	0.210	0.057	0.007	0.002	0.005	0.296	0.080	0.010	0.002	0.007	0.131	0.036	0.004	0.001	0.003	0.041	0.011	0.001	0.000	0.001	0.032	0.009	0.001	0.000	0.001	0.049
5	0.206	0.056	0.007	0.002	0.005	0.291	0.079	0.010	0.002	0.007	0.129	0.035	0.004	0.001	0.003	0.041	0.011	0.001	0.000	0.001	0.032	0.009	0.001	0.000	0.001	0.064
6	0.202	0.055	0.007	0.002	0.005	0.285	0.078	0.010	0.002	0.007	0.128	0.035	0.004	0.001	0.003	0.041	0.011	0.001	0.000	0.001	0.032	0.009	0.001	0.000	0.001	0.080

7	0.197	0.054	0.007	0.002	0.005	0.279	0.076	0.009	0.002	0.007	0.126	0.034	0.004	0.001	0.003	0.040	0.011	0.001	0.000	0.001	0.031	0.009	0.001	0.000	0.001	0.098
8	0.192	0.052	0.006	0.002	0.005	0.273	0.074	0.009	0.002	0.007	0.124	0.034	0.004	0.001	0.003	0.040	0.011	0.001	0.000	0.001	0.031	0.008	0.001	0.000	0.001	0.117
9	0.187	0.051	0.006	0.002	0.005	0.267	0.073	0.009	0.002	0.007	0.121	0.033	0.004	0.001	0.003	0.039	0.011	0.001	0.000	0.001	0.030	0.008	0.001	0.000	0.001	0.137
10	0.181	0.049	0.006	0.002	0.005	0.259	0.071	0.009	0.002	0.007	0.119	0.032	0.004	0.001	0.003	0.038	0.010	0.001	0.000	0.001	0.030	0.008	0.001	0.000	0.001	0.160
11	0.176	0.048	0.006	0.001	0.004	0.252	0.068	0.008	0.002	0.006	0.116	0.032	0.004	0.001	0.003	0.037	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001	0.184
12	0.169	0.046	0.006	0.001	0.004	0.243	0.066	0.008	0.002	0.006	0.113	0.031	0.004	0.001	0.003	0.037	0.010	0.001	0.000	0.001	0.028	0.008	0.001	0.000	0.001	0.210
13	0.163	0.044	0.005	0.001	0.004	0.234	0.064	0.008	0.002	0.006	0.109	0.030	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.027	0.007	0.001	0.000	0.001	0.239
14	0.155	0.042	0.005	0.001	0.004	0.224	0.061	0.008	0.002	0.006	0.105	0.029	0.004	0.001	0.003	0.034	0.009	0.001	0.000	0.001	0.026	0.007	0.001	0.000	0.001	0.269
15	0.148	0.040	0.005	0.001	0.004	0.214	0.058	0.007	0.002	0.005	0.101	0.027	0.003	0.001	0.003	0.033	0.009	0.001	0.000	0.001	0.025	0.007	0.001	0.000	0.001	0.302
16	0.140	0.038	0.005	0.001	0.004	0.203	0.055	0.007	0.002	0.005	0.096	0.026	0.003	0.001	0.002	0.032	0.009	0.001	0.000	0.001	0.024	0.007	0.001	0.000	0.001	0.338
17	0.131	0.036	0.004	0.001	0.003	0.191	0.052	0.006	0.002	0.005	0.091	0.025	0.003	0.001	0.002	0.030	0.008	0.001	0.000	0.001	0.023	0.006	0.001	0.000	0.001	0.376
18	0.122	0.033	0.004	0.001	0.003	0.179	0.049	0.006	0.001	0.004	0.086	0.023	0.003	0.001	0.002	0.028	0.008	0.001	0.000	0.001	0.021	0.006	0.001	0.000	0.001	0.416
19	0.113	0.031	0.004	0.001	0.003	0.166	0.045	0.006	0.001	0.004	0.080	0.022	0.003	0.001	0.002	0.027	0.007	0.001	0.000	0.001	0.020	0.005	0.001	0.000	0.001	0.458
20	0.104	0.028	0.003	0.001	0.003	0.152	0.041	0.005	0.001	0.004	0.074	0.020	0.002	0.001	0.002	0.025	0.007	0.001	0.000	0.001	0.018	0.005	0.001	0.000	0.000	0.501
21	0.094	0.026	0.003	0.001	0.002	0.138	0.038	0.005	0.001	0.003	0.067	0.018	0.002	0.001	0.002	0.023	0.006	0.001	0.000	0.001	0.017	0.005	0.001	0.000	0.000	0.547
22	0.084	0.023	0.003	0.001	0.002	0.124	0.034	0.004	0.001	0.003	0.061	0.017	0.002	0.001	0.002	0.020	0.006	0.001	0.000	0.001	0.015	0.004	0.001	0.000	0.000	0.592
23	0.074	0.020	0.002	0.001	0.002	0.110	0.030	0.004	0.001	0.003	0.054	0.015	0.002	0.000	0.001	0.018	0.005	0.001	0.000	0.000	0.014	0.004	0.000	0.000	0.000	0.638
24	0.065	0.018	0.002	0.001	0.002	0.096	0.026	0.003	0.001	0.002	0.048	0.013	0.002	0.000	0.001	0.016	0.004	0.001	0.000	0.000	0.012	0.003	0.000	0.000	0.000	0.683
25	0.056	0.015	0.002	0.000	0.001	0.083	0.023	0.003	0.001	0.002	0.041	0.011	0.001	0.000	0.001	0.014	0.004	0.000	0.000	0.000	0.010	0.003	0.000	0.000	0.000	0.725
26	0.048	0.013	0.002	0.000	0.001	0.071	0.019	0.002	0.001	0.002	0.035	0.010	0.001	0.000	0.001	0.012	0.003	0.000	0.000	0.000	0.009	0.002	0.000	0.000	0.000	0.766
27	0.04	0.01	0.00	0.00	0.00	0.06	0.01	0.00	0.00	0.00	0.03	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.803

	0	1	1	0	1	0	6	2	0	1	0	8	1	0	1	0	3	0	0	0	8	2	0	0	0	
28	0.032	0.009	0.001	0.000	0.001	0.048	0.013	0.002	0.000	0.001	0.024	0.007	0.001	0.000	0.001	0.008	0.002	0.000	0.000	0.000	0.006	0.002	0.000	0.000	0.000	0.839
29	0.025	0.007	0.001	0.000	0.001	0.038	0.010	0.001	0.000	0.001	0.019	0.005	0.001	0.000	0.000	0.007	0.002	0.000	0.000	0.000	0.005	0.001	0.000	0.000	0.000	0.873
30	0.020	0.005	0.001	0.000	0.000	0.029	0.008	0.001	0.000	0.001	0.015	0.004	0.001	0.000	0.000	0.005	0.001	0.000	0.000	0.000	0.004	0.001	0.000	0.000	0.000	0.902

Figure 3. Markov trace: ranibizumab arm, 1 year of treatment, aged 64 years at baseline

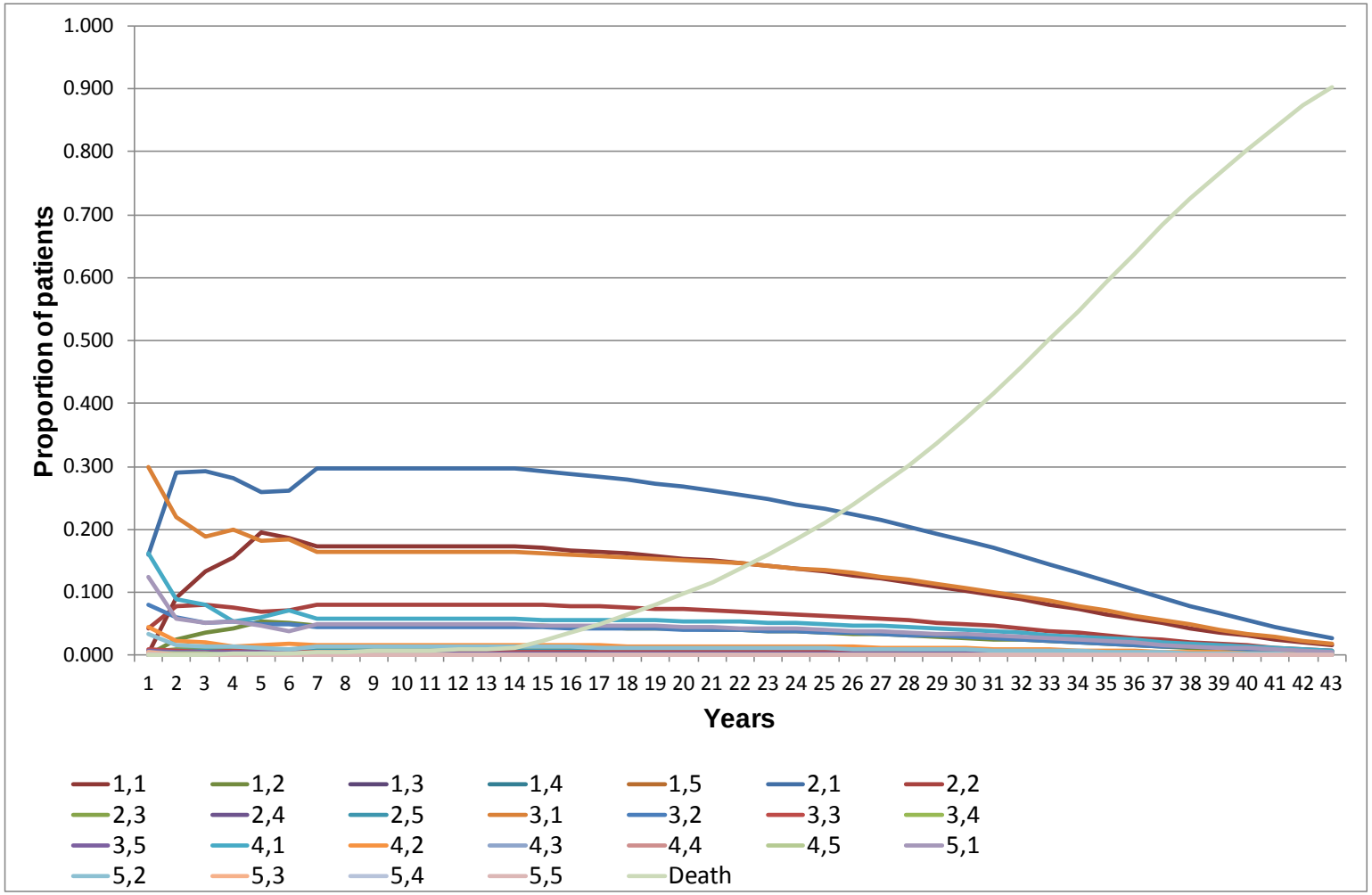


Table 105. Markov trace: ranibizumab arm, 1 year of treatment, aged 64 years at baseline

Years	1,1	1,2	1,3	1,4	1,5	2,1	2,2	2,3	2,4	2,5	3,1	3,2	3,3	3,4	3,5	4,1	4,2	4,3	4,4	4,5	5,1	5,2	5,3	5,4	5,5	Death
Week 0	0.002	0.001	0.000	0.000	0.000	0.159	0.043	0.005	0.001	0.004	0.298	0.081	0.010	0.002	0.007	0.162	0.044	0.005	0.001	0.004	0.125	0.034	0.004	0.001	0.003	0.000
Week 0-4	0.090	0.025	0.003	0.001	0.002	0.290	0.079	0.010	0.002	0.007	0.220	0.060	0.007	0.002	0.006	0.088	0.024	0.003	0.001	0.002	0.057	0.016	0.002	0.000	0.001	0.001
Week 4-8	0.134	0.036	0.004	0.001	0.003	0.292	0.079	0.010	0.002	0.007	0.189	0.051	0.006	0.002	0.005	0.080	0.022	0.003	0.001	0.002	0.051	0.014	0.002	0.000	0.001	0.002
Week 8-12	0.155	0.042	0.005	0.001	0.004	0.281	0.076	0.009	0.002	0.007	0.199	0.054	0.007	0.002	0.005	0.055	0.015	0.002	0.000	0.001	0.055	0.015	0.002	0.000	0.001	0.002
Week 12-16	0.196	0.053	0.007	0.002	0.005	0.259	0.070	0.009	0.002	0.006	0.183	0.050	0.006	0.002	0.005	0.061	0.016	0.002	0.001	0.002	0.047	0.013	0.002	0.000	0.001	0.003
Week 16-20	0.186	0.051	0.006	0.002	0.005	0.263	0.071	0.009	0.002	0.007	0.185	0.050	0.006	0.002	0.005	0.071	0.019	0.002	0.001	0.002	0.039	0.011	0.001	0.000	0.001	0.004
Week 20-24	0.174	0.047	0.006	0.001	0.004	0.298	0.081	0.010	0.002	0.007	0.164	0.045	0.006	0.001	0.004	0.058	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.005
Week 24-28	0.174	0.047	0.006	0.001	0.004	0.298	0.081	0.010	0.002	0.007	0.164	0.045	0.006	0.001	0.004	0.058	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.006
Week 28-32	0.174	0.047	0.006	0.001	0.004	0.298	0.081	0.010	0.002	0.007	0.164	0.045	0.005	0.001	0.004	0.058	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.007
Week 32-36	0.174	0.047	0.006	0.001	0.004	0.297	0.081	0.010	0.002	0.007	0.164	0.045	0.005	0.001	0.004	0.058	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.007
Week 36-40	0.174	0.047	0.006	0.001	0.004	0.297	0.081	0.010	0.002	0.007	0.164	0.045	0.005	0.001	0.004	0.057	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.008
Week 40-44	0.173	0.047	0.006	0.001	0.004	0.297	0.081	0.010	0.002	0.007	0.164	0.045	0.005	0.001	0.004	0.057	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.009
Week 44-48	0.173	0.047	0.006	0.001	0.004	0.297	0.081	0.010	0.002	0.007	0.164	0.045	0.005	0.001	0.004	0.057	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.010
Week 48-52	0.173	0.047	0.006	0.001	0.004	0.296	0.081	0.010	0.002	0.007	0.163	0.044	0.005	0.001	0.004	0.057	0.016	0.002	0.000	0.001	0.049	0.013	0.002	0.000	0.001	0.011
2	0.170	0.046	0.006	0.001	0.004	0.292	0.080	0.010	0.002	0.007	0.162	0.044	0.005	0.001	0.004	0.057	0.016	0.002	0.000	0.001	0.048	0.013	0.002	0.000	0.001	0.022
3	0.168	0.046	0.006	0.001	0.004	0.288	0.078	0.010	0.002	0.007	0.160	0.044	0.005	0.001	0.004	0.057	0.015	0.002	0.000	0.001	0.048	0.013	0.002	0.000	0.001	0.035
4	0.165	0.045	0.006	0.001	0.004	0.284	0.077	0.009	0.002	0.007	0.159	0.043	0.005	0.001	0.004	0.056	0.015	0.002	0.000	0.001	0.047	0.013	0.002	0.000	0.001	0.049
5	0.161	0.044	0.005	0.001	0.004	0.279	0.076	0.009	0.002	0.007	0.157	0.043	0.005	0.001	0.004	0.056	0.015	0.002	0.000	0.001	0.047	0.013	0.002	0.000	0.001	0.064

6	0.158	0.043	0.005	0.001	0.004	0.273	0.074	0.009	0.002	0.007	0.154	0.042	0.005	0.001	0.004	0.055	0.015	0.002	0.000	0.001	0.046	0.013	0.002	0.000	0.001	0.080
7	0.154	0.042	0.005	0.001	0.004	0.268	0.073	0.009	0.002	0.007	0.152	0.041	0.005	0.001	0.004	0.055	0.015	0.002	0.000	0.001	0.046	0.012	0.002	0.000	0.001	0.098
8	0.150	0.041	0.005	0.001	0.004	0.262	0.071	0.009	0.002	0.007	0.149	0.041	0.005	0.001	0.004	0.054	0.015	0.002	0.000	0.001	0.045	0.012	0.001	0.000	0.001	0.117
9	0.146	0.040	0.005	0.001	0.004	0.255	0.069	0.009	0.002	0.006	0.146	0.040	0.005	0.001	0.004	0.053	0.014	0.002	0.000	0.001	0.044	0.012	0.001	0.000	0.001	0.137
10	0.142	0.039	0.005	0.001	0.004	0.248	0.067	0.008	0.002	0.006	0.143	0.039	0.005	0.001	0.004	0.052	0.014	0.002	0.000	0.001	0.043	0.012	0.001	0.000	0.001	0.160
11	0.137	0.037	0.005	0.001	0.003	0.241	0.065	0.008	0.002	0.006	0.139	0.038	0.005	0.001	0.003	0.051	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001	0.184
12	0.133	0.036	0.004	0.001	0.003	0.232	0.063	0.008	0.002	0.006	0.135	0.037	0.005	0.001	0.003	0.049	0.013	0.002	0.000	0.001	0.041	0.011	0.001	0.000	0.001	0.210
13	0.127	0.035	0.004	0.001	0.003	0.224	0.061	0.007	0.002	0.006	0.130	0.035	0.004	0.001	0.003	0.048	0.013	0.002	0.000	0.001	0.039	0.011	0.001	0.000	0.001	0.239
14	0.122	0.033	0.004	0.001	0.003	0.214	0.058	0.007	0.002	0.005	0.125	0.034	0.004	0.001	0.003	0.046	0.013	0.002	0.000	0.001	0.038	0.010	0.001	0.000	0.001	0.269
15	0.116	0.031	0.004	0.001	0.003	0.204	0.056	0.007	0.002	0.005	0.120	0.033	0.004	0.001	0.003	0.044	0.012	0.001	0.000	0.001	0.037	0.010	0.001	0.000	0.001	0.302
16	0.109	0.030	0.004	0.001	0.003	0.194	0.053	0.006	0.002	0.005	0.114	0.031	0.004	0.001	0.003	0.042	0.012	0.001	0.000	0.001	0.035	0.009	0.001	0.000	0.001	0.338
17	0.103	0.028	0.003	0.001	0.003	0.182	0.050	0.006	0.002	0.005	0.108	0.029	0.004	0.001	0.003	0.040	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001	0.376
18	0.096	0.026	0.003	0.001	0.002	0.170	0.046	0.006	0.001	0.004	0.101	0.028	0.003	0.001	0.003	0.038	0.010	0.001	0.000	0.001	0.031	0.008	0.001	0.000	0.001	0.416
19	0.089	0.024	0.003	0.001	0.002	0.158	0.043	0.005	0.001	0.004	0.094	0.026	0.003	0.001	0.002	0.035	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001	0.458
20	0.081	0.022	0.003	0.001	0.002	0.145	0.039	0.005	0.001	0.004	0.087	0.024	0.003	0.001	0.002	0.033	0.009	0.001	0.000	0.001	0.027	0.007	0.001	0.000	0.001	0.502
21	0.073	0.020	0.002	0.001	0.002	0.131	0.036	0.004	0.001	0.003	0.079	0.022	0.003	0.001	0.002	0.030	0.008	0.001	0.000	0.001	0.024	0.007	0.001	0.000	0.001	0.547
22	0.066	0.018	0.002	0.001	0.002	0.118	0.032	0.004	0.001	0.003	0.071	0.019	0.002	0.001	0.002	0.027	0.007	0.001	0.000	0.001	0.022	0.006	0.001	0.000	0.001	0.592
23	0.058	0.016	0.002	0.000	0.001	0.104	0.028	0.003	0.001	0.003	0.064	0.017	0.002	0.001	0.002	0.024	0.007	0.001	0.000	0.001	0.020	0.005	0.001	0.000	0.000	0.638
24	0.051	0.014	0.002	0.000	0.001	0.091	0.025	0.003	0.001	0.002	0.056	0.015	0.002	0.000	0.001	0.021	0.006	0.001	0.000	0.001	0.017	0.005	0.001	0.000	0.000	0.683
25	0.044	0.012	0.001	0.000	0.001	0.079	0.022	0.003	0.001	0.002	0.049	0.013	0.002	0.000	0.001	0.019	0.005	0.001	0.000	0.000	0.015	0.004	0.001	0.000	0.000	0.725
26	0.03	0.01	0.00	0.00	0.00	0.06	0.01	0.00	0.00	0.00	0.04	0.01	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.766

	7	0	1	0	1	7	8	2	1	2	1	1	1	0	1	6	4	1	0	0	3	4	0	0	0	
27	0.031	0.008	0.001	0.000	0.001	0.056	0.015	0.002	0.000	0.001	0.035	0.009	0.001	0.000	0.001	0.014	0.004	0.000	0.000	0.000	0.011	0.003	0.000	0.000	0.000	0.803
28	0.025	0.007	0.001	0.000	0.001	0.046	0.013	0.002	0.000	0.001	0.029	0.008	0.001	0.000	0.001	0.011	0.003	0.000	0.000	0.000	0.009	0.002	0.000	0.000	0.000	0.839
29	0.020	0.005	0.001	0.000	0.001	0.036	0.010	0.001	0.000	0.001	0.023	0.006	0.001	0.000	0.001	0.009	0.002	0.000	0.000	0.000	0.007	0.002	0.000	0.000	0.000	0.873
30	0.015	0.004	0.001	0.000	0.000	0.028	0.008	0.001	0.000	0.001	0.017	0.005	0.001	0.000	0.000	0.007	0.002	0.000	0.000	0.000	0.005	0.001	0.000	0.000	0.000	0.902

Given the large number of HS, the proportions of the model cohort presented in the tables above for each HS are summarised in Table 106 below per aggregated HS for both aflibercept and ranibizumab.

For the first year the probabilities have been detailed for each 4-week. Thereafter and for purposes of brevity, the final cycle of each year was reported only after treatment duration (i.e. from Year 2 onwards).

Table 106. Proportion of the cohort in each aggregated health state and per treatment arm

	Aflibercept						Ranibizumab					
Years	**1**	**2**	**3**	**4**	**5**	**Death**	**1**	**2**	**3**	**4**	**5**	**Death**
Week 0	0.003	0.213	0.399	0.216	0.168	0.000	0.003	0.213	0.399	0.216	0.168	0.000
Week 0-4	0.148	0.431	0.271	0.093	0.056	0.001	0.121	0.388	0.295	0.118	0.077	0.001
Week 4-8	0.230	0.417	0.223	0.080	0.049	0.002	0.180	0.390	0.253	0.107	0.069	0.002
Week 8-12	0.268	0.394	0.233	0.052	0.051	0.002	0.208	0.377	0.266	0.073	0.074	0.002
Week 12-16	0.336	0.352	0.208	0.059	0.041	0.003	0.262	0.347	0.244	0.081	0.062	0.003
Week 16-20	0.319	0.362	0.210	0.071	0.034	0.004	0.249	0.352	0.248	0.095	0.052	0.004
Week 20-24	0.298	0.415	0.181	0.056	0.045	0.005	0.233	0.399	0.220	0.077	0.065	0.005
Week 24-28	0.298	0.415	0.180	0.056	0.045	0.006	0.233	0.399	0.220	0.077	0.065	0.006
Week 28-32	0.297	0.415	0.180	0.056	0.045	0.007	0.233	0.398	0.220	0.077	0.065	0.007
Week 32-36	0.297	0.414	0.180	0.056	0.045	0.007	0.233	0.398	0.220	0.077	0.065	0.007
Week 36-40	0.297	0.414	0.180	0.056	0.045	0.008	0.232	0.398	0.219	0.077	0.065	0.008
Week 40-44	0.297	0.414	0.180	0.056	0.045	0.009	0.232	0.397	0.219	0.077	0.065	0.009
Week 44-48	0.296	0.413	0.180	0.056	0.045	0.010	0.232	0.397	0.219	0.077	0.065	0.010
Week 48-52	0.296	0.413	0.180	0.056	0.045	0.011	0.232	0.397	0.219	0.077	0.065	0.011
2	0.291	0.408	0.178	0.056	0.044	0.022	0.228	0.391	0.217	0.076	0.065	0.022
3	0.287	0.402	0.177	0.056	0.044	0.035	0.224	0.386	0.215	0.076	0.064	0.035
4	0.281	0.396	0.175	0.055	0.044	0.049	0.220	0.380	0.212	0.075	0.063	0.049
5	0.276	0.389	0.173	0.055	0.043	0.064	0.216	0.373	0.210	0.075	0.063	0.064
6	0.270	0.382	0.171	0.054	0.042	0.080	0.211	0.366	0.207	0.074	0.062	0.080
7	0.264	0.374	0.169	0.054	0.042	0.098	0.207	0.358	0.203	0.073	0.061	0.098
8	0.257	0.366	0.166	0.053	0.041	0.117	0.201	0.350	0.200	0.072	0.060	0.117
9	0.250	0.357	0.163	0.052	0.040	0.137	0.196	0.342	0.196	0.071	0.059	0.137
10	0.243	0.347	0.159	0.051	0.040	0.160	0.190	0.332	0.191	0.069	0.058	0.160
11	0.235	0.337	0.155	0.050	0.039	0.184	0.184	0.322	0.186	0.068	0.056	0.184
12	0.227	0.326	0.151	0.049	0.038	0.210	0.177	0.311	0.181	0.066	0.055	0.210
13	0.218	0.314	0.146	0.048	0.036	0.239	0.170	0.299	0.174	0.064	0.053	0.239
14	0.208	0.301	0.141	0.046	0.035	0.269	0.163	0.287	0.168	0.062	0.051	0.269
15	0.198	0.287	0.135	0.044	0.034	0.302	0.155	0.274	0.161	0.060	0.049	0.302
16	0.187	0.272	0.129	0.042	0.032	0.338	0.146	0.259	0.153	0.057	0.047	0.338
17	0.176	0.256	0.122	0.040	0.030	0.376	0.138	0.244	0.145	0.054	0.044	0.376
18	0.164	0.239	0.115	0.038	0.029	0.416	0.128	0.228	0.136	0.051	0.042	0.416
19	0.151	0.222	0.107	0.036	0.027	0.458	0.119	0.211	0.126	0.047	0.039	0.458
20	0.139	0.204	0.099	0.033	0.025	0.501	0.109	0.194	0.116	0.044	0.036	0.502
21	0.126	0.185	0.090	0.030	0.023	0.547	0.098	0.176	0.106	0.040	0.033	0.547
22	0.113	0.166	0.081	0.027	0.020	0.592	0.088	0.158	0.096	0.036	0.030	0.592
23	0.100	0.147	0.072	0.024	0.018	0.638	0.078	0.140	0.085	0.032	0.026	0.638
24	0.087	0.129	0.064	0.022	0.016	0.683	0.068	0.122	0.075	0.029	0.023	0.683
25	0.075	0.111	0.055	0.019	0.014	0.725	0.059	0.106	0.065	0.025	0.020	0.725
26	0.064	0.095	0.047	0.016	0.012	0.766	0.050	0.090	0.056	0.021	0.017	0.766
27	0.053	0.080	0.040	0.014	0.010	0.803	0.042	0.076	0.047	0.018	0.015	0.803
28	0.043	0.065	0.033	0.011	0.008	0.839	0.034	0.062	0.038	0.015	0.012	0.839
29	0.034	0.051	0.026	0.009	0.007	0.873	0.027	0.049	0.030	0.012	0.010	0.873
30	0.026	0.039	0.020	0.007	0.005	0.902	0.020	0.037	0.023	0.009	0.007	0.902

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 two tables below (Table 107 and Table 108) show the cumulative discounted QALYs for the two treatment arms under base-case assumptions. A similar presentation format as above is provided, where cumulative QALYs are shown for each individual cycle of Year 1 and for the last cycle of each Year thereafter. An additional table (Table 109) was added that summarises cumulative QALYS per aggregated HS for both treatment arms.

Table 107. QALYs (discounted) accrued over time – aflibercept arm, 1 year of treatment

Years	1,1	1,2	1,3	1,4	1,5	2,1	2,2	2,3	2,4	2,5	3,1	3,2	3,3	3,4	3,5	4,1	4,2	4,3	4,4	4,5	5,1	5,2	5,3	5,4	5,5
Week 0	0.002	0.001	0.000	0.000	0.000	0.142	0.038	0.005	0.001	0.003	0.262	0.071	0.009	0.002	0.006	0.140	0.038	0.005	0.001	0.003	0.107	0.029	0.004	0.001	0.003
Week 0-4	0.104	0.027	0.003	0.001	0.002	0.286	0.078	0.009	0.002	0.007	0.178	0.048	0.006	0.001	0.004	0.060	0.016	0.002	0.001	0.001	0.036	0.010	0.001	0.000	0.001
Week 4-8	0.161	0.041	0.005	0.001	0.004	0.277	0.075	0.009	0.002	0.007	0.146	0.040	0.005	0.001	0.004	0.052	0.014	0.002	0.000	0.001	0.031	0.008	0.001	0.000	0.001
Week 8-12	0.188	0.048	0.006	0.001	0.004	0.261	0.071	0.009	0.002	0.006	0.153	0.042	0.005	0.001	0.004	0.033	0.009	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001
Week 12-16	0.236	0.061	0.007	0.002	0.005	0.233	0.063	0.008	0.002	0.006	0.137	0.037	0.005	0.001	0.003	0.038	0.010	0.001	0.000	0.001	0.026	0.007	0.001	0.000	0.001
Week 16-20	0.224	0.058	0.007	0.002	0.005	0.240	0.065	0.008	0.002	0.006	0.138	0.038	0.005	0.001	0.003	0.046	0.012	0.002	0.000	0.001	0.022	0.006	0.001	0.000	0.001
Week 20-24	0.209	0.054	0.007	0.002	0.005	0.276	0.075	0.009	0.002	0.007	0.119	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
Week 24-28	0.209	0.054	0.007	0.002	0.005	0.275	0.075	0.009	0.002	0.007	0.118	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
Week 28-32	0.209	0.054	0.007	0.002	0.005	0.275	0.075	0.009	0.002	0.007	0.118	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
Week 32-36	0.209	0.054	0.007	0.002	0.005	0.275	0.075	0.009	0.002	0.007	0.118	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
Week 36-40	0.209	0.054	0.007	0.002	0.005	0.275	0.075	0.009	0.002	0.007	0.118	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
Week 40-44	0.208	0.054	0.007	0.002	0.005	0.274	0.075	0.009	0.002	0.007	0.118	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
Week 44-48	0.208	0.053	0.007	0.002	0.005	0.274	0.075	0.009	0.002	0.007	0.118	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
Week 48-52	0.208	0.053	0.007	0.002	0.005	0.274	0.074	0.009	0.002	0.007	0.118	0.032	0.004	0.001	0.003	0.036	0.010	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
2	0.198	0.051	0.006	0.002	0.005	0.261	0.071	0.009	0.002	0.006	0.113	0.031	0.004	0.001	0.003	0.035	0.009	0.001	0.000	0.001	0.027	0.007	0.001	0.000	0.001
3	0.188	0.048	0.006	0.001	0.004	0.249	0.068	0.008	0.002	0.006	0.108	0.029	0.004	0.001	0.003	0.034	0.009	0.001	0.000	0.001	0.026	0.007	0.001	0.000	0.001
4	0.178	0.046	0.006	0.001	0.004	0.237	0.064	0.008	0.002	0.006	0.104	0.028	0.003	0.001	0.003	0.032	0.009	0.001	0.000	0.001	0.025	0.007	0.001	0.000	0.001

5	0.169	0.043	0.005	0.001	0.004	0.225	0.061	0.007	0.002	0.005	0.099	0.027	0.003	0.001	0.002	0.031	0.008	0.001	0.000	0.001	0.024	0.007	0.001	0.000	0.001
6	0.160	0.041	0.005	0.001	0.004	0.213	0.058	0.007	0.002	0.005	0.095	0.026	0.003	0.001	0.002	0.030	0.008	0.001	0.000	0.001	0.023	0.006	0.001	0.000	0.001
7	0.151	0.039	0.005	0.001	0.003	0.202	0.055	0.007	0.002	0.005	0.090	0.024	0.003	0.001	0.002	0.028	0.008	0.001	0.000	0.001	0.022	0.006	0.001	0.000	0.001
8	0.142	0.036	0.004	0.001	0.003	0.191	0.052	0.006	0.002	0.005	0.086	0.023	0.003	0.001	0.002	0.027	0.007	0.001	0.000	0.001	0.021	0.006	0.001	0.000	0.001
9	0.134	0.034	0.004	0.001	0.003	0.180	0.049	0.006	0.001	0.004	0.081	0.022	0.003	0.001	0.002	0.026	0.007	0.001	0.000	0.001	0.020	0.005	0.001	0.000	0.000
10	0.125	0.032	0.004	0.001	0.003	0.169	0.046	0.006	0.001	0.004	0.077	0.021	0.003	0.001	0.002	0.024	0.007	0.001	0.000	0.001	0.019	0.005	0.001	0.000	0.000
11	0.117	0.030	0.004	0.001	0.003	0.158	0.043	0.005	0.001	0.004	0.072	0.020	0.002	0.001	0.002	0.023	0.006	0.001	0.000	0.001	0.018	0.005	0.001	0.000	0.000
12	0.109	0.028	0.003	0.001	0.002	0.148	0.040	0.005	0.001	0.004	0.068	0.018	0.002	0.001	0.002	0.022	0.006	0.001	0.000	0.001	0.016	0.004	0.001	0.000	0.000
13	0.101	0.026	0.003	0.001	0.002	0.138	0.037	0.005	0.001	0.003	0.063	0.017	0.002	0.001	0.002	0.020	0.006	0.001	0.000	0.001	0.015	0.004	0.001	0.000	0.000
14	0.093	0.024	0.003	0.001	0.002	0.127	0.035	0.004	0.001	0.003	0.059	0.016	0.002	0.000	0.001	0.019	0.005	0.001	0.000	0.000	0.014	0.004	0.000	0.000	0.000
15	0.086	0.022	0.003	0.001	0.002	0.117	0.032	0.004	0.001	0.003	0.055	0.015	0.002	0.000	0.001	0.018	0.005	0.001	0.000	0.000	0.013	0.004	0.000	0.000	0.000
16	0.078	0.020	0.002	0.001	0.002	0.108	0.029	0.004	0.001	0.003	0.050	0.014	0.002	0.000	0.001	0.016	0.004	0.001	0.000	0.000	0.012	0.003	0.000	0.000	0.000
17	0.071	0.018	0.002	0.001	0.002	0.098	0.027	0.003	0.001	0.002	0.046	0.013	0.002	0.000	0.001	0.015	0.004	0.001	0.000	0.000	0.011	0.003	0.000	0.000	0.000
18	0.064	0.016	0.002	0.000	0.001	0.088	0.024	0.003	0.001	0.002	0.042	0.011	0.001	0.000	0.001	0.014	0.004	0.000	0.000	0.000	0.010	0.003	0.000	0.000	0.000
19	0.057	0.015	0.002	0.000	0.001	0.079	0.022	0.003	0.001	0.002	0.038	0.010	0.001	0.000	0.001	0.012	0.003	0.000	0.000	0.000	0.009	0.003	0.000	0.000	0.000
20	0.051	0.013	0.002	0.000	0.001	0.070	0.019	0.002	0.001	0.002	0.034	0.009	0.001	0.000	0.001	0.011	0.003	0.000	0.000	0.000	0.008	0.002	0.000	0.000	0.000
21	0.044	0.011	0.001	0.000	0.001	0.062	0.017	0.002	0.001	0.001	0.030	0.008	0.001	0.000	0.001	0.010	0.003	0.000	0.000	0.000	0.007	0.002	0.000	0.000	0.000
22	0.038	0.010	0.001	0.000	0.001	0.053	0.015	0.002	0.000	0.001	0.026	0.007	0.001	0.000	0.001	0.009	0.002	0.000	0.000	0.000	0.006	0.002	0.000	0.000	0.000
23	0.033	0.008	0.001	0.000	0.001	0.046	0.012	0.002	0.000	0.001	0.022	0.006	0.001	0.000	0.001	0.007	0.002	0.000	0.000	0.000	0.005	0.001	0.000	0.000	0.000
24	0.028	0.007	0.001	0.000	0.001	0.039	0.011	0.001	0.000	0.001	0.019	0.005	0.001	0.000	0.000	0.006	0.002	0.000	0.000	0.000	0.005	0.001	0.000	0.000	0.000
25	0.02	0.00	0.00	0.00	0.00	0.03	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

	3	6	1	0	1	2	9	1	0	1	6	4	1	0	0	5	1	0	0	0	4	1	0	0	0
26	0.019	0.005	0.001	0.000	0.000	0.027	0.007	0.001	0.000	0.001	0.013	0.004	0.000	0.000	0.000	0.004	0.001	0.000	0.000	0.000	0.003	0.001	0.000	0.000	0.000
27	0.015	0.004	0.000	0.000	0.000	0.022	0.006	0.001	0.000	0.001	0.011	0.003	0.000	0.000	0.000	0.004	0.001	0.000	0.000	0.000	0.003	0.001	0.000	0.000	0.000
28	0.012	0.003	0.000	0.000	0.000	0.017	0.005	0.001	0.000	0.000	0.008	0.002	0.000	0.000	0.000	0.003	0.001	0.000	0.000	0.000	0.002	0.001	0.000	0.000	0.000
29	0.009	0.002	0.000	0.000	0.000	0.013	0.004	0.000	0.000	0.000	0.007	0.002	0.000	0.000	0.000	0.002	0.001	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000
30	0.007	0.002	0.000	0.000	0.000	0.010	0.003	0.000	0.000	0.000	0.005	0.001	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000	0.001	0.000	0.000	0.000	0.000

Table 108. QALYs (discounted) accrued over time – ranibizumab arm, 1 year of treatment

Years	1,1	1,2	1,3	1,4	1,5	2,1	2,2	2,3	2,4	2,5	3,1	3,2	3,3	3,4	3,5	4,1	4,2	4,3	4,4	4,5	5,1	5,2	5,3	5,4	5,5
Week 0	0.002	0.001	0.000	0.000	0.000	0.142	0.038	0.005	0.001	0.003	0.262	0.071	0.009	0.002	0.006	0.140	0.038	0.005	0.001	0.003	0.107	0.029	0.004	0.001	0.003
Week 0-4	0.085	0.022	0.003	0.001	0.002	0.257	0.070	0.009	0.002	0.006	0.194	0.053	0.006	0.002	0.005	0.076	0.021	0.003	0.001	0.002	0.049	0.013	0.002	0.000	0.001
Week 4-8	0.126	0.032	0.004	0.001	0.003	0.259	0.070	0.009	0.002	0.006	0.166	0.045	0.006	0.001	0.004	0.069	0.019	0.002	0.001	0.002	0.044	0.012	0.001	0.000	0.001
Week 8-12	0.146	0.038	0.005	0.001	0.003	0.250	0.068	0.008	0.002	0.006	0.175	0.047	0.006	0.001	0.004	0.048	0.013	0.002	0.000	0.001	0.047	0.013	0.002	0.000	0.001
Week 12-16	0.184	0.047	0.006	0.001	0.004	0.230	0.063	0.008	0.002	0.006	0.160	0.044	0.005	0.001	0.004	0.053	0.014	0.002	0.000	0.001	0.040	0.011	0.001	0.000	0.001
Week 16-20	0.175	0.045	0.005	0.001	0.004	0.233	0.063	0.008	0.002	0.006	0.163	0.044	0.005	0.001	0.004	0.061	0.017	0.002	0.001	0.002	0.034	0.009	0.001	0.000	0.001
Week 20-24	0.164	0.042	0.005	0.001	0.004	0.265	0.072	0.009	0.002	0.006	0.145	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
Week 24-28	0.164	0.042	0.005	0.001	0.004	0.264	0.072	0.009	0.002	0.006	0.144	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
Week 28-32	0.164	0.042	0.005	0.001	0.004	0.264	0.072	0.009	0.002	0.006	0.144	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
Week 32-36	0.163	0.042	0.005	0.001	0.004	0.264	0.072	0.009	0.002	0.006	0.144	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
Week 36-40	0.163	0.042	0.005	0.001	0.004	0.264	0.072	0.009	0.002	0.006	0.144	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
Week 40-44	0.163	0.042	0.005	0.001	0.004	0.264	0.072	0.009	0.002	0.006	0.144	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
Week 44-48	0.163	0.042	0.005	0.001	0.004	0.263	0.072	0.009	0.002	0.006	0.144	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
Week 48-52	0.163	0.042	0.005	0.001	0.004	0.263	0.072	0.009	0.002	0.006	0.144	0.039	0.005	0.001	0.004	0.050	0.014	0.002	0.000	0.001	0.042	0.011	0.001	0.000	0.001
2	0.155	0.040	0.005	0.001	0.004	0.251	0.068	0.008	0.002	0.006	0.138	0.037	0.005	0.001	0.003	0.048	0.013	0.002	0.000	0.001	0.040	0.011	0.001	0.000	0.001
3	0.147	0.038	0.005	0.001	0.003	0.239	0.065	0.008	0.002	0.006	0.132	0.036	0.004	0.001	0.003	0.046	0.012	0.002	0.000	0.001	0.038	0.010	0.001	0.000	0.001
4	0.140	0.036	0.004	0.001	0.003	0.227	0.062	0.008	0.002	0.005	0.126	0.034	0.004	0.001	0.003	0.044	0.012	0.001	0.000	0.001	0.037	0.010	0.001	0.000	0.001

5	0.132	0.034	0.004	0.001	0.003	0.216	0.059	0.007	0.002	0.005	0.120	0.033	0.004	0.001	0.003	0.042	0.011	0.001	0.000	0.001	0.035	0.009	0.001	0.000	0.001
6	0.125	0.032	0.004	0.001	0.003	0.204	0.056	0.007	0.002	0.005	0.114	0.031	0.004	0.001	0.003	0.040	0.011	0.001	0.000	0.001	0.033	0.009	0.001	0.000	0.001
7	0.118	0.030	0.004	0.001	0.003	0.193	0.053	0.006	0.002	0.005	0.109	0.030	0.004	0.001	0.003	0.038	0.010	0.001	0.000	0.001	0.032	0.009	0.001	0.000	0.001
8	0.111	0.029	0.003	0.001	0.003	0.183	0.050	0.006	0.001	0.004	0.103	0.028	0.003	0.001	0.003	0.037	0.010	0.001	0.000	0.001	0.030	0.008	0.001	0.000	0.001
9	0.105	0.027	0.003	0.001	0.002	0.172	0.047	0.006	0.001	0.004	0.097	0.027	0.003	0.001	0.002	0.035	0.009	0.001	0.000	0.001	0.029	0.008	0.001	0.000	0.001
10	0.098	0.025	0.003	0.001	0.002	0.162	0.044	0.005	0.001	0.004	0.092	0.025	0.003	0.001	0.002	0.033	0.009	0.001	0.000	0.001	0.027	0.007	0.001	0.000	0.001
11	0.092	0.024	0.003	0.001	0.002	0.151	0.041	0.005	0.001	0.004	0.087	0.024	0.003	0.001	0.002	0.031	0.008	0.001	0.000	0.001	0.025	0.007	0.001	0.000	0.001
12	0.085	0.022	0.003	0.001	0.002	0.141	0.038	0.005	0.001	0.003	0.081	0.022	0.003	0.001	0.002	0.029	0.008	0.001	0.000	0.001	0.024	0.007	0.001	0.000	0.001
13	0.079	0.020	0.002	0.001	0.002	0.131	0.036	0.004	0.001	0.003	0.076	0.021	0.003	0.001	0.002	0.027	0.007	0.001	0.000	0.001	0.022	0.006	0.001	0.000	0.001
14	0.073	0.019	0.002	0.001	0.002	0.122	0.033	0.004	0.001	0.003	0.070	0.019	0.002	0.001	0.002	0.026	0.007	0.001	0.000	0.001	0.021	0.006	0.001	0.000	0.001
15	0.067	0.017	0.002	0.001	0.002	0.112	0.030	0.004	0.001	0.003	0.065	0.018	0.002	0.001	0.002	0.024	0.006	0.001	0.000	0.001	0.019	0.005	0.001	0.000	0.000
16	0.061	0.016	0.002	0.000	0.001	0.103	0.028	0.003	0.001	0.002	0.060	0.016	0.002	0.000	0.001	0.022	0.006	0.001	0.000	0.001	0.018	0.005	0.001	0.000	0.000
17	0.056	0.014	0.002	0.000	0.001	0.093	0.025	0.003	0.001	0.002	0.055	0.015	0.002	0.000	0.001	0.020	0.005	0.001	0.000	0.000	0.016	0.004	0.001	0.000	0.000
18	0.050	0.013	0.002	0.000	0.001	0.084	0.023	0.003	0.001	0.002	0.050	0.013	0.002	0.000	0.001	0.018	0.005	0.001	0.000	0.000	0.015	0.004	0.000	0.000	0.000
19	0.045	0.012	0.001	0.000	0.001	0.075	0.020	0.002	0.001	0.002	0.045	0.012	0.001	0.000	0.001	0.017	0.004	0.001	0.000	0.000	0.013	0.004	0.000	0.000	0.000
20	0.040	0.010	0.001	0.000	0.001	0.067	0.018	0.002	0.001	0.002	0.040	0.011	0.001	0.000	0.001	0.015	0.004	0.000	0.000	0.000	0.012	0.003	0.000	0.000	0.000
21	0.035	0.009	0.001	0.000	0.001	0.059	0.016	0.002	0.000	0.001	0.035	0.010	0.001	0.000	0.001	0.013	0.004	0.000	0.000	0.000	0.011	0.003	0.000	0.000	0.000
22	0.030	0.008	0.001	0.000	0.001	0.051	0.014	0.002	0.000	0.001	0.030	0.008	0.001	0.000	0.001	0.011	0.003	0.000	0.000	0.000	0.009	0.002	0.000	0.000	0.000
23	0.026	0.007	0.001	0.000	0.001	0.044	0.012	0.001	0.000	0.001	0.026	0.007	0.001	0.000	0.001	0.010	0.003	0.000	0.000	0.000	0.008	0.002	0.000	0.000	0.000
24	0.022	0.006	0.001	0.000	0.000	0.037	0.010	0.001	0.000	0.001	0.022	0.006	0.001	0.000	0.001	0.008	0.002	0.000	0.000	0.000	0.007	0.002	0.000	0.000	0.000
25	0.01	0.00	0.00	0.00	0.00	0.03	0.00	0.00	0.00	0.00	0.01	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00

	8	5	1	0	0	1	8	1	0	1	9	5	1	0	0	7	2	0	0	0	6	2	0	0	0
26	0.015	0.004	0.000	0.000	0.000	0.025	0.007	0.001	0.000	0.001	0.015	0.004	0.001	0.000	0.000	0.006	0.002	0.000	0.000	0.000	0.005	0.001	0.000	0.000	0.000
27	0.012	0.003	0.000	0.000	0.000	0.020	0.006	0.001	0.000	0.000	0.013	0.003	0.000	0.000	0.000	0.005	0.001	0.000	0.000	0.000	0.004	0.001	0.000	0.000	0.000
28	0.009	0.002	0.000	0.000	0.000	0.016	0.004	0.001	0.000	0.000	0.010	0.003	0.000	0.000	0.000	0.004	0.001	0.000	0.000	0.000	0.003	0.001	0.000	0.000	0.000
29	0.007	0.002	0.000	0.000	0.000	0.012	0.003	0.000	0.000	0.000	0.008	0.002	0.000	0.000	0.000	0.003	0.001	0.000	0.000	0.000	0.002	0.001	0.000	0.000	0.000
30	0.005	0.001	0.000	0.000	0.000	0.009	0.002	0.000	0.000	0.000	0.006	0.002	0.000	0.000	0.000	0.002	0.001	0.000	0.000	0.000	0.002	0.000	0.000	0.000	0.000

Table 109. QALYs (discounted) accrued over time – aflibercept and ranibizumab arms, aggregated HS, 1 year of treatment

	Aflibercept					Ranibizumab				
Years	**1**	**2**	**3**	**4**	**5**	**1**	**2**	**3**	**4**	**5**
Week 0	0.003	0.189	0.351	0.187	0.144	0.003	0.189	0.351	0.187	0.144
Week 0-4	0.137	0.383	0.238	0.081	0.048	0.112	0.344	0.259	0.102	0.066
Week 4-8	0.213	0.370	0.196	0.069	0.042	0.166	0.346	0.222	0.092	0.059
Week 8-12	0.248	0.349	0.204	0.045	0.044	0.193	0.334	0.234	0.064	0.063
Week 12-16	0.312	0.312	0.183	0.051	0.035	0.243	0.307	0.215	0.070	0.053
Week 16-20	0.295	0.321	0.185	0.061	0.029	0.231	0.312	0.218	0.082	0.045
Week 20-24	0.276	0.368	0.159	0.049	0.038	0.216	0.354	0.193	0.067	0.056
Week 24-28	0.276	0.368	0.158	0.049	0.038	0.216	0.354	0.193	0.067	0.056
Week 28-32	0.276	0.368	0.158	0.049	0.038	0.216	0.353	0.193	0.067	0.056
Week 32-36	0.275	0.368	0.158	0.049	0.038	0.216	0.353	0.193	0.067	0.056
Week 36-40	0.275	0.367	0.158	0.049	0.038	0.215	0.353	0.193	0.067	0.056
Week 40-44	0.275	0.367	0.158	0.049	0.038	0.215	0.353	0.193	0.067	0.056
Week 44-48	0.275	0.367	0.158	0.049	0.038	0.215	0.352	0.192	0.067	0.056
Week 48-52	0.274	0.366	0.158	0.048	0.038	0.215	0.352	0.192	0.066	0.056
2	0.261	0.349	0.151	0.047	0.037	0.204	0.335	0.184	0.064	0.053
3	0.248	0.333	0.145	0.045	0.035	0.194	0.319	0.176	0.061	0.051
4	0.235	0.317	0.139	0.043	0.034	0.184	0.304	0.168	0.059	0.049
5	0.223	0.301	0.133	0.041	0.032	0.174	0.288	0.161	0.056	0.047
6	0.211	0.285	0.126	0.040	0.031	0.165	0.273	0.153	0.054	0.045
7	0.199	0.270	0.120	0.038	0.029	0.156	0.259	0.145	0.051	0.042
8	0.187	0.255	0.114	0.036	0.028	0.147	0.244	0.138	0.049	0.040
9	0.176	0.240	0.109	0.034	0.026	0.138	0.230	0.130	0.047	0.038
10	0.165	0.226	0.103	0.033	0.025	0.129	0.216	0.123	0.044	0.036
11	0.154	0.212	0.097	0.031	0.023	0.121	0.203	0.116	0.042	0.034
12	0.144	0.198	0.091	0.029	0.022	0.113	0.189	0.109	0.039	0.032
13	0.133	0.184	0.085	0.027	0.021	0.104	0.176	0.101	0.037	0.030
14	0.123	0.170	0.079	0.025	0.019	0.096	0.163	0.094	0.034	0.028
15	0.113	0.157	0.073	0.024	0.018	0.089	0.150	0.087	0.032	0.026
16	0.103	0.144	0.068	0.022	0.016	0.081	0.137	0.080	0.029	0.024
17	0.094	0.131	0.062	0.020	0.015	0.073	0.125	0.073	0.027	0.022
18	0.085	0.118	0.056	0.018	0.014	0.066	0.113	0.066	0.025	0.020
19	0.076	0.106	0.050	0.017	0.012	0.059	0.101	0.060	0.022	0.018
20	0.067	0.094	0.045	0.015	0.011	0.052	0.089	0.053	0.020	0.016
21	0.059	0.082	0.040	0.013	0.010	0.046	0.078	0.047	0.018	0.014
22	0.051	0.072	0.035	0.011	0.008	0.040	0.068	0.041	0.015	0.012
23	0.043	0.061	0.030	0.010	0.007	0.034	0.058	0.035	0.013	0.011
24	0.036	0.052	0.025	0.008	0.006	0.029	0.049	0.030	0.011	0.009
25	0.030	0.043	0.021	0.007	0.005	0.024	0.041	0.025	0.009	0.008
26	0.025	0.036	0.018	0.006	0.004	0.020	0.034	0.021	0.008	0.006
27	0.020	0.029	0.014	0.005	0.004	0.016	0.027	0.017	0.006	0.005
28	0.016	0.023	0.011	0.004	0.003	0.012	0.022	0.013	0.005	0.004
29	0.012	0.017	0.009	0.003	0.002	0.009	0.016	0.010	0.004	0.003
30	0.009	0.013	0.007	0.002	0.002	0.007	0.012	0.008	0.003	0.002

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:

Table 110 below reports discounted life years (LY) and discounted QALYs accrued for each model HS for the treatment (aflibercept) and the comparator (ranibizumab). Costs associated with each model health state are also presented. Results are presented for the base-case analysis.

Table 110. Model outputs (discounted) by clinical outcomes

	Aflibercept			Ranibizumab		
Outcome	**LY**	**QALY**	**Cost (£)**	**LY**	**QALY**	**Cost (£)**
1,1	4.070	[redacted]	[redacted]	3.186	[redacted]	[redacted]
1,2	1.107	[redacted]	[redacted]	0.866	[redacted]	[redacted]
1,3	0.136	[redacted]	[redacted]	0.107	[redacted]	[redacted]
1,4	0.034	[redacted]	[redacted]	0.027	[redacted]	[redacted]
1,5	0.102	[redacted]	[redacted]	0.080	[redacted]	[redacted]
2,1	5.841	[redacted]	[redacted]	5.582	[redacted]	[redacted]
2,2	1.589	[redacted]	[redacted]	1.518	[redacted]	[redacted]
2,3	0.196	[redacted]	[redacted]	0.187	[redacted]	[redacted]
2,4	0.049	[redacted]	[redacted]	0.047	[redacted]	[redacted]
2,5	0.147	[redacted]	[redacted]	0.140	[redacted]	[redacted]
3,1	2.712	[redacted]	[redacted]	3.243	[redacted]	[redacted]
3,2	0.737	[redacted]	[redacted]	0.882	[redacted]	[redacted]
3,3	0.091	[redacted]	[redacted]	0.109	[redacted]	[redacted]
3,4	0.023	[redacted]	[redacted]	0.027	[redacted]	[redacted]
3,5	0.068	[redacted]	[redacted]	0.081	[redacted]	[redacted]
4,1	0.878	[redacted]	[redacted]	1.185	[redacted]	[redacted]
4,2	0.239	[redacted]	[redacted]	0.322	[redacted]	[redacted]
4,3	0.029	[redacted]	[redacted]	0.040	[redacted]	[redacted]
4,4	0.007	[redacted]	[redacted]	0.010	[redacted]	[redacted]
4,5	0.022	[redacted]	[redacted]	0.030	[redacted]	[redacted]
5,1	0.673	[redacted]	[redacted]	0.977	[redacted]	[redacted]
5,2	0.183	[redacted]	[redacted]	0.266	[redacted]	[redacted]
5,3	0.023	[redacted]	[redacted]	0.033	[redacted]	[redacted]
5,4	0.006	[redacted]	[redacted]	0.008	[redacted]	[redacted]
5,5	0.017	[redacted]	[redacted]	0.025	[redacted]	[redacted]
LY, life years; QALY, quality-adjusted life year						

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.

Disaggregated discounted incremental clinical and economic outcomes are reported by HS in Table 111 and Table 112 below.

Table 111. Summary of QALY gain (discounted) by health state

Health	QALY	QALY	Increment	Absolute	% absolute

state	aflibercept	ranibizumab		increment	increment
1,1	[redacted]				
1,2					
1,3					
1,4					
1,5					
2,1					
2,2					
2,3					
2,4					
2,5					
3,1					
3,2					
3,3					
3,4					
3,5					
4,1					
4,2					
4,3					
4,4					
4,5					
5,1					
5,2					
5,3					
5,4					
5,5					
Total					

QALY, quality-adjusted life year

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

Table 112. Summary of costs (discounted) by health state

Health state	Cost aflibercept (£)	Cost ranibizumab (£)	Increment (£)	Absolute increment (£)	% absolute increment
1,1	[redacted]				
1,2					
1,3					
1,4					
1,5					
2,1					
2,2					
2,3					
2,4					
2,5					
3,1					
3,2					
3,3					
3,4					
3,5					
4,1					
4,2					
4,3					
4,4					
4,5					
5,1					
5,2					

5,3	[redacted]
5,4	
5,5	
Total	

QALY, quality-adjusted life year

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

Table 113 below presents the breakdown of discounted costs for the intervention and comparator as well as the increment, absolute increment and percentage absolute increment.

Table 113. Summary of predicted resource use (discounted) by category of cost

Health state	Cost aflibercept (£)	Cost ranibizumab (£)	Increment (£)	Absolute increment (£)	% absolute increment
Technology cost	[redacted]				
Administration and monitoring cost					
AE cost (blindness)					
Total					

Note that in Table 113 above, some the results presented for the row “AE (blindness) represent the costs associated with blindness only since AEs were not modelled in the base-case analyses.

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.

Ranibizumab is considered the standard of care for CRVO with MO. The base-case analysis consisted of one treatment comparator pair namely aflibercept 2mg versus ranibizumab 0.5 mg.

The results of the base-case analysis showed that compared with ranibizumab, aflibercept was associated with marginal gains in LYs (incremental LYs: 0.001), QALYs (incremental QALYs: 0.054) and costs (incremental costs: £[redacted]). Compared to ranibizumab, aflibercept was deemed cost-effective in the treatment of MO secondary to CRVO (ICER: £[redacted]/QALY).

Table 114. Base-case results: aflibercept vs. ranibizumab

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	18.977	[redacted]	-	-	-	-
Ranibizumab	[redacted]	18.976	[redacted]	[redacted]	0.001	0.054	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Aflibercept was associated with similar life expectancy to ranibizumab over the lifetime (30 years) horizon. These results were based on the treatment effects calculated based on i) week 0-24: the pooled 24-week COPERNICUS and GALILEO clinical trial outcomes and the RR (ranibizumab vs. aflibercept) of gaining ≥ 15 letters of BCVA calculated through the NMA reported in Section 6.7 and ii) week 25-52: assumption that vision achieved by patients in either arms at week 24 was maintained throughout the rest of the year. The RR suggested no statistically significant difference in clinical effect between the two treatments (RR: [redacted]). Aflibercept was associated with slightly higher costs compared to ranibizumab, primarily reflecting higher technology costs (when using NHS list price). Overall, aflibercept was associated with costs savings for administration and monitoring visits (see Table 114 above) reflecting that less of these visits are necessary when patients are treated with aflibercept compared with ranibizumab.

Sensitivity analyses

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

Deterministic sensitivity analysis was performed by means of one-way and multivariate sensitivity analysis, where one parameter or group of related parameters was varied relative to its base case value. The method adopted and the parameters tested were described in Section 7.6.2.

Overall, there were 25 sensitivity analyses conducted for the base-case analysis. A tornado plot for the top 15 most sensitive parameters based on the ICER measure at a willingness to pay of £20,000 per QALY was used to illustrate the results of the analyses. Note the tornado diagrams were designed to hide ICERs when aflibercept is dominant or dominated. This is why for several parameters, only one bar, showing either results of the “low” or the “high” variation, can be seen.

The tornado diagram (Figure 23) shows variation in the ICER from a base-case of £[redacted]. The key drivers of the cost-effectiveness of aflibercept vs. ranibizumab were the frequency of injections with ranibizumab in Year 1, the RR of gaining ≥ 15 letters with ranibizumab compared with aflibercept, the frequency of injections with aflibercept in Year 1 and the rate of monitoring patients with both ranibizumab and aflibercept in Year 1. Additional drivers of the results were the utility values.

The bars of the diagram that are not shown - as generating results outside the North East cost-effectiveness quadrant - indicate that:

- aflibercept is [redacted] when using the lower values for the Year 1 frequency of administration with ranibizumab, the lower rate of aflibercept administration visits in month 7-12 and the higher rate of Year 1 monitoring visits for patients treated with ranibizumab.

- aflibercept is [redacted] when using the higher RR value.

Figure 23. Tornado plot – ICER of aflibercept vs. ranibizumab, 1 year of treatment, lifetime horizon

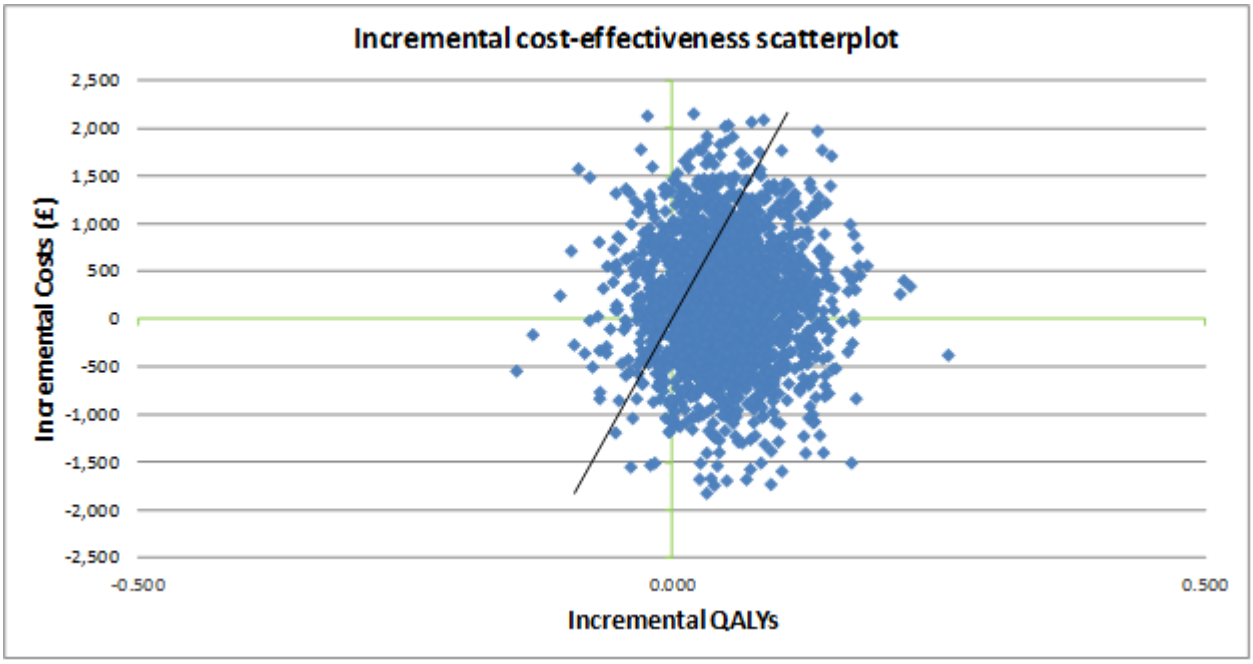
[redacted]

7.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

The probabilistic sensitivity analysis (PSA) was run with 2,000 simulations. PSA outputs are represented graphically by i) plotting incremental cost and effectiveness pairs on the cost-effectiveness plane (CE scatter plot) ii) presenting the likelihood of aflibercept being cost-effective at a range of willingness-to-pay (WTP) thresholds.

The results of the PSA graphed as a scatter plot are presented in Figure 24 below):

Figure 24. Scatterplot for aflibercept vs. ranibizumab, 1 year of treatment, lifetime horizon



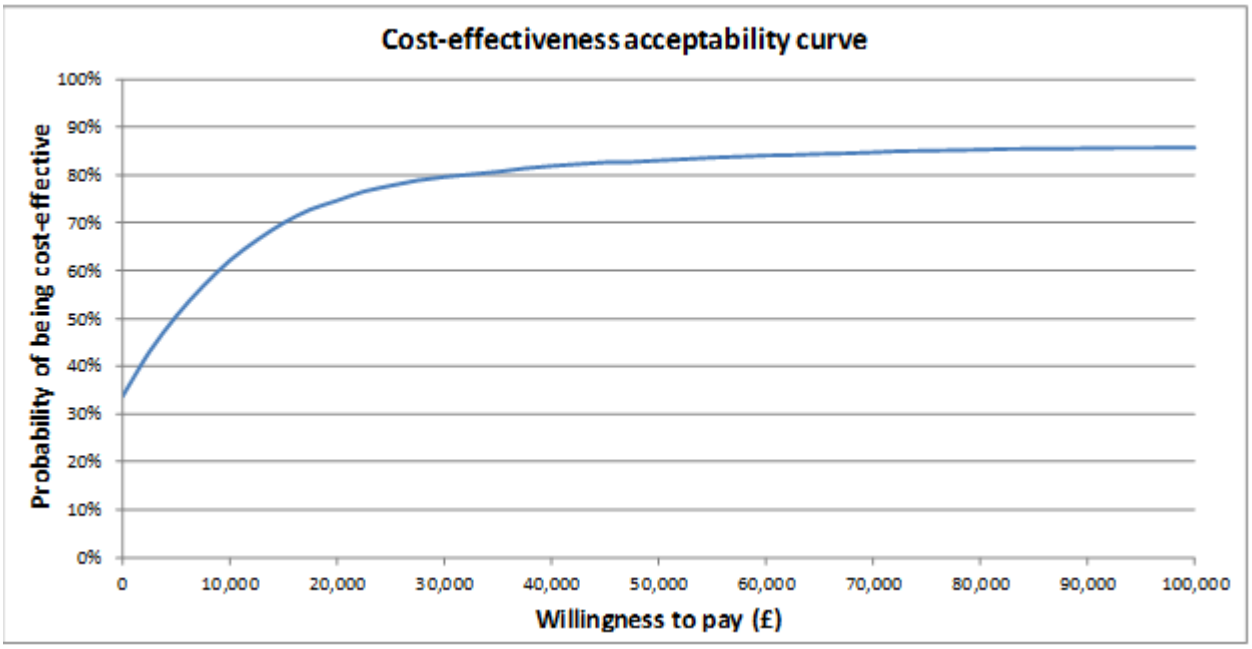
The PSA demonstrated that, when using NHS list price, compared to ranibizumab, the likelihood aflibercept is more effective and more costly (and potentially cost-effective) is 54%, and the likelihood aflibercept is more effective and less costly (i.e. dominant) is 33.85%. The probability of aflibercept being less effective and more costly (i.e. dominated) is 7.20%. In 4.95% of the simulations, aflibercept was both less effective and less costly than ranibizumab. These probabilities are summarised in Table 115 below:

Table 115. PSA simulations per CE quadrant for aflibercept vs. ranibizumab

More costly and more effective	Dominant	Dominated	Less costly and less effective
54.0%	33.85%	7.20%	4.95%

In addition, the analysis indicated that aflibercept would be considered cost-effective versus ranibizumab across a range of hypothetical WTP thresholds as shown in the CEAC (Figure 25). At a threshold of £20,000 per QALY, the probability of aflibercept being cost-effective in comparison with ranibizumab, the current standard of care was 74.6%.

Figure 25. CE plane for aflibercept vs. ranibizumab, 1 year of treatment, lifetime horizon



7.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

The five following scenario analyses (see Section 7.6.1) were conducted:

a) Treatment duration:

- Extending treatment duration from 1 year in the base-case to 2 and 4 years;

b) Using utility values from the literature (Czoski-Murray 2009 or "Brazier") instead of trial-based utility values in the base-case;

c) Modelling AEs as opposed to discarding them in the base-case;

d) Comparing aflibercept vs. dexamethasone as opposed to vs. ranibizumab in the base-case. This analysis was included as a scenario analysis for completeness (see Section 2.7)

The deterministic results for each analysis are presented below. For scenario analysis e), where aflibercept is compared to dexamethasone, PSA scatter plots are presented in addition.

Treatment duration scenario analyses

i) Extending treatment duration from 1 year in the base-case to 2 years

The results of the 2-year treatment scenario analysis (Table 116) showed that compared with ranibizumab, aflibercept was associated with slightly higher LYs (incremental LYs: 0.001), QALYs (incremental QALYs: 0.054) and costs (incremental costs: £[redacted]), when using NHS list price. Compared to ranibizumab, aflibercept was deemed cost-effective in the treatment of MO secondary to CRVO (ICER: £[redacted]).

Table 116. Scenario results: aflibercept vs. ranibizumab – 2-year treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	18.977	[redacted]	-	-	-	-
Ranibizumab	[redacted]	18.976	[redacted]	[redacted]	0.001	0.054	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

When extending treatment duration from 1 to 2 years, incremental QALYs remained unchanged, reflecting the assumption of “maintained vision” applied to model treatment effectiveness in Year 2. Incremental costs varied from £[redacted] in the base-case to £[redacted] in this scenario reflecting the assumptions around Year 2 resource use made for aflibercept and ranibizumab, of respectively 3.5 vs. 3.8 administration and 4.8 vs. 5.8 monitoring visits.

ii) Extending treatment duration from 1 year in the base-case to 4 years

The results of the 4-year treatment scenario analysis (Table 117) showed that compared with ranibizumab, aflibercept was associated with slightly higher LYs (incremental LYs: 0.001), QALYs (incremental QALYs: 0.054) but lower costs (incremental costs: -£[redacted]), when using NHS list price. Compared to ranibizumab, aflibercept was deemed [redacted] in the treatment of MO secondary to CRVO.

Table 117. Scenario results: aflibercept vs. ranibizumab – 4-year treatment

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	18.977	[redacted]	-	-	-	-
Ranibizumab	[redacted]	18.976	[redacted]	[redacted]	0.001	0.054	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

When extending treatment duration from 1 to 4 years, incremental QALYs remained unchanged, as explained above for the 2-year treatment duration scenario. Incremental costs varied from £[redacted] in the base-case to -£[redacted] in this scenario reflecting the assumptions around resource use made for aflibercept and ranibizumab.

The annual frequency of administration and monitoring was the following for aflibercept and ranibizumab respectively:

- Administration: Year 3: 3.0 vs. 3.0; Year 4: 1.8 vs. 2.2
- Monitoring: Year 3: 3.8 vs. 4.4; Year 4: 3.2 vs. 3.8.

Using utility values from the literature (Czoski-Murray 2009 or "Brazier")

The results of scenario analysis using utility values derived from Czoski-Murray et al. 2009 as opposed to trial-based utility values (Table 118) showed that compared with ranibizumab, aflibercept was associated with slightly higher LYs (incremental LYs: 0.001), QALYs (incremental QALYs: 0.028) and costs (incremental costs: £[redacted]), when using NHS list price. Compared to ranibizumab, aflibercept was deemed cost-effective in the treatment of MO secondary to CRVO (ICER: £[redacted]/QALY).

Table 118. Scenario results: aflibercept vs. ranibizumab – Czoski-Murray utility values

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	18.977	[redacted]	-	-	-	-
Ranibizumab	[redacted]	18.976	[redacted]	[redacted]	0.001	0.028	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

As expected, replacing the trial-based with literature-based utility values impacted incremental QALYs only. The incremental QALYs decreased from 0.054 in the base-case to 0.028 in the scenario.

This results from both:

i) the fact the literature-based values are BSE values and were applied as such in the model, whereas the trial-based values are WSE values and were applied as such in the model and

ii) the patients' baseline distribution across HS and transition probabilities applied in the model.

Specifically, 74% of patients treated at baseline (either arm) have a BCVA of ≥ 80 letters in their FE and are likely to have the same FE BCVA over the treatment duration given that the model assumes FE BCVA remains constant of time (see Section 7.3.2). Furthermore, the majority of SE transitions applied over the first 24 weeks of treatment reflect movement to a HS with improved BCVA in the SE (see Table 54 to Table 59 in Section 7.3.2). Consequently, a greater HRQL benefit will be achieved in patients that both have a FE baseline BCVA of ≥ 80 letters and a SE BCVA improvement over the first 24 weeks of treatment (thereafter "maintained vision" is assumed). Given that the literature-based utilities offer no utility benefit for these patients (see Table 78 in Section 7.4.9), BCVA change using this dataset will have a lower impact on HRQL that using the WSE dataset.

Modelling AEs

The results of the scenario analysis including AEs (Table 119) showed that compared with ranibizumab, aflibercept was associated with slightly higher LYs (incremental LYs: 0.001), QALYs (incremental QALYs: 0.054) and costs (incremental costs: £[redacted]), when using NHS list price. Compared to ranibizumab, aflibercept was deemed cost-effective in the treatment of MO secondary to CRVO (ICER: £[redacted] QALY).

Table 119. Scenario results: aflibercept vs. ranibizumab – adverse events included

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	18.977	[redacted]	-	-	-	-

Ranibizumab	[redacted]	18.976	[redacted]	[redacted]	0.001	0.054	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Including AEs impacts both QALYs and costs as AE are associated with both disutilities and unit costs. Given the very small rates of AEs used in the model, the impact on health and benefits taken separately is minor. Total QALY gains decrease by 0.001 QALY in each arm, generating therefore the same incremental QALY gain as in the base-case ([redacted]). The impact on incremental costs is also minor (a decrease of £[redacted]), with more AE cost than aflibercept, reflecting higher rates of cataracts. Overall, the impact on the ICER, which decreased from £[redacted]n the base-case to £[redacted] in this scenario reflects the small impact on a low incremental costs and supports the argument that the base-case is a conservative analysis.

Comparing aflibercept vs. dexamethasone

This scenario analysis was included for completeness but note that as per the decision problem rationale (see Section 2.7), dexamethasone is not considered to be standard of care. The 1-year results of the analysis comparing aflibercept with dexamethasone and including AEs (Table 120) showed that compared with dexamethasone, aflibercept was associated with slightly higher LYs (incremental LYs: 0.001), higher QALYs (incremental QALYs: 0.189) and significantly higher costs (incremental costs: £[redacted]), when using NHS list price. Compared to dexamethasone, and assuming a WTP threshold of £20,000/QALY, aflibercept was deemed cost-effective in the treatment of MO secondary to CRVO (ICER: £[redacted]/QALY).

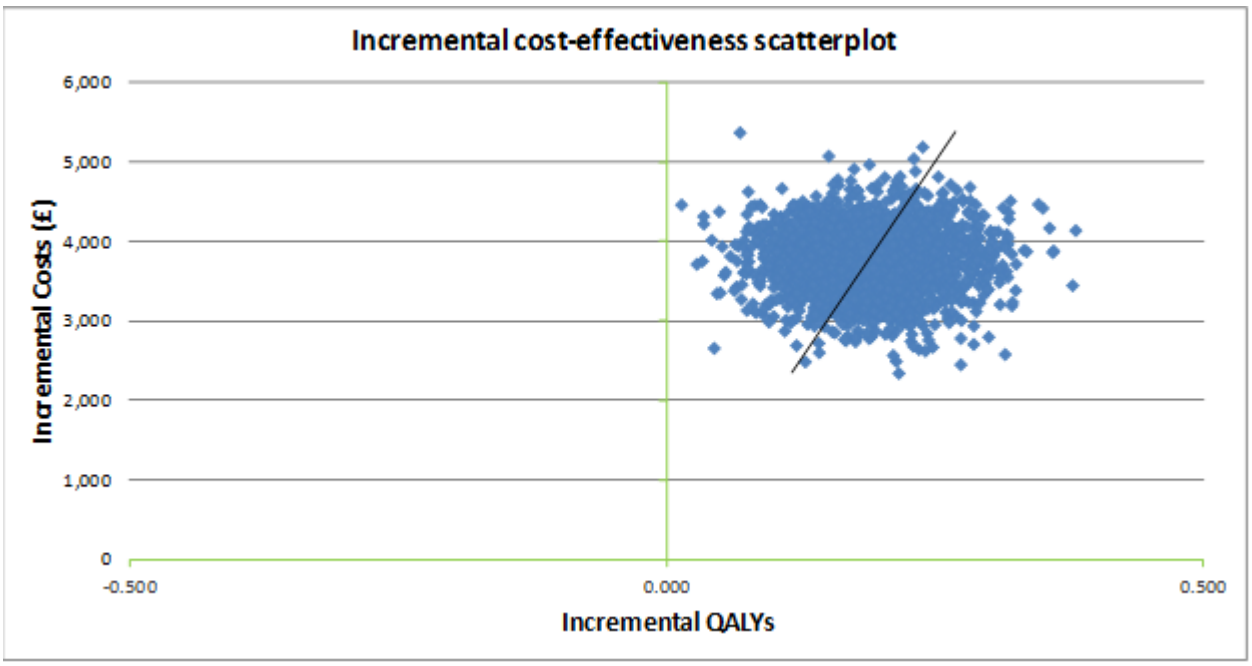
Table 120. Scenario results: aflibercept vs. dexamethasone

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)
Aflibercept	[redacted]	18.977	[redacted]	-	-	-	-
Dexamethasone	[redacted]	18.976	[redacted]	[redacted]	0.001	0.189	[redacted]
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

The additional QALY gain (of 0.189 vs.0.054 in the base-case) reflected the differential RR (dexamethasone vs. aflibercept compared against ranibizumab vs. aflibercept) of

gaining ≥ 15 letters of BCVA generated in the NMA (Section 6.7). A similar conservative approach as in the base-case analysis was followed whereby it was assumed that that vision achieved by patients in either arms at week 24 was maintained throughout the rest of the year despite significant differences favouring aflibercept shown in the NMA for the first 24 weeks. The RR (dexamethasone vs. aflibercept) was associated with statistically significant differences between the treatment effects of the interventions (RR: [redacted]). Incremental costs associated with aflibercept resulted primarily from additional technology costs, which predominantly reflected the lower frequency of administration of dexamethasone (4 injections) compared with aflibercept (8.3), despite the per-injection price of dexamethasone being slightly higher (£870) than the per-injection price of aflibercept (£816), when using NHS list price .

Figure 26. Scatterplot for aflibercept vs. dexamethasone, 1 year of treatment, lifetime horizon



A PSA was conducted on the results of this analysis using 2,000 simulations. The results are presented in the scatter plot below (Figure 26)

The PSA demonstrated that compared to dexamethasone, the likelihood aflibercept is more effective and more costly (and potentially cost-effective) is 100%, and that it is unlikely that aflibercept is more effective and less costly (i.e. dominant). Likewise, it is unlikely that aflibercept is less effective and more costly (i.e. dominated). These probabilities are summarised in Table 121 below.

Table 121. PSA simulations per CE quadrant for aflibercept vs. dexamethasone

More costly and more effective	Dominant	Dominated	Less costly and less effective
100%	0%	0%	0%

7.7.10 What were the main findings of each of the sensitivity analyses?

The main findings were the following:

- When using NHS list price, aflibercept was found to be cost-effective relative to ranibizumab by generating improved LYs/QALYs at marginal additional cost (ICER: £[redacted] /QALY).

- The deterministic sensitivity analysis has shown that results were most sensitive to the number of injections (primarily injections with ranibizumab), the RR of gaining ≥ 15 letters with ranibizumab compared with aflibercept, the frequency of injections with aflibercept in Year 1 and the rate of monitoring patients with both ranibizumab and aflibercept in Year 1. Additional drivers of the results were the utility values.1. However when the values of the parameters were tested within plausible ranges, the ICER falling in the North East quadrant showed that aflibercept remained cost-effective, with the exception of when the lower frequency of injections with ranibizumab was used.

- The OWSA also demonstrated that aflibercept was [redacted] when varying the values of several parameters, while it was [redacted] on one occasion only, when using the higher RR value.

- Results from the probabilistic sensitivity analysis have shown that aflibercept is 33.85% likely to dominate ranibizumab and 54% likely to be more costly and more effective; in the majority of simulations, aflibercept was cost-effective compared with ranibizumab, with a 74.6% likelihood of being cost-effective at a threshold of £20,000/QALY.

- Scenario analyses were performed to test how key model assumptions impacted the base-case results. Inputs tested in the scenarios included using literature-based vs. trial-based utility values, extending treatment duration to 2 and 4 years and

modelling AEs. Results have shown that aflibercept was [redacted] in the 4-year treatment scenario and was cost-effective in all other scenarios.

- In the scenario analysis comparing aflibercept to dexamethasone as opposed to ranibizumab (standard of care), the ICER was £[redacted] /QALY, when assuming 4 dexamethasone injections (based on retreatment every 4 months) and 6 monitoring visits. Aflibercept was associated with more additional QALYs compared with dexamethasone (0.189) than compared with ranibizumab (0.054). Despite a similar list price (aflibercept: £816; dexamethasone: £870), aflibercept was found to be overall more expensive than dexamethasone (incremental total cost: £[redacted]). This primarily reflects the assumptions made around injection frequency in 1 year of treatment (aflibercept: 8.3; dexamethasone: 4).

In summary, the base-case results demonstrated that compared with ranibizumab, aflibercept is cost-effective in the treatment of patients with MO secondary to CRVO. The robustness of these results was confirmed by the outputs of both the OWSA and the PSA.

7.7.11 What are the key drivers of the cost-effectiveness results?

The cost-effectiveness results are mainly driven by the following:

- The number of injections

– Number of injections is a key driver of the model since the annual number of injections has a direct impact on the drug cost component which has shown to be another key driver of the base case results. The rates of injections for ranibizumab impacted more significantly the results that those for aflibercept.

- The RR of gaining vision (ranibizumab vs. aflibercept)

– The RR of gaining vision is a key driver in all analyses comparing aflibercept versus ranibizumab as this determines the differences in the treatment effects between the two therapies.

- Frequency of monitoring

– Results are driven by the number of monitoring visits for aflibercept and ranibizumab.

- Utility values

– WSE trial-based utility values also represented a driver of the CE results, but to a lesser extent than the parameters listed above.

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.

Two clinicians were involved at the stage of developing the model to ensure key assumptions (e.g. around model structure and disease progression) underlying the model were robust. Furthermore, a Physician survey (see Section 7.5.4) was conducted to estimate values for resource use inputs. Unit costs' values were aligned with that used in previous HTA submissions in ophthalmic indications(8;20). WSE trial-based utility values used for the base-case analysis were additionally put in perspective with BSE literature-based utility values derived from Czoski-Murray *et al.* 2009(80) in a scenario analysis (see Section 0 and Section7.4.9). This analysis showed that, when applied to the "whole person", WSE values generated a greater health benefit than BSE values, despite the span of the BSE values being greater than that of the WSE values. This reflected the baseline distribution of patients by BCVA range and the HRQL benefit associated with BCVA change in a population which affected eye is predominantly the WSE.

In addition, a check of internal validity was performed to ensure that outputs were logical and accurate within the framework set by the model. This was ensured by quality control of the model by the model developers, and a model audit performed by an experienced health economist outside the team of developers in which extreme value scenarios were tested to cross check that the model behaved logically.

The model was additionally validated against the underlying trial data as shown in Table 122 below for the first 24 weeks of treatment and for the remaining of the treatment period respectively. Both the 24-week and 52-week validations suggest reasonable consistency of results. Taking the 24-week example, the trials suggest an additional treatment effect of aflibercept over ranibizumab of 4.1 letters, while the model estimates an additional

treatment effect of 3.2 letters. This suggests a conservative analysis with reasonable integrity.

Table 122. Mean BCVA gain (number of letters) at week 24 – Trial vs. model outputs

	Baseline BCVA	24-week BCVA	Treatment effect	Aflibercept treatment effect	Source
Trial data					
Aflibercept	52.0	69.7	18.2 ((69.7-52)-(49.4-49.9))	4.1	24-week integrated data (see Section 6.5)
Sham	49.9	49.4	-	-	24-week integrated data (see Section 6.5)
Ranibizumab	48.1	63.0	14.1 ((63-48.1))-(50-49.2))	-	Brown *et al.* 2010(30)
Sham	49.2	50.0	-	-	Brown *et al.* 2010(30)
Model outputs*					
Aflibercept	53.0	70.7	17.7	3.2	Model output
Ranibizumab	53.0	67.5	14.5	-	Model output

*Mean BCVA estimated assuming a mid-point BCVA for each modeled HS.

Table 123. Mean BCVA gain (number of letters) at week 52 – Trial vs. model outputs

	Baseline BCVA	52-week BCVA	Absolute difference	Aflibercept treatment effect	Source
Trial data					
Aflibercept	53.6*	70.4	13.0 ((70.4-53.6)-(54.7-50.9))	6.4	52-week GALILEO data (see Section 6.5)
Sham	50.9*	54.7	-	-	52-week GALILEO data (see Section 6.5)
Ranibizumab	48.1	62.0	6.6 ((62.0-48.1)-(56.5-49.2))	-	Brown *et al.* 2010(30);Campochiaro *et al.* 2011(35)
Sham	49.2	56.5	-	-	Brown *et al.* 2010(30); Campochiaro *et al.* 2011(35)
Model outputs					
Aflibercept	53.0	70.3	17.3	3.1	Model output
Ranibizumab	53.0	67.2	14.2	-	Model output

*Note the GALILEO data were used for 52-week validation and therefore baseline data are different from data presented in the table above in which 24-week integrated data were used for baseline.

Note that 52-week CRUISE results for the ranibizumab arm as reported by Campochiaro *et al.* 2010 also include sham patients due to the cross-over design of the trial. In contrast, 52-week results for the aflibercept arm were taken from the GALILEO trial, i.e. no sham patients were included in this arm.

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.

Subgroup analyses were not part of the current evaluation since the target population includes all those patients with MO secondary to CRVO requiring anti-VEGF treatment.

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.

No subgroup analyses were conducted on patients' perfusion[9] status on the basis that, trial analyses demonstrated that the baseline perfusion status did not affect response rates: pooled trial results showed that at week 24 (before cross-over in COPERNICUS), mean change from baseline in BCVA letter score was 18.3 versus -4.1 for VEGF Trap-Eye versus sham treatment in nonperfused/indeterminable (10 disc areas of non-perfusion) eyes and 17.5 versus 0.8 letters in perfused eyes, with p=0.1054 (see Section 6.5).

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?

Neither the systematic literature review nor the ISPOR congress abstracts search conducted on the economic literature identified EE that included aflibercept (see Section 7.1.1).

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?

The scope of the appraisal considers adults with MO secondary to CRVO. The economic evaluation is relevant to all groups of patients who could potentially use the technology as identified in the decision problem in Section 5. The NMA used to derive RR applied in the economic evaluation (see Section 6.7 included studies of MO secondary to CRVO only.

[9] Baseline retinal perfusion status, determined by fluorescein angiography (FA), was measured for each trial subject using the following criteria: i) perfused: 10 or greater disc areas (DA) of capillary nonperfusion on FA; ii) non-perfused: <10 DA of capillary nonperfusion on FA.

The GALILEO and COPERNICUS study participants were elderly (mean age 63-66 years according to treatment group), predominantly white, and a majority were male. There are no obvious inconsistencies between the modelled population and the prevalent CRVO.

7.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths of the analysis

The evaluation presented builds on existing evaluations of other interventions in CRVO(8;20). The model has the flexibility to track change of BCVA in the two eyes (assuming BCVA in the FE remains constant over time) and to project costs and consequences of unilateral treatment for the "whole person" (base-case and scenario analysis). This is consistent with the requirement of the NICE reference case.

Model health states were defined based on BCVA ranges of 15 letters compared to 10 letters in previous appraisals(8;20). A 15-letter BCVA range was deemed an appropriate measure of vision improvement/treatment effectiveness given that it is considered "clinically meaningful" by clinical experts and that it is also commonly used as a primary endpoint in clinical trials in ophthalmology, including in the COPERNICUS and GALILEO trials. Focus on this endpoint promotes the interpretability of model outcomes by ensuring their clinical relevance.

WSE trial-based utilities independent of SE/FE were applied in the model (base-case analysis); these utilities were generated through robust analysis of the trial data which followed rigorous methodological standards (see Section 7.4.9). By nature, these utilities are specific to the CRVO population. They were assigned to model HS based on the BCVA score achieved across the two eyes, i.e. the HRQoL impact of BCVA change was captured for the "whole person" in the base-case analysis. The results generated in the base-case analysis were put in perspective with those from a scenario analysis in which utility values were derived from the literature (Czoski-Murray *et al.* 2009(80)). The publication used for the scenario analysis derived BSE utility values from the preferences of the healthy population. Additional health benefits were generated when using the trial-based compared with literature-based utility values reflecting that WSE utility values

applied to the “whole person” translated into more benefits than BSE values applied to the “whole person”.

Patient-level data from two identically designed trials were used to inform the 4-week transition probabilities applied in the first 24 weeks of treatment. Therefore the model captured all potential movements observed in the study eye in the trials, for short and accurate time intervals. This adds to the integrity of the analysis performed as due to the short cycle lengths, assumptions relating to the distribution of treatment effect over time were not necessary.

Assumptions regarding resource use for Year 1 (base-case) and Year 2 (scenario analysis), primarily for the frequency of administration and monitoring, were conservatively based on trial data.

Limitations of this analysis

The de novo model tracks BCVA in the SE while BCVA is assumed to be constant in the FE, i.e. while the model tracks BCVA in the two eyes, it does not track BCVA change in the SE in relationship with BCVA change in the FE. Consequently, the de novo model is not a full “two-eye” model. A full “two-eye” model could not be developed because patient level data for BCVA change in the SE in relationship with BCVA change in the FE are not available. Given this data gap, the model structure underpinning this evaluation is deemed the best approximation of a “two-eye” model. However, while this represents a more “advanced” model than the models submitted in previous HTAs in this disease area, limitations remain.

Due to the absence of direct efficacy data, a NMA comparing aflibercept and ranibizumab was conducted (see Section 6.7). The study groups considered in the NMA were however heterogeneous: while the COPERNICUS and GALILEO trials included patients irrespective of their perfusion status, the vast majority of patients enrolled in the CRUISE trial were perfused patients. Since aflibercept trial analyses demonstrated that the baseline perfusion status did not affect response rates (see Section 7.9.5), the difference between the study groups was deemed negligible. Furthermore, as a result of the cross-over design of the COPERNICUS and COPERNICUS trials at week 24, this NMA was conducted over the first 24 weeks of treatment. The lack of robust relative efficacy data for active

treatments beyond 6 months was acknowledged and therefore a conservative assumption of “maintained vision” for each arm was made.

In line with previous evaluations in CRVO, the absence of long-term efficacy and resource use data creates uncertainty around long-term impact of treatment and clinical management of patients. However, PSA outputs suggests that despite underlying uncertainty the model results are stable, with aflibercept considered cost-effective relative to ranibizumab in 74.6% of the simulations conducted, assuming a WTP of £20,000/QALY.

The optimal duration of treatment is not yet certain. In the current model, treatment duration of one year was deemed conservative and applied in the base-case analysis. However scenario analyses projecting benefit and costs and assuming treatment durations of two and four years were conducted. For these extended treatment periods, it was assumed that vision improvement achieved at Year 1 was maintained at Year 2 or at Year 5 i.e. no additional vision improvement was modelled. Application of this assumption may underestimate the longer term benefits of treatment. However, in the absence of comparable data for ranibizumab and aflibercept this seemed a reasonably conservative approach given that individual data for the two products suggest that short-term benefits are maintained in the longer term.

In order to derive estimates for resource use inputs (frequency of administration and monitoring), a survey of five physicians was conducted. This approached seemed the most conservative given the absence of long-term resource use data. The outputs of the survey that were used as model resource use inputs with base-case values tested in OWSA. Post-treatment frequency of monitoring was assumed to be the same across the two treatment arms and was therefore not modeled explicitly. While reliance on survey outputs and assumptions is a limitation of the analysis, the approach is consistent with both the lack of published evidence relating to resource data and long-term treatment effects, and with the methods used to support model inputs in previous HTA submissions. Despite limitations, the current model presents a robust analysis of the relative costs and benefits of the two treatments considered.

7.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

Extensive sensitivity and scenario analyses were performed testing the uncertainty around parameters in the model which could have had an impact on the final results. Further evidence generation could improve the robustness of the analyses and the accuracy of the input values. In particular, long-term follow-up of treatment and monitoring frequency, disease progression as well as effects after Year 2 would be beneficial.

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.

The population eligible for treatment comprises CRVO patients with MO suffering from vision impairment (VI) and meeting criteria for active treatment. Given that CRVO is a unilateral disease, the projected number of patients treated is based on the projected number of eyes treated.

In order to estimate a projected eligible CRVO population from year 2014 to 2018, the following parameters have been considered:

- Total projected England and Wales population > 45 years of age from 2014 to 2018. This was estimated on the basis of population projections (2010-based) for 2014 and a fixed annual growth rate index of 0.7% for subsequent years, calculated using projections data from the ONS(99). Note this age cohort is selected to reflect disease epidemiology, see Klein *et al.* 2008(69) below.

- Incidence of CRVO as a whole. This was estimated from Klein *et al.* 2008(69), reporting the 15-year incidence rate of CRVO in a 43-84 year US population (males and females) from the Beaver Dam Eye study. To our knowledge, no study was conducted to this date to estimate the incidence of CRVO in the UK. The Beaver

Dam Eye study represents the most robust data source available to date and use of these data is consistent with the approach taken in previous CRVO HTA submissions(62;63).

- Proportion of CRVO patients eligible for treatment in the UK each year. This comprised patients experiencing VI due to MO secondary to CRVO. Based on the CVO study 1993(100), we assumed that 84% of patients with CRVO had MO at diagnosis. It was furthermore assumed that 100% of patients with MO secondary to CRVO experienced VI. These assumptions are in line with previous CRVO HTA submissions(62;63).

- The treated population modelled in these analyses was assumed to be comprised of anti-VEGF patients only, given that ranibizumab was deemed to be the standard of care for the treatment of MO secondary to CRVO at the time of the launch of aflibercept (see Section 2.7).

- The treated population was therefore further adjusted to reflect the fact that a proportion of this population will be treated with anti-VEGF only when aflibercept is introduced on the market. Based on the previous Novartis manufacturer submission in CRVO, it was assumed that approximately 40% of the eligible MO secondary CRVO population with VI was treated with anti-VEGF. This proportion was based on the ratio of:

    - The number of patients treated with ranibizumab in Year 1 estimated by dividing Total year 1 cost with blindness (£17.4 million – Table C17 – Novartis submission) by the Year 1 per patient total treatment cost with ranibizumab (£9,552 – Table C12 – Novartis submission),

    - Eligible population (4,674 – see section 7.2, page 295, Novartis submission)

The annual projected number of eligible patients used in the budget impact analysis is reported in Table 124 below:

Table 124. Population used in the Budget Impact Analysis

	2014	2015	2016	2017	2018
Population (45+) in	24,778,196	24,951,643	25,126,305	25,302,189	25,479,304

England and Wales (UK)					
Incident population with CRVO in UK	8,259	8,317	8,375	8,434	8,493
Proportion of patients with VI due to MO secondary to RVO	6,938	6,986	7,035	7,085	7,134
Total treated population (n)	5,689	5,729	5,769	5,809	5,850
Total population treated with anti-VEGF (n)	2,276	2,292	2,308	2,324	2,340

In Year 1, the total treated population with MO secondary to CRVO is estimated to be 2,276 patients. This estimate is in line with the number of patients indicated in Section 2.2.

8.2 What assumption(s) were made about current treatment options and uptake of technologies?

Spontaneous Resolution

The treated population was estimated as described above. However, a proportion of CRVO patients were not expected to require the full course of treatment due to spontaneous resolution of their condition. In line with published evidence, it was assumed that 36% of CRVO patients (McIntosh *et al.* 2010(70)) would cease treatment after an average of 6 months. As a result, the annual eligible population for treatment was adjusted accordingly. This is in line with the approach taken in a previous HTA submission in CRVO(63).

Other treatments

To help understand the economic impact of aflibercept uptake and use, cost savings were estimated under two scenarios; a world with aflibercept and a world without aflibercept. Ranibizumab was considered the standard of care against which new treatments should be benchmarked (see Section 2.7). Therefore the eligible population for treatment in a world without aflibercept is assumed to be represented by 100% ranibizumab market share. In a world with aflibercept, the uptake of aflibercept was assumed to increase over time through displacement of ranibizumab (see Section 8.3 below).

8.3 What assumption(s) were made about market share (when relevant)?

It is assumed that the uptake of aflibercept will displace a portion of ranibizumab share every year. The assumed market shares projections in the world with aflibercept are shown in Table 125 below.

Table 125. Projected market shares: world with aflibercept

	Year 1 (06/2014)	Year 2 (06/2015)	Year 3 (06/2016)	Year 4 (06/2017)	Year 5 (06/2018)
Aflibercept uptake	[redacted]				
Ranibizumab	83%	56%	44%	38%	33%

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).

In addition to technology costs, the following additional costs were modelled in the cost-effectiveness analysis (see Section 7.5 and were therefore also incorporated into the budget impact analysis:

- Cost of treatment administration,
- Cost of follow-up monitoring visits.

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?

The budget impact model outputs were directly derived from the cost-effectiveness analyses and unit costs are as previously reported (see Section 7.5). Unit costs were all derived from the following sources: BNF-65(92), NHS reference costs(95) and the published literature (see section 7.1).

The cost of administration entailed the technology cost and the cost of administration by an ophthalmologist. These are presented in Table 126 below:

Table 126. Drug and administration costs

	Cost (£)	**Reference in submission**
Aflibercept - drug only	816.00	Section 7.5

Ranibizumab - drug only	742.17	Section 7.5
Administration cost	257.45	Section 7.5

The cost of patient monitoring at hospital was different for the first visit and follow-up visits. While follow-up visits consisted of a clinical examination (assumed to take place during an ophthalmologist visit) and an OCT only, it was considered that patients assessed for the first time also required a FA. The costs used to model patient monitoring are summarised in Table 127 below:

Table 127. Unit costs associated with monitoring visits

	Cost (£)	Reference in the submission
Visual acuity visit	79.74	Section 7.5
OCT	117.26	Section 7.5
FA	117.26	Section 7.5

Treatment costs (technology and administration costs) and monitoring costs were combined with rates of occurrence that are summarised in Table 128 below:

Table 128. Frequency of administration and monitoring in Year 1

	Frequency of administration	Frequency of monitoring	Reference in the submission
Aflibercept	8.30	9.25	Section 7.5
Ranibizumab	8.80	9.90	Section 7.5

These rates cover the treatment duration assumed in the base-case cost-effectiveness analysis (one year). They were derived from trial data and a Physician survey.

Treatment of MO secondary to CRVO tends to be expensive as patients require frequent injections and monitoring visits for years. Treatment with ranibizumab in the UK is administered on a PRN (per needed) schedule, meaning that patients require monthly monitoring to assess whether they need a treatment injection(9). Treatment with aflibercept for MO secondary to CRVO does not require patients to be monitored monthly or between injections, unless treatment intervals are extended where it is at the discretion of the treating physician (see *draft SmPC* for details). Furthermore, based on the trial data used in the cost-effectiveness model, the number of injections required by a patient treated

with aflibercept in year 1 is lower than the number of injections required with ranibizumab, leading to a saving on administration costs to the NHS (see Section 8.7 below), given that injections are performed by an experienced ophthalmologist.

8.6 Were there any estimates of resource savings? If so, what were they?

The introduction of aflibercept was not predicted to accrue significant cost savings for the treatment of blindness given the similar efficacy at preventing progression to blindness compared with ranibizumab. Therefore the cost of blindness was not included in the budget impact analyses.

Resource savings were predicted in terms of avoidance of ophthalmologist visits, as ranibizumab was anticipated to be associated with more administration and monitoring visits than aflibercept. To put this in perspective, for the cohort considered, over the 5 year period, a total of 0.5 administration and 0.65 monitoring visits were avoided in the aflibercept arm relative to the ranibizumab arm.

8.7 What is the estimated annual budget impact for the NHS in England and Wales?

As shown in Table 129, the base-case analysis yielded a total £1,161,319 net budget impact of aflibercept over the time period 2014-2018 (i.e. a 1.1% increase based on a total £105,011,102 budget impact in a world without aflibercept).

Table 129. Budget impact of aflibercept (base-case results - summary)

Year	Without aflibercept	With aflibercept	Budget impact	%
2014	20,710,240	20,789,115	78,875	0.38%
2015	20,855,212	21,060,787	205,575	0.99%
2016	21,001,199	21,264,671	263,472	1.25%
2017	21,148,207	21,441,950	293,743	1.39%
2018	21,296,244	21,615,899	319,654	1.50%
Total	105,011,102	106,172,422	1,161,319	1.11%

As expected, a positive net budget impact was observed in all years following the launch of aflibercept given the higher total costs associated with aflibercept: the costs savings associated with lower administration and monitoring costs were systematically outbalanced by the drug costs (Table 130):

Table 130. Budget impact of aflibercept (base-case results – cost breakdown)

	Drug	% change	Admin & monitoring	% change	Total	% change
2014	93,505	0.63%	-14,630	-0.25%	78,875	0.38%
2015	243,707	1.63%	-38,132	-0.65%	205,575	0.99%
2016	312,343	2.07%	-48,871	-0.82%	263,472	1.25%
2017	348,229	2.29%	-54,486	-0.91%	293,743	1.39%
2018	378,947	2.48%	-59,292	-0.99%	319,654	1.50%
Total	1,376,731	1.83%	-215,412	-0.73%	1,161,319	1.11%

An analysis was also performed using the discounted price from the Patient's Access Scheme for aflibercept (see PAS template for details).

8.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

The direct costs of treating adverse events have not been included in the budget impact model. This is in line with the approach taken in the base-case cost-effectiveness analysis (see Section 7.3.2 for rationale). The scenario analysis conducted on the CEA which assesses the impact of including AEs found little difference on overall outcome (see Section 7.7.9) and suggests that impact on the BIM would be minimal

9 References

See end of document

10 Appendices

10.1 Appendix 1

10.1.1 SPC/IFU, scientific discussion or drafts – draft attached

10.2 Appendix 2: Search strategy for section 6.1 (Identification of studies)

The following information should be provided.

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 following databases were searched:

- EMBASE (OvidSP)
- MEDLINE (OvidSP)
- MEDLINE In-Process Citations (OvidSP)
- **Cochrane library accessed via Ovid**

Cochrane Central Register of Controlled Trials <April 2012>,
Cochrane Database of Systematic Reviews <2005 to April 2012>,
Cochrane Methodology Register <2nd Quarter 2012>,
Database of Abstracts of Reviews of Effects <2nd Quarter 2012>

The date on which the search was conducted.

The searches were conducted on the 11th March 2013.

The date span of the search.

From the beginning of 2002 to 11th March 2013.

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).

Table 131: Clinical - EMBASE Search via OVID for randomised controlled trials

#	Main CRVO terms	
1.	central retina vein occlusion/	1,542
2.	central retina$ vein$ occlu$.mp.	2,104
3.	central retina$ vein$ obstruct$.mp.	30
4.	retina$ centra$ vein$ occlu$.mp.	11
5.	CRVO.mp.	754
6.	central vein$ occlu$.mp.	164
7.	central vein$ obstruct$.mp.	30
8.	CVO.mp.	161
9.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	3,512
10.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	8,536
11.	(central adj2 RVO).mp.	60
12.	(central adj2 retina$ vein$ occlu$).mp.	2,108
13.	central.mp. and exp retina vein occlusion/	2,424
14.	*OR/#1-13*	10,020
	Clinical studies terms	
15.	randomized controlled trial/	321,405
16.	exp clinical trial/	909,465
17.	double blind procedure/	104,717
18.	single blind procedure/	17,065
19.	crossover procedure/	36,339
20.	randomization/	57,314
21.	experimental design/	7,918
22.	control group/	42,414
23.	placebo/	180,822
24.	(clin$ adj3 trial$).mp.	999,125
25.	randomi?ed controlled trial$.mp.	378,743
26.	RCT.mp.	11,513
27.	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	170,066
28.	placebo$.mp.	255,684
29.	(random$ adj2 allocat$).mp.	21,441
30.	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).mp.	5,407,634
31.	(crossover$ or (cross adj over$)).mp.	64,712
32.	*OR/#15-31*	5,529,720
	Comparator terms	
33.	exp angiogenesis inhibitor/	65,066
34.	bevacizumab/	25,066
35.	avastin.mp.	6,760
36.	bevacizumab.mp.	25,724
37.	(nsc 704865 or nsc704865).mp.	4
38.	ranibizumab/	2,947
39.	ranibizumab.mp.	3,022
40.	lucentis.mp.	1,350
41.	rhuFab V2.mp.	11
42.	eylea.mp.	57
43.	aflibercept/	947
44.	vegf trap eye.mp.	40

#	Main CRVO terms	
45.	vascular endothelial growth factor trap.mp.	68
46.	vasculotropin trap.mp.	55
47.	VEGF Trap.mp.	330
48.	("ave 0005" or ave0005).mp.	63
49.	anti vegf inhibitors.mp.	11
50.	exp dexamethasone/	81,594
51.	dexamethasone.mp.	89,430
52.	ozurdex.mp.	140
53.	best support$ care.mp.	1,709
54.	support$ care.mp.	11,680
55.	bsc.mp.	1,568
56.	symptom$ care.mp.	163
57.	laser coagulation/	14,924
58.	photocoagulat$.mp.	7,128
59.	laser coagulat$.mp.	13,177
60.	light coagulat$.mp.	28
61.	(panretinal photocoagulat$ or pan-retinal photocoagulat$).mp	910
62.	*OR/#33-61*	178,460
63.	*#14 (CRVO terms) AND #32 (Clinical studies terms) AND #62 (Comparator terms)*	450
64.	*Limit #63 to English language and years 2001-2013*	344
	Study terms to be excluded	
65.	case study/	16,718
66.	case report.mp.	1,411,501
67.	abstract report/	3,120
68.	letter/	687,195
69.	*OR/#65-68*	1,970,216
70.	*#32 NOT #69*	5,400,145
71.	*#14 (CRVO terms) AND #70 (Clinical studies terms/Excluded study terms) AND #62 (Comparator terms)*	422
72.	*Limit #71 to English language and years 2001-2013*	320

Table 132: Clinical - MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) for randomised controlled trials

#	Main CRVO terms	Hits
1.	central retina$ vein$ occlu$.mp.	1,321
2.	central retina$ vein$ obstruct$.mp.	43
3.	retina$ centra$ vein$ occlu$.mp.	9
4.	CRVO.mp.	608
5.	CVO.mp.	162
6.	central vein$ occlu$.mp.	146
7.	central vein$ obstruct$.mp.	18
8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	2,565
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	7,002
10.	(central adj2 RVO).mp.	46
11.	(central adj2 retina$ vein$ occlu$).mp.	1,327
12.	central.mp. and retinal vein occlusion/	1,396
13.	*OR/#1-12*	*8,117*
	Clinical studies terms	
14.	randomized controlled trial/	343,373
15.	randomized controlled trial as topic/	83,799
16.	exp clinical trial/	706,640
17.	exp clinical trials as topic/	262,429
18.	double-blind method/	118,452

#	Main CRVO terms	Hits
19.	single-blind method/	17,153
20.	random allocation/	76,571
21.	placebos/	31,395
22.	control groups/	1,378
23.	clinical trial, phase i.pt.	12,793
24.	clinical trial, phase ii.pt.	20,528
25.	clinical trial, phase iii.pt.	7,627
26.	clinical trial, phase iv.pt.	776
27.	controlled clinical trial.pt.	85,408
28.	randomized controlled trial.pt.	343,373
29.	multicenter study.pt.	152,647
30.	clinical trial.pt.	475,091
31.	(clin$ adj3 trial$).mp.	745,790
32.	randomi?ed controlled trial$.mp.	443,553
33.	RCT.mp.	7,002
34.	((singl$ or doubl$ or trebl$ or tripl$) adj3 (blind$ or mask$)).mp.	167,266
35.	placebo$.mp.	160,327
36.	(random$ adj2 allocat$).mp.	9,3721
37.	((random$ or control$ or clinical$) adj2 (trial$ or stud$)).mp.	1,256,061
38.	(crossover$ or (cross adj over$)).mp.	64,671
39.	*OR/#14-38*	1,428,161
	Comparator terms	
40.	exp angiogenesis inhibitor/	30,760
41.	bevacizumab.mp.	7,546
42.	avastin.mp.	916
43.	(nsc 704865 or nsc704865).mp.	0
44.	ranibizumab.mp.	1,395
45.	lucentis.mp.	199
46.	rhuFab V2.mp.	3
47.	eylea.mp.	11
48.	aflibercept.mp.	254
49.	vegf trap eye.mp.	35
50.	vascular endothelial growth factor trap.mp.	52
51.	vasculotropin trap.mp.	0
52.	VEGF Trap.mp.	227
53.	(ave 0005 or ave0005).mp.	4
54.	anti vegf inhibitors.mp.	7
55.	exp dexamethasone/	42,327
56.	dexamethasone.mp.	55,354
57.	ozurdex.mp.	44
58.	best support$ care.mp.	968
59.	support$ care.mp.	14,785
60.	bsc.mp.	1,420
61.	symptom$ care.mp.	140
62.	exp light coagulation/	10,467
63.	laser coagulat$.mp.	6,560
64.	light coagulat$.mp.	4,711
65.	photocoagulat$.mp.	7,352
66.	(panretinal photocoagulat$ or pan-retinal photocoagulat$).mp	772
67.	*OR/#40-66*	*118,924*
68.	*#13 (CRVO terms) AND #39 (Clinical studies terms) AND #67 (Comparator terms)*	*157*
69.	*limit #68 to English language and years 2001-2013*	*109*
	Study terms to be excluded	
70.	case report/	1,606,685
71.	case report.mp.	187,849
72.	Historical article/	289,896

#	Main CRVO terms	Hits
73.	abstract report.mp.	4
74.	letter/	782,097
75.	*OR/#70-74*	*2,256,321*
76.	*#39 NOT #75*	*1,381,781*
77.	*#13 (CRVO terms) AND #76 (Clinical studies terms/ excluded study terms) AND #67 (Comparator terms)*	*152*
78.	*limit #77 to English language and years 2001-2013*	*106*

Table 133: Clinical - Cochrane library Search, for randomised controlled trials

#	Main CRVO terms	
1.	central retina$ vein$ occlu$.mp.	100
2.	central retina$ vein$ obstruct$.mp.	3
3.	retina$ centra$ vein$ occlu$.mp.	0
4.	CRVO.mp.	68
5.	CVO.mp.	9
6.	central vein$ occlu$.mp.	24
7.	central vein$ obstruct$.mp.	0
8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	147
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	523
10.	(central adj2 RVO).mp.	1
11.	(central adj2 retina$ vein$ occlu$).mp.	70
12.	central.mp. and retinal vein occlusion/	104
13.	*OR/#1-12*	*568*
	Comparator terms	
14.	exp angiogenesis inhibitor/	544
15.	bevacizumab.mp.	534
16.	avastin.mp.	78
17.	(nsc 704865 or nsc704865).mp.	1
18.	ranibizumab.mp.	185
19.	lucentis.mp.	44
20.	rhuFab V2.mp.	8
21.	eylea.mp.	1
22.	aflibercept.mp.	8
23.	vegf trap eye.mp.	6
24.	vascular endothelial growth factor trap.mp.	6
25.	vasculotropin trap.mp.	0
26.	VEGF Trap.mp.	24
27.	ave?0005.mp.	1
28.	anti vegf inhibitors.mp.	0
29.	exp dexamethasone/	2,054
30.	dexamethasone.mp.	3,955
31.	ozurdex.mp.	4
32.	best support$ care.mp.	307
33.	support$ care.mp.	1,204
34.	bsc.mp.	141
35.	symptom$ care.mp.	16
36.	laser coagulation/	360
37.	exp light coagulation/	513
38.	laser coagulat$.mp.	477
39.	light coagulat$.mp.	168
40.	photocoagulat$.mp.	850
41.	(panretinal photocoagulat$ or pan-retinal photocoagulat$).mp	133
42.	*OR/#14-41*	*7,186*

#	Main CRVO terms	
43.	*#13 (CRVO terms) AND #42 (Comparator terms)*	*85*
44.	*limit #43 to English language and years 2001-2013*	*64*

Details of any additional searches, such as searches of company databases (include a description of each database).

Searches of relevant conference abstracts that were published from 2010 were undertaken from the following websites:

- American Academy of Ophthalmology (AAO); http://www.aao.org/
- Association for Research in Vision and Ophthalmology (ARVO); http://www.arvo.org
- European Association for Vision and Eye Research (EVER); http://www.ever.be/news.php
- Nordic Congress of Ophthalmology (NOK); http://www.nok2012.fi/index.html
- World Ophthalmology Congress (WOC); http://www.woc2012.org/

Also, supplementary searches were undertaken on the following resources to identify grey literature and ongoing studies:

- NIH ClinicalTrials.gov (http://www.clinicaltrials.gov/)
- WHO International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)

Databases and abstract books were searched using an approach that strived to mimic that of the core searches but within the limitations set by the above-listed websites.

The table below summarises the search strategies used to find relevant conference abstracts from the selected ophthalmic societies, presenting the search string used and the corresponding number of hits. Due to the varying nature of the search engines found on the ophthalmic societies' Web sites, different search strategies were employed.

Table 134: Search strategies for conferences websites

Conference name	Conference website/database	Search terms	Studies after duplicates removal
The Association for Research in Vision and Ophthalmology (ARVO)	http://www.arvo.org Search: http://www.arvo.org/Annual_Meeting/Abstracts/Annual_Meeting_Abstract_Search/	crvo (in presentation title) OR crvo (in abstract body) OR "central retinal vein occlusion" (in presentation title) OR "central retinal vein occlusion" (in abstract body)	ARVO 2011: 29 ARVO 2012: 55
American Academy of Ophthalmology (AAO)	http://www.aao.org/ Search: http://aao.scientificposters.com/aaoSearch.cfm	1) Retina Vitreous (poster topic) AND VEGF Trap-Eye; 2) Retina Vitreous (poster topic) AND aflibercept; 3) Retina Vitreous (poster topic) AND ave 0005; 4)	AAO 2012: 30 AAO 2011: 31 AAO 2010: 33

Conference name	Conference website/database	Search terms	Studies after duplicates removal
		Retina Vitreous (poster topic) AND eylea; 5) Retina Vitreous (poster topic) AND ranibizumab; 6) Retina Vitreous (poster topic) AND lucentis; 7) Retina Vitreous (poster topic) AND bevacizumab; 8) Retina Vitreous (poster topic) AND avastin; 9) Retina Vitreous (poster topic) AND ozurdex; 10) Retina Vitreous (poster topic) AND dexamethasone	
World Ophthalmology Congress (WOC)	http://www.woc2012.org/ Abstract book: http://woc2012.org/files/abstract_book_woc2012.pdf	Abstract book: crvo OR "central retinal vein occlusion"	WOC 2012: 29
European Association for Vision and Eye Research (EVER)	http://www.ever.be/news.php Abstract book 2012: http://www.ever.be/view_room_day_fill.php?ev_id=10 Abstract book 2011: http://www.ever.be/view_room_day_fill.php?ev_id=9	Abstract book: crvo OR "central retinal vein occlusion"	EVER 2012: 10 EVER 2011: 6
Nordic Congress of Ophthalmology (NOK)	http://www.nok2012.fi/index.html Abstract book 2012: http://www.nok2012.fi/PDF/NOK_2012_Abstracts.pdf	Abstract book: crvo OR "central retinal vein occlusion"	NOK 2012: 9

The inclusion and exclusion criteria.

Please see Table 2 (section 6.2.1).

The data abstraction strategy.

All references identified through searches were exported to Reference Manager 11 databases. The databases were merged and deduplicated and exported to an Excel spreadsheet. Two reviewers independently screened each reference for relevance and any disagreements were resolved through 'reconciliation' (discussion between the two reviewers) or through 'arbitration' by a third independent reviewer. The 'majority view' determined inclusion or exclusion. Excluded publications were disregarded. Publications that appeared to be potentially relevant were ordered for a full review of the text and assessed for inclusion by two reviewers using the same approach as the initial abstract screening.

Searches were limited to evidence published between 2002-2013 and in the English language.

The following data were extracted from the selected publications:

Study characteristics: Author, title, year, country, study design, duration.
Patient demographics
Details of intervention and comparators: drugs used, duration and intensity
Efficacy and safety outcomes, including HRQoL data
plus sufficient information to complete the quality assessments of each study.

10.3 Appendix 3: Quality assessment of RCT(s) (section 6.4)

	COPERNICUS		GALILEO	
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**	**How is the question addressed in the study?**	**Grade (yes/no/not clear/ N/A)**
Was randomisation carried out appropriately?	Patients were randomised in a 3:2 ratio using a centralised interactive voice randomisation system (IVRS), and stratified by geographic region (North America vs. rest of the world), and by using a baseline best-corrected visual acuity (BCVA) score (>20/200 [35 to 73 letters] and ≤20/200 [34 to 24 letters].	Yes	Patients were randomised in a 3:2 ratio [redacted] and stratified by region (Europe vs. Asia/Pacific) and baseline best -corrected visual acuity (BCVA) (≤20/200 vs. >20/200).	Yes
Was the concealment of treatment allocation adequate?	Randomisation was via IVRS. This was a double-masked study.	Yes	[redacted] This was a double-masked study.	[redacted]
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Baseline patient demographic and disease characteristics were comparable for the treatment groups	Yes	Baseline patient demographic and disease characteristics were comparable for the treatment 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)?	Patients and investigators were masked as to treatment assignment. All outcome assessors were masked including those assessing adverse events, efficacy and retreatment during PRN phase, visual acuity examiners, NEI VFQ-25 administrators, independent OCT scan reading centre and angiographic image reading centre. [redacted] All aflibercept and sham treatments were packaged in identical treatment kits with identical labelling, except for the kit number (unique to the patient). Sham injections were performed by pressing an empty, needleless syringe barrel to the conjunctival surface to simulate an injection. [redacted]	Yes	All other site personnel were masked to treatment assignment, including the physician assessing adverse events, supervising the assessment of efficacy and deciding on the need for retreatment during the PRN phase. Examiners testing visual acuity and administering National Eye Institute 25-item Visual Function Questionnaire (NEI VFQ-25) were masked to treatment assignment. [redacted] All aflibercept and sham treatments were packaged in identical treatment kits with identical labelling, except for the kit number (unique to the patient). All Sham procedure was performed by pressing an empty, needleless syringe to the conjunctival surface. OCT, fluoroscein angiography and fundus photography were evaluated centrally by masked reviewers. Electrocardiograms (ECGs) were read by a central reader. Blood and urine samples evaluated centrally. The study remained masked for the entire 76 week study period.	Yes

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No. At Week 24, 5 (4.3%) patients had discontinued the study in the aflibercept arm and 14 (18.9%) patients in the sham control group had discontinued from the study. By [redacted] patients had discontinued the study in the aflibercept arm and [redacted] patients in the sham control group had discontinued from the study.	No	No. At Week 24, 10 (9.4%) patients had discontinued the study in the aflibercept arm and 15 (21.1%) patients in the sham control group had discontinued from the study. The sham group had a higher percentage of patients discontinuing study primarily due to AEs and lack of efficacy; this had no major impact on the analysis of the primary endpoint (with discontinued patients before week 24 judged as nonresponders), as similar results were obtained after imputing the missing values with the LOCF approach, using observed cases, or excluding patients who discontinued prior to week 24 and received fewer than five injections. By [redacted] patients had discontinued the study in the aflibercept arm and [redacted] patients in the sham control group had discontinued from the study. Again, sensitivity analyses confirmed this had no impact on outcomes.	Not unexpected as they were in patients in the sham group. Yes these were explained and adjusted for.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results of all pre-specified outcomes have been reported in full.	No	Results of all pre-specified outcomes have been reported in full.	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?	Primary efficacy analyses were conducted using the full analysis set (FAS) (includes all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment). Sensitivity analyses included per protocol and observed cases, pure LOCF analyses. Patients who discontinued prematurely (before week 24) and had fewer than 5 injections of aflibercept or sham were evaluated as non-responders; otherwise, missing values were imputed using last observation carried forward (LOCF) analyses.	No.	Primary efficacy analyses were conducted using the full analysis set (FAS) (includes all randomised patients who received any study drug and had a baseline and at least one post-baseline assessment). Sensitivity analyses included [redacted], pure LOCF and observed cases analyses or excluding patients who discontinued study prior to week 24 and received fewer than five injections. . Patients who discontinued prematurely (before week 24) were evaluated as non-responders; otherwise, missing values were imputed using last observation carried forward (LOCF) analyses.	No.

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination

10.4 Appendix 4: Search strategy for section 6.7 (Indirect and mixed treatment comparisons)

See Appendix 10.2.

10.5 Appendix 5: Quality assessment of comparator RCT(s) in section 6.7 (Indirect and mixed treatment comparisons)

Trial no. (acronym)	**CRUISE (NCT00485856)**		**ROCC (NCT00567697)**	
	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was the method used to generate random allocations adequate?	Eligible patients were randomized 1:1:1 to receive monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections, using a dynamic randomization method proposed by Signorini et al 1993. Randomization was stratified by baseline BCVA letter score (≤34 [approximate Snellen equivalent <20/200], 35–54 [approximate Snellen equivalent 20/200 to <20/80], ≥55 [approximate Snellen equivalent <20/80]) and study centre.	Yes	The study states that this 6-month, prospective, multicentre, sham-controlled, monitored study was randomized 1:1 to receive intravitreal injections of ranibizumab 0.5mg/0.05mL or Sham each month for 3 months and double masked, but fails to provide adequate detail of the methods used.	Not clear
Was the allocation adequately concealed?	Not clear whether the allocation was adequately concealed.	Not clear	Not clear whether the allocation was adequately concealed.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Patient demographics and baseline ocular characteristics were similar across treatment groups	Yes	Demographics were not mentioned for each group. BCVA score was similar (45±23 (SD) ETDRS letters in the ranibizumab group and 41± 23 ETDRS letters for the Sham group. The overall mean macular thickness was 661±161 (SD) µm in the ranibizumab group and 587 ± 154 µm in the Sham group	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)?	Patients, certified BCVA examiners, and evaluating physicians were masked to treatment and dose. Injecting physicians, who did not perform examinations or outcome assessments, were masked to dose but not treatment.	Yes	The investigating physician and nurse were masked towards the injecting physician and nurse and vice versa	Yes
Were there any unexpected imbalances in	Four patients (3.0%) in the 0.3 mg group, 10 patients(7.7%) in the 0.5 mg	No	No imbalances between groups were reported.	No

Trial no. (acronym)	**CRUISE (NCT00485856)**		**ROCC (NCT00567697)**	
drop-outs between groups? If so, were they explained or adjusted for?	group, and 16 patients (12.3%) in the sham group discontinued treatment at or before month 5.			
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results of all pre-specified outcomes have been reported in full	No	Results of all pre-specified outcomes have been reported in full	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?	Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomized. Missing values for efficacy outcomes were imputed using the last observation-carried-forward method.	Yes	Efficacy analysis was performed in the per-protocol patient population, which was considered to be appropriate considering the explanatory nature of the trial. The study did not report how missing data was dealt with.	No
Source	Brown et al. 2010		Kinge et al. 2010	

Trial no. (acronym)	**GENEVA 008 and 009**	
	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was the method used to generate random allocations adequate?	Patients were randomised using a 1:1:1 allocation ratio. Randomisation was performed centrally (using an interactive voice response system) and stratified by the underlying cause of RVO (BRVO or CRVO).	Yes
Was the allocation adequately concealed?	Centralised, interactive voice response system used.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No clinically relevant differences between groups were observed for demographic and disease characteristics at baseline	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)?	Patients were masked with regard to study treatment, and the key efficacy variables were collected and evaluated by follow-up investigators who were also masked with regard to study treatment.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No unexpected imbalances.	No
Is there any evidence to	Results of all pre-specified outcomes have been reported in	No

suggest that the authors measured more outcomes than they reported?	full	
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 ITT population was included in the primary analysis. In general, the last observation carried forward (LOCF) method was used to replace missing post-baseline data unless the response variable for changes from baseline was unambiguously determined based on the available information.	Yes
Source	Haller et al. 2010	

Trial no. (acronym)	**Epstein et al. 2012a & Epstein et al. 2012b**		**Wittstrom et al. 2012**	
	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Was the method used to generate random allocations adequate?	Although mentioned that study participant was randomly assigned with equal probability to IVB injections (study group) or sham injections (control group), it was not clarified what method was used.	Not clear	Not clear how the randomisation was generated.	Not clear
Was the allocation adequately concealed?	Randomization was done at the day of the first injection by sealed envelopes drawn by staff not involved in patient treatment or follow-up.	Yes	Not clear whether the allocation was adequately concealed.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Patient demographic and disease characteristics were comparable for the treatment groups	Yes	Patient demographic and disease characteristics were comparable for the treatment 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)?	Study patients were masked to the treatment given. Staff performing VA testing, optical coherence tomography (OCT), fundus photographs, and follow-up investigators were masked to treatment group.	Yes	Not clear whether the blinding was adequate.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	N/A	No	It is not stated how the imbalances were adjusted.	Yes

Trial no. (acronym)	**Epstein et al. 2012a & Epstein et al. 2012b**		**Wittstrom et al. 2012**	
	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)	How is the question addressed in the study?	Grade (yes/no/not clear/N/A)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Results of all pre-specified outcomes have been reported in full	No	N/A	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?	Analysis at 6 month, included patients that comprised the intent-to-treat population, in whom the last observation carried forward method was used for missing data for all efficacy parameters. At 12 month, it is not clear what type of analysis the study used.	Not clear	N/A	No
Source	Epstein *et al.* 2012a & Epstein *et al.* 2012b		Wittstrom *et al.* 2012	

10.6 Appendix 6: Search strategy for section 6.8 (Non-RCT evidence)

Alongside the clinical systematic literature review update, systematic searches were conducted which objective was to identify sources for the following inputs of the economic model:

- risk of mortality associated with blindness in RVO patients and
- risk of mortality associated with RVO in RVO patients.

10.6.1 The following information should be provided.

- 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 Medline database was used through the Ovid platform to conduct this search.

10.6.2 The date on which the search was conducted.

The searches were performed on the 3rd of April 2013.

10.6.3 The date span of the search.

The searches covered the period 01.01.200 to 03.04.2013.

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).

Table 136 and Table 135 below present the search strings developped for each of the reviews:

Table 135. Search strings - Risk of mortality associated with blindness in RVO patients

MEDLINE	Search strings	Hits
Visual Impairment Terms		
1	*Visual Acuity/	8,134
2	*Blindness/	10,479
3	*Vision Disorders/	12,279
4	*Vision, Low/	1,534
5	visual acuity.ti.	3,363
6	((visual$ or vision or sight) and (impair$ or defect$ or loss$ or disorder$)).ti.	8,046
7	**or/1-6**	**35,025**
Mortality Terms		
8	*Life expectancy/	4,984
9	*Mortality/	16,714
10	*Survival/	980
11	*Survival Analysis/	1,929
12	*Survival rate/	567
13	*Cause of death/	8,000
14	life expectancy.ti.	2,009
15	mortality.ti.	72,908
16	survival.ti.	85,226
17	mortality.fs.	383,210
18	**or/8-17**	**477,436**
19	**7 and 18**	**151**
Excluded types of publications		
20	letter.pt.	783,975
21	editorial.pt	323,926
22	comment.pt.	527,715
23	**or/20-22**	**1,225,209**
24	**19 not 23**	**143**
25	**Limit 24 to English Language**	**130**
26	**Limit 25 to 2000-2013**	**83**

Table 136. Search strings - Risk of mortality associated with RVO in RVO patients

MEDLINE	Search strings	Hits
Disease Terms - RVO		
1	exp retinal vein occlusion/	2,651
2	retina$ vein$ occlu$.ti,ab.	2,676
3	retina$ vein$ obstruct$.ti,ab.	101
4	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).ti,ab.	143
5	RVO.ti,ab.	355
6	**or/1-5**	**3,706**
Mortality Terms		
7	life expectancy/	13,077
8	exp mortality/	259,078
9	survival/	3,658
10	Survival rate/	115,112

MEDLINE	Search strings	Hits
11	exp survival analysis/	162,300
12	cause of death/	32,946
13	life expectancy.ti,ab.	17,265
14	mortality.ti,ab.	415,864
15	survival.ti,ab.	529,911
16	mortality.fs.	383,210
17	or/7-16	1,159,091
18	**6 and 17**	**64**
Excluded types of publications		
19	letter.pt.	783,975
20	editorial.pt	323,926
21	comment.pt.	527,715
22	**or/19-21**	**1,225,209**
23	**18 not 22**	**143**
24	**Limit 23 to English language**	**54**

10.6.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Not applicable.

10.6.6 The inclusion and exclusion criteria.

The same eligibility criteria were use to review abstracts and full texts of studies identified by the two reviews. They are presented in Table 137 below:

Table 137. Eligibility criteria for the risk of mortality associated with blindness/RVO in RVO patients

Patient population	Inclusion	Exclusion
Patient population	VA <35 letters in both eyes	-
Interventions	-	-
Comparator	-	-
Outcome measures	Mortality rate e.g. Hazard ratio	-
Study design	· Observational studies · systematic reviews/meta-analyses	· Clinical trials · Editorials OR · Notes OR · Comments OR · Letters OR
Restrictions	· Language: English OR · Published since 01.01.2000	· Non-English studies OR · Studies published before 01.01.2000

10.6.7 The data abstraction strategy.

<u>Risk of mortality associated with blindness in RVO patients and</u>

The search identified 83 publications that were assessed based on their title and abstract against the eligibility criteria described above. At the title/abstract review stage, 23 publications were included and were further screened at the full text review stage.

Table 138 lists the publications that were eligible for inclusion after full text review. After the full text review, 11 publications were excluded for either of these two reasons: i) no mortality rate was reported for blind patients or ii) the definition of blindness provided in the publication differed from that used in the economic model. The remaining 12 publications were then further assessed to select the most suitable study to be used in the economic model. The rationale is briefly described in the last column of Table 138. Studies that were conducted in a setting other than the UK or that strictly involved an elderly population were considered inappropriate to populate the economic model.

Table 138. List of publications included after full text review, mortality associated with blindness

Author	Year	Title	Useful for the model
Berdeaux *et al.(101)*	2007	Self-reported visual impairment and mortality: a French nationwide perspective	No - French patients
Cacciatore *et al.(102)*	2004	Disability and 6-year mortality in elderly population. Role of visual impairment	No - elderly patients (mean age 74.2)
Christ *et al.(19)*	2008	Assessment of the effect of visual impairment on mortality through multiple health pathways: structural equation modeling	Yes
Foong *et al.(103)*	2008	Visual acuity and mortality in a chinese population. The Tanjong Pagar Study	No - Chinese patients
Freeman *et al.(104)*	2005	Visual acuity change and mortality in older adults	No - elderly patients
Kulmala *et al.(105)*	2008	Visual acuity and mortality in older people and factors on the pathway	No - elderly patients
Lee *et al.(106)*	2002	Visual acuity impairment and mortality in US adults	No - elderly patients
Li *et al.(107)*	2011	Visual impairment and mortality in a rural adult population (the Southern Harbin eye study)	No - Chinese patients
Pion *et al.(108)*	2005	Excess mortality associated with blindness in the onchocerciasis focus of the Mbam Valley, Cameroon	No - Cameroon patients
Thiagarajan *et al.(18)*	2005	Cause-specific visual impairment and mortality: results from a population-based study of older people in the United Kingdom	No - elderly patients
Tournier *et al.(109)*	2008	Depression and mortality in the visually-impaired, community-dwelling, elderly population of Quebec	No - elderly patients in Canada
Wang *et al.(110)*	2001	Visual impairment, age-related cataract, and mortality	No - Australian patients

The publication by Christ *et al.* 2008(19), which was used in the Novartis RVO HTA submission(63), was considered the most appropriate source to populate the model. This paper reports that severe visual impairment (VI), which was coded as blindness in both eyes, increases the hazard rate by 1.54 (95% CI:1.28 –1.86) relative to no VI, taking into consideration both direct effects and indirect effects of mortality associated with visual impairment.

Risk of mortality associated with RVO in RVO patients.

The search identified 54 publications that were assessed based on their title and abstract against the eligibility criteria described above. At the title/abstract review stage, 8 publications were included and were further screened at the full text review stage.

Four papers were retained after full text review and are listed in Table 139 below: three studies related to CRVO patients and one to BRVO patients. These studies however present contradictory results: while three studies (Tsaloumas *et al.* 2000(21), Cugati *et al.* 2007(15) and Xu *et al.* 2007) clearly established that an increased risk of mortality can be attributed to RVO, one study (Christoffersen *et al.* 2007 (no reference available)*)* concluded that RVO was not associated with a greater risk of mortality.

Table 139. List of publications included after full text review, mortality associated with RVO

Author	Year	Title	Useful for the model
Christoffersen et al. (no reference available)	2007	Mortality in patients with branch retinal vein occlusion.	No, BRVO patients
Cugati et al(15)	2007	Retinal vein occlusion and vascular mortality: pooled data analysis of 2 population-based cohorts	Yes, potentially, yet pooled analyses of the Beaver Dam Eye Study (USA) and Blue Mountains Eye Study (Australia)
Tsaloumas et al.(21)	2000	Nine year follow-up study of morbidity and mortality in retinal vein occlusion	Yes, potentially, as UK based study
Xu et al.(111)	2007	Retinal vein occlusions and mortality: the Beijing Eye Study	Yes, potentially, yet study conducted in Chinese patients

Christoffersen *et al.* found that mortality in BRVO patients was similar to that of the background population. In contrast, Cugati *et al.(15)* reported no significant difference overall in the mortality between individuals with and without RVO among participants of all ages, however, in persons aged less than 70 years, baseline RVO was associated with higher cardiovascular mortality. The study by Tsaloumas *et al.(21)* found that the percentage of deaths from myocardial infarction in the RVO population was significantly higher compared to the percentage of deaths in the West Midlands population as a whole. In addition, the study by Xu *et al.(111)* found that mortality rates were significantly higher in persons with RVO than in those without RVO.

Given conflicting evidence and in line with the approache used in the Novartis RVO HTA submission(63), mortality associated with RVO was not included in the economic model.

10.7 Appendix 7: Quality assessment of non-RCT(s) in section 6.8 (Non-RCT evidence)

Not applicable

10.8 Appendix 8: Search strategy for section 6.9 (Adverse events)

Not applicable – see section 10.2

10.9 Appendix 9: Quality assessment of adverse event data in section 6.9 (Adverse events)

Not applicable – see section 10.2

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.

The searches were conducted on Embase, Medline (including Medline (R) in process), NHS EED and EconLitusing the OVID platform.

10.10.2 The date on which the search was conducted.

The search was conducted on March the 11th, 2013.

10.10.3 The date span of the search.

The searches spanned from January the 1st, 2001 to March the 11th, 2013.

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 search strategies used for Embase, MEdline, NHS EED and EconLit are summarised in Table 140, Table 141, Table 142, Table 143 respectively.

Table 140. Economic - EMBASE Search via OVID, 2001 to 2013

#	**Main CRVO terms**	Hits
1.	central retina vein occlusion/	1,542
2.	CRVO.mp.	754
3.	central retina$ vein$ occlu$.mp.	2,104
4.	central retina$ vein$ obstruct$.mp.	30
5.	retina$ centra$ vein$ occlu$.mp.	11
6.	CVO.mp.	161
7.	central vein$ occlu$.mp.	164

8.	central vein$ obstruct$.mp.	30
9.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	3,512
10.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	8,536
11.	(central adj2 RVO).mp.	60
12.	(central adj2 retina$ vein$ occlu$).mp.	2,108
13.	central.mp. and exp retina vein occlusion/	2,424
14.	*OR/#1-13*	10,020
	Additional RVO terms	
15.	exp retina vein occlusion/	4,365
16.	retina vein/	958
17.	retina$ vein$ occlu$.mp.	4,687
18.	retina$ vein$ obstruct$.mp.	67
19.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	7,284
20.	RVO.mp.	474
21.	*OR/#15-20*	7,873
22.	*#14 or #21*	14,215
	Cost terms	
23.	exp pharmacoeconomics/	143,588
24.	exp socioeconomics/	134,656
25.	pharmacoeconomic$.mp.	10,484
26.	(pharmaco adj economic$).mp.	428
27.	exp health economics/	503,872
28.	health economic$.mp.	22,311
29.	exp economic aspect/	874,709
30.	economic aspect$.mp.	57,897
31.	economic evaluati$.mp.	12,860
32.	cost utility analysis/	4,558
33.	cost utili$ analys$.mp.	5,286
34.	(cost$ or (cost$ adj2 (effective$ or utili$ or benefit$ or minimi$ or stud$ or effic$ or effect$))).mp.	542,377
35.	(economic$ and (evaluat$ or analys$ or model$)).mp.	150,609
36.	health care utilization/	33,991
37.	health care utili$.mp.	35,411
38.	resource$ utili$.mp.	7,080
39.	(resource$ adj3 utili$).mp.	9,768
40.	resour$ us$.mp.	7,399
41.	cost of illness/	13,659
42.	cost of illness.mp.	14,418
43.	hospitalization cost/	1,740
44.	hospital$ cost$.mp.	16,893
45.	cost minimization analysis/	2,221
46.	cost minimi?ation analys$.mp.	2,484
47.	exp "health care cost"/	179,012
48.	health care cost$.mp.	116,726
49.	cost effectiveness analysis/	84,964
50.	cost effectiveness analys$.mp.	86,944
51.	cost benefit analysis/	58,227
52.	cost benefit analys$.mp.	59,520
53.	(cba or cea or cua).mp.	26,735
54.	"cost control"/	39,790
55.	(cost adj estimate$).mp.	1,655
56.	(unit$ adj cost$).mp.	43,861
57.	exp economic evaluation/	184,713
58.	exp economics/	178,062

59.	(econom$ or cost$ or pric$ or pharmacoeconomic$).mp.	813,122
60.	budget$.mp.	28,840
61.	expenditure$.mp.	43,103
62.	markov$.mp.	14,104
63.	(monte adj carlo).mp.	28,619
64.	(decision adj2 (tree$ or analys$ or model$)).mp.	16,312
65.	*OR/#23-64*	1,270,597
	Comparator terms	
66.	exp angiogenesis inhibitor/	65,325
67.	bevacizumab/	25,066
68.	avastin.mp.	6,760
69.	bevacizumab.mp.	25,724
70.	(nsc 704865 or nsc704865).mp.	4
71.	ranibizumab/	2,947
72.	ranibizumab.mp.	3,022
73.	lucentis.mp.	1,350
74.	rhuFab V2.mp.	11
75.	eylea.mp.	57
76.	aflibercept/	949
77.	("ave 0005" or ave0005).mp.	63
78.	vegf trap eye.mp.	40
79.	vascular endothelial growth factor trap.mp.	68
80.	vasculotropin trap.mp.	55
81.	VEGF Trap.mp.	330
82.	Anti vegf inhibitors.mp.	11
83.	exp dexamethasone/	81,594
84.	dexamethasone.mp.	89,430
85.	ozurdex.mp.	140
86.	best support$ care.mp.	1,709
87.	support$ care.mp.	11,680
88.	bsc.mp.	1,568
89.	symptom$ care.mp.	163
90.	laser coagulation/	14,924
91.	photocoagulat$.mp.	7,128
92.	laser coagulat$.mp.	13,177
93.	light coagulat$.mp.	28
94.	(panretinal photocoagulat$ or pan-retinal photocoagulat$).mp.	910
95.	*OR/#66-94*	178,460
96.	*#14 (CRVO terms) AND #65 (Cost terms) AND #95 (Comparator terms)*	39
97.	*limit #96 to English language and years 2001-2013*	35
98.	*#22 (CRVO + RVO terms) AND #65 (Cost terms) AND #95 (Comparator terms)*	87
99.	*limit #98 to English language and years 2001-2013*	81

Table 141. Economic - MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R), 2001 to 2013

#	Main CRVO search terms	Hits
1.	central retina$ vein$ occlu$.mp.	1,321
2.	central retina$ vein$ obstruct$.mp.	43
3.	retina$ centra$ vein$ occlu$.mp.	9
4.	CRVO.mp.	608
5.	CVO.mp.	162
6.	central vein$ occlu$.mp.	146
7.	central vein$ obstruct$.mp.	18

8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	2,565
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	7,002
10.	(central adj2 RVO).mp.	46
11.	(central adj2 retina$ vein$ occlu$).mp.	1,327
12.	central.mp. and retinal vein occlusion/	1,396
13.	*OR/#1-12*	8,117
	Additional RVO terms	
14.	retinal vein occlusion/	2,649
15.	retina$ vein$ occlu$.mp.	3,428
16.	retina$ vein$ obstruct$.mp.	101
17.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	143
18.	RVO.mp.	362
19.	*OR/#14-18*	3,716
20.	*#13 OR #19*	10,037
	Cost terms	
21.	economics, pharmaceutical/	2,391
22.	Economics/	26,425
23.	exp economics, medical/	13,295
24.	exp economics, hospital/	18,413
25.	economics, nursing/	3,869
26.	pharmacoeconomic$.mp.	3,065
27.	(pharmaco adj economic$).mp.	258
28.	health economic$.mp.	3,417
29.	economic aspect$.mp.	1,708
30.	economic evaluation$.mp.	5,795
31.	cost utili$ analys$.mp.	1,337
32.	(cost$ or (cost$ adj2 (effective$ or utili$ or benefit$ or minimi$ or stud$ or effic$ or effect$))).mp.	398,454
33.	(economic$ and (evaluat$ or analys$ or model$)).mp.	90,432
34.	(economic$ or cost$ or pric$ or pharmacoeconomic$).mp.	566,368
35.	budget$.mp.	23,084
36.	expenditure$.mp.	44,032
37.	(low adj cost$).mp.	21,871
38.	(high adj cost$).mp.	9,822
39.	health care utili$.mp.	3,649
40.	resource$ utili$.mp.	4,655
41.	(resource$ adj3 utili$).mp.	6,787
42.	Resource$ us$.mp.	5,379
43.	Cost allocation/	1,920
44.	Cost control/	19,525
45.	Cost savings/	7,974
46.	cost of illness/	15,817
47.	cost of illness.mp.	16,184
48.	hospital costs/	7,113
49.	hospital$ cost$.mp.	11,521
50.	exp "fees and charges"/	26,059
51.	exp budgets/	11,623
52.	exp costs and cost analysis/	169,451
53.	cost-benefit analysis/	55,658
54.	(cba or cea or cua).mp.	40,646
55.	cost minimi?ation analys$.mp.	441
56.	models, economic/	5,472
57.	markov chains/	8,574
58.	monte carlo method/	17,945

59.	decision tree/	8,259
60.	(decision adj2 (tree$ or analys$ or model$)).mp.	16,475
61.	markov$.mp.	14,354
62.	(monte adj carlo).mp.	31,638
63.	exp health care costs/	42,367
64.	health care cost$.mp.	30,492
65.	(health care adj2 cost$).mp.	32,266
66.	(cost$ adj3 estimate$).mp.	10,305
67.	(unit adj3 cost$).mp.	2,219
68.	Direct service costs/	981
69.	Drug costs/	11,297
70.	Health expenditures/	12,756
71.	cost effectiveness analys$.mp.	5,950
72.	cost benefit analys$.mp.	56,834
73.	*OR/#21-72*	*715,296*
	Comparator terms	
74.	exp angiogenesis inhibitor/	30,760
75.	bevacizumab.mp.	7,546
76.	avastin.mp.	916
77.	(nsc 704865 or nsc704865).mp.	0
78.	ranibizumab.mp.	1,395
79.	lucentis.mp.	199
80.	rhuFab V2.mp.	3
81.	eylea.mp.	11
82.	aflibercept.mp.	254
83.	vegf trap eye.mp.	35
84.	vascular endothelial growth factor trap.mp.	52
85.	vasculotropin trap.mp.	0
86.	VEGF Trap.mp.	227
87.	(ave 0005 or ave0005).mp.	4
88.	anti vegf inhibitors.mp.	7
89.	exp dexamethasone/	42,327
90.	dexamethasone.mp.	55,354
91.	ozurdex.mp.	44
92.	best support$ care.mp.	968
93.	support$ care.mp.	14,785
94.	bsc.mp.	1,420
95.	symptom$ care.mp.	140
96.	exp light coagulation/	10,467
97.	laser coagulat$.mp.	6,560
98.	light coagulat$.mp.	4,711
99.	photocoagulat$.mp.	7,352
100.	(panretinal photocoagulat$ or pan-retinal photocoagulat$).mp	772
101.	*OR/#74-100*	*118,972*
102.	*#13 (CRVO terms) AND #72 (Cost terms) AND #101 (Comparator terms)*	7
103.	*limit #102 to English language and years 2001-2013*	5
104.	*#20 (CRVO + RVO terms) AND #72 (Cost terms) AND #101 (Comparator terms)*	16
105.	*limit #104 to English language and years 2001-2013*	14

Table 142. Economic - NHS Economic Evaluation Database (NHS EED) via OVID, 2001 to 2013

#	Main CRVO search terms	Hits
1.	central retina$ vein$ occlu$.mp.	0
2.	central retina$ vein$ obstruct$.mp.	0
3.	retina$ centra$ vein$ occlu$.mp.	0

4.	CRVO.mp.	0
5.	CVO.mp.	0
6.	central vein$ occlu$.mp.	0
7.	central vein$ obstruct$.mp.	0
8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	8
10.	(central adj2 RVO).mp.	0
11.	(central adj2 retina$ vein$ occlu$).mp.	0
12.	central.mp. and retinal vein occlusion/	0
13.	*OR/#1-12*	*8*
	Additional RVO terms	
14.	retinal vein occlusion/	2
15.	retina$ vein$ occlu$.mp.	2
16.	retina$ vein$ obstruct$.mp.	1
17.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
18.	RVO.mp.	0
19.	*OR/#14-18*	2
20.	*#13 OR #19*	10
	Comparator terms	
21.	angiogenesis inhibitor.mp.	0
22.	bevacizumab.mp.	22
23.	avastin.mp.	0
24.	(nsc 704865 or nsc704865).mp.	0
25.	ranibizumab.mp.	16
26.	lucentis.mp.	1
27.	rhuFab V2.mp.	1
28.	eylea.mp.	0
29.	aflibercept.mp.	0
30.	(ave 0005 or ave0005).mp.	0
31.	vegf trap eye.mp.	0
32.	vascular endothelial growth factor trap.mp.	0
33.	vasculotropin trap.mp.	0
34.	VEGF Trap.mp.	0
35.	anti vegf inhibitors.mp.	0
36.	exp dexamethasone/	13
37.	dexamethasone.mp.	27
38.	ozurdex.mp.	0
39.	best support$ care.mp.	65
40.	support$ care.mp.	162
41.	bsc.mp.	35
42.	symptom$ care.mp.	0
43.	laser coagulation/	18
44.	photocoagulat$.mp.	30
45.	laser coagulat$.mp.	20
46.	light coagulat$.mp.	0
47.	(panretinal photocoagulat$ or pan-retinal photocoagulat$).mp.	2
48.	*OR/#21-47*	257
49.	*#13 (CRVO terms) AND #48 (Comparator terms)*	0
50.	*#20 (CRVO + RVO terms) AND #48 (Comparator terms)*	2

Table 143. Economic - Econlit Search via OVID, 2001 to 2013

#	Main CRVO search terms	Hits

1.	central retina$ vein$ occlu$.mp.	0
2.	central retina$ vein$ obstruct$.mp.	0
3.	retina$ centra$ vein$ occlu$.mp.	0
4.	CRVO.mp.	0
5.	CVO.mp.	2
6.	central vein$ occlu$.mp.	0
7.	central vein$ obstruct$.mp.	0
8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	21
10.	(central adj2 RVO).mp.	0
11.	(central adj2 retina$ vein$ occlu$).mp.	0
12.	*OR/#1-11*	*23*
	Additional RVO terms	
13.	retina$ vein$ occlu$.mp.	2
14.	retina$ vein$ obstruct$.mp.	2
15.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
16.	RVO.mp.	0
17.	*OR/#13-16*	*2*
18.	*#12 OR #17*	*23*
	Comparator terms	
19.	angiogenesis inhibitor.mp.	0
20.	bevacizumab.mp.	0
21.	avastin.mp.	0
22.	(nsc 704865 or nsc704865).mp.	0
23.	ranibizumab.mp.	0
24.	lucentis.mp.	0
25.	rhuFab V2.mp.	0
26.	eylea.mp.	0
27.	aflibercept.mp.	0
28.	(ave 0005 or ave0005).mp.	0
29.	vegf trap eye.mp.	0
30.	vascular endothelial growth factor trap.mp.	0
31.	vasculotropin trap.mp.	0
32.	VEGF Trap.mp.	0
33.	anti vegf inhibitors.mp.	0
34.	Exp dexamethasone/	0
35.	dexamethasone.mp.	0
36.	ozurdex.mp.	0
37.	best support$ care.mp.	2
38.	support$ care.mp.	14
39.	bsc.mp.	86
40.	symptom$ care.mp.	0
41.	Laser coagulation/	1
42.	laser coagulat$.mp.	0
43.	photocoagulat$.mp.	0
44.	light coagulat$.mp.	0
45.	(panretinal photocoagulat$ or pan-retinal photocoagulat$).mp.	2
46.	*#OR/19-45*	*101*
47.	*#12 (CRVO terms) AND #46 (Comparator terms)*	*0*
48.	*#18 (CRVO + RVO terms) AND #46 (Comparator terms)*	*0*

10.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Table 144 below summarises the search strategies used to find relevant conference abstracts from ISPOR congresses, presenting the search strings used and the corresponding number of hits.

Table 144. Search strategies for ISPOR conferences

Search terms	Studies after duplicates removal
Economic evaluations and costing/resource use studies: Disease/disorder: eye disorders Topic: cost studies Subtopic: all Quality of life studies: Disease/disorder: eye disorders Topic: patient reported outcomes & patient preference studies (PRO) Subtopic: all	Economic evaluations and costing/resource use studies: ISPOR Berlin 2012: 10 ISPOR USA 2012: 6 ISPOR USA 2011: 7 ISPOR Spain 2011: 16 ISPOR Czech Rep. 2010: 8 Quality of life studies: ISPOR Berlin 2012: 3 ISPOR USA 2012: 0 ISPOR USA 2011: 2 ISPOR Spain 2011: 6 ISPOR Czech Rep. 2010: 4

The ISPOR congress abstracts search identified five studies summarised in Table 145 below:

Table 145. Abstracts of RVO economic evaluations presented at ISPOR congresses

Reference	Abstract
Duff et al. 2012	OBJECTIVES: Quantify the cost effectiveness of treatments for macular oedema (MO) secondary to branch or central retinal vein occlusion (BRVO, CRVO) from U.S. payer/societal perspectives. METHODS: A Markov model consisting of five visual acuity (VA) health states and death was developed to quantify clinical outcomes, costs, and quality-adjusted life-years (QALYs) associated with no treatment (observation) or two-year treatment with ranibizumab monotherapy (six monthly injections; as needed thereafter), laser photocoagulation (BRVO only), ranibizumab plus laser (BRVO only), triamciniolone acetonide (CRVO only), or dexamethasone intravitreal implant. Transition probabilities were based on patient-level data for ranibizumab (± laser) and published literature for the remaining alternatives. Health state-specific costs and utilities were accrued for 13 years—approximate median survival of an RVO patient—with costs and QALYs discounted 3% annually. Costs associated with treatment, adverse events, and impaired vision were expressed in 2011 U.S. dollars. Incremental cost-effectiveness ratios (ICERs) were calculated comparing the least costly alternative to the next most costly strategy. Deterministic and probabilistic sensitivity analyses were conducted. RESULTS: Ranibizumab demonstrated superior efficacy relative to other strategies in both BRVO and CRVO but was most costly ($26,732 and $32,850; BRVO and CRVO, respectively). Other strategy costs ranged from $10,622 (observation in

Reference	Abstract
	BRVO) to $16,090 (dexamethasone intravitreal implant in CRVO patients). QALYs were greatest for ranibizumab (6.75 and 6.10; BRVO and CRVO, respectively) compared to a range of 4.88 (observation in CRVO) to 5.93 (laser in BRVO). Dexamethasone intravitreal implant was dominated in BRVO as was no treatment in CRVO. ICERs for ranibizumab were favorable ($19,270/QALY vs laser in BRVO; $34,204/QALY vs dexamethasone intravitreal implant in CRVO). At a threshold of $50,000/QALY, probabilistic analyses suggested ranibizumab to be cost effective in 99.7% (BRVO) and 88.3% (CRVO) of simulations. CONCLUSIONS: In patients with MO secondary to BRVO or CRVO, ranibizumab is a cost-effective treatment alternative.
Haig et al. 2012	OBJECTIVES: The value of ranibizumab as compared to standard care (laser photocoagulation in BRVO and observation in CRVO) was assessed within the framework of a cost-utility analysis (CUA) from the Canadian health care and societal perspectives. METHODS: Cost-utility of ranibizumab to the Canadian health care system was analyzed using a Markov model that followed a cohort of 66 or 68 year old patients (with BRVO or CRVO) over a lifetime time horizon. The model included 8 heath states as defined by best corrected visual acuity (BCVA) and 1 absorbing state for death. Year 1 health state transitions were based on data from the BRAVO and CRUISE trials, while year 2 transitions were based on data from the HORIZON extension trial. From year 3 onwards, health state transitions were based on fixed probabilities of maintaining or worsening BCVA. Health state utilities were derived from both the literature and a Canadian utility study in RVO patients. Resource use and costs were collected from clinical trials, published literature, and standard Canadian sources. Costs and outcomes were discounted at 5% as recommended by Canadian guidelines. RESULTS: From the health care perspective, patients receiving ranibizumab for BRVO accrued an additional 0.22 quality-adjusted life years (QALYs) with a total estimated incremental cost of CAD$8,080, resulting in $36,725 per QALY gained. In CRVO, 0.41 QALYs and $11,466 were estimated, resulting in $28,046 per QALY gained. From the societal perspective, considering costs related to productivity losses, the analyses resulted in an incremental cost per QALY gained of $11,266 for BRVO and $2,103 for CRVO. CONCLUSIONS: Compared to standard care (laser photocoagulation in BRVO and observation in CRVO), ranibizumab shows cost-effectiveness within commonly accepted cost per QALY thresholds from both the health care and societal perspectives.
Hayward et al. 2011	OBJECTIVES: Ozurdex (dexamethasone 700 µg intravitreal implant in applicator) was the first EMA licensed pharmacotherapy for macular oedema following central and branch retinal vein occlusion (CRVO, BRVO), a leading cause of vision loss. The objective of this analysis was to evaluate the cost-effectiveness of Ozurdex compared with a strategy of observation for the treatment of macular oedema (MO) following CRVO, and for BRVO patients with macular haemorrhage (BRVO-MH) or who have failed prior laser treatment (BRVO-PL). The analysis was performed from a UK NHS perspective. METHODS: A cost-utility model was developed to estimate the lifetime costs and effects of Ozurdex compared with observation in patients with CRVO, BRVO-MH and BRVO-PL based on the GENEVA 008 and GENEVA 009 studies. Patients in the model could move between six BCVA defined health states (best corrected visual acuity) based on the number of letters read correctly on the Early Treatment of Diabetic Retinopathy Study (ETDRS) chart. Cost data were obtained from literature and NHS reference costs. Utility values ranged between 0.599 and 0.862 and were derived from a preference-based scoring algorithm, the Visual Function Questionnaire Utility Index (VFQ-UI), valued by members of the general population using time-trade off (TTO).

Reference	Abstract
	RESULTS: Ozurdex was shown to be cost-effective relative to observation with ICERs of £16,522, £17,741 and £6,361 for patients with CRVO, BRVO-MH and BRVO-PL respectively. One-way sensitivity analysis demonstrated that the proportion of patients affected in the baseline defined worse-seeing eye was a key driver of cost-effectiveness. Probabilistic sensitivity analysis demonstrated that at a threshold of £30,000, Ozurdex was a cost effective option in 85.2% of simulations for CRVO, 82.1% of simulations for BRVO-MH and 98.2% of simulations for BRVO-PL. CONCLUSIONS: Ozurdex is a cost-effective treatment option from a UK NHS perspective for macular oedema secondary to CRVO, BRVO-MH and BRVO-PL. [poster available]
Kowalski et al. 2011	OBJECTIVES: Macular oedema (MO) following retinal vein occlusion (RVO) is a common cause of vision loss. The objective of this research was to assess the lifetime incremental cost-effectiveness of dexamethasone intravitreal implant 0.7mg (DEX) treatment versus observation for MO following central or branch RVO (CRVO or BRVO) from a US payer perspective. METHODS: An Excel-based Markov model with 6 heath states based on visual acuity (VA) plus one absorbing (Death) state was developed. Transition matrices were derived using individual patient-level data pooled from two identical phase III studies. Enrolled study patients at baseline had mean age of 65 years and study-eye VA of 20/80. DEX patients were assumed to receive up to 6-treatments over 3 years. Direct medical costs included drug, procedure, maintenance care, and adverse events. Additional directs costs and mortality was assigned to patients who became legally blind (=20/200 in BSE). Utility scores were directly calculated from study data via the Visual Function Questionnaire – Utility Index and health states differentially valued by whether the treated eye was the better- (BSE) or worse-seeing-eye (WSE). 90% of patients were assumed to have RVO in their WSE at model entry and a time-dependent risk of fellow eye occurrence (FEO) was incorporated. Costs and outcomes were discounted at 3%. Deterministic and probabilistic sensitivity analyses were conducted. RESULTS: Reference case ICERs were $23,416 and $20,597 per QALY for BRVO and CRVO (respectively); and sensitive to the percent of patients incurring the RVO in the BSE, risk of FEO, and cost of vision loss. Probabilistic sensitivity analyses demonstrated that the ICERs fall below a threshold of $50,000 per QALY in 87% and 92% of simulations for BRVO and CRVO, respectively. CONCLUSIONS: Using a threshold of $50,000, DEX treatment compared to observation is supported as a cost-effective treatment option for MO following BRVO or CRVO.
Tylor et al. 2012	OBJECTIVES: To evaluate the cost-effectiveness of ranibizumab versus best supportive care and grid laser photocoagulation therapy in patients with macular oedema (MO) secondary to branch or central retinal vein occlusion (BRVO or CRVO). METHODS: A Markov model was developed to compare treatment with ranibizumab to best supportive care (CRVO) and grid laser photocoagulation therapy (BRVO) in patients with MO secondary to RVO. Data from the BRAVO and CRUISE clinical trials were used to estimate transition probabilities between health states, defined by best corrected visual acuity (BCVA) and the frequency of adverse events. Costs and utilities from published sources were associated with each treatment and the model health states, and these were combined to predict the incremental costs and outcomes for a cohort treated over a lifetime horizon. The model included the costs associated with fellow eye involvement and the cost of blindness. A health system perspective in the UK was used. RESULTS: In CRVO, ranibizumab lead to a gain of 0.539 QALYs at an incremental cost of £9,216. The incremental cost-effectiveness ratio (ICER) was £17,103 per QALY. In BRVO, ranibizumab was shown to produce a gain of 0.518 QALYs

Reference	Abstract
	at an incremental cost of £8,141. The ICER was £15,710 per QALY. Both results were below the threshold range of £20,000 to £30,000 which is regarded as representing acceptable cost-effectiveness in the UK. Probabilistic sensitivity analysis suggests that the probability of cost-effectiveness for ranibizumab at a £20,000 threshold is 60% in CRVO and 57% in BRVO. CONCLUSIONS: Ranibizumab is a cost-effective therapy for treating patients with MO secondary to both BRVO and CRVO compared to current standard of care in the UK (laser in BRVO and observation in CRVO).

10.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 7.1)

The quality assessment of the two studies identified by the EE search is summarised in Section 7.1.3 above. No comments were deemed necessary to complement the grade provided for each question of the assessment.

The quality assessment of the 2 studies identified by the RU search is summarised in Table 146 below. No comments were deemed necessary to complement the grade provided for each question of the assessment.

Table 146. Quality assessment for resource use studies

Study question	**Fekrat *et al.* 2010**	**Augustin *et al.* 2012**
1. Was the research question stated?	Yes	Yes
Study Design		
1 Was the research question stated?	Yes	Yes
2. Was the economic importance of the research question stated?	Yes	N/A
3. Was/were the viewpoint(s) of the analysis clearly stated and justified?	Yes	Yes
4. Was a rationale reported for the choice of the alternative programmes or interventions compared?	No	N/A
5. Were the alternatives being compared clearly described?	Yes	N/A
6. Was the form of economic evaluation stated?	Yes	N/A
7. Was the choice of form of economic evaluation justified in relation to the questions addressed?	Yes	N/A
Data collection		
8. Was/were the source(s) of effectiveness estimates used stated?	N/A	N/A
9. Were details of the design and results of the effectiveness study given (if based on a single study)?	N/A	N/A
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)?	N/A	N/A
11. Were the primary outcome measure(s) for the economic evaluation clearly stated?	Yes	Yes
12. Were the methods used to value health states and other benefits stated?	N/A	N/A
13. Were the details of the subjects from whom valuations were obtained given?	N/A	Yes
14. Were productivity changes (if included) reported separately?	N/A	N/A
15. Was the relevance of productivity changes to the study question discussed?	N/A	N/A
16. Were quantities of resources reported separately from their unit cost?	No	Yes
17. Were the methods for the estimation of quantities and unit costs described?	Yes	Yes

18. Were currency and price data recorded?	Yes	Yes
19. Were details of price adjustments for inflation or currency conversion given?	No	Yes
20. Were details of any model used given?	N/A	N/A
21. Was there a justification for the choice of model used and the key parameters on which it was based?	N/A	N/A
Analysis and interpretation of results		
22. Was the time horizon of cost and benefits stated?	Yes	Yes
23. Was the discount rate stated?	N/A	N/A
24. Was the choice of rate justified?	N/A	N/A
25. Was an explanation given if cost or benefits were not discounted?	N/A	N/A
26. Were the details of statistical test(s) and confidence intervals given for stochastic data?	No	N/A
27. Was the approach to sensitivity analysis described?	N/A	N/A
28. Was the choice of variables for sensitivity analysis justified?	N/A	N/A
29. Were the ranges over which the parameters were varied stated?	N/A	N/A
30. Were relevant alternatives compared? (That is, were appropriate comparisons made when conducting the incremental analysis?)	N/A	N/A
31. Was an incremental analysis reported?	No	N/A
32. Were major outcomes presented in a disaggregated as well as aggregated form?	Yes	N/A
33. Was the answer to the study question given?	Yes	Yes
34. Did conclusions follow from the data reported?	Yes	N/A
35. Were conclusions accompanied by the appropriate caveats?	Yes	Yes
36. Were generalisability issues addressed?	No	Yes
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 searches were conducted on Embase, Medline (including Medline (R) in process), NHS EED and EconLitusing the OVID platform.

10.12.2 The date on which the search was conducted.

The search was conducted on March the 11th, 2013.

10.12.3 The date span of the search.

The searches spanned from January the 1st, 2001 to March the 11th, 2013.

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).

The search strategies used for Embase, MEdline, NHS EED and EconLit are summarised in Table 147, Table 148, Table 149, and Table 150 respectively.

Table 147. Quality of life - EMBASE Search via OVID, 2001 to 2013

#	**Main CRVO terms**	Hits
1.	central retina vein occlusion/	1,542
2.	CRVO.mp.	754
3.	central retina$ vein$ occlu$.mp.	2,104
4.	central retina$ vein$ obstruct$.mp.	30
5.	retina$ centra$ vein$ occlu$.mp.	11

6.	CVO.mp.	161
7.	central vein$ occlu$.mp.	164
8.	central vein$ obstruct$.mp.	30
9.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	3,512
10.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	8,536
11.	(central adj2 RVO).mp.	60
12.	(central adj2 retina$ vein$ occlu$).mp.	2,108
13.	central.mp. and exp retina vein occlusion/	2,424
14.	*OR/#1-13*	10,020
	Additional RVO terms	
15.	exp retina vein occlusion/	4,365
16.	retina vein/	958
17.	retina$ vein$ occlu$.mp.	4,687
18.	retina$ vein$ obstruct$.mp.	67
19.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	7,284
20.	RVO.mp.	474
21.	*OR/#15-20*	7,873
22.	*#14 or #21*	14,215
	Additional AMD terms	
23.	retina macula age related degeneration/	10,126
24.	age related macular degeneration.mp.	10,956
25.	retina macula age related degeneration.mp.	10,126
26.	macular degeneration.mp.	12,843
27.	AMD.mp	8,347
28.	ARMD.mp.	776
29.	*OR/#23-28*	18,941
30.	*#14 OR #21 OR #29*	32,706
	Additional DMO terms	
31.	exp diabetic retinopathy/	21,084
32.	exp retina macula cystoid oedema/	2,698
33.	exp diabetic macular oedema/	1,517
34.	(macula$ adj2 (oedema$1 or oedema$1)).mp.	9,906
35.	DME.mp	1,535
36.	DMO.mp.	282
37.	CME.mp.	5,858
38.	CSME.mp.	168
39.	OR/#31-38	34,800
40.	*#14 OR #21 OR #29 OR #39*	63,897
	QOL terms	
41.	exp "quality of life"/	225,841
42.	quality of life.mp.	261,874
43.	(hrql or hrqol or qol or hql or hqol).mp.	37,727
44.	health related quality of life.mp.	25,678
45.	quality adjusted life year/	10,329
46.	(qaly$ or qualy$ or quality adjusted life or life quality or quality adjusted survival).mp.	19,572
47.	life expectancy/	24,059
48.	life expectancy.mp.	32,424
49.	exp disability/	81,570
50.	disease free survival/	31,744
51.	disease free survival.mp.	45,026
52.	q twist.mp.	142
53.	(health utili$ index or hui or hui2 or hui 2 or hui 3 or hui 3).mp.	1,781
54.	(utili$ approach$ or health gain).mp.	658

55.	((utili$ or preference$) and (value$ or weight$ or scor$ or index$)).mp.	476,777
56.	Daily life activity/	47,637
57.	willingness to pay.mp.	2,843
58.	WTP.mp.	1,065
59.	(quality of well being or qwb).mp.	388
60.	assessment of quality of life.mp.	1,516
61.	(person trade off$ or person tradeoff$ or standard gamble$ or sg or time trade off or time tradeoff or tto).mp.	7,764
62.	(disutili$ or daly or disabili$ adjusted life).mp.	2,074
63.	(health$ year$ equivalen$ or hye$ or health utilit$).mp.	2,622
64.	rosser index.mp.	28
65.	Short Form 36/	9,414
66.	(short form 36 or shortform 36 or sf36 or sf 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).mp.	22,120
67.	(short form 6d or shortform 6d or sf6d or sf 6d).mp.	558
68.	(eq5d or eq 5d or euroqol 5d or euroqol).mp.	5,380
69.	(categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or visual analog scal$ or VAS or magnitude estimat$).mp.	55,526
70.	visual analog scale/	29,288
71.	exp health status/	112,774
72.	(health status or health state$).mp.	91,250
73.	health survey/	134,496
74.	wellbeing/	27,286
75.	well?being.mp.	31,624
76.	National Eye Institute Visual Function Questionnaire/	158
77.	visual function questionnaire.mp.	430
78.	NEI VFQ.mp.	305
79.	*OR/#41-78*	*1,147,407*
80.	*#14 (CRVO terms) AND #79 (QOL terms)*	*486*
81.	*limit 80 to English language and years 2001-2013*	*384*
82.	*#22 (CRVO + RVO terms) AND #79 (QOL terms)*	*586*
83.	*limit 82 to English language and years 2001-2013*	*469*
84.	*#30 (CRVO + RVO + AMD terms) AND #79 (QOL terms)*	*1,973*
85.	*limit 84 to English language and years 2001-2013*	*1,632*
86.	*#40 (CRVO + RVO + AMD +DMO terms) AND #79 (QOL terms)*	*3,875*
87.	*limit 86 to English language and years 2001-2013*	*3,092*

Table 148. Quality of life - MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) Search, 2001 to 2013

#	Main CRVO search terms	Hits
1.	central retina$ vein$ occlu$.mp.	1,323
2.	central retina$ vein$ obstruct$.mp.	43
3.	retina$ centra$ vein$ occlu$.mp.	9
4.	CRVO.mp.	608
5.	CVO.mp.	162
6.	central vein$ occlu$.mp.	146
7.	central vein$ obstruct$.mp.	18
8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	2,568
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	7,004
10.	(central adj2 RVO).mp.	46
11.	(central adj2 retina$ vein$ occlu$).mp.	1,329
12.	central.mp. and retinal vein occlusion/	1,396

13.	*OR/#1-12*	8,120
	Additional RVO terms	
14.	retinal vein occlusion/	2,649
15.	retina$ vein$ occlu$.mp.	3,430
16.	retina$ vein$ obstruct$.mp.	101
17.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	143
18.	RVO.mp.	362
19.	*OR/#14-18*	3,718
20.	*#13 OR #19*	10,040
	Additional AMD terms	
21.	exp Macular degeneration/	14,379
22.	macular degeneration.mp.	14,219
23.	age related macular degeneration.mp.	8,861
24.	retina macula age related degeneration.mp.	0
25.	ARMD.mp.	633
26.	AMD.mp.	6,091
27.	(age adj3 macular degeneration).mp.	8,917
28.	*OR/#21-27*	19,492
29.	*#13 OR #19 OR #28*	*28,727*
	Additional DMO terms	
30.	diabetic retinopathy/	17,567
31.	macular oedema/	3,752
32.	(macula$ adj2 (oedema$1 or oedema$1)).mp.	6,731
33.	DME.mp	1,368
34.	DMO.mp.	469
35.	CME.mp.	3,781
36.	CSME.mp.	147
37.	OR/#30-36	*26,818*
38.	*#13 OR #19 OR #28 OR #37*	*50,550*
	QOL terms	
39.	quality of life/	105,253
40.	quality of life.mp.	170,963
41.	(hrql or hrqol or qol or hql or hqol).mp.	24,218
42.	health related quality of life.mp.	18,834
43.	Quality adjusted life years/	6,026
44.	(qaly$ or qualy$ or quality adjusted life or life quality or quality adjusted survival).mp.	12,318
45.	life expectancy/	13,061
46.	life expectancy.mp.	25,479
47.	disease free survival/	36,933
48.	disease free survival.mp.	49,906
49.	q twist.mp.	81
50.	(health utili$ index or hui or hui2 or hui 2 or hui 3 or hui 3).mp.	1,029
51.	(utili$ approach$ or health gain).mp.	538
52.	((utili$ or preference$) and (value$ or weight$ or scor$ or index$)).mp.	352,134
53.	willingness to pay.mp.	1,973
54.	WTP.mp.	747
55.	(quality of well?being or qwb).mp.	162
56.	assessment of quality of life.mp.	1,072
57.	(person trade off$ or person tradeoff$ or standard gamble$ or sg or time trade off or time tradeoff or tto).mp.	1,452
58.	(disutili$ or daly or disabili$ or disabili$ adjusted life).mp.	165,148
59.	(health$ year$ equivalen$ or hye$ or health utili$).mp.	1,875
60.	rosser index.mp.	22
61.	(short form 36 or shortform 36 or sf36 or sf 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form	14,186

	thirty six).mp.	
62.	(short form 6d or shortform 6d or sf6d or sf 6d).mp.	337
63.	(eq5d or eq 5d or euroqol 5d or euroqol).mp.	3,241
64.	(categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or visual analog scal$ or VAS or magnitude estimat$).mp.	35,565
65.	exp health status/	94,308
66.	(health status or health state$).mp.	97,813
67.	exp health surveys/	373,910
68.	exp health status indicatiors/	177,652
69.	exp activities of daily living/	47,359
70.	value of life/	5,263
71.	well?being.mp.	4,568
72.	National Eye Institute Visual Function Questionnaire.mp.	226
73.	visual function questionnaire.mp.	316
74.	NEI VFQ.mp.	244
75.	*OR/#39-74*	*1,179,385*
76.	*#13 (CRVO terms) AND #75 (QOL terms)*	*380*
77.	*Limit #76 to English language and years 2001-2013*	*264*
78.	*#20 (CRVO + RVO terms) AND #75 (QOL terms)*	*424*
79.	*Limit #78 to English language and years 2001-2013*	*289*
80.	*#29 (CRVO + RVO + AMD terms) AND #75 (QOL terms)*	*1,801*
81.	*Limit #80 to English language and years 2001-2013*	*1,33*
82.	*#38 (CRVO + RVO + AMD+ DMO terms) AND #75 (QOL terms)*	*3,467*
83.	*Limit #82 to English language and years 2001-2013*	*2,319*

Table 149. Quality of life -NHS Economic Evaluation Database (NHS EED) via OVID, 2001 to 2013

#	Main CRVO search terms	Hits
1.	central retina$ vein$ occlu$.mp.	0
2.	central retina$ vein$ obstruct$.mp.	0
3.	retina$ centra$ vein$ occlu$.mp.	0
4.	CRVO.mp.	0
5.	CVO.mp.	0
6.	central vein$ occlu$.mp.	0
7.	central vein$ obstruct$.mp.	0
8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	8
10.	(central adj2 RVO).mp.	0
11.	(central adj2 retina$ vein$ occlu$).mp.	0
12.	central.mp. and retinal vein occlusion/	0
13.	*OR/#1-12*	*8*
	Additional RVO terms	
14.	retinal vein occlusion/	2
15.	retina$ vein$ occlu$.mp.	2
16.	retina$ vein$ obstruct$.mp.	1
17.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
18.	RVO.mp.	0
19.	*OR/#14-18*	*2*
20.	*#13 OR #19*	*10*
	Additional AMD terms	
21.	exp macular degeneration/	38
22.	macular degeneration.mp.	42
23.	age related macular degeneration.mp.	36

24.	retina macula age related degeneration.mp.	0
25.	ARMD.mp.	1
26.	AMD.mp.	18
27.	(age adj3 macular degeneration).mp.	36
28.	*OR/#21-27*	*41*
29.	*#13 OR #19 OR #28*	*53*
	Additional DMO terms	
30.	Diabetic retinopathy/	24
31.	(macula$ adj2 (oedema$1 or oedema$1)).mp.	21
32.	DME.mp	1
33.	DMO.mp.	0
34.	CME.mp.	3
35.	CSME.mp.	1
36.	*OR/#30-35*	*42*
37.	*#13 OR #19 OR #28 OR #36*	*92*
	QOL terms	
38.	quality of life/	1,049
39.	quality of life.mp.	5,041
40.	(hrql or hrqol or qol or hql or hqol).mp.	181
41.	health related quality of life.mp.	363
42.	quality adjusted life years/	2,272
43.	(qaly$ or qualy$ or quality adjusted life or life quality or quality adjusted survival).mp.	3,755
44.	life expectancy/	313
45.	life expectancy.mp.	1,187
46.	disease free survival/	119
47.	disease free survival.mp.	163
48.	q twist.mp.	5
49.	(health utili$ index or hui or hui2 or hui 2 or hui 3 or hui 3).mp.	127
50.	(utili$ approach$ or health gain).mp.	67
51.	((utili$ or preference$) and (value$ or weight$ or scor$ or index$)).mp.	4,924
52.	willingness to pay.mp.	709
53.	WTP.mp.	67
54.	(quality of well?being or qwb).mp.	13
55.	assessment of quality of life.mp.	33
56.	(person trade off$ or person tradeoff$ or standard gamble$ or sg or time trade off or time tradeoff or tto).mp.	484
57.	(disutili$ or daly or disabili$ or disabili$ adjusted life).mp.	756
58.	(health$ year$ equivalen$ or hye$ or health utili$).mp.	285
59.	rosser index.mp.	5
60.	(short form 36 or shortform 36 or sf36 or sf 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).mp.	221
61.	(short form 6d or shortform 6d or sf6d or sf 6d).mp.	39
62.	(eq5d or eq 5d or euroqol 5d or euroqol).mp.	586
63.	(categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or visual analog scal$ or VAS or magnitude estimat$).mp.	144
64.	exp health status/	191
65.	(health status or health state$).mp.	1,701
66.	exp health surveys/	1,524
67.	exp health status indicatiors/	407
68.	exp activities of daily living/	99
69.	value of life/	112
70.	well?being.mp.	13
71.	National Eye Institute Visual Function Questionnaire.mp.	0
72.	visual function questionnaire.mp.	0
73.	NEI VFQ.mp.	0

74.	*OR/#38-73*	*7923*
75.	*#13 (CRVO terms) AND #74 (QOL terms)*	*4*
76.	*Llimit #75 to English language and years 2001-2013*	*4*
77.	*#20 (CRVO + RVO terms) AND #74 (QOL terms)*	*6*
78.	*Limit #77 to English language and years 2001-2013*	*6*
79.	*#29 (CRVO + RVO + AMD terms) AND #74 (QOL terms)*	*45*
80.	*Limit #79 to English language and years 2001-2013*	*43*
81.	*#37 (CRVO + RVO + AMD + DMO terms) AND #74 (QOL terms)*	*78*
82.	*Limit #81 to English language and years 2001-2013*	*68*

Table 150. Quality of life – Econlit Search via OVID, 2001 to 2013

#	Main CRVO search terms	Hits
1.	central retina$ vein$ occlu$.mp.	0
2.	central retina$ vein$ obstruct$.mp.	0
3.	retina$ centra$ vein$ occlu$.mp.	0
4.	CRVO.mp.	0
5.	CVO.mp.	2
6.	central vein$ occlu$.mp.	0
7.	central vein$ obstruct$.mp.	0
8.	(central adj2 retina$ adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
9.	(central adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	21
10.	(central adj2 RVO).mp.	0
11.	(central adj2 retina$ vein$ occlu$).mp.	0
12.	*OR/#1-11*	*23*
	Additional RVO terms	
13.	retina$ vein$ occlu$.mp.	2
14.	retina$ vein$ obstruct$.mp.	2
15.	(retina adj2 (vein$ or occlu$ or obstruct$ or clos$ or stricture$ or steno$ or block$ or embolism$)).mp.	0
16.	RVO.mp.	0
17.	*OR/#13-16*	*2*
18.	*#12 OR #17*	*23*
	Additional AMD terms	
19.	macular degeneration.mp.	2
20.	age related macular degeneration.mp.	2
21.	retina macula age related degeneration.mp.	0
22.	ARMD.mp.	1
23.	AMD.mp.	14
24.	(age adj3 macular degeneration).mp.	2
25.	*OR/#19-24*	*16*
26.	*#12 OR #17 OR #25*	*39*
	Additional DMO terms	
27.	(diabet$ adj2 macula$ adj2 (oedema$1 or oedema$1)).mp.	1
28.	diabetic retinopathy.mp.	4
29.	DME.mp	5
30.	DMO.mp.	6
31.	CME.mp.	62
32.	CSME.mp.	11
33.	*OR/#27-32*	*89*
34.	*#12 OR #17 OR #25 OR #33*	*128*
	QOL terms	
35.	quality of life.mp.	1,921
36.	(hrql or hrqol or qol or hql or hqol).mp.	112

37.	health related quality of life.mp.	114
38.	(qaly$ or qualy$ or quality adjusted life or life quality or quality adjusted survival).mp.	419
39.	life expectancy.mp.	1,303
40.	disease free survival.mp.	0
41.	q twist.mp.	0
42.	(health utili$ index or hui or hui2 or hui 2 or hui 3 or hui 3).mp.	73
43.	(utili$ approach$ or health gain).mp.	154
44.	((utili$ or preference$) and (value$ or weight$ or scor$ or index$)).mp.	41,742
45.	willingness to pay.mp.	3,416
46.	WTP.mp.	1,055
47.	(quality of well?being or qwb).mp.	4
48.	assessment of quality of life.mp.	8
49.	(person trade off$ or person tradeoff$ or standard gamble$ or sg or time trade off or time tradeoff or tto).mp.	173
50.	(disutili$ or daly or disabili$ or disabili$ adjusted life).mp.	2,567
51.	(health$ year$ equivalen$ or hye$ or health utili$).mp.	109
52.	rosser index.mp.	0
53.	(short form 36 or shortform 36 or sf36 or sf 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).mp.	32
54.	(short form 6d or shortform 6d or sf6d or sf 6d).mp.	30
55.	(eq5d or eq 5d or euroqol 5d or euroqol).mp.	84
56.	(categor$ scal$ or linear scal$ or linear analog$ scal$ or visual scal$ or visual analog scal$ or VAS or magnitude estimat$).mp.	101
57.	(health status or health state$).mp.	1,566
58.	health surveys.mp.	195
59.	well?being.mp.	557
60.	National Eye Institute Visual Function Questionnaire.mp.	0
61.	visual function questionnaire.mp.	0
62.	NEI VFQ.mp.	0
63.	*OR/#35-62*	*51,244*
64.	*#12 (CRVO terms) AND #63 (QOL terms)*	*2*
65.	*#18 (CRVO + RVO terms) AND #63 (QOL terms)*	*2*
66.	*#26 (CRVO + RVO + AMD terms) AND #63 (QOL terms)*	*5*
67.	*#34 (CRVO + RVO + AMD + DMO terms) AND #63 (QOL terms)*	*12*
68.	*limit 67 to English language and years 2001-2013*	*11*

10.12.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Table 151 below summarises the search strategies used to find relevant conference abstracts from ISPOR congresses, presenting the search strings used and the corresponding number of hits.

Table 151. Search strategies for conferences websites

Conference name	Conference website/database	Search terms	Studies after duplicates removal

International Society for Pharmacoeconomics and Outcomes Research (ISPOR)	http://ispor.org/ Search (Outcomes Research Digest): http://www.ispor.org/research_study_digest/research_index.asp	Economic evaluations and costing/resource use studies: Disease/disorder: eye disorders Topic: cost studies Subtopic: all Quality of life studies: Disease/disorder: eye disorders Topic: patient reported outcomes & patient preference studies (PRO) Subtopic: all	Economic evaluations and costing/resource use studies: ISPOR Berlin 2012: 10 (update) ISPOR USA 2012: 6 ISPOR USA 2011: 7 ISPOR Spain 2011: 16 ISPOR Czech Rep. 2010: 8 Quality of life studies: ISPOR Berlin 2012: 3 (update) ISPOR USA 2012: 0 ISPOR USA 2011: 2 ISPOR Spain 2011: 6 ISPOR Czech Rep. 2010: 4

The ISPOR congress abstracts search identified three studies summarised in Table 152 below:

Table 152. Abstracts of CRVO/RVO/AMD/DMO HRQL studies presented at ISPOR congresses

Reference	Abstract
Balshaw et al. 2012	OBJECTIVES: Retinal vein occlusion (RVO) is the second most common vascular disorder of the retina, affecting approximately 28,000 new patients every year in Canada, but little is known about their health utility. A Canadian Observational Utility Study was conducted to estimate utility values for RVO patients with different levels of visual acuity (VA). METHODS: A total of 202 participants with RVO, where 37% had CRVO and 63% had BRVO, were enrolled from 20 sites across Canada. Participantss had RVO in either their best-seeing eye (17%) or worse-seeing eye (83%). Spectacle corrected VA was measured and patient health utility was collected using the Health Utilities Index questionnaire (HUI3). VA was recorded as a fraction (Snellen Score) and the value of this fraction was expressed as logMAR. A linear regression model was used to predict utility values from logMAR in the affected eye adjusting for key clinical covariates (age, duration of disease, logMAR in fellow eye). The baseline characteristics of participants from randomized controlled clinical trials (BRAVO, CRUISE) were used to generate predicted health utilities relevant in the context of these studies. RESULTS: For the 202 participants (ages 39 to 92, median 72) the mean (SD) HUI utility value was 0.80 (0.20), ranging from 0.18 to 1 (n=169) and logMAR score was 0.62 (0.42), ranging from 0 to 1.60 (n=202). The correlation between VA and utility was significant (r = -0.21, p=0.004, n=169) and the regression model indicated that a one unit increase in logMAR score was associated with 0.085 unit decrease in utility. Based on the regression model, HUI-based utilities decrease from 0.87 (logMAR -0.15) to 0.74 (logMAR 1.45) for typical patients in the randomized studies (mean age=67, logMAR fellow eye=0.09, disease duration=3.4 months). CONCLUSIONS: RVO is a debilitating ophthalmologic condition leading to reduced health utility with worsening of visual acuity.
Knudsen et al. 2011	OBJECTIVES: Evidence is limited on the extent to which health state utility decrements differ between changes in the better-seeing and worse-seeing eyes following treatment. This study presents estimates of the utility levels as a function of the visual acuity in the treated eye stratified by the condition of the fellow (untreated) eye in patients treated for visual impairment caused by diabetic macular oedema (DMO). METHODS: Data from RESTORE clinical trial with (12 months follow up of ranibizumab treatment for DMO) were analyzed. 8 health states were defined by BCVA in the treated eye. Mean utility was estimated using multivariate regression (repeated measures analysis). The regression was tested for confounders including disease severity. The influence of BCVA in the fellow eye on the health index was explored by separating treated

Reference	Abstract
	eyes into cohorts according to visual acuity of the fellow eye: better, equal or worse. Results were compared with other published studies. RESULTS: The utility ranged from 0.86 (SE=0.014) with BCVA 76-100 letters (Snellen score) to 0.55 (SE=0.083) with BCVA 0-25 letters (unadjusted model). Disease severity had a non-significant effect on this range (p>0.05). BCVA of the worse seeing eye had a significant impact on the utility (utility decrement -0.11 from 76-100 letters to 36-45 letters), with better seeing eyes demonstrating a utility decrement -0.14 from 76-100 letters to 36-45 letters. Results were inconclusive for health states below 35 letters due to small numbers. CONCLUSIONS: This explorative analysis reveals that visual acuity of a worse seeing eye has a significant impact on utility and may be comparable to the impact on the better seeing eye. Importantly, these findings are supported by improvements in quality of life observed using the National Eye Institute Visual Function Questionnaire-25 (NEI VFQ-25) for DMO patients treated with ranibizumab in the worse seeing eye in RESTORE
Liu et al. 2012	OBJECTIVES: To investigate whether a 1-line (5 letters) average change in best corrected visual acuity (BCVA) is associated with changes in health-related quality of life (HRQoL) in patients with diabetic macular oedema (DMO). METHODS: Data from a 12-month randomized trial of dexamethasone intravitreal implant plus laser or laser alone for DMO were analyzed. HRQoL was assessed by the National Eye Institute 25-Item Visual Function Questionnaire (VFQ-25). Patients were categorized into groups based on time-weighted average BCVA change from baseline: worsened (BCVA =-5), no change (-5 [...].

10.12.6 The inclusion and exclusion criteria.

The eligibility criteria for the quality of life search are summarised in Table 153 below:

Table 153. Eligibility criteria for the quality of life search

Quality of life	Inclusion	Exclusion
Patient population	Adult patients with CRVO, BRVO, RVO, AMD or DMO	Patients with pathologies other than CRVO, BRVO, RVO, AMD or DMO
Interventions	-	-
Comparators	-	-
Outcome measures	• Utility values (visual acuity, treatment adverse events, CRVO complications) stratified by visual acuity or disease severity • HRQoL studies that could inform the process of mapping the NEI-VFQ scores collected during the COPERNICUS and GALILEO trials to EQ-5D utility values	Studies that reported utilitily values not stratified by visual acuity or disease severity of CRVO, BRVO, RVO, AMD or DMO
Study design	• Reports of utility elicitation exercises **OR** • Reports of utility validation exercises **OR** • HRQoL studies that could inform the process of mapping (see “Outcomes measures” cell above in this table) • Reports of economic evaluations using utility measures gathered during the studies.	• Abstracts only*
Restrictions	• Language: English • Published in past 11 years	• Non-English studies • Studies published beyond 11 past years

10.12.7 The data abstraction strategy.

A data extraction form was developed and pilot tested. Two reviewers independently extracted the data from each study and resolved their disagreements by discussion or by consulting a third author. For non-English articles, one author extracted data.

Data was collected in relation to:

- Demographic characteristics (e.g. age, sex) and patient recruitment;
- Intervention and comparators;
- Sample size;
- Response rate;
- Description of health states;
- Adverse events;
- Method of elicitation;
- Method of valuation;
- Mapping;
- Results.

A summary of each of the 13 publications reviewed is provided below:

Aspinall *et al.* 2007(78) was a utility elicitation study in 122 patients in a Scottish (UK) setting with AMD; included patients had a mean age of 77.8 (SD±6.7) years. Utilities were elicited using TTO. Health states were defined according to BCVA ranges using LogMAR scale. The health states were logMAR <0.1; 0.12-0.40; 0.42-0.70; 0.72-1.30; and >1.30 and the corresponding health-related utility values were found to be 0.93 (95%CI: 0.86, 0.99); 0.86 (95%CI: 0.78, 0.93); 0.74 (95%CI: 0.67, 0.83); 0.68 (95%CI: 0.57, 0.79); and 0.76 (95%CI: 0.37, 1.15) respectively. The findings presented by Aspinall *et al.* 2007 are

subject to a single counterintuitive result. Participants with the worst visual acuity valued their current health state higher (BCVA: >1.30, utility value: 0.76) than participants in the two preceding health states (BCVA: 0.72-1.30, utility value: 0.68 and BCVA: 0.42-0.70, utility value: 0.74). This finding may be a result of disease duration, assuming those with the worst visual acuity have been affected for longer, and as a result they have adapted to their current visual impairment. Overall, the results presented in this study are of moderate quality. Although a high proportion of participants were unwilling to trade-off any of their remaining lifetime for perfect vision, all but one of the resulting health states report utility values consistent with what would be expected of a chronic indication.

Au Eong *et al*. 2012(79) was a utility elicitation and valuation study in 338 patients in Singapore with AMD conducted over the time period April 2006 to December 2007. Patients were included in the study if they had dry or wet AMD in one or both eyes, were ≥40 years of age, and could give informed consent; patients were excluded if they had significant ocular co-morbidities in either eye. Included patients had a mean age of 68.1 (SD±9.4) years. Utilities were elicited using TTO, EQ-5D and two SG methods; the first, SG (Death) used perfect health and death as the upper and lower health state anchors, and the second, SG (Blindness) modified the lower anchor, to binocular blindness rather than death. Health states were defined according to clinical severity of AMD. The health states were dry/normal; dry/dry; wet/normal; wet/dry; and wet/wet and the corresponding EQ-5D health-related utility values were found to be 0.87 (SD±0.12); 0.91 (SD±0.11); 0.90 (SD±0.11); 0.85 (SD±0.18); and 0.83 (SD±0.19) respectively. For TTO, the utility values were 0.88 (SD±0.19); 0.82 (SD±0.23); 0.77 (SD±0.19); 0.78 (SD±0.26); and 0.78 (SD±0.26), respectively. For the SG (death) the elicited utility values were 0.97 (SD±0.12); 0.88 (SD±0.23); 0.74 (SD±0.31); 0.80 (SD±0.33); and 0.86 (SD±0.29), respectively; and for SG (Blindness) the elicited utility values were 0.96 (SD±0.12); 0.92 (SD±0.12); 0.87 (SD±0.20); 0.85 (SD±0.27); and 0.94 (SD±0.14), respectively. The reported utility values for each method of elicitation are inconsistent and counterintuitive to expected outcomes; clinically inferior health states were valued more highly than clinically superior health states, which suggests inherent baseline differences between the patients in each of the AMD severity health states. The results of the two SG procedures suggests another caveat; by nature of the questions posed to participants, which anchored the lower health state to death and binocular blindness, it would be expected that the resulting utility values

would be lower when assuming a risk of binocular blindness versus a risk of death, however, the opposite was apparent. Overall, the results presented in this study are of low quality.

Brown *et al.* 2002a(55) was a utility elicitation study 333 patients with diabetic retinopathy and 246 patients with AMD . Patients were included in the study if they had visual acuity loss occurring primarily as secondary to diabetic retinopathy or had either dry or exudative AMD. Patients were excluded if Alzheimer's disease or other forms of dementia that were judged to negate the possibility of giving rational answers were apparent, there was visual acuity loss occurring secondary to multiple causes, or the inability or unwillingness to answer study questions once they were posed was demonstrated. Included patients had a mean age of 73.2 (SD±9.8) years. Utilities were elicited using TTO. Health states were defined according to BCVA level using Snellen. The BCVA health states were 20/20 to 20/25; 20/30 to 20/40; 20/50-20/100 and ≤20/200 and the corresponding health-related utility values were found to be 0.84 (95% CI: 0.82, 0.86); 0.80 (95% CI: 0.75, 0.85); 0.71 (95% CI: 0.65, 0.77); and 0.59 (95% CI: 0.53, 0.65), respectively. The findings presented by Brown *et al.* 2002a are consistent with what would be expected of a chronic indication; the utility values elicited for each health state consistently decline as patients progress to worse health states. The large sample size and relatively small confidence intervals (95%) are indicative of robust results. Overall, the results presented in this study are deemed to be of high quality, and would be useful in informing an economic evaluation.

Czoski-Murray *et al.* 2009(80) was a utility elicitation and valuation study in 108 persons from the English (Sheffield) general population. Patients were excluded if they had known ocular pathology, high myopia (>5.00 diopters spherical equivalent), a recent increase in floaters, or any of a number of high-risk medical complaints. Included patients had a mean age of 32 years (SD±12.5) years. Utilities were elicited using TTO. BCVA results were presented using the LogMAR scale. Three sets of vision impairing contact lenses (LogMAR 0.6; 1.0; and 1.4) were assessed, resulting in the following health states ≤0.30 (≥20/40); 0.31 to 0.60 (20/40 to 20/80); 0.61 to 1.30 (20/80 to 20/400); and ≥1.31 (≤20/400) and the corresponding (overall) health-related utility values were found to be 0.706 (95% CI: 0.606, 0.805); 0.681 (95% CI: 0.623, 0.740); 0.511 (95% CI: 0.449, 0.573); and 0.314 (95% CI: 0.217, 0.410), respectively. The combined findings across all three of the contact lenses are consistent with *a priori* expectations, such that utility values

decrease as patients' progress to the worse health states. The novel methodology implemented by Czoski-Murray *et al.* 2009 gave a sample of the general population a more pragmatic opportunity to value AMD related health states. Overall, the results presented in this study are deemed to be of high quality, and would be useful for informing an economic evaluation.

Espallargues *et al.*2005(81) was a utility elicitation and valuation study in 209 patients in Sheffield, England with AMD over the time period October 2003 to March 2004. Patients were included in the study if previously diagnosed with AMD, and excluded if known to have other ocular co-morbidities (e.g., glaucoma, uveitis, cataract, amblyopic, corneal scarring, vitreous haemorrhage, optic neuropathy, or other eye conditions that could cause visual impairment). Included patients had a mean age of 79.6 years (range 43-96 years). Utilities were estimated using TTO, VAS, EQ-5D, HUI-3, SF-6D and VF-14. Health states were defined according to VA using LogMAR. The health states were logMAR ≤0.3; 0.31-0.60; 0.61-1.3; 1.31-2.00; and >2.00 and the corresponding health-related utility values were found to range from: 0.73 to 0.47 for TTO; from 71.1 to 59.7 for VAS, from 0.75 to 0.63 for EQ-5D, and from 0.5 to 0.1 for HUI-3. The results presented by Espallargues *et al.*2005 are varied in terms of consistency. The TTO utility values adhere to the trend expected of a chronic condition, decreasing as health states worsen. While the HUI-3 results appear to overestimate the disutility associated with AMD, the corresponding utility values behave consistently, decreasing as a patient moves from better to worse health states. The utility values were assessed via the EQ-5D and VAS fail to depict the expected trend of a chronic indication as health states worsen; inconsistencies arise as worse visual acuity health states are valued more highly than less severe visual acuity states. Overall, the inconsistencies that arise across elicitation methods and relatively large standard deviations suggest that the results presented in this study are of low/moderate quality.

Lee *et al*. 2008(82) was a utility elicitation study in 44 patients in the US with AMD over the time period June 1998 to October 1999. Patients were required to have an eye examination on the day they enrolled, be at least 18 years old, and have sufficient literacy in English to understand the utility assessment instruments. Subjects ≥ 65 years old were excluded if they failed any mental acuity questions on a short form derived from the NEI-VFQ-25. Included patients had a mean age of 75.4 years (SD± 6.2) years. The health states were mild to moderate and severe AMD and the corresponding health-related utility

values elicited via a scale where 1=perfect health and 0=death, were found to be 0.89 (SD±0.23) and 0.76 (SD±0.30), respectively. Results are consistent with a priori expectations, reporting higher utilities for better health states and lower utility scores for worse health states. However, the small sample size and stratification of participants by only two health states (mild to moderate AMD and severe AMD) casts doubt over the robustness of the study results, which may therefore be inadequate for the purpose of informing an economic analysis. Overall, the quality of this study was deemed to be low.

Lotery *et al.* 2007(83) was a utility valuation study in 75 patients and 91 elderly non-AMD (controls) in the UK with Neovascular AMD over the time period April 2005 to October 2005. Patients were required to have bilateral subfoveal NV-AMD as HRQoL and functional status impairment have been shown to be correlated with VA in the better seeing eye. Controls had best-corrected Snellen VA of >20/40 in the better eye and were free from serious ocular pathologies. Patients that participated in an investigational drug study within the 30 days prior to the survey were excluded. Included patients had a mean age of 79.6 (SD±6.43). Utilities were elicited using EQ-5D. Health states were defined according to severity level in the better seeing eye. The health states were normal (>20/40); mild (20/40 – 20/80); moderate (20/80 – 20/200); severe (20/200 – 20/400); and near blind (<20/400) and the corresponding health-related utility values were found to be 0.52; 0.66; 0.72; 0.79; and 0.70, respectively, while the combined estimate for all AMD patients was 0.67, and the utility for controls was 0.77. As expected, the utility score for all AMD patients was significantly different from the control group (p = 0.0273). However, the stratified results presented by Lotery et al. 2007118111 are beset with inconsistencies: participants with normal AMD (>20/40) in their better seeing eye valued their current health state lower than all other AMD participants included in the trial implying that an unambiguously better health state was given a lower value in comparison with another more severe health state. Overall, the quality of this study was deemed to be low, and therefore of little use in informing an economic evaluation.

Sahel *et al.* 2007(84) was a utility valuation study in 360 patients from France, Germany, and Italy with AMD. Patients were included in the study if they were 50 years or older and visited the centre because of AMD during the enrolment period (for any reason), had a clinical record at the centre that contained all of the critical information required by the study, were able to answer and complete the questionnaires personally or with help from a

caregiver, and gave their written consent; patients were excluded if they had dry AMD and had participated in any other study or clinical trial, had a mental disability, or impaired VA due mainly to an eye disease other than AMD. Included patients had a mean age of 77 (SD±8.0) years. Utilities were estimated using HUI-3. Health states were defined according to BEVA/WEVA using Snellen fractions. Four health states were defined, including: 1) BEVA 20/40 or better and a WEVA of 20/200 or better for best acuity; 2) BEVA 20/40 or better and WEVA worse than 20/200 for intermediate acuity; 3) BEVA less than 20/40 and WEVA 20/200 or better for intermediate acuity; and 4) BEVA less than 20/40 and WEVA less than 20/200 for worst acuity. The corresponding HUI-3 French health-related utility values were 0.64; 0.59; 0.44; and 0.35, respectively; German health related utility values were 0.64; 0.58; 0.37; and 0.38, respectively, while the Italian values were 0.62; 0.60; 0.37; and 0.47, respectively. The combined (all three countries) utilities were consistent with *a priori* expectations of a chronic indication; however, inconsistency was apparent in both the German and Italian results, with both countries attaching a greater utility value to worse health states than less severe states, and the Italian data also proving inconsistent when comparing the best and second best health states. It appears that the HUI-3 generally overestimates the disutility associated with AMD in comparison to other methods of elicitation. While the combined results are consistent, the statistical moments (SE, SD or CI) detailing the robustness of the findings are withheld. Thus, the overall quality of these findings was deemed low.

Shah *et al.* 2004(85) was a utility elicitation study in 136 patients in the US with AMD and diabetes retinopathy over the time period November 2001 to January 2003. Patients were included in the study if they were at least 21 years of age with BCVA equal to or worse than 20/40 in at least one eye, and excluded if any other ocular disease was a greater contributor to vision loss than AMD or diabetic retinopathy, if they had a different ophthalmic problem in the second eye, the cause of visual loss was doubtful, or if they had Alzheimer's disease or other forms of dementia. Included patients had a mean age of 67.5 years (range: 25 to 92 years). Utilities were elicited using TTO. Health states were defined according to VA. The health states were VA 20/20 to 20/40; VA 20/50 to 20/100; and VA 20/200 to NLP and the corresponding health-related utility values were found to be 0.88 (95% CI: 0.87, 1.00); 0.90 (95% CI: 0.853, 1.00); and 0.76 (95% CI: 0.73, 0.87) respectively. The results presented by Shah *et al*.2004 are inconsistent with *a priori*

expectations, reporting a higher utility value clinically worse health states versus a less severe states. The overall quality of this study was deemed to be low.

Sharma *et al.* 2002(77) was a utility elicitation and valuation study in 323 patients in the US who visited a retina clinic in a tertiary hospital in Philadelphia. Patients were included in the study if they had 20/40 vision or worse in at least one eye and were deemed competent to answer the required questions, and excluded if any of the following were present: communication barriers, developmental disability, psychiatric illness. Included patients had a mean age of 67.5 (SD± 11.9) years. Utilities were elicited using TTO and SG. Health states were defined according to visual acuity in the better seeing eye using Snellen fractions. The health states were 6/7.5 or better; 6/9 to 6/15; 6/18 to 6/30;6/60 to 6/120; and CF to NLP and the corresponding health-related utility values were found to be 0.908 (95% CI: 0.875, 0.942); 0.797 (95% CI: 0.762, 0.833); 0.708 (95% CI: 0.653, 0.764); 0.621 (95% CI: 0.555, 0.687); and 0.473 (95% CI: 0.323, 0.624), respectively for TTO; and 0.948 (95% CI:0.924, 0.972); 0.897 (95% CI:0.869, 0.925); 0.769 (95% CI:0.696, 0.842); 0.742 (95% CI:0.672, 0.812); and 0.603 (95% CI:0.451, 0.754), respectively for SG. The findings presented by Sharma *et al.*2002 follow the trend expected when considering a chronic indication. Utility values declined in line with worsening clinical health states for both the TTO and SG metrics. Overall, utility values elicited via the TTO metric were lower than the SG utility values, which is a common occurrence related to the nature of the methods of utility elicitation. Overall, the quality of this study was deemed to be moderate.

Soubrane *et al.* 2007(86) was a utility valuation study in 401 NV-AMD patients and 471 controls from Canada, France, Germany, Spain and the UK. Patients were excluded if they were under 50 years old or had participated in an investigational drug study within the 30 days prior to the survey. Included NV-AMD patients had a mean age of 78.1 and controls had a mean age of 63.8 (SD±8.4) years. Utilities were assessed using EQ-5D. Health states were defined according to VA level using Snellen fractions. The health states were VA >20/40; VA 20/40 to >20/80; VA 20/80 to >20/200; and VA 20/200 to >20/400; the corresponding health-related utility values were found to be 0.69; 0.75; 0.72; 0.72; and 0.69 for the respective NV-AMD severity levels, while overall utility in the control group was found to be 0.75. The findings presented by Soubrane *et al.* 2007 suffer from inconsistent utility valuations of worsening health states. The inconsistencies of the results are demonstrated by the best clinical health state evaluated having the lowest utility score,

which is on par with that of the worst health state. The results are likely to be compromised by the poor sensitivity of the EQ-5D metric when valuing vision related health states. The overall quality of this study was deemed to be low.

Stein *et al.* 2003a(87) was a utility elicitation study in 324 patients in the US, 115 of whom had AMD, with two control groups, 142 from the general population, and 62 providers of care, over the time period February 2000 to February 2001. Patients were included in the study if they were 18 years or older and had the ability to complete a self administered questionnaire. Included patients had a mean age of 75.1 (SD± 7.92); included general population controls had a mean age of 44.3(SD± 13.32); and care provider controls had a mean age of 29(SD±7.32). Utilities were elicited using TTO. Health states were defined according to BCVA using Snellen fractions for the patient population while the control groups were asked to assume they had each of the following AMD health states. The health states were mild AMD (BCVA 20/30); moderate AMD (BCVA 2/40 to 20/100); and severe AMD (BCVA ≥20/200) and the corresponding health-related utility values were found to be 0.832 (95% CI: 0.762, 0.901), 0.732 (95% CI: 0.669, 0.795), and 0.566 (95% CI: 0.487, 0.654), respectively, for the patient population; 0.96 (95% CI: 0.95, 0.97), 0.918 (95% CI: 0.902, 0.934), and 0.857 (95% CI: 0.834, 0.879), respectively, for the general population; and 0.929 (95% CI: 0.904, 0.954), 0.877 (95% CI:0.846, 0.909), and 0.821 (95% CI: 0.785, 0.857), respectively, for the clinical population. The results are consistent across all three subgroups; utility scores decrease for each of the worsening health states which is expected with a chronic indication. The three health states (mild, moderate and severe AMD) received the highest valuations from the general population, followed by the clinician and patient populations, respectively. The overall quality of this study is deemed to be high.

Yanagi *et al.* 2011(88) was a utility elicitation study in 48 patients in Japan with bilateral exudative AMD. Patients were included in the study if they had a definite diagnosis of bilateral exudative AMD and excluded if they had other diseases such as idiopathic choroidal neovascularisation (CNV) and myopic CNV. Included patients had a mean age of 75.9 (range 59-91) years. Utilities were elicited using TTO and SG. Health states were defined according to BCVA. The health states were BCVA 0.01–0.15; BCVA 0.2-0.3; BVCA 0.4-0.6; BVCA 0.7-1.0 and the corresponding health-related utility values were found to be 0.534 (95% CI: 0.400, 0.667); 0.574 (95% CI: 0.487, 0.660); 0.613 (95% CI:

0.523, 0.703); and 0.653 (95% CI: 0.513, 0.793), respectively, for TTO; and 0.686 (95% CI:0.535, 0.838); 0.695 (95% CI: 0.595, 0.794); 0.703 (95% CI:0.601, 0.804); and 0.711 (95% CI:0.555, 0.867), respectively, for SG. The findings presented by Yanagi *et al.* 2011 are consistent across both methods of elicitation; clinically superior health states were given higher utility values. The values for each health state were lower for the TTO versus SG, a trend found consistently within the literature. Overall, the quality of this study was deemed to be low due to the particularly small sample size.

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.

As resource use (RU) systematic literature review was conducted alongside the EE systematic literature review, please refer to Appendix 10 Section 10.10.1.

10.13.2 The date on which the search was conducted.

Please refer to Appendix 10 Section 10.10.2.

10.13.3 The date span of the search.

Please refer to Appendix 10 Section 10.10.3.

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).

Please refer to Appendix 10 Section 10.10.4.

10.13.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

Please refer to Appendix 10 Section 10.12.5.

10.13.6 The inclusion and exclusion criteria.

Please refer to Section 7.7.1.

10.13.7 The data abstraction strategy.

A data extraction form was developed and pilot tested. Two reviewers independently extracted the data from each study and resolved their disagreements by discussion or by consulting a third author. Data was collected in relation to:

- Study characteristics including type of analysis, study population, coutnry/settimg, interventions, patient age, source of cost data;
- Study results including direct medical costs and any relevant resource use data.

10.14 Related procedures for evidence submission

10.15 Cost-effectiveness models

NICE accepts executable economic models using standard software – that is, Excel, TreeAge Pro, R or WinBUGs. If you plan to submit a model in a non-standard package, NICE should be informed in advance. NICE, in association with the ERG, will investigate whether the requested software is acceptable, and establish if you need to provide NICE and the ERG with temporary licences for the non-standard software for the duration of the appraisal. NICE reserves the right to reject economic models in non-standard software. A fully executable electronic copy of the model must be submitted to NICE with full access to the programming code. Care should be taken to ensure that the submitted versions of the model program and the written content of the evidence submission match.

NICE will need to distribute an executable version of the model to consultees and commentators because it will be used by the Appraisal Committee to assist their decision-making. On distribution of the appraisal consultation document (ACD) or final appraisal determination (FAD), and the evaluation report produced after the first committee meeting, NICE will advise consultees and commentators by letter that the manufacturer or sponsor has developed a model as part of their evidence submission for this technology appraisal. The letter asks consultees to inform NICE if they wish to receive an electronic copy of the model. If a request is received, NICE will release the model as long as it does not contain information that was designated confidential by the model owner, or the confidential material can be redacted by the model owner without producing severe limitations on the functionality of the model. The letter to consultees indicates clearly that NICE will distribute an executable copy, that the model is protected by intellectual property rights, and can be used only for the purposes of commenting on the model's reliability and informing a response to the ACD or FAD.

Manufacturers and sponsors must ensure that all relevant material pertinent to the decision problem has been disclosed to NICE at the time of submission. There will be no subsequent opportunity to submit information unless it has been specifically requested by NICE.

When making a submission, manufacturers and sponsors should check that:

- an electronic copy of the submission has been given to NICE with all confidential information highlighted and underlined
- an executable electronic copy of the economic model has been submitted
- the checklist of confidential information (provided by NICE along with invitation to submit) has been completed and submitted.

10.16 Disclosure of information

To ensure that the appraisal process is as transparent as possible, NICE considers it highly desirable that evidence pivotal to the Appraisal Committee's decisions should be publicly available. NICE recognises that because the appraisal is being undertaken close to the time of regulatory decisions, the status of information may change during the STA process. However, at the point of issuing the FAD or ACD to consultees and commentators, all the evidence seen by the Committee should be available to all consultees and commentators.

Under exceptional circumstances, unpublished evidence is accepted under agreement of confidentiality. Such evidence includes 'commercial in confidence' information and data that are awaiting publication ('academic in confidence'). Further instructions on the specification of confidential information, and its acceptability, can be found in the agreement between the Association of the British Pharmaceutical Industry (ABPI) and NICE (www.nice.org.uk).

When data are 'commercial in confidence' or 'academic in confidence', it is the manufacturer's or sponsor's responsibility to highlight such data clearly, and to provide reasons why they are confidential and the timescale within which they will remain confidential. The checklist of confidential information should be completed: if it is not provided, NICE will assume that there is no confidential information in the submission. It is the responsibility of the manufacturer or sponsor to ensure that the confidential information checklist is kept up to date.

The manufacturer or sponsor must ensure that any confidential information in their evidence submission is clearly underlined and highlighted. NICE is assured that information marked 'academic in confidence' can be presented and discussed during the public part of the Appraisal Committee meeting. NICE is confident that such public

presentation does not affect the subsequent publication of the information, which is the prerequisite allowing for the marking of information as ‘academic in confidence’.

Please therefore underline all confidential information, and separately highlight information that is submitted under ‘commercial in confidence’ in turquoise and information submitted under ‘academic in confidence’ in yellow.

The manufacturer or sponsor will be asked to supply a second version of the submission with any information that is to remain confidential removed. The confidential information should be ‘blacked out’ from this version, taking care to retain the original formatting as far as possible so that it is clear which data have been removed and where from. For further details on how the document should be redacted/stripped, see the checklist of confidential information.

The last opportunity to review the confidential status of information in an STA, before publication by NICE as part of the consultation on the ACD, is 2 weeks before the Appraisal Committee meeting; particularly in terms of ‘academic in confidence’ information. The ‘stripped’ version will be issued to consultees and commentators along with the ACD or FAD, and made available on NICE’s website 5 days later.

It is the responsibility of the manufacturer or sponsor to ensure that the ‘stripped’ version of the submission does not contain any confidential information. NICE will ask manufacturers and sponsors to reconsider restrictions on the release of data if there appears to be no obvious reason for the restrictions, or if such restrictions would make it difficult or impossible for NICE to show the evidential basis for its guidance. Information that has been put into the public domain, anywhere in the world, cannot be marked as confidential.

Confidential information submitted will be made available for review by the ERG and the Appraisal Committee. Confidential information may be distributed to all consultees with the permission of the manufacturer or sponsor. NICE will at all times seek to protect the confidentiality of the information submitted, but nothing will restrict the disclosure of information by NICE that is required by law (including in particular, but without limitation, the Freedom of Information Act 2000).

The Freedom of Information Act 2000, which came into force on 1 January 2005, enables any person to obtain information from public authorities such as NICE. The Act obliges NICE to respond to requests about the recorded information it holds, and it gives people a right of access to that information. This obligation extends to submissions made to NICE. Information that is designated as 'commercial in confidence' may be exempt under the Act. On receipt of a request for information, NICE will make every effort to contact the designated company representative to confirm the status of any information previously deemed 'commercial in confidence' before making any decision on disclosure.

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