NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Single Technology Appraisal (STA)

Ranibizumab (Lucentis®) for the treatment of visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)

Submitted by Novartis Pharmaceuticals UK Ltd.

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Abbreviations

Abbreviation	Definition
AAO	American Association of Ophthalmology
ABPI	Association of the British Pharmaceutical Industry
ACD	Appraisal Consultation Document
AE	Adverse Event
AMD	Age-Related Macular Degeneration
ANCOVA	ANalysis of COVAriance
ANOVA	ANalysis Of VAriance
APD	Afferent Pupillary Defect
ARVO	Association for Research in Vision and Ophthalmology
ATC	Anatomical Therapeutic Chemical
ATE	Arterial Thromboembolism
BCVA	Best Corrected Visual Acuity
BNF	British National Formulary
BRVO	Branch Retinal Vein Occlusion
BSE	Best Seeing Eye
BVOS	Branch Vein Occlusion Study
CA	Carbonic Anhydrase
CEA	Cost Effectiveness Analysis
CEAC	Cost-Effectiveness Acceptability Curve
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
CFT	Central Foveal Thickness
CMT	Central Macular Thickness
CRD	Centre for Reviews and Dissemination
CRT	Central Retinal Thickness
CRVO	Central Retinal Vein Occlusion
CSR	Clinical Study Report
CVA	cerebrovascular accident
CVOS	Central Vein Occlusion study
DA	Disc Area

DEX	Dexamethasone
DMO	Diabetic Macular Oedema
EFT	Excess Foveal Thickness
EMA	European Medicines Agency
EPAR	European public assessment report
EQ-5D	EuroQol-5D
ERG	Evidence Review Group
ERM	Epiretinal Membrane
ETDRS	Early Treatment Diabetic Retinopathy Study
EU	European Union
EURETINA	European Society of Retina Specialists
EVER	European Association for Vision and Eye Research
FA	Fluorescein angiography
FAD	Final Appraisal Decision
FDA	Food and Drug Administration (USA)
GMC	General Medical Council
GP	General Practitioner
HEED	Health Economic Evaluation Database
HR	Hazard Ratio
HRG	Healthcare Resource Group
HRQL	Health Related Quality of Life
HRVO	HemiRetinal Vein Occlusion
HSCS	Health and Social Care Services
ICER	Incremental Cost Effectiveness Ratio
IFU	Instructions For Use
IOP	IntraOcular Pressure
ITT	Intention To Treat
IVT	IntrViTreal
IVTA	IntraViTreal triAmcinolone
LS	Least Squares
LYG	Life Years Gained
MH	Macular Hole
MI	Myocardial Infarction
MO	Macular Oedema
MTC	Mixed Treatment Comparison

NA	Not Applicable
NCT	National Clinical Trial
NEI VFQ-25	National Eye Institute Visual Functioning Questionnaire - 25
NHMS	National Health Medical Survey
NHS	National Health Service
NHS EED	National Health Service Economic Evaluation Database
NS	Not Significant
OCT	Optical Coherence Tomography
ONS	Office of National Statistics
OPCS	Office of Population Censuses and Survey
OR	Odds Ratio
PbR	Payment by Results
PDR	Proliferative Diabetic Retinopathy
PDT	PhotoDynamic Therapy
PRN	Pro Re Nata (dosed as needed)
PROQOLID	Patient Reported Outcome and Quality of Life Instruments Database
PSA	Probabilistic Sensitivity Analysis
PSS	Personal Social Services
PSSRU	Personal and Social Services Research Unit
QALY	Quality Adjusted Life Year
QoL	Quality of Life
RAPD	Relative Afferent Pupillary Defect
RCT	Randomised Controlled Trial
RCO	Royal College of Ophthalmologists
RD	Retinal Detachment
RePEc	Research Papers in Economics
RNIB	Royal National Institute of Blind People
RR	Risk Ratio
RVO	Retinal Vein Occlusion
SAE	Serious Adverse Event
SCC	Statistical Coordinating Centre
SD	Standard Deviation
SF-36	Short Form 36

SG	Standard Gamble
SMC	Scottish Medicines Consortium
SPC	Summary of Product Characteristics
STA	Single Technology Appraisal
TTO	Time Trade-Off
UK	United Kingdom
USA	United States of America
USD	United States Dollar
VA	Visual Acuity
VAT	Value Added Tax
VEGF	Vascular Endothelial Growth Factor
VEGF-A	Vascular Endothelial Growth Factor A
VR	Vitreous Retinal
VR-QOL	Vision-related Quality of Life
WMD	Weighted Mean Difference
WSE	Worst Seeing Eye
WTP	Willingness To Pay

The term '**laser'** is used throughout the document to refer to **grid laser photocoagulation.**

Executive summary

The Technology and Indication

Ranibizumab (Lucentis®) has received a positive opinion from the EMA for the treatment of **visual impairment due to macula oedema (MO) secondary to retinal vein occlusion (RVO)** and is due to receive full marketing approval during the second quarter of 2011.

Ranibizumab is a humanised recombinant monoclonal antibody fragment that selectively binds to human Vascular Endothelial Growth Factor A (VEGF-A) and prevents it from binding to its receptors. VEGF-A is an important mediator of vascular leakage in MO caused by RVO.

Posology

Ranibizumab is available as a 10 mg/ml solution for intravitreal injection and costs £742.17 per 0.23 ml vial. The licensed dose is 0.5 mg given as a single intravitreal injection.

Treatment is initiated with monthly injections. The interval between two doses should not be shorter than 1 month. Patients should be monitored monthly for their disease activity. Stopping treatment is recommended when the patient's visual acuity (VA) is stable for at least three consecutive months. Treatment should be resumed when monitoring indicates a loss of visual acuity due to MO secondary to RVO. Patients should be treated with monthly injections until stabilisation is reached again.

Comparators

Laser photocoagulation is the main comparators of ranibizumab for BRVO and best supportive care is the main comparator of ranibizumab for CRVO. Dexamethasone implant (Ozurdex®) may be considered best alternative care, although it is not routinely used in the NHS currently, and is therefore also considered a relevant comparator.

The pivotal phase III trial that studied ranibizumab versus sham injections in the treatment of MO secondary to BRVO permitted the use of laser therapy after month 3 in both arms of the trial. The frequency of laser use was considerably greater in the

sham arm and therefore it can be considered that BRAVO directly compared ranibizumab therapy to standard of care including laser treatment. The pivotal phase III trial for ranibizumab in CRVO patients was CRUISE, which compared ranibizumab to sham injection; equivalent to best supportive care.

There are no head-to-head trials comparing ranibizumab directly to dexamethasone implant and the population, design and reporting of the randomised controlled trials for these agents did not permit a reliable indirect comparison. Despite these limitations of the data, a comparison to dexamethasone implant is of interest and attempts were made to incorporate the available data into the economic model. It is acknowledged that there are severe limitations to this approach, and the results should be considered exploratory and uncertain.

Characteristics of the Main Trials

- BRAVO was a large, randomised, double-blind, sham injection controlled trial of ranibizumab (0.3 mg and 0.5 mg) in patients with MO secondary to BRVO. Laser treatment was permitted in BRAVO, reflecting standard of care for patients with MO secondary to BRVO.
- CRUISE was a large randomised, double-blind, sham injection controlled trial of ranibizumab (0.3 mg and 0.5 mg) in patients with MO secondary to CRVO.
- Patients who completed the BRAVO and CRUISE 12 month trials entered the HORIZON extension study, for which 12 month data is presented.
- One pivotal non-RCT was identified (Campochiaro 2008/2010), which reports 2 year experience with ranibizumab treatment for MO secondary to RVO.

Key Efficacy and Safety Results

<u>Rapid and significant improvements in visual acuity</u>

- The large and high-quality BRAVO and CRUISE trials demonstrated that compared with sham injections, intraocular injections with ranibizumab 0.5 mg provided significant improvements in visual acuity over 6 months in patients with MO secondary to BRVO and CRVO, respectively.
  - In the BRAVO study at Month 6, patients in the 0.5 mg ranibizumab group had gained a mean (95% confidence interval (CI)) of 18.3 (16.0 – 20.6) letters from baseline best corrected visual acuity (BCVA) score, compared with a gain of only 7.3 (5.1 – 9.5) letters in the sham group ($p<0.0001$).

- In the CRUISE study at month 6, patients in the 0.5 mg ranibizumab treatment group had gained a mean of 14.9 (95% CI: 12.6 – 17.2) letters from baseline BCVA score, compared with the sham treatment group, where no statistically significant change in mean BCVA was observed at 6 months (0.8 [-2 to 3.6]; p<0.0001 for 0.5 mg ranibizumab vs. sham).

- These improvements in BCVA seen in both BRVO and CRVO patients were both rapid and clinically meaningful.
  - Significantly greater improvements from baseline in mean BCVA letter score were observed with ranibizumab treatment as early as Day 7 in both BRVO and CRVO patients (P<0.0001 vs. sham).
  - For both BRVO and CRVO patients, a significantly greater proportion of patients receiving 0.5 mg ranibizumab experienced a gain in BCVA of 15 letters or more during the 6-month treatment phase of the study (61.1% and 47.7%, respectively), compared to BRVO and CRVO patients who were randomised to receive sham-injection (28.8% and 16.9%, respectively; P<0.0001 for 0.5 mg ranibizumab vs. sham).

<u>Meaningful improvements in vision-related function</u>

- The observed improvement in visual acuity with ranibizumab treatment was associated with meaningful improvements in patient-reported vision-related function in both BRAVO and CRUISE.
  - For BRVO patients, the observed improvement (mean improvement [95% CI]) at month 6 from baseline in the NEI VFQ-25 composite score was significantly greater in patients treated with ranibizumab 0.5 mg (10.4 [8.3 – 12.4] points) than in patients treated with sham injection (5.4 [3.6 – 7.3] points, P<0.005 for 0.5 mg ranibizumab vs. sham).
  - The observed improvement (mean improvement [95% CI]) at month 6 from baseline in the NEI VFQ-25 composite score was also significantly greater in CRVO patients treated with ranibizumab 0.5 mg (6.2 [4.3 – 8.0] points) than in CRVO patients treated with sham injection (2.8 [0.8 – 4.7] points, P<0.05 for 0.5 mg ranibizumab vs. sham).

<u>Long-term sustained efficacy</u>

- The 6-month observational periods of BRAVO and CRUISE demonstrate that the continuation of ranibizumab treatment on a PRN basis maintains the positive

visual acuity and vision-related functional outcomes that were observed at the 6 month time point.

- The results from the HORIZON (Cohort 2) study indicate that the improvement in BCVA from BRAVO and CRUISE baseline seen in the ranibizumab treatment groups is sustained to 24 months.
  - From BRAVO baseline, BRVO patients receiving sham/0.5 mg and 0.5 mg ranibizumab achieved mean changes in BCVA of +15.6 and +17.5 letters, respectively. From CRUISE baseline, CRVO patients receiving sham/0.5 mg and 0.5 mg ranibizumab achieved mean changes in BCVA of +7.6 and +12.6 letters, respectively.
- Ranibizumab treatment was also found to provide long-term benefits to patients with MO secondary to RVO in the non-RCT Campochiaro 2008/2010, particularly for patients with MO secondary to BRVO.

Safety overview

- Ranibizumab has been found to be safe and well tolerated in over 750 patients with MO secondary to RVO in clinical trials. Ocular adverse events occurred at a lower frequency in the ranibizumab treatment arms of the BRAVO and CRUISE studies than in the sham arm during the 6 month treatment period.
- The favourable safety profile for ranibizumab in patients with visual impairment due to MO secondary to RVO is similar to that previously seen in patients with wet age-related macular degeneration (AMD) and DMO.

Economic Evaluation

Model structure

A markov model was employed, where patients moved between nine different health states at monthly cycles. The health states were based on eight different intervals of BCVA and a ninth absorbing state, 'death'. Health states were defined as bands of 10 EDTRS letters (2 lines) based on the assumption that 2 line changes are clinically significant. The model follows a cohort of 1,000 hypothetical generated patients, of whom each patient may experience a different health pathway over the course of the model. The model predicts changes in each patient's quality of life, resource use and costs.

In the primary analysis of the model for both MO secondary to BRVO and MO secondary to CRVO, ranibizumab was compared to the standard of care in this group of patients. For BRVO, ranibizumab was compared to laser therapy and data for the comparator group was based on the BRAVO trial, in which 57.6% of patients in the control standard care arm received laser treatment in the first 6 months of treatment. For CRVO, ranibizumab was compared to observation as per the CRUISE trial, which represents standard of care in this population.

Pivotal assumptions

The pivotal assumptions underlying the model are as follows:

- In BRAVO and CRUISE there was considerable HRQL gain (assessed using the NEI-VFQ 25 questionnaire) associated with treating eyes which were predominantly worse seeing. However, it has not yet been possible to translate these HRQL gains into utilities for use in a cost-utility analysis. Furthermore, there is a general paucity of data on costs and utility of changing vision in the worse-seeing eye in MO secondary to RVO, or indeed in other ocular conditions. In line with previous appraisals relating to ocular disease, the model therefore assumes treatment in the better-seeing eye (BSE) for the base case analysis.

Base-case results

Table 1 and Table 2 present the base case results for BRVO and CRVO respectively.

For BRVO, the incremental cost-effectiveness ratio (ICER) of ranibizumab compared to standard care (laser) was £24,610 per QALY gained.

Table 1 Base-case cost-effectiveness results for BRVO

	Standard of Care (laser)	**Ranibizumab**
Technology acquisition cost	£0	£7,501
Other costs	£11,990	£11,216
Total costs	£11,990	£18,717
Difference in total costs	N/A	£6,727
LYG	12.561	12.625
LYG difference	N/A	0.064
QALYs	7.705	7.978
QALY difference	N/A	0.273
ICER	N/A	**£24,610**
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

For CRVO, the incremental cost-effectiveness ratio (ICER) of ranibizumab compared to standard care (observation) was £11,428 per QALY gained.

Table 2 Base-case cost-effectiveness results for CRVO

	Standard of Care (observation)	**Ranibizumab**
Technology acquisition cost	£0	£9,098
Other costs	£20,727	£17,229
Total costs	£20,727	£26,327
Difference in total costs	N/A	£5,600
LYG	12.149	12.283
LYG difference	N/A	0.134
QALYs	7.061	7.551
QALY difference	N/A	0.490
ICER	N/A	**£11,428**
LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio		

Comparison to dexamethasone implant

The results must be interpreted with caution as sensitivity analysis showed that the ICERs were sensitive to changes in efficacy of either agent. For BRVO, the incremental cost-effectiveness ratio (ICER) of ranibizumab compared to dexamethasone implant was £10,883 per QALY gained. For CRVO, the incremental cost-effectiveness ratio (ICER) of ranibizumab compared to standard care (observation) was £12,027 per QALY gained.

Sensitivity analysis

For BRVO, the probability of ranibizumab being cost-effective compared to standard of care (including laser therapy) at a willingness to pay (WTP) threshold of £20,000 was 42.0%, and at a WTP threshold of £30,000 was 56.6%.

For CRVO, the probability of ranibizumab being cost-effective compared to best supportive care at a WTP threshold of £20,000 was 60.9%, and at a WTP threshold of £30,000 was 80.0%.

The direction of the deterministic sensitivity analysis results follows prior expectation: decreasing the effectiveness of ranibizumab, increasing natural deterioration of vision, decreasing the cost of blindness or increasing the frequency of ranibizumab injections increases the ICER. Probabilistic sensitivity analysis showed an inverse relationship between incremental cost and incremental effectiveness, as iterations that produce a greater effectiveness will have both a greater QALY gain and lower cost associated with blindness.

The results of the model were particularly sensitive to the proportion of patients affected in their best-seeing eye. This is due to the fact that changes in utility due to changes in visual acuity in the worse-seeing eye could not be modelled.

Sub-group Analyses

In both BRAVO and CRUISE, the significant group differences observed for improvement of visual acuity from baseline were maintained when results were analysed by subgroups based on baseline BCVA, CFT and time from RVO diagnosis to screening for trial entry. For ranibizumab versus standard of care in BRVO, the majority of subgroup ICERs were between £20,000 and £30,000 per QALY. For

ranibizumab versus best supportive care in CRVO, the majority were below £20,000 per QALY. These detailed subgroup results should be interpreted with caution, as there were very small numbers by subgroup and treatment group in several of the analyses.

Section A – Decision problem

Manufacturers and sponsors will be requested to submit section A in advance of the full submission (for details on timelines, see the NICE document 'Guide to the single technology appraisal (STA) process' – www.nice.org.uk). A (draft) summary of product characteristics (SPC) for pharmaceuticals or information for use (IFU) for devices, a (draft) assessment report produced by the regulatory authorities (for example, the European Public Assessment Report (EPAR)), and a (draft) technical manual for devices should be provided (see section 9.1, appendix 1).

1 Description of technology under assessment

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

Brand name: Lucentis
Approved name: ranibizumab
Therapeutic class: Ophthalmologicals; antineovascularisation agent, Anatomical Therapeutic Chemical (ATC) code: S01LA04 (1)

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

Ranibizumab is a humanised recombinant monoclonal antibody fragment that selectively binds to human Vascular Endothelial Growth Factor A (VEGF-A) and prevents it from binding to its receptors. VEGF-A is an important mediator of vascular leakage in Macular Oedema (MO) caused by Retinal Vein Occlusion (RVO).

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

Ranibizumab is currently being reviewed by the Committee for Medicinal Products for Human Use (CHMP; European Medicines Agency) for the treatment of visual

impairment due to MO secondary to RVO; a positive opinion was issued on 18th March 2011 and final approval is expected in the second quarter of 2011.

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 licence).

The [draft] EPAR that includes visual impairment due to MO secondary to RVO, the indication that is the focus of this submission, is not available at time of writing.

The EPAR for ranibizumab in the treatment of neovascular (wet) age-related macular degeneration (wet AMD) and diabetic macular oedema (DMO) discusses the safety concerns associated with the product, but concludes that the efficacy benefits of ranibizumab in these indications are greater than the risks [2]. In wet AMD, ranibizumab was deemed to be more effective at preventing a worsening of vision than its comparators and in DMO, ranibizumab was deemed more effective at improving vision than its comparators [2]. The main risks discussed are the common side effects that have occurred in more than 1 in 10 patients in clinical trials, which include increased intraocular pressure (pressure within the eye), headache, vitritis (inflammation within the eye), vitreous detachment (separation of the fluid in the eye from the back of the eye) and visual disturbance, among others.

A relevant condition attached to the current marketing authorisation is that the manufacturer, Novartis, must provide doctors and patients with an information pack detailing the safe use and the risks of using ranibizumab [2].

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

Ranibizumab has received a positive opinion from the CHMP and is expected to receive final approval for marketing authorisation for the treatment of:

- Visual impairment due to macular oedema secondary to retinal vein occlusion (the indication that is the focus of this submission)

Ranibizumab already has a European marketing authorisation for the following indications:

- wet age-related macular degeneration
- visual impairment due to diabetic macular oedema.

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 following trials are expected to provide further evidence in the next 12 months to support the use of ranibizumab in the treatment of MO caused by RVO:

Phase III studies

- 12 month data from the BRAVO and CRUISE studies, which were randomised, double-masked, sham-injection controlled Phase III studies of ranibizumab in the treatment of visual impairment due to MO secondary to BRVO and CRVO, respectively, have been presented as a poster at the Association for Research in Vision and Ophthalmology (ARVO) Annual Meeting, May 2010, and are due to be published in full in May 2011 (BRAVO) and June 2011 (CRUISE).

Extension studies

- The HORIZON study (NCT00379795) was a 24 month, open-label extension of both the BRAVO and CRUISE studies. The study was primarily designed to assess the long-term safety of ranibizumab. Patients were administered 0.5 mg ranibizumab *pro re nata* (prn), and were followed up at 3 monthly intervals. This extension study has now finished and the primary results have recently been presented at the Macular Society 34th Annual Meeting in Boca Raton, Florida [3]. The full results are expected to be published in late 2011.
- RETAIN (NCT01198327) is an extended follow-up study of patients who complete the HORIZON study. Ranibizumab will be dosed as needed and there will be the option to treat non-perfused areas of the retina with scatter photocoagulation. The aim of the study is to assess whether visual benefits are maintained when peripheral laser is used or whether it would be more beneficial to continue with intermittent injections of ranibizumab. The estimated primary completion date for RETAIN is September 2011.

Phase II studies

- The RABAMES Phase II study (NCT00562406), which was a 6 month pilot study that compared 0.5 mg ranibizumab injections, laser photocoagulation and a combination of both for MO due to BRVO, has now finished and is due to release results by the end of 2011.
- The RELATE study (NCT01003106) is an ongoing Phase I/II study that aims to compare the 0.5 mg dose of ranibizumab to a 2.0 mg dose for the treatment of MO secondary to either CRVO or BRVO. Patients in both dosing arms are then randomised to receive laser treatment at areas of non-perfusion outside the fovea or no further treatment. Collection of the final data for the primary endpoint is due to occur in November 2011.
- A Phase I open-label, randomised study (NCT01028248) is currently ongoing that is investigating a 2.0 mg dose of ranibizumab compared to the 0.5 mg

dose in patients with MO secondary to CRVO only. The expected primary completion date for this study is June 2011.

- A 40 patient Phase II study (NCT01123564) sponsored by the University of Pecs in Hungary is also comparing the efficacy of intravitreal ranibizumab to laser photocoagulation for patients with MO secondary to CRVO. This study is due to complete in September 2011.

Korean Studies

- A Phase IIIb, open-label, nonrandomised study (NCT00942864) of ranibizumab in MO due to RVO is currently underway in a Korean population. The results of this study will have less relevance to a UK population.
- A second Korean study (NCT01189526), sponsored by the Seoul Retina Investigator Group, is investigating intravitreal ranibizumab in comparison to macular laser photocoagulation for MO following BRVO in a randomised fashion. Again, the results of this study will have less relevance to a UK population.

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

[redacted] Ranibizumab is available in the UK, with marketing authorisation for the treatment of wet AMD and visual impairment due to DMO.

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

Ranibizumab is licensed in the United States of America (USA) for the treatment of MO following RVO [4], which is the indication that is the focus of this submission.

Ranibizumab also has regulatory approval for wet AMD in the European Union (EU) [5] and the USA [4], and for the treatment of visual impairment due to DMO in the EU only [5].

Genentech Inc. is the originator company and retains the commercial rights for North America (excluding Canada), whilst Novartis is the proprietor of those rights for the rest of the world, including the UK.

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?

[redacted]

Ranibizumab is currently undergoing the following health technology assessment in the UK:

- NICE is currently reviewing ranibizumab for the treatment of visual impairment due to DMO via single technology appraisal (STA).

- The SMC is also appraising ranibizumab for the treatment of visual impairment due to DMO and final guidance is expected in July 2011.

- NICE has produced multiple technology appraisal (MTA) TA155, which assessed available treatments for AMD and currently recommends ranibizumab for this indication.

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 A1 Unit costs of technology being appraised

Pharmaceutical formulation	10 mg/ml solution for intravitreal injection
Acquisition cost (excluding VAT)	£742.17 per 0.23 ml vial
Method of administration	Intravitreal injection
Doses	0.5 mg given as a single intravitreal injection (injection volume 0.05 ml)
Dosing frequency *[based on draft SPC]*	Treatment is initiated with monthly injections. The interval between two doses should not be shorter than 1 month. Patients should be monitored monthly for their disease activity. Stopping treatment is recommended when the patient's visual acuity (VA) is stable for at least three consecutive months. Patients should continue to be monitored for their disease activity. Treatment should be resumed when monitoring indicates a loss of visual acuity due to MO secondary to RVO. Patients should be treated with monthly injections until stabilisation is reached again. As demonstrated in the HORIZON study which followed patients 3 monthly, less frequent disease monitoring than monthly may be possible subsequent to visual stability being achieved for branch RVO (BRVO).
Average length of a course of treatment	Treatment duration depends on patient response. Data from the BRAVO, CRUISE and HORIZON studies indicates a declining need for further ranibizumab subsequent to treatment initiation.
Average cost of a course of treatment	The cost of a course of treatment depends on patient response.
Anticipated average interval between courses of treatments	The treatment interval should not be shorter than 1 month.
Anticipated number of repeat courses of treatments *[based on draft SPC]*	Treatment is resumed with monthly injections when monitoring indicates loss of visual acuity due to MO secondary to RVO, and continued until stable visual acuity is reached again for at least three

	consecutive monthly assessments.
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?

Fluorescein angiography (FA) is required in all patients with RVO to detect ischaemia [6]. The results of this test impact upon treatment choice, but as all patients will receive this investigation at diagnosis regardless of treatment there is no additional resource use associated with ranibizumab introduction. For patients with macular haemorrhage, FA may be required at more frequent intervals to ensure resolution of haemorrhage prior to laser treatment. This would not be the case for ranibizumab-treated patients with macular haemorrhage.

Assessment of best corrected visual acuity (BCVA) (during a routine outpatient appointment) should be undertaken monthly to monitor disease activity [7]. Assessment of MO (with Optical Coherence Tomography (OCT)) may also be undertaken monthly.

The Royal College of Ophthalmologists (RCO) guidelines for intravitreal injection procedures recommend administration in an enclosed, dedicated clean room, sterilisation of peri-operative equipment, and a specified mode of administration and post-injection management [8]. These guidelines apply to intravitreal injection of all products, including ranibizumab.

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

Patients should be monitored monthly for their disease activity, which is likely to include assessment of BCVA and of MO using OCT. As demonstrated in the HORIZON study, less frequent disease monitoring than monthly may be possible, subsequent to visual stability being achieved for BRVO.

Regular monitoring is part of the recommended best supportive care for any patient with MO secondary to RVO (monthly intervals for CRVO, 3 monthly intervals for BRVO [6]). Thus ranibizumab is not expected to impose substantial further requirements for patient monitoring, although treatment frequency will increase. The

RCO guidelines note that due to the effectiveness of the intravitreal anti-VEGF therapies in all types of RVO, there will be a greater number of patients eligible for treatment [6].

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?

Ranibizumab can be administered as monotherapy or in combination with laser photocoagulation. When given on the same day, ranibizumab injection should be administered at least 30 minutes after laser photocoagulation [5]. Section 1.6 provides more details on current trials that are investigating the safety and efficacy of concomitant ranibizumab and laser photocoagulation therapy in treating visual impairment due to MO secondary to RVO.

In terms of administration, broad-spectrum antimicrobial eye drops should be given before and after each injection [5, 9]. In addition, the periocular skin, eyelid and ocular surface should be disinfected and adequate anaesthesia should be applied immediately prior to the injection [5].

2 Context

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

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

Retinal vein occlusion (RVO) is a major cause of visual impairment in the UK, secondary only to diabetic retinopathy [6, 10]. Macular oedema (MO), the accumulation of fluid in the macula of the eye, is a common complication of RVO and is a major contributor to the loss of vision. Vision loss is associated with a high burden of disease, both in terms of reduced health-related quality of life (HRQL) and substantial economic costs [11-15].

RVO particularly affects older people, as incidence and prevalence increases with age. In a study of 4068 people, it has been found that incident RVO was associated with baseline age (odds ratio [OR] per 10 years, 1.70; 95% confidence interval [CI], 1.36-2.12).[16] Australian data indicates that the prevalence is 0.7% for those younger than 60 years, 1.2% for those 60 to 69 years, 2.1%, for those 70 to 79 years and 4.6% for people 80 years or older [17]. Other risk factors for RVO include hypertension, hyperlipidaemia, glaucoma and diabetes.

Aetiology
RVO occurs when there is a blockage in the venous system of the retina. The primary cause is often thrombus (blood clot) formation, but other causes can include external compression or vasculitis.[6] Occlusion can occur in the central retinal vein, leading to central RVO (CRVO) or in one of the branch veins, leading to branch RVO (BRVO). CRVO is approximately six times less prevalent than BRVO [18], but it is a more serious condition.

Following RVO, increased vascular permeability leads to MO. This condition is known to be associated with hypoxia (lack of oxygen) in the retina, and the degree of hypoxia corresponds to the impairment of visual acuity [10]. MO is the primary cause of visual loss in BRVO patients [19] and one of the leading causes of visual impairment in CRVO patients [20]. A reduction in the permeability of the retinal blood vessels would lead to a reduction in the volume of oedema in the macula and thus ameliorate vision.

Both types of RVO can either be ischaemic, where there is reduced blood supply to the retina (also known as non-perfused), or non-ischaemic, where blood supply remains relatively normal. There may be differing definitions of ischaemia [6, 21]. The definition for ischaemic RVO used by the Central Vein Occlusion Study (CVOS) was the presence of more than 10 fluorescein angiography disc areas of capillary non-perfusion [22], whereas for the Branch Vein Occlusion Study (BVOS) it was 5 disc areas [23]. Patients with severe ischaemic may be defined as those who present with brisk afferent pupillary defect (APD) [24, 25]. The presence of APD has been found to be a highly sensitive and reliable indicator of ischaemia [26].

Approximately 20% of CRVO patients are reported to have ischaemic disease [27], although as previously stated there is discrepancy over the definitions of ischaemia used in the literature [6]. The proportion of BRVO patients with ischaemia is not well established. Furthermore, ischaemia can occur in the macula or at peripheral sites of the retina; it is only that occurring in the macula that is relevant to the decision problem in this submission. Patients with ischaemic RVO, where retinal capillaries have closed, are at greatest risk of experiencing neovascularisation (growth of abnormal blood vessels), which can lead to glaucoma or vitreous haemorrhage. Ischaemic RVO has different treatment paradigms to the non-ischaemic conditions (see Section 2.4).

Course of the Disease

Although some patients can experience an improvement in MO and thus VA, in general the condition persists and vision declines over time. The aim of treatment, therefore, is to reduce MO and improve or prevent further deterioration in VA.

A systematic review of the literature describing the natural history of untreated CRVO concluded that VA generally decreases over time [27]. In the small proportion of studies that reported a spontaneous improvement in VA for patients over a defined time period (ranging from 3 to 40 months), their final VA was never greater than 20/40 (approximately equivalent to 70 ETDRS letters) [27]. Further evidence suggests that for those CRVO patients with an initial VA of 20/50 to 20/200 (approximately equivalent to 65 - 35 ETDRS letters), only 20% of eyes are likely to improve spontaneously [6]. A similar review of the course of BRVO found that of the eyes that had MO at presentation, 18 to 41% may show some degree of resolution, but that on average VA did not improve above 20/40 (approximately equivalent to 73 ETDRS letters) [28]. Furthermore, approximately 20% of untreated BRVO eyes with MO experience a significant deterioration of vision over time [8, 23].

Thus, although both CRVO and BRVO can improve spontaneously, in the majority of cases it does not resolve and may progress to a chronic state in which the prognosis and response to treatment is poor [29-31]. Chronic MO is associated with persistent hypoxia, which may lead to permanent structural damage in the macula and thus irreversible visual impairment [10]. Additionally, haemorrhage into the vitreous is more likely to occur when MO is persistent; this contributes to a worsening of VA and poor prognosis [10]. It is therefore important to treat MO due to RVO at an early stage.

Empirical data from randomised controlled trials in BRVO support the early treatment of MO:

- The recent triamcinolone SCORE study in BRVO found that in the standard of care group (laser photocoagulation or deferral of laser treatment until haemorrhage clears) patients with a baseline MO duration of greater than 3 months gained significantly fewer letters of BCVA at 12 months than those with a baseline MO duration of less than 3 months [32].
- In both the untreated and laser-treated arms of the BVOS study, patients with disease duration of more than 12 months were less likely to achieve two lines or more in BCVA after one year than those patients who had a shorter disease duration at baseline [23].

Studies such as these reveal the strong requirement for prompt treatment of MO secondary to RVO in order to improve or maintain VA. However to date, no

publication has established a reliable method to identify those patients whose MO will resolve spontaneously.

CRVO and BRVO can occur in both eyes at the same time. A systematic review of studies of the natural history of BRVO found that 5%-6% of patients at baseline had bilateral BRVO, with 10% developing fellow-eye involvement over time [28]. Studies in CRVO report a large range in the percentage of CRVO patients at baseline who have bilateral RVO (0.4% from CVOS study including 711 eyes to 43% in Pollack et al., which included only 7 eyes). The majority of studies reported that under 10% of CRVO patients showed bilateral RVO at baseline [27]. One study reported that 5% of CRVO cases develop RVO in the fellow eye over a 1 year period [27]. There was no data identified describing the incidence of fellow eye macular oedema caused by RVO.

Quality of Life

Loss of VA is associated with a considerable reduction in HRQL, due to the increased difficulty experienced when performing everyday tasks such as driving and the impact it may have on the patient's ability to work [11, 14]. It has specifically been reported that both CRVO and BRVO are associated with a decrease in vision-related QoL scores (as measured by the VFQ-25) and this reduction in QoL was related to the degree of VA [11, 12].

Although QoL is usually reported as a function of the better-seeing eye, this does not necessarily mean that there will be no QoL benefits in treating the worse-seeing eye; studies in both BRVO and CRVO have found that QoL scores were associated with the level of VA in the affected eye, even if the other eye had good vision [12, 24, 25]. There is also evidence from ranibizumab-treatment of wet AMD that treatment of the worse-seeing eye still improves patient-reported vision-related functioning [33]. A further argument for treating the worse-seeing eye is to maintain VA in that eye in case of future loss in the better-seeing eye, due to RVO or other eye conditions.

Mortality

It has been noted in some studies that for patients younger than 65-70 years, RVO is associated with a higher mortality rate than that seen in the general population [34, 35]. This is likely to be multifactorial in cause. For example, a large (N=549) UK hospital-based study has reported that over a nine year period patients with RVO experienced a higher rate of death from myocardial infarction than those without RVO [36]. This finding is corroborated by a smaller UK study (N=89), which found that patients with RVO had a higher risk of cardiovascular disease than the norm [37]. However, other data exists that did not find any association between RVO and cardiovascular mortality [34].

2.2 How many patients are assumed to be eligible? How is this figure derived?

There are no data specific to England and Wales on the incidence and prevalence of RVO ([27], [28]. There were no data identified describing the incidence of visual impairment due to MO secondary to RVO; the data relating to MO in patients with RVO was also limited. Furthermore, the majority of published epidemiological evidence is derived from population-based studies using scheduled appointments or

screening to identify cases (rather than through symptomatic presentation). In UK clinical practice, a proportion of cases are expected to remain undiagnosed due to the absence of symptoms. Thus, it is difficult to determine with any certainty the eligible population in England and Wales.

Novartis is currently working to refine estimates of the numbers of patients with visual impairment due to MO secondary to RVO in the UK, through primary research. As described in more detail in section 6, an assumption based estimate of incident cases of visual impairment due to MO secondary to BRVO and CRVO, respectively, can be derived but is uncertain.

2.3 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.

No NICE guidance or protocol has been published to date for the pharmacological treatment of visual impairment due to MO secondary to RVO; however, the dexamethasone intravitreal implant (Ozurdex) is undergoing a NICE single technology appraisal for this indication. In November 2010, the SMC did not recommend dexamethasone intravitreal implant for the treatment of MO secondary to RVO for use in NHS Scotland [38].

NICE have published Interventional Procedure Guidance 334, which states that current evidence on the efficacy and safety of arteriovenous crossing sheathotomy for BRVO is inadequate, and advises that this procedure should only be used within the context of research [39]. This decision was based on evidence from one RCT (40 patients), 3 non-randomised controlled studies (68, 40 and 36 patients) and one case series (60 patients).

2.4 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.

In light of the recent European approval of dexamethasone intravitreal implant and the imminently anticipated marketing authorisation of ranibizumab in this indication, the Royal College of Ophthalmologists (RCO) published interim guidelines in December 2010 for the management of RVO in which the treatment of MO secondary to CRVO and BRVO was considered separately [6].

The recent RCO guidelines are used to outline the current clinical pathway of care in which ranibizumab is placed. The RCO grade the evidence as follows:

- Grade A - At least one meta-analysis, systematic review, or good quality RCT directly applicable to the target population; or a body of evidence consisting principally of RCTs, directly applicable to the target population, and demonstrating overall consistency of results.
- Grade B - A body of evidence including high quality systematic reviews of case-control or cohort studies, directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from RCTs.
- Grade C - A body of evidence including studies rated as well conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal, directly applicable to the target population and demonstrating overall consistency of results; or extrapolated evidence from studies rated as high quality systematic reviews of case-control or cohort studies.
- Grade D - Evidence from non-analytic studies, e.g. case reports, case series or expert opinion.

<u>CRVO</u>

The RCO guidelines assess the evidence of various treatments specifically relating to MO secondary to CRVO. However, they do not provide recommendations on this exact indication [6]:

- For all non-ischaemic CRVO, the RCO conclude that there is Grade A evidence (at least one good quality RCT directly applicable to the target population) to support the use of dexamethasone intravitreal implant (licensed) or ranibizumab (off label at the time of guidance but has robust clinical evidence of efficacy)
- The RCO guidelines note that randomised controlled trials have failed to indicate VA benefit (despite a reduction in MO severity with treatment) with grid laser photocoagulation in MO secondary to CRVO, although a trend in favour of treatment has been observed in younger patients [6]. Laser photocoagulation is therefore not recommended for the management of CRVO.
- Follow-up after treatment for non-ischaemic CRVO will normally be required for up to 2 years. The development of disc collaterals or the resolution of the macular oedema should lead to discharge from clinical supervision [6].
- For ischaemic CRVO, the RCO advise only regular monitoring of the condition, (best supportive care) preferably at monthly intervals [6]. This regular monitoring is part of best supportive care that is provided for non-ischaemic CRVO, particularly as up to 30% of non-ischaemic CRVO cases can develop into the ischaemic condition [6].

<u>BRVO</u>

- The RCO guidelines recommend that for patients with MO secondary to non-ischaemic BRVO seen within 3 months of BRVO onset, pharmacotherapy with dexamethasone intravitreal implant (licensed) or ranibizumab (off label at the time of guidance but has robust clinical evidence of efficacy,) should be considered [6]. These recommendations are based on Grade A evidence for both therapies.
- Laser photocoagulation may also be considered in patients seen 3 months after the initial BRVO event and following absorption of the majority of the haemorrhage [6]. This recommendation is based on Grade A evidence.

- The RCO note that there is some evidence to suggest that BRVO patients with severe visual loss (<6/60 vision) and those in whom symptoms have been present for more than 12 months are unlikely to benefit from laser photocoagulation [6].
- For ischaemic BRVO, the RCO guidelines advise that monitoring for neovascularisation at 3-monthly intervals for up to 12 months should be performed as part of best supportive care [6].

The RCO reviewed the evidence of several other potential treatments for MO secondary to CRVO and BRVO.

- The Trivaris preparation of intravitreal triamcinolone acetonide (IVTA) has been observed to produce anatomical and functional improvement of MO due to CRVO and BRVO, though only to a similar magnitude to laser in BRVO [6]. Furthermore, laser was considered to have a more favourable benefit-risk profile than Trivaris in BRVO [6]. Although FDA approved, the RCO guideline indicates that the Trivaris preparation is not available for use in clinical practice anywhere in the world [6]. Kenalog is the triamcinolone formulation available in the UK and is specifically contraindicated for intraocular. The evidence review conducted by the RCO highlights that in addition to the known risks of cataract and raised intraocular pressure (IOP) seen with the preservative-free Trivaris, the presence of a preservative in Kenalog may also lead to an increased risk of sterile endophthalmitis when administered intraocularly. Endophthalmitis, eye inflammation, increased IOP and visual disturbances including vision loss have been reported with intravitreal administration of Kenalog [40]. Furthermore, the manufacturers of Kenalog advise that the intraocular injection of corticosteroid formulations containing benzyl alcohol, such as Kenalog, is not recommended because of retinal toxicity from the benzyl alcohol [41].
- The RCO notes that evidence for bevacizumab is limited to non-analytic studies, such as case reports, case series or expert opinion; the weakest level of evidence [6]. Unlicensed bevacizumab is therefore not recommended by the RCO to treat MO due to RVO. Clinical experts have provided feedback at previous NICE scoping meetings that unlicensed bevacizumab is not routinely used to treat macular oedema due to RVO. In light of the RCO guidance, it is unlikely that unlicensed bevacizumab would be considered routine treatment for RVO or best supportive care at the time of this appraisal.
- The RCO guidelines report that a phase II trial provides evidence for the efficacy of pegaptanib in MO secondary to CRVO, though response to treatment in the long-term remains unclear (Grade C evidence).
- Periocular administration (orbital floor or retrobulbar) of triamcinolone has demonstrated efficacy in the treatment of MO in BRVO, however the observed results are only short lived [6] (Grade C evidence).
- In agreement with the advice provided by NICE, the RCO guidelines also recommend against the use of arteriovenous sheathotomy in routine clinical practice in this indication [6] (Grade A evidence).

Inclusion of ranibizumab in the clinical care pathway for MO secondary to RVO has therefore already been proposed by the RCO, and in this context ranibizumab offers an alternative treatment option, with a distinct mechanism of action to dexamethasone intravitreal implant and laser photocoagulation, for the immediate management of this condition. It is of note that in its submission to NICE the manufacturer of dexamethasone intravitreal implant assumed that dexamethasone

intravitreal implant would be used only in those in whom laser therapy was inappropriate (due to macular haemorrhage) or in those in whom it had failed. Therefore ranibizumab may be the only alternative treatment option to laser therapy for a majority of patients affected by MO following BRVO.

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

Dexamethasone intravitreal implant was not recommended by the SMC for use in Scotland as "the manufacturer did not present a sufficiently robust clinical and economic analysis to gain acceptance by SMC" [38]. Guidance from NICE is awaited. There were higher rates of raised intra-ocular pressure (IOP) and cataract observed in pivotal studies [38]. Considering that dexamethasone intravitreal implant is the only pharmacological intervention currently licensed for this indication, there is scope for a second pharmacological agent with an alternative mechanism of action and potential for improved safety. Therefore, ranibizumab can provide an additional option for the treatment of visual impairment due to MO following RVO. In fact, as described above, ranibizumab may be the only additional treatment option in a broad number of patients.

The lack of a licensed pharmacological therapy for this condition may have resulted in the experimental use of unlicensed bevacizumab and the preserved triamcinolone preparation Kenalog (a corticosteroid), neither of which were developed for or are licensed for ocular use. The efficacy and safety of such unlicensed use of these therapies have not been evaluated in regulatory standard RCTs, and neither agent is recommended for use in the management of MO secondary to RVO by the RCO [6]. Furthermore, Kenalog is specifically contraindicated for intraocular administration [40] and the manufacturers of bevacizumab have highlighted safety concerns regarding the unlicensed intraocular use of this product [42].

Rapid treatment of MO secondary to RVO is known to be important in terms of good prognosis (refer to Section 2.1), but laser photocoagulation treatment is not recommended for the management of MO within 3 months of the initial BRVO event to allow some reduction in haemorrhage. There is therefore a need for therapies that can be dosed immediately after presentation of MO following RVO.

Ranibizumab provides an alternative option for a first-line, licensed pharmacological agent for the immediate treatment of visual impairment due to MO secondary to RVO, which is achieved through a distinct mechanism of action from that of the currently licensed dexamethasone intravitreal implant.

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

The current standard of care for non-ischaemic MO due to BRVO is a grid pattern of laser photocoagulation. Laser should be used after 3 months of the occlusion, following absorption of the majority of the haemorrhage. This is the main comparator for ranibizumab in non-ischaemic BRVO.

The standard of care, and main comparator, is best supportive care for the following subgroups:

- Patients with visual impairment due to MO secondary to both ischaemic and non-ischaemic CRVO
- Patients with MO secondary to BRVO who have severe visual loss (less than 6/60 vision) or whose symptoms have been present for over a year
- Patients with visual impairment due to MO secondary to ischaemic BRVO.

In light of the recently published RCO guidelines [6], dexamethasone intravitreal implant has been identified as a comparator for ranibizumab in the treatment of visual impairment due to MO secondary to CRVO or BRVO. Although this recently approved agent is not used routinely in NHS clinical practice as yet, it may be considered to represent the best alternative care to the current standard of care.

In contrast to the final NICE scope for this appraisal, bevacizumab is not considered a comparator to ranibizumab for this single technology appraisal. The use of unlicensed bevacizumab is not routine practice across the NHS, according to clinical experts at NICE scoping meetings for technology appraisals in this indication. Furthermore, given the absence of approval for bevacizumab, it cannot be considered best practice. Thus bevacizumab does not fulfil the criteria defined by NICE for inclusion as an unlicensed comparator. According to NICE guidance, relevant comparator technologies may also include those that do not have a marketing authorisation for the indication defined in the scope **but that are used routinely for the indication in the NHS.** Furthermore, the guidance states that relevant comparators are identified, with consideration given specifically to **routine** and **best practice in the NHS** [43].

There are also issues arising from the extent of the data for bevacizumab in this indication; the RCO notes that evidence for bevacizumab is limited to non-analytic studies, such as case reports, case series or expert opinion [6]. On this basis, they do not recommend the use of unlicensed bevacizumab to treat MO due to RVO. It is not clear whether evidence considered inadequate for clinical decision making should be considered adequate for considerations of relative clinical or cost effectiveness. The lack of reliable efficacy data for bevacizumab in the treatment of MO secondary to RVO renders an indirect comparison of ranibizumab and unlicensed bevacizumab unviable.

The use of intravitreal bevacizumab represents the use of a product that does not have regulatory approval for any ocular indications, is not presented in a licensed formulation for administration in the eye and does not have approval for compounding into smaller doses for ocular use. Potential systemic and ocular safety signals for bevacizumab mean that it is inappropriate to include this intervention in an appraisal before safety and quality have been assessed by the regulatory authorities [42, 44, 45]. The implications of these safety signals are a need for a large pharmacovigilance programme, as identified by stakeholders during the exploratory work by NICE regarding the feasibility of an appraisal of bevacizumab for eye conditions [46]. There are also liability consequences of unlicensed use. However, the uncertain costs of these activities cannot be incorporated adequately into an economic analysis using the existing NICE guidance for technology appraisal. Therefore inclusion of unlicensed bevacizumab as a comparator to ranibizumab in this submission is considered unnecessary, in light of NICE guidance, as well as inappropriate and implausible.

To conclude, laser photocoagulation and best supportive care are the main comparators of ranibizumab. Dexamethasone may be considered best alternative care, although it is not routinely used in the NHS currently, and is therefore also a comparator in this appraisal.

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

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

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

The main resource use associated with ranibizumab is monthly hospital outpatient visits, which include the staffing requirements for monitoring of disease activity. Tests required for monitoring are likely to be limited to assessment of BCVA and OCT. It is anticipated that care will most frequently be provided in ophthalmology units under the supervision of consultant ophthalmologists. Non-consultant grade ophthalmologists, specialist and other grade nurses, optometrists, orthoptists and technicians may also be involved in delivering care to ranibizumab-treated patients. In addition to staff time, administration costs may include those associated with maintaining a clean room and sterile equipment, anaesthesia and anti-microbial eye drops. It is expected that the majority of patients will receive intravitreal injections during an outpatient ophthalmologist appointment.

The location of care, staff delivering treatment and frequency of monitoring and tests are likely to vary between ophthalmology units depending on local practice. Table A2 illustrates resource use estimates and their data sources. All resource use estimates have been validated by NHS ophthalmologists that currently treat patients with visual impairment due to MO.

Table A2: Anticipated resource use associated with ranibizumab treatment

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

Abbreviations: BCVA, best corrected visual acuity; OCT, optical coherence tomography; SPC, summary of product characteristics

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

Ranibizumab has been routinely used in the NHS since 2008 for the treatment of wet AMD. Appropriate facilities for the administration of intravitreal injections are therefore already well established.

Regular monitoring is part of the recommended best supportive care for any patient with MO secondary to RVO (monthly intervals for CRVO, 3 monthly intervals for BRVO [6]). Thus ranibizumab is not expected to impose substantial further requirements on the NHS infrastructure.

3 Equity and equality

NICE considers equity in terms of how the effects of a health technology may deliver differential benefits across the population. Evidence relevant to equity considerations may also take a variety of forms and come from different sources. These may include general-population-generated utility weightings applied in health economic analyses, societal values elicited through social survey and other methods, research into technology uptake in different population groups, evidence on differential treatment effects in different population groups, and epidemiological evidence on risks or incidence of the condition in different population groups.

3.1 Identification of equity and equalities issues

3.1.1 Please specify any issues relating to equity or equalities in NICE guidance, or protocols for the condition for which the technology is being used.

Currently, there is no NICE guidance relating to the treatment of MO secondary to RVO.

3.1.2 Are there any equity or equalities issues anticipated for the appraisal of this technology (consider issues relating to current legislation and any issues identified in the scope for the appraisal)?

No equity or equalities issues were identified at scoping or subsequently.

3.1.3 How have the clinical and cost-effectiveness analyses addressed these issues?

Not applicable

4 Statement of the decision problem

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

Table A3 Decision problem

	Final scope issued by NICE	**Decision problem addressed in the submission**	**Rationale if different from the scope**
Population	People with macular oedema caused by retinal vein occlusion (RVO)	People with visual impairment due to macular oedema secondary to retinal vein occlusion (RVO)	This is the expected indication.
Intervention	Ranibizumab	Ranibizumab	
Comparator(s)	CRVO: i. Best supportive care (ischaemic only) ii. Bevacizumab iii. Dexamethasone implant BRVO: i. Best supportive care (ischaemic only) ii. Bevacizumab iii. Dexamethasone implant iv. Grid pattern photocoagulation	CRVO: i. Best supportive care ii. Dexamethasone implant BRVO: i. Dexamethasone implant ii. Grid pattern photocoagulation	Very few patients fulfilled the definition of ischaemia in the two key phase III RCTs for ranibizumab (0 in BRAVO and 2 in CRUISE), likely because patients with brisk afferent pupillary defect, which equates to ischaemia, were excluded from the trials. Therefore the subgroup of ischaemic RVO only cannot be considered separately. Bevacizumab is not used routinely in clinical practice in the NHS. In the absence of a regulatory assessment of, in particular safety and quality, and insufficient evidence for efficacy, bevacizumab cannot be considered best practice. Thus, unlicensed bevacizumab is not an appropriate comparator according to NICE guidance (Section 5.7).
Outcomes	The outcome measures to be considered include: • Visual acuity (the affected eye) • Visual acuity (the whole	The outcome measures to be considered include: • Visual acuity (the affected eye) • Adverse effects of treatment	Bilateral visual acuity outcomes were not recorded in the phase III trials.

	person) • Adverse effects of treatment • Health-related quality of life	• Health-related quality of life	
Economic analysis	The reference case stipulates that the cost effectiveness of treatments should be expressed in terms of incremental cost per quality-adjusted life year. The reference case stipulates that the time horizon for estimating clinical and cost effectiveness should be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective.	A cost utility analysis will be presented, with results expressed in terms of incremental cost per quality-adjusted life year. The time horizon for estimating clinical and cost effectiveness will be sufficiently long to reflect any differences in costs or outcomes between the technologies being compared The cost perspective is that of NHS and Personal Social Services.	
Subgroups to be considered	If the evidence allows, consideration will be given to subgroups according to: • type of RVO (BRVO and CRVO) • the presence or absence of ischaemia • baseline visual acuity • baseline structural damage to the central fovea • perfusion at the back of the eye • duration of	Consideration will be given to subgroups according to: • type of RVO (BRVO and CRVO) • baseline visual acuity • duration of macular oedema (time since diagnosis)	From the key phase III RCTs, no data were available for the subgroups ischaemic vs. non ischaemic patients, perfusion at the back of the eye and damage to the central fovea. The common definition of ischaemia used in RVO is based on perfusion: a case of greater than 10 fluorescein angiography disc areas of capillary non-perfusion is classed as ischaemia.[22] Although this characteristic was measured at baseline in BRAVO and CRUISE, very few patients actually fulfilled this definition of ischaemia (0 in BRAVO and 2 in CRUISE). This is likely due to the fact that patients with brisk afferent pupillary defect, which equates to severe ischaemia, were

	macular oedema (time since diagnosis)		excluded from the trials.
Special considerations, including issues related to equity or equality	Guidance will only be issued in accordance with the marketing authorisation	Guidance will only be issued in accordance with the marketing authorisation	

Section B – Clinical and cost effectiveness

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

Table B1 Reference case

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)

5 Clinical evidence

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

5.1 Identification of studies

Summary of Identification of Studies

- A systematic review was performed to identify randomised controlled trials that assessed the efficacy of ranibizumab in the treatment of visual impairment due to MO secondary to RVO.
- A wide range of electronic databases was searched and the results were reviewed independently by two investigators against pre-defined inclusion and exclusion criteria.

5.1.1 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 9.2, appendix 2.

A systematic review was performed to identify randomised controlled trials (RCTs) of ranibizumab in the treatment of MO secondary to CRVO or BRVO. The full search strategy used is detailed in Section 9.2, appendix 2.

A range of databases indexing published research were searched including those required by the NICE for STA submissions: MEDLINE, MEDLINE In-Process, EMBASE and the Cochrane Library. In addition, CINAHL, the Science Citation Index and clinical trials databases were also searched. Abstracts from the three most recent conferences proceedings of the following conferences were also searched via the conference websites: Association for Research in Vision and Ophthalmology

(ARVO), European Association for Vision and Eye Research (EVER), Nordic Ophthalmological Societies: Biannual Nordic Congress of Ophthalmology, American Association of Ophthalmology (AAO), EURETINA Congress (European Society of Retina Specialists).

The structure of the search strategy was as follows:

- Macular oedema/edema OR RVO/CRVO/BRVO

AND

- Ranibizumab (Lucentis)

NOT

- Animal studies

The titles and abstracts (if available) of the articles identified were then assessed by two researchers according to the inclusion/exclusion criteria described below in Section 5.2.1 and were eliminated if they were not relevant. Any judgment based on titles/abstracts where there was not agreement was reviewed again by both researchers and an agreement was reached. In cases where elimination based on the titles and/or abstract was not possible the full publication was reviewed in the same way by two researchers.

5.2 Study selection

Summary of Study Selection

- Three RCTs were identified from the systematic review:
  - BRAVO was a large, randomised, double-blind, sham injection controlled trial of ranibizumab (0.3 mg and 0.5 mg) in patients with MO secondary to BRVO.
  - CRUISE was a large randomised, double-blind, sham injection controlled trial of ranibizumab (0.3 mg and 0.5 mg) in patients with MO secondary to CRVO.
  - ROCC was a small randomised, double-blind, sham injection controlled trial of ranibizumab (0.5 mg) in patients with MO secondary to CRVO.
- Patients who completed the BRAVO and CRUISE 12 month trials entered the HORIZON extension study.
- One pivotal non-RCT was identified (Campochiaro 2008/2010), which reports 2 year experience with ranibizumab treatment for MO secondary to RVO.

5.2.1 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.

The searches were limited to human studies in the large bibliographic databases (such as MEDLINE). No date limits were applied. The searches were limited to English language studies only.

Studies were selected based on the following inclusion criteria:

Table B2 Eligibility criteria used in search strategy

Clinical effectiveness		
Inclusion criteria	Population	• Trials that fulfil the specific criteria for the UK/EU licence population were eligible for inclusion. • Participants must have included adults (aged 18 or over) with visual impairment due to macular oedema secondary to retinal vein occlusion. • The diagnosis of vein occlusion should have been established by fluorescein angiography, optical coherence tomography (OCT) or a clinical assessment. • Trials could include participants with concomitant ocular disease such as cataract or diabetic retinopathy.

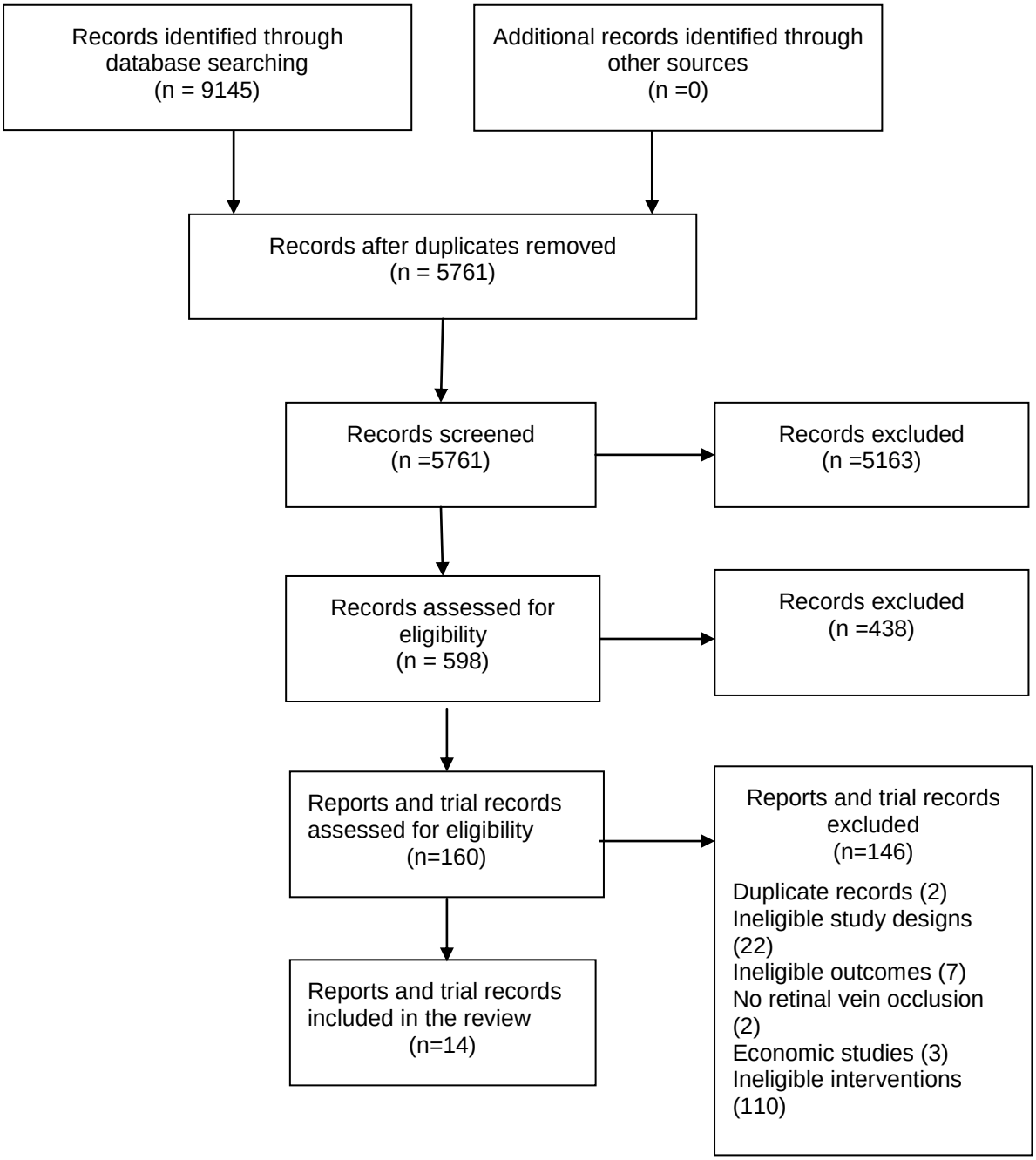
	Interventions	• Trials that evaluated ranibizumab used within its licensed dosage indication
		• Ranibizumab could be given concomitantly with laser photocoagulation therapy
		• The following comparators were eligible:
		  • Bevacizumab (Avastin)
		  • Dexamethasone (Ozurdex intravitreal implant)
		  • Laser photocoagulation
		  • Placebo (i.e. sham injections)
		  • Mixed treatments
		  • Observation/watchful waiting

	Outcomes	The primary outcomes for the review were the proportion of patients with an improvement in best corrected visual acuity, as measured by an improvement from baseline to six months of 10 or more letters read on an Early Treatment Diabetic Retinopathy Study Chart at four metres, equivalent to 0.2 logMAR. Any additional follow-up times will be reported. Studies reporting certain secondary outcomes, including QALYs, blindness avoided, structural damage to the central fovea, ischaemia and adverse events, were also eligible for inclusion.
	Study design	• Eligible study types were RCTs of any duration, including cross-over RCTs if data were presented at cross-over. Studies published as abstracts or conference presentations were eligible for the primary analysis of clinical effectiveness if adequate data are provided. • Studies conducted in any country where ranibizumab has regulatory approval were eligible for inclusion. • Data from unpublished studies was eligible for inclusion.
	Language restrictions	English

Exclusion criteria	Population	• Non-human • Mixed patient populations for which the results for RVO patients were not reported separately
	Interventions	Studies not involving ranibizumab used within its licensed dosage indication
	Outcomes	-
	Study design	Non-RCT study designs or articles reporting results of RCTs published elsewhere, eg. reviews, meta-analyses/pooled analyses, editorials, notes, comments or letters.
	Language restrictions	All non-English language articles

5.2.2 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 5.2.4.

Figure B1 Flow diagram showing study identification process for ranibizumab RCTs



The 14 articles identified by the review relate to three RCTs (BRAVO, CRUISE and ROCC), which are described below in Section 5.2.4 (Table B3). A Phase II study (Campochiaro 2008[47, 48]) was initially included in the systematic review as the participants were randomized to the study arms. However, it was subsequently excluded because the arms were both ranibizumab treatment arms (0.3 mg and 0.5 mg ranibizumab) and thus there was no control group.

5.2.3 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.

The fourteen articles identified by the review relate to three RCTs (BRAVO, CRUISE and ROCC), which are described below in Table B4.

The following is an alphabetical list of the publications identified for each trial, in which the primary papers for each trial are highlighted in bold:

BRAVO (NCT00486018)

- Bhisitkul, R. B., S. Gray, et al. (2010). "Anatomical Outcomes of the BRAVO Study of Intravitreal Ranibizumab in Patients With Macular Edema Following Branch Retinal Vein Occlusion." ARVO Meeting Abstracts 51(5): 6400.
- **Campochiaro, P. A., J. S. Heier, et al. (2010). "Ranibizumab for macular edema following branch retinal vein occlusion: six-month primary end point results of a phase III study." Ophthalmology 117(6): 1102-1112.e1101.**
- Ho, A. C., S. Gray, et al. (2010). "Ranibizumab in Patients With Macular Edema Following Retinal Vein Occlusion: 12-Month Outcomes of BRAVO and CRUISE." ARVO Meeting Abstracts 51(5): 6452.
- Singer, M., S. Gray, et al. (2010). "Subgroup Analyses of Visual Acuity Outcomes in the BRAVO Study of Intravitreal Ranibizumab in Patients With Macular Edema Following Branch Retinal Vein Occlusion." ARVO Meeting Abstracts 51(5): 3561. (extracted)
- Suner, I. J., R. Varma, et al. (2010). "Improvements in Reading Speed After 6 Months of Ranibizumab Treatment in Bravo and Cruise." ARVO Meeting Abstracts 51(5): 945.
- Varma, R., N. M. Bressler, et al. (2010). "Ranibizumab Improves Patient-Reported Near and Distance Vision Activities in Patients With Macular Edema Following Retinal Vein Occlusion." ARVO Meeting Abstracts 51(5): 5212.

CRUISE (NCT00485836)

- **Brown, D. M., P. A. Campochiaro, et al. (2010). "Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study." Ophthalmology 117(6): 1124-1133.e1121.**
- Feiner, L., R. Rubio, et al. (2010). "Anatomical Outcomes of the CRUISE Study of Intravitreal Ranibizumab in Patients With Macular Edema Following Central Retinal Vein Occlusion." ARVO Meeting Abstracts 51(5): 3564.
- Regillo, C. D., R. Rubio, et al. (2010). "Subgroup Analyses of Visual Acuity Outcomes in the CRUISE Study of Intravitreal Ranibizumab in Patients with Macular Edema Following Central Retinal Vein Occlusion." ARVO Meeting Abstracts 51(5): 3566.
- NCT record NCT00485836

Information on BRAVO and CRUISE presented in Section 5.5 was also supplemented with data from the manufacturer's clinical study reports, where necessary.

ROCC (NCT00567697)

- Kinge, B., P. Stordahl, et al. (2008). "The Rocc-study: A Randomized Study Comparing the Safety and Efficacy of Ranibizumab (lucentis®) to Sham in Patients With Macular Edema Secondary to Central Retinal Vein Occlusion (crvo)." Investigative Ophthalmology and Visual Science 49: E- abstract 2701.
- Kinge, B., P. B. Stordahl, et al. (2008). "The ROCC-study. A randomized study comparing the safety and efficacy of ranibizumab to sham in patients with macular edema secondary to CRVO (central retinal vein occlusion)." Acta Ophthalmologica 86(Suppl 241): 414-412.
- **Kinge, B., P. B. Stordahl, et al. (2010). "Efficacy of ranibizumab in patients with macular edema secondary to central retinal vein occlusion: results from the sham-controlled ROCC study." American Journal of Ophthalmology 150(3): 310-314.**
- ROCC ClinicalTrials.gov record

Complete list of relevant RCTs

5.2.4 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 B3 List of relevant RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
NCT00486018 **(BRAVO)** [25]	0.3 mg ranibizumab injection, 0.5 mg ranibizumab injection	Sham injection	Patients (≥ 18 years) with foveal centre-involved MO secondary to BRVO (N=397)	Campochiaro 2010 [25]
NCT00485836 **(CRUISE)** [24]	0.3 mg ranibizumab injection, 0.5 mg ranibizumab injection	Sham injection	Patients (≥ 18 years) with foveal centre-involved MO secondary to CRVO (N=392)	Brown 2010[24]
NCT00567697 **(ROCC)**[49]	0.5 mg ranibizumab injection	Sham injection	Patients (≥ 18 years) with MO secondary to CRVO (N=32)	Kinge 2010 [49]

5.2.5 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.

All three RCTs (BRAVO, CRUISE and ROCC) compared ranibizumab to sham injections, where a needleless hub of a syringe was placed against the eye and the plunger of the syringe was depressed to mimic an injection.

The BRAVO trial permitted PRN grid laser treatment in both sham and ranibizumab treatment groups after 3 months of observation, based upon the precedent of the BVO Study (see Section 5.3.2).[8, 23] Thus, the comparator arm in BRAVO is equivalent to UK standard of care incorporating laser therapy, which was identified as a key comparator in BRVO for ranibizumab under the decision problem in Section A (Section 2.6). This is also in line with the RCO Guidelines for management of BRVO.[6]

The RCO Guidelines for management of BRVO do not recommend concomitant use of laser and pharmacotherapy and this practice is not expected to occur frequently in clinical practice once ranibizumab is introduced.[7] A post-hoc analysis of the BRAVO trial results has demonstrated that the receipt of laser therapy by approximately 20% of patients in the ranibizumab arms did not inflate the efficacy results for ranibizumab. [50] In patients who did not receive laser therapy, numerically superior improvements in BCVA and the percentage of patients achieving an increase of at least 15 ETDRS letters were seen for each ranibizumab group compared to those who did receive laser therapy (see Appendix 19, Section 10.7 for full details).[50] Therefore, although combination treatment with ranibizumab and laser is anticipated to occur rarely in clinical practice, the results for ranibizumab plus laser patients from the BRAVO trial have been retained when presenting the clinical results and within the economic model so as not to bias the results through exclusion of those patients with a poorer response to ranibizumab.

No RCTs were identified that compare ranibizumab directly to dexamethasone biodegradable implant, which was the other appropriate comparator for ranibizumab identified in Section A (Section 2.6).

The decision problem for this submission states that best supportive care should be the comparator for patients with ischaemic RVO only. However, it should be noted

that very few patients fulfilled the definition of ischaemia in the two key RCTs for ranibizumab (0 in BRAVO and 2 in CRUISE) and therefore this sub group cannot be considered separately. Furthermore, given that neither dexamethasone nor bevacizumab are routinely available in the UK best supportive care is an important comparator, particularly in CRVO.

5.2.6 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.

The ROCC study was a small RCT in patients with MO secondary to CRVO (N=15 in ranibizumab treatment group), for which there is only has 6 month data available. As a larger number of patients with MO secondary to CRVO have been studied in the CRUISE study for a longer period of time, the ROCC study was not deemed to be a pivotal trial for ranibizumab in this patient population. Therefore the methodology and results of ROCC are not presented in the main body of this submission, but can be found in the supplementary appendix (Section 10.1, appendix 14).

List of relevant non-RCTs

5.2.7 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 5.8 and key details should be presented in a table; the following is a suggested format.

Non-RCTs that investigated the long term use of ranibizumab in the treatment of visual impairment due to MO secondary to RVO were deemed relevant to the decision problem, as they provide additional information to that reported by the RCTs. Only one such non-RCT was identified: Campochiaro 2008/2010, a randomised but uncontrolled dose comparison Phase II study of ranibizumab treatment for visual impairment due to MO secondary to BRVO.

Several large retrospective observational studies that assessed the safety of ranibizumab in wet AMD in clinical practice were identified during the review of data for this submission. Although these studies do not investigate the indication under consideration in this submission, they were deemed valuable for demonstrating in particular the systemic safety of intraocular injections of 0.5 mg ranibizumab and are thus discussed in Section 5.9.

Table B4 List of relevant non-RCTs

Trial no. (acronym)	Study Design	Intervention	Population	Objectives	Primary study ref.	Justification for inclusion
NCT00407355 **(Campochiaro 2008/2010)**	24 month, open label, uncontrolled, randomised dose comparison study	0.3 mg ranibizumab or 0.5 mg ranibizumab dosed monthly for 3 months then dosed PRN	Adult patients with MO caused by either BRVO or CRVO	To determine the long term effects of ranibizumab treatment	Campochiaro 2010[48]	This study reports on the long term outcomes of ranibizumab therapy, although in a small population (N=40)

5.3 Summary of methodology of relevant RCTs

Summary of methodology of relevant RCTs

- In BRAVO and CRUISE, eligible patients (with MO secondary to BRVO and CRVO, respectively) were randomised 1:1:1 to receive monthly intraocular injection of 0.3 mg, 0.5 mg of ranibizumab or sham injections, for a 6-month treatment period. This was followed by a 6-month observation period, in which all patients could receive ranibizumab PRN if they met pre-specified retreatment criteria.
    - In BRAVO only, patients were able to receive grid laser photocoagulation once during the treatment period and once during the observation period, beginning at months 3 and 9, respectively, in order to reflect standard of care.
- The primary efficacy endpoint in BRAVO and CRUISE was mean change from baseline BCVA letter score (using ETDRS charts) at Month 6.
- Secondary endpoints for the studies included mean changes from baseline BCVA letter score and CFT over time to Month 12, as well as the proportion of patients who gained ≥ 15, or lost < 15 ETDRS letters from baseline BCVA over time to Month 12. The mean change from baseline in the NEI VFQ-25 near and distance activities subscale over time up to 12 months were also secondary outcomes of BRAVO and CRUISE.
- The intention-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using the last-observation-carried-forward method.
- At baseline, patient demographics and ocular characteristics of study participants were similar across the three randomly allocated treatment groups within BRAVO and CRUISE.
- HORIZON (Cohort 2) was an open-label, single arm, multicentre follow-up study, in which patients who had completed the 12-month BRAVO and CRUISE trials could receive 0.5 mg ranibizumab on a PRN basis. Patients were followed in HORIZON for up to 24 months, during which time, the long-term safety and efficacy of ranibizumab was evaluated.

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

Methods

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

The design of the BRAVO and CRUISE trials are practically identical, with the obvious difference being that BRAVO included patients with MO secondary to BRVO, and CRUISE included patients with MO secondary to CRVO. This difference in patient population meant that concomitant grid laser photocoagulation was allowed after 3 months in BRAVO, though not in CRUISE (grid laser photocoagulation is not recommended for the management of patients with MO secondary to CRVO[6]). Thus, the comparator arm in BRAVO is equivalent to standard of care incorporating laser therapy.

The conditions for eligibility for both laser therapy and PRN ranibizumab therapy in the second 6 months of BRAVO were that a patient must have a Snellen equivalent BCVA of ≤20/40 or mean central subfield thickness of ≥250 μm. In addition to these requirements patients were required to have no macular haemorrhages and a gain of less than 5 letters in BCVA or a decrease of less than 50 μm in mean central subfield thickness compared to the visit 3 months prior to the current visit in order to qualify for laser therapy.

Table B5 Comparative summary of methodology of the RCTs

Trial no. (acronym)	NCT00486018 BRAVO [25]	NCT00485836 CRUISE [51]
Location	93 investigational centres in the United States	95 investigational centres in the United States
Design	A phase III prospective, randomised, sham-injection controlled, double-masked multicenter clinical trial. The study included a 28 day screening period (days -28 to -1) and a 6-month treatment period (Day 0 to Month 6), during which patients received monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab or sham injections. This was followed by a 6-month observation period (Month 6 through to completion of the study at Month 12, with a final visit at month 12), during which all patients (including those initially randomised to sham injection) could receive monthly intraocular ranibizumab if they met pre-specified functional and anatomic criteria: Snellen equivalent study eye BCVA ≤ 20/40 according to the ETDRS chart or mean central subfield thickness ≥ 250 µm according to OCT. Please see Figure B2 for a diagram of the BRAVO study design. During the 6-month treatment period, study visits occurred on days 0 and 7 and months 1-6. At each visit, patients were given a complete eye examination with OCT assessment of central foveal thickness. Patient-reported visual function was assessed with the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) at day 0 and months 1, 3 and 6. **Rescue laser photocoagulation** Rescue grid laser photocoagulation was allowed based upon the precedent of the BVOS.[23] As in BVOS, patients were eligible for laser treatment once during the treatment period and once during the observation period, beginning at months 3 and 9, respectively. Starting from month 3 or 9, patients were eligible for laser treatment if haemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤20/40 or mean central subfield thickness ≥250 µm, and compared with the visit 3 months before the current visit, patient had a gain of <5 letters in BCVA or a decrease of <50 µm in mean central subfield thickness. If rescue laser was not given at month 3, the same criteria were applied at month 4, and if rescue laser was not given at month 4, the same criteria were	A phase III prospective, randomised, sham-injection controlled, double-masked multicenter clinical trial. The study included a 28 day screening period (days -28 to -1) and a 6-month treatment period (Day 0 to Month 6), during which patients received monthly intraocular injections of 0.3 mg or 0.5 mg ranibizumab or sham injections. This was followed by a 6-month observation period (Month 6 through to completion of the study at Month 12, with a final visit at month 12), during which all patients (including those initially randomised to sham injection) could receive monthly intraocular ranibizumab if they met pre-specified functional and anatomic criteria: Snellen equivalent study eye BCVA ≤20/40 according to the ETDRS chart or mean central subfield thickness ≥ 250 µm according to OCT. Please see Figure B3 for a diagram of the CRUISE study design. During the 6-month treatment period, study visits occurred on days 0 and 7 and months 1-6. At each visit, patients were given a complete eye examination with OCT assessment of central foveal thickness. Patient-reported visual function was assessed with the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25) at day 0 and months 1, 3 and 6.

Trial no. (acronym)	NCT00486018 BRAVO [25]	NCT00485836 CRUISE [51]
	applied at month 5. This same process applied to rescue laser photocoagulation during the observation period for months 9, 10 and 11.	
Duration of study	The study duration was 12 months excluding the 28-day screening period (6 month treatment period, followed by 6 month observation period) The study was conducted between July 2007 and November 2008	
Method of randomisation	Eligible patients were randomised at Day 0 in a 1:1:1 ratio to one of three treatment arms (monthly injections of 0.3 mg or 0.5 mg ranibizumab or sham injections) through an interactive voice response system. Randomisation was stratified by baseline BCVA letter score (≤ 34, 35-54, or ≥ 55 letters [approximate Snellen equivalent groups of <20/200, 20/200 to <20/80 or ≥20/80, respectively]) and study centre. A dynamic randomisation method was used which was designed to achieve overall balance, balance within each category defined by visual acuity score, and balance within each study centre between the three treatment arms. One eye was chosen as the study eye for each patient. If both eyes were eligible, the eye with the worse BCVA at screening was selected.	
Method of blinding (care provider, patient and outcome assessor)	Patients, certified BCVA examiners, evaluating physicians, central reading centre personnel and the Sponsor were masked to treatment and dose throughout the study. Injecting physicians, who did not perform examinations or outcome assessments, were masked to dose but not treatment. Masking was maintained until after completion of the study (after all subjects have either completed the visit at month 12 or discontinued early from the study.	

Trial no. (acronym)	**NCT00486018 BRAVO [25]**	**NCT00485836 CRUISE [51]**
Intervention(s) (n =) and comparator(s) (n =)	**Interventions**: 0.3 mg ranibizumab (n=134) 0.5 mg ranibizumab (n=131)**Comparator**: Sham injection (n=132) Patients received their assigned treatment at day 0 and months 1-5 for a maximum of 6 injections. Injection procedures were identical to those previously described.[52, 53] Briefly, when administering intraocular injections, topical anaesthetic drops were given, a lid speculum was inserted, and after subconjunctival injection of 2% lidocaine and cleaning of the injection site with 5% povidone iodine, a 30-gauge needle was inserted through the pars plana, and 0.05 mL of ranibizumab was injected. Patients who were randomized to the sham group were treated similarly to those in the ranibizumab groups, except that a needleless hub of a syringe was placed against the injection site; and the plunger of the syringe was depressed to mimic an injection. The ability to count fingers with the study eye was assessed 15 minutes after injection, and intraocular pressure was measured within 50–70 minutes of an injection.	**Interventions**: 0.3 mg ranibizumab (n=132) 0.5 mg ranibizumab (n=130)**Comparator**: Sham injection (n=130) Patients received their assigned treatment at day 0 and months 1-5 for a maximum of 6 injections. Injection procedures were identical to those previously described.[52, 53] Briefly, when administering intraocular injections, topical anaesthetic drops were given, a lid speculum was inserted, and after subconjunctival injection of 2% lidocaine and cleaning of the injection site with 5% povidone iodine, a 30-gauge needle was inserted through the pars plana, and 0.05 mL of ranibizumab was injected. Patients who were randomized to the sham group were treated similarly to those in the ranibizumab groups, except that a needleless hub of a syringe was placed against the injection site; and the plunger of the syringe was depressed to mimic an injection. The ability to count fingers with the study eye was assessed 15 minutes after injection, and intraocular pressure was measured within 50–70 minutes of an injection.
Primary outcomes (including scoring methods and timings of assessments)	Mean change from baseline in BCVA at 6 months* * BCVA was measured in the study eye based on the ETDRS visual acuity charts and assessed at a starting test distance of 4 metres	
Secondary outcomes (including scoring methods and timings of assessments)	(All ocular efficacy outcome measures refer to the study eye only) Secondary efficacy outcomes: • Mean change from baseline in BCVA over time up to 6 and 12 months • Proportion of subjects who gained ≥ 15 letters in BCVA* at 6 and 12 months compared with baseline • Proportion of subjects who lose < 15 letters in BCVA at 6 and 12 months compared with baseline • Proportion of subjects with a central foveal thickness of ≤ 250 µm, assessed by OCT, at 6 and 12 months • Mean absolute change from baseline in central foveal thickness, assessed by OCT, over time up to 6 months and at 12 months • Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months and at 12 months	

Trial no. (acronym)	NCT00486018 BRAVO [25]	NCT00485836 CRUISE [51]
	• Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months and at 12 months Exploratory efficacy outcomes (not all exploratory outcomes considered in BRAVO have been listed here, however the full list of exploratory outcomes can be provided to NICE on request): • Percentage of patients with Snellen equivalent BCVA ≥ 20/40 at month 6 and 12 months • Percentage of patients with Snellen equivalent BCVA ≤ 20/200 at month 6 and 12 months • Mean change from baseline extra foveal thickness** over time to months 6 and 12 • Mean change from baseline in the NEI VFQ-25 composite score (of near and distance activities subscales) over time up to 6 months and at 12 months • Mean change from baseline in the number of correctly read words per minute on the reading speed test over time at 6 months and at 12 months Safety outcome measures: • The incidence and severity of ocular and non-ocular adverse events • Changes and abnormalities in clinical laboratory parameters and ocular safety assessments (e.g., IOP and slitlamp) • Incidence of positive serum antibodies to ranibizumab • Changes in vital signs * BCVA was measured in the study eye based on the ETDRS visual acuity charts and assessed at a starting test distance of 4 metres ** Excess foveal thickness is defined as the amount of foveal thickness greater than 212 µm. A value of 212 µm or below is equal to 0 excess foveal thickness	

Trial no. (acronym)	NCT00486018 BRAVO [25]	NCT00485836 CRUISE [51]
Duration of follow-up	6 months (observation period from month 6 to 12) **HORIZON (Cohort 2) (NCT00379795)**[3] Patients who completed the 12-month BRAVO trial could enter the open-label, single arm, multicentre HORIZON (Cohort 2) extension study. Patients could receive intravitreal ranibizumab 0.5 mg at ≥ 30 day intervals if they had central subfield thickness ≥ 250 µm or MO that affected visual acuity. Enrolled patients were followed for up to 24 months or until study termination (30 days after FDA approval of ranibizumab for RVO treatment). Efficacy outcomes included changes in BCVA and CFT from HORIZON (Cohort 2) baseline to month 12 of the extension study. Key ocular and non-ocular safety events for the study duration (24-months or study termination) were summarised. **RETAIN (NCT01198327)**[54] The RETAIN study is an open-label, single arm extended follow-up study that evaluates the long-terms safety of ranibizumab in patients with MO secondary to RVO, who were originally enrolled in BRAVO and subsequently followed in the HORIZON extension trial. The primary and secondary outcomes of RETAIN are measured at 12 months.	
Abbreviations used in table: AEs, adverse events; BCVA, best-corrected visual activity letter score; CFT, central foveal thickness; EFT, excess foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; MO, macular oedema; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; OCT, optical coherence tomography; RVO, retinal vein occlusion;		

Figure B2 BRAVO study design

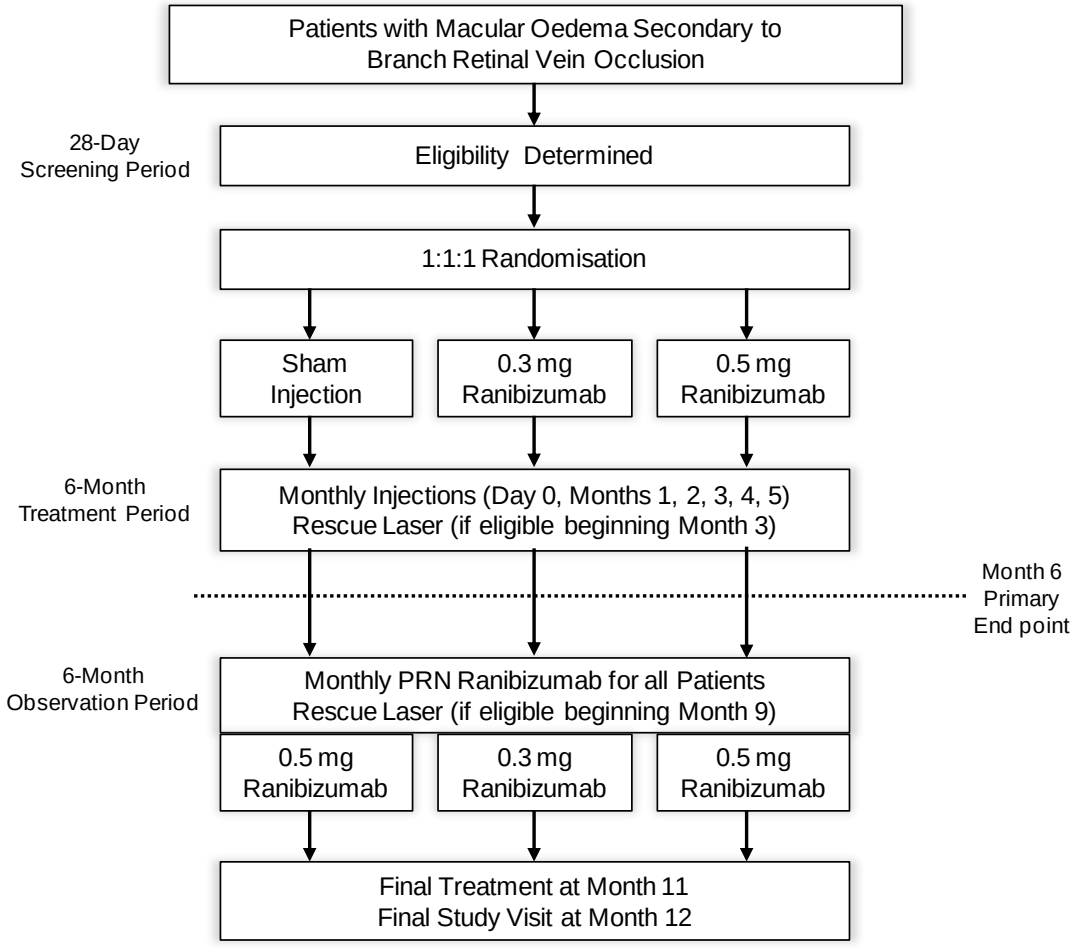
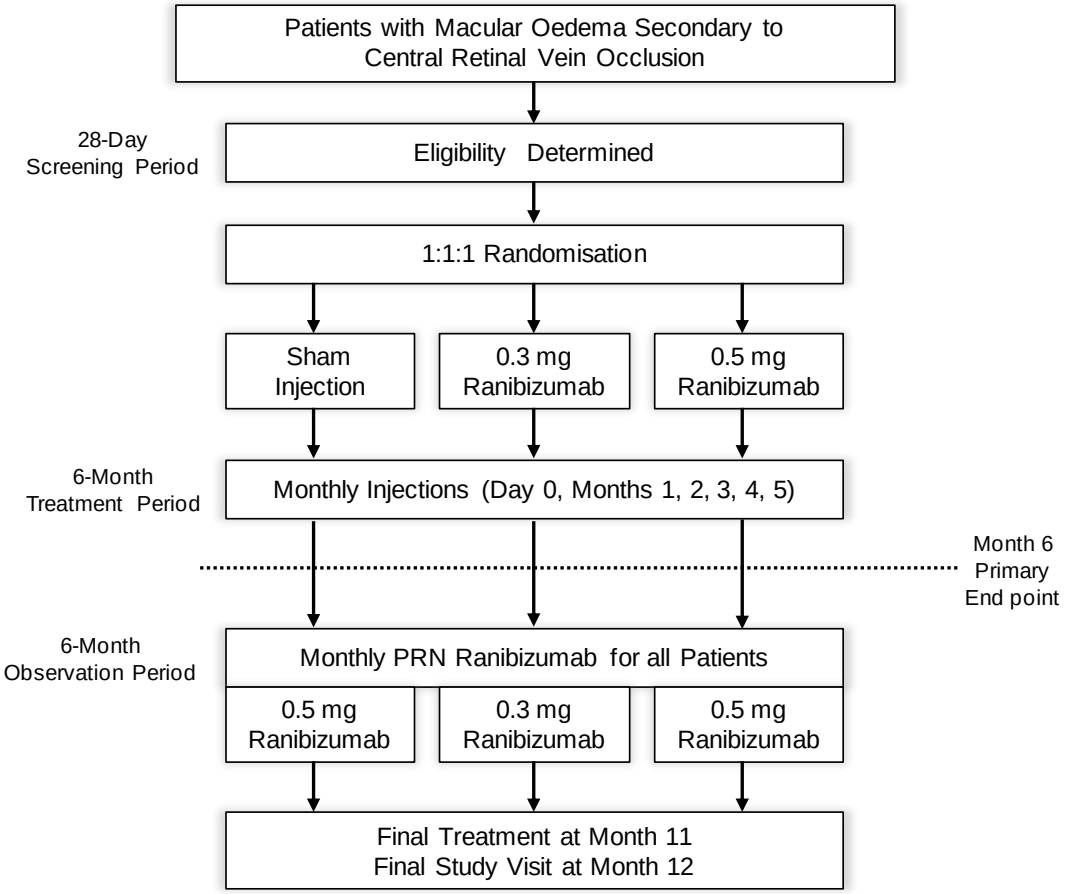


Figure B3 CRUISE study design



Participants

5.3.3 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.

They key difference in eligibility criteria between BRAVO and CRUISE is that in BRAVO, the MO must be secondary to BRVO, and in CRUISE, MO must be secondary to CRVO. BRAVO also allowed a slightly lower BCVA at baseline (20/400) than CRUISE (20/320). Aside from these differences, all other key eligibility criteria were the same.

Table B6 Eligibility criteria in the RCTs

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
NCT00486018 BRAVO[25] **and** **NCT00485836 CRUISE[51]**	Criteria pertains to study eye, except where noted otherwise • Age ≥ 18 years of age • Mean central subfield thickness ≥ 250 µm from 2 OCT measurements (central 1 mm diameter circle with a Stratus OCT3) on 2 measurements, one at screening confirmed by University of Wisconsin Fundus Photograph Reading Center, the other on day 0 confirmed by the investigating physician	Criteria pertains to study eye, except where noted otherwise • Prior episode of RVO • Brisk afferent pupillary defect (ie. obvious and unequivocal) • >10-letter improvement in BCVA between screening and day 0 • History of radial optic neurotomy or sheathotomy • Intraocular corticosteroid use in study eye within 3 months before day 0 • History or presence of wet or dry AMD • Panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before day 0 or anticipated within 4 months after day 0 • Laser photocoagulation for MO within 4 months before day 0 (for patients who had previously received grid laser photocoagulation, the area of leakage at day 0 must have extended into the fovea [ie. prior laser treatment was inadequate], and there could be no evidence of laser damage to the fovea) • Evidence upon examination of any diabetic retinopathy • CVA or MI within 3 months before day 0 • Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro-VEGF treatment within 6 months before day 0

NCT00486018 BRAVO[25] only	Criteria pertains to study eye, except where noted otherwise • Foveal centre-involved MO secondary to BRVO* diagnosed within 12 months before study invitation • BCVA 20/40 to 20/400 Snellen equivalent using the ETDRS charts * BRVO was defined as an eye that had retinal haemorrhage or other biomicroscopic evidence of RVO (e.g., telangiectatic capillary bed) and a dilated (or previously dilated) venous system in one quadrant or less of the retina drained by the affected vein. Hemiretinal vein occlusion (HRVO) is an RVO that involves 2 altitudinal quadrants. In this study, eyes with HRVO were treated the same as eyes with BRVO. The presence of BRVO and HRVO was assessed by fluorescein angiography.	
NCT00485836 CRUISE[51] only	Criteria pertains to study eye, except where noted otherwise • Foveal centre-involved MO secondary to CRVO† diagnosed within 12 months before study initiation • BCVA 20/40 to 20/320 Snellen equivalent using the ETDRS charts †CRVO was defined as an eye that had retinal haemorrhage or other biomicroscopic evidence of RVO (eg. telangiectatic capillary bed) and a dilated (or previously dilated) venous system in ≥3 quadrants of the retina drained by the affected vein.	
NCT00379795 HORIZON (Cohort 2)[55]	• For entrance to the HORIZON (Cohort 2) open-label extension study to BRAVO and CRUISE, patients must have first completed the 12-month BRAVO or CRUISE trial to which they were initially enrolled. • Expectation by the investigator that the subject may potentially benefit from intravitreal anti-VEGF treatment	• Concurrent use of systemic anti-VEGF agents • History of intraocular surgery (including cataract extraction, scleral buckle, etc.) within 1 month prior to Day 0 of this extension study • Use of RVO treatments not approved by the Food and Drug Administration (FDA) in the study eye • Use of intravitreal bevacizumab in the study eye and/or fellow eye • Macular edema in the study eye due to other causes than RVO such as diabetes for Cohort 2
Abbreviations used in table: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; CVA, cerebrovascular accident; ETDRS, Early Treatment Diabetic Retinopathy Study; HRVO, Hemiretinal vein occlusion; MO, macular oedema; MI, myocardial infarction; RVO, retinal vein occlusion; VEGF, vascular endothelial growth factor		

5.3.4 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.

In both BRAVO and CRUISE the patient demographics and baseline ocular characteristics were similar across the randomly allocated treatment groups (Table B7 and Table B8). The ranibizumab 0.3 mg arm has not been presented here as this is not a licensed dose.

It is noteworthy that baseline BCVA letter score and CFT are worse in the CRUISE patients compared with BRAVO patients. This is expected as occlusion occurring in the central retinal vein (CRVO) results in more oedema and is therefore a more serious condition than occlusion occurring in one of the branch veins (BRVO).

[redacted]

Table B7 Baseline characteristics of participants in BRAVO[25]

Trial no. (acronym) **Baseline characteristic**	**Sham injection**	**Ranibizumab 0.5 mg**
NCT00486018 BRAVO[25] **(n = 397)**	**(n = 132)**	**(n = 131)**
Patient demographics		
Age (yrs)		
Mean (SD)	65.2 (12.7)	67.5 (11.8)
Median	64.0	67.0
Range	26–89	41–91
Gender, n (%)		
Male	74 (56.1)	71 (54.2)
Female	58 (43.9)	60 (45.8)
Race,* n (%)		
White	108 (81.8)	107 (81.7)
Black/ African American	13 (9.8)	13 (9.9)
Other	8 (6.0)	5 (3.8)
Unavailable	4 (3.0)	6 (4.6)
Baseline ocular characteristics in study eye		
Months from RVO diagnosis to screening		
Mean (SD)	3.7 (3.7)	3.3 (3.1)
Median	2	2
Range	0-16	0-13
Distribution, n (%)		
≤ 3	85 (64.4)	88 (67.2)
>3 to ≤ 6	17 (12.9)	20 (15.3)
> 6 to ≤ 9	12 (9.1)	14 (10.7)
> 9 to ≤ 12	16 (12.1)	7 (5.3)
>12	2 (1.5)	2 (1.5)
HRVO classification,† n (%)	17 (13.1)	17 (13.2)
BCVA		
ETDRS letter score		
Mean (SD)	54.7 (12.2)	53.0 (12.5)
Range	16–73	22–79
Distribution, n (%)		
< 34	9 (6.8)	13 (9.9)
35-54	50 (37.9)	49 (37.4)
≥ 55	73 (55.3)	69 (52.7)
Approximate Snellen equivalent, median	20/80	20/80

Trial no. (acronym) Baseline characteristic	Sham injection	Ranibizumab 0.5 mg
IOP (mmHg),[¶] mean (SD)	14.8 (3.0)	14.9 (3.3)
Taking IOP-lowering medication, n (%)	10 (7.6)	16 (12.2)
Phakic eye,** n (%)	93 (78.8)	94 (80.3)
Imaging data		
CFT(µm), mean (SD)	488.0 (192.2)	551.7 (223.5)
Total macular volume (mm^3),[‡] mean (SD)	9.641 (1.831)	9.839 (2.151)
Total area of retinal haemorrhage, central subfield (DA), calculated,[††] mean (SD)	0.121 (0.137)	0.117 (0.131)
Area of fluorescein leakage within grid (DA),[¶¶] median	7	7
>10 DA of capillary nonperfusion (%)	0	0
Baseline ocular characteristics in fellow eye		
Fellow eye BCVA		
ETDRS letter score, mean (SD)	79.8 (17.4)	81.4 (13.8)
[redacted]		
[redacted]		
[redacted]		
Fellow eye vision compared with study eye, n (%)		
Better	121 (91.7)	125 (95.4)
Worse	8 (6.1)	4 (3.1)
Same	3 (2.3)	2 (1.5)
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		
[redacted]		

Abbreviations used in table: BCVA, best-corrected visual acuity; CFT, central foveal thickness; DA, disc area; ETDRS, Early Treatment Diabetic Retinopathy Study; HRVO, hemiretinal vein occlusion; IOP, intraocular pressure; RVO, retinal vein occlusion; SD, standard deviation.
*Multiracial patients were counted in each race category that they indicated. Number of patients in Other category may be overestimated. Number assessed in sham and 0.5 mg groups was [†]130, 129; [¶]131, 130; **118, 117; [‡]81, 85; [††]129, 131; [¶¶]131, 130.

Table B8 Baseline characteristics of participants in CRUISE[51]

Trial no. (acronym) **Baseline characteristic**	**Sham injection**	**Ranibizumab 0.5 mg**
NCT00485836 CRUISE[51] **(n = 392)**	**(n = 130)**	**(n = 130)**
Patient demographics		
Age (yrs)		
Mean (SD)	65.4 (13.1)	67.6 (12.4)
Median	66	70
Range	20–91	40–91
Gender, n (%)		
Male	72 (55.4)	80 (61.5)
Female	58 (44.6)	50 (38.5)
Race,* n (%)		
White	113 (86.9)	108 (83.1)
Black/ African American	8 (6.2)	10 (7.7)
Other	7 (5.4)	7 (5.4)
Unavailable	3 (2.3)	5 (3.8)
Baseline ocular characteristics in study eye		
Months from RVO diagnosis to screening		
Mean (SD)	2.9 (2.9)	3.3 (3.7)
Median	2	2
Range	0–14	0–27
Distribution, n (%)		
≤ 3	91 (70.0)	94 (72.3)
>3 to ≤ 6	27 (20.8)	17 (13.1)
> 6 to ≤ 9	4 (3.1)	10 (7.7)
> 9 to ≤ 12	7 (5.4)	6 (4.6)
>12	1 (0.8)	3 (2.3)
BCVA		
ETDRS letter score		
Mean (SD)	49.2 (14.7)	48.1 (14.6)
Range	16–71	21–73
Distribution, n (%)		
< 34	26 (20.0)	30 (23.1)
35-54	49 (37.7)	50 (38.5)
≥ 55	55 (42.3)	50 (38.5)
Approximate Snellen equivalent, median	20/100	20/100
IOP (mmHg), mean (SD)	15.1 (3.1)	15.1 (3.4)
IOP-lowering medication, n (%)	13 (10.0)	22 (16.9)
Phakic eye, † n (%)	88 (80.7)	83 (72.8)
Imaging data		

CFT(μm),‡ mean (SD)	687.0 (237.6)	688.7 (253.1)
Total macular volume (mm^3),§ mean (SD)	10.700 (2.303)	10.308 (2.033)
Total area of retinal haemorrhage, central subfield (DA), calculated,†† mean (SD)	0.080 (0.113)	0.093 (0.117)
Area of fluorescein leakage within grid (DA),¶ median	15	14
>10 DA of capillary nonperfusion** (%)	0	2
Baseline ocular characteristics in fellow eye		
Fellow eye BCVA		
ETDRS letter score, mean (SD)	78.9 (18.6)	78.8 (17.4)
[redacted]	[redacted]	[redacted]
Fellow eye vision compared with study eye, n (%)		
Better	117 (90.0)	120 (92.3)
Worse	8 (6.2)	7 (5.4)
Same	5 (3.8)	3 (2.3)
[redacted]		
[redacted]	[redacted]	[redacted]

Abbreviations used in table: BCVA, best-corrected visual acuity; CFT, central foveal thickness; DA, disc area; ETDRS, Early Treatment Diabetic Retinopathy Study; IOP, intraocular pressure; RVO, retinal vein occlusion; SD, standard deviation.
*Multiracial patients were counted in each race category that they indicated. No. of patients in Other category may be overestimated. Number assessed in sham and 0.5 mg groups was †109, 114; ‡129, 130; §86, 74; †† 128, 126; ¶128, 129; **112, 109.

Table B9 Baseline characteristics of participants in HORIZON (Cohort 2)[3, 55]

Study eye characteristic	Patients from BRAVO		Patients from CRUISE	
	Sham/ 0.5 mg (n = 97)	Ranibizumab 0.5 mg (n = 104)	Sham/ 0.5 mg (n = 98)	Ranibizumab 0.5 mg (n = 99)
Patient demographics				
Mean age (SD), years	66.2 (12.2)	68.3 (12.3)	66.0 (12.5)	68.2 (11.6)
Male, n (%)	54 (55.7)	58 (55.8)	57 (58.2)	60 (60.6)
Baseline ocular characteristics in study eye				
BCVA			[redacted]	[redacted]
ETDRS letter score				
Mean (SD)	68.1 (15.6)	72.2 (13.8)	59.8 (18.4)	64.7 (16.7)
Range	14–94	28–99	15–90	4–94
Distribution				
≤ 34, n (%)	4 (4.1)	2 (1.9)	9 (9.4)	4 (4.1)
35 to 54, n (%)	16 (16.5)	10 (9.6)	24 (25.0)	20 (20.4)
≥ 54, n (%)	77 (79.4)	92 (88.5)	63 (65.6)	74 (75.5)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean (SD) central foveal thickness, µm	196.7 (107.4)	187.0 (80.8)	200.3 (132.7)	202.6 (123.7)
	[redacted]	[redacted]	[redacted]	[redacted]

Abbreviations used in table: BCVA, best-corrected visual acuity; ETDRS Early Treatment Diabetic Retinopathy Study; SD, standard deviation

Outcomes

5.3.5 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, 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.

All visual acuity outcomes of BRAVO and CRUISE relate to the study eye only. The same outcomes are reported in both BRAVO and CRUISE and so Table B10 provides details of the outcomes for both of these studies combined.

Table B10 Primary and secondary outcomes of BRAVO[25] and CRUISE[24]

	Outcome(s) and measures	Reliability/validity/ current use in clinical practice	Relevance to decision problem
Primary Outcome	Mean change from baseline in BCVA score in study eye at 6 months. BCVA was measured based on the ETDRS visual acuity charts and assessed at a starting test distance of 4 metres	The change in best corrected visual acuity (BCVA) using an Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.[56] The proportion of patients that achieved a certain change is more relevant to the economic case, however.	High BCVA is a key outcome defined in the decision problem.
Secondary Outcomes	Mean change from baseline in BCVA in study eye up to month 12, and the proportion of subjects gaining ≥ 15 or losing < 15 letters ETDRS letters in study eye at 6 and 12 months compared with baseline. BCVA was measured based on the ETDRS visual acuity charts and assessed at a starting test distance of 4 metres	As mentioned above, the ETDRS chart is the gold standard measure for visual acuity in clinical practice. Although previous research has often defined 'clinically significant vision loss' as a loss of at least 15 letters (3 lines) on the ETDRS chart, a loss of just 10 letters (2 lines) can be associated with a substantial decline in health-related quality of life (e.g. inability to drive, increased dependency, role limitations, impaired mental health), suggesting that this degree of vision loss can be considered clinically significant.[57]	Medium
	Patient-reported outcomes were measured using the National Eye Institute Visual Functioning Questionnaire-25 (NEI VFQ-25). The mean change in composite NEI VFQ-25 score over time, from baseline up to 6 months, was calculated.	The National Eye Institute Visual Functioning Questionnaire (NEI VFQ) was developed to test the psychometric properties of diseases that cause vision loss, in order to evaluate vision-related quality of life.[11] Reliable and valid questionnaires with 51 questions (NEI VFQ-51) and a reduced version with 25 questions (NEI VFQ-25) have been created and used to survey patients with a range of conditions that manifest with vision loss.[11] BRVO[58] and CRVO[11] have both been associated with a decrease in vision-related quality of life as measured with the (NEI VFQ-25). The NEI VFQ-25 addresses 12 subscales; 11 of which consist of vision-targeted questions, and the remaining 1 relates to general health.[59] The NEI VFQ-25 subscale scores are an average of the items in the subscale transformed to a 0 to 100 scale, where 100 represents the best possible score on the measure and 0 represents the worst.[59] The composite NEI VFQ-25 score is an un-weighted average of the responses to all items except for the general health rating question.[59]	High Health-related quality of life is a key outcome defined in the decision problem.
	Anatomical outcomes were measured as the proportion of subjects	Measurement of fovea thickness by OCT is described as one of the minimum clinical services required for effective	Low

	with a central foveal thickness (CFT) of ≤ 250 µm at 6 and 12 months, and the mean absolute change from baseline in CFT over time up to 12 months. CFT is assessed on optical coherence tomography (OCT).	management of RVO by the RCO.[8] Its use in decision making regarding treatment in clinical practice is greater, however, than its value as an outcome indicator for patients in clinical trials. This is due to the only modest correlation observed between the centre point thickness as measured by OCT and visual acuity. A wide range of visual acuity may therefore be observed for a given degree of retinal oedema. Thus this outcome is not relevant to the decision problem as presented to NICE.[60]	
Abbreviations used in table: ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, Optical coherence tomography; RCO, Royal College of Ophthalmology; VA, visual acuity			

Table B11 Primary and secondary outcomes of HORIZON (Cohort 2)

	Outcome(s) and measures	Reliability/validity/ current use in clinical practice	Relevance to decision problem
Primary Outcome	Mean change from HORIZON baseline in BCVA score in study eye up to 24 months. BCVA was measured based on the ETDRS visual acuity charts.	As above	High
Secondary Outcomes	[redacted] BCVA was measured based on the ETDRS visual acuity charts.	As above	Medium
	Mean change from baseline in CFT over time up to 12 months. CFT is assessed on optical coherence tomography (OCT).	As above	Low
Abbreviations used in table: BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, Optical coherence tomography;			

Statistical analysis and definition of study groups

5.3.6 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.

Table B12 Summary of statistical analyses in BRAVO and CRUISE

Hypothesis objective	The primary objective of BRAVO and CRUISE was to assess the treatment difference in the mean change from baseline BCVA score at month 6. The H_0 therefore assumes that mean change in BCVA from baseline to Month 6, is not significantly different between ranibizumab treatment groups and sham injection.
Statistical analysis	For each efficacy outcome of the 6-month treatment period, 2 pairwise comparisons were made: 0.3 mg ranibizumab versus sham and 0.5 mg ranibizumab versus sham. Unless otherwise noted, efficacy outcome analyses were stratified by baseline BCVA letter score in the study eye (≤ 34 vs. 35 – 54 vs. ≥ 55). For the primary outcome, the mean change from baseline BCVA at month 6 was compared between each ranibizumab group and the sham injection group, using an analysis of variance model stratified by baseline BCVA, with no additional adjustments for covariates, and using the Hochberg-Bonferroni multiple comparison procedure to maintain an overall type I error rate of 0.05. If the p-values for both comparisons are ≤ 0.05, then both ranibizumab groups will be considered statistically significantly different from the sham injection control group. If the p-value for the comparison of one ranibizumab group with the sham injection control group is > 0.05, the other ranibizumab group will be considered statistically significantly different from the control group only if the p-value for its comparison with the control group is ≤ 0.05/2 (0.025). Cochran-Mantel-Haenszel chi-square tests, stratified by baseline BCVA, were used for secondary and exploratory binary end point group comparisons (for BRAVO only: except for percentage of patients who had lost < 15 letters from baseline BCVA at month 6 and percentage of patients who had Snellen equivalent ≤ 20/200 at month 6, for which the Fisher exact test was used because the percentage of patients meeting that end point was high [for the former] and low [for the latter] in all treatment groups). All statistical tests were two-sided. Analysis of variance or analysis of covariance models were used to analyse continuous outcome measures. In addition to p-values for statistical tests, the estimates and confidence intervals (CIs) were provided for the mean (for continuous variables) or proportion (for binary variables) for each treatment group and the difference in means or proportions between two treatment groups. All CIs were two-sided and at the 95% level. To manage the type I error rate while testing multiple secondary efficacy endpoints for statistical significance, a type I error rate of 0.05 was allocated for each dose, and a staged hierarchical testing procedure was used with a Hochberg-Bonferroni procedure at each stage. To determine the earliest time point at which statistically significant between-group differences were obtained for mean change from baseline BCVA, CFT, EFT, and the NEI VFQ-25 composite score, a hierarchical testing procedure for significance at each time point was performed sequentially for each end point, beginning with month 6 and working backward to the time point at which the test for between-group differences resulted in P>0.05. Additional analyses were performed to assess sensitivity of the results to the statistical methods used. National Eye Institute VFQ-25 scores were calculated according to published guidelines. The mean of all of the NEI VFQ-25 subscales was used to calculate the overall composite score (available from: http://www.rand.org/health/surveys_tools.html; accessed December 15, 2009). The incidence of ocular and non-ocular AEs and serious AEs was summarized by treatment group. In addition, efficacy data from the observation period were summarised separately for the sham/0.5 mg group; descriptive summaries of changes in key efficacy outcomes for month 6 were performed. During the sixth month observation period all subjects (including those initially randomised to the sham injection group) were eligible (and the

	majority did cross over) to receive monthly PRN retreatment with intravitreal injections of ranibizumab if they met the protocol-specified retreatment criteria. Therefore, efficacy analyses based on the 6-month observation period (months 6 to 12) data did not involve formal comparisons between treatment groups and were based on descriptive statistics only. Safety endpoints were analysed for the safety-evaluable population (randomised subjects who received at least one injection of study drug [ranibizumab or sham] during the 6-month treatment period), with subjects grouped according to the actual treatment received.
Sample size, power calculation	The determination of sample size was based on the primary efficacy end point of mean change from baseline in BCVA score at month 6, assuming: • for patients in BRAVO, a mean change from baseline in BCVA score at 6 months of +12, +10 and +2 letters for the 0.5 mg, 0.3 mg and sham-treated subjects, respectively • for patients in CRUISE, a mean change from baseline in BCVA score at 6 months of +8, +6 and -2 letters for the 0.5 mg, 0.3 mg and sham-treated subjects, respectively • for patients in both BRAVO and CRUISE, a standard deviation for the change from baseline in BCVA score at 6 months of 20 letters for each of the ranibizumab groups and 28 letters for the sham-injection group The sample size of 390 subjects (130 subjects per treatment group) provides 90% power in the ITT analysis to detect a statistically significant difference between one or both ranibizumab groups and the control group in the primary outcome. Calculations were based on a 1:1:1 randomisation ratio (0.5 mg ranibizumab vs. 0.3 mg ranibizumab vs. sham injection), a two-sided test for equality of means using a Normal approximation and assuming unequal variances (for comparison of each ranibizumab group vs. sham injection), and the Hochberg-Bonferroni multiple comparison procedure with an overall α level of 0.05. The power of the Hochberg-Bonferroni multiple comparison procedure was evaluated using Monte Carlo simulations.
Data management, patient withdrawals	Unless otherwise noted, the intention-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using last-observation-carried-forward method. Supportive analyses based on observed data (with no imputation of missing data) and worst-outcome imputation were performed for key efficacy endpoints.
Abbreviations: AE, adverse event; BCVA, best corrected visual acuity; CFT, central foveal thickness; EFT, extra foveal thickness; PRN, *pro re nata* (dosed as needed)	

Table B13 Summary of statistical analyses in HORIZON

Hypothesis objective	The primary objective of HORIZON was to evaluate long-term efficacy of open-label ranibizumab 0.5 mg
Statistical analysis	During this open-label extension study, all subjects were eligible to receive monthly PRN retreatment with intravitreal injections of ranibizumab provided they met the pre-specified treatment criteria. Therefore, efficacy analyses based on the open-label extension study data did not involve formal comparisons between treatment groups and were based on descriptive statistics only.
Sample size, power calculation	N/A
Data management, patient withdrawals	Summaries of efficacy outcomes at months 18, 21 and 24 based on observed data, and the number of patients with observed data varied at each time point. Therefore analysis is per-protocol with no imputation for missing data.
Abbreviations: N/A, not applicable; PRN, *pro re nata* (dosed as needed)	

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

In both BRAVO and CRUISE, mean change in visual acuity from baseline at 6 months, and the proportion of patients gaining ≥ 15 ETDRS letters by 6 months was evaluated by the following subgroups:

- Baseline BCVA letter score groups of: ≤ 34, 35 – 54 and ≥ 55
- Baseline CFT (μm) groups of: < 450 and ≥ 450, and
- Time from diagnosis of BRVO or CRVO to screening (in BRAVO and CRUISE, respectively): < 3 months and ≥ 3 months.

All subgroup analyses were pre-planned, and randomisation in these trials was stratified by baseline the BCVA letter score groups highlighted above.

Participant flow

5.3.8 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.

The CONSORT flow charts for BRAVO and CRUISE are provided below in Figure B4 and Figure B5.

Figure B4 BRAVO CONSORT flow diagram for participant flow

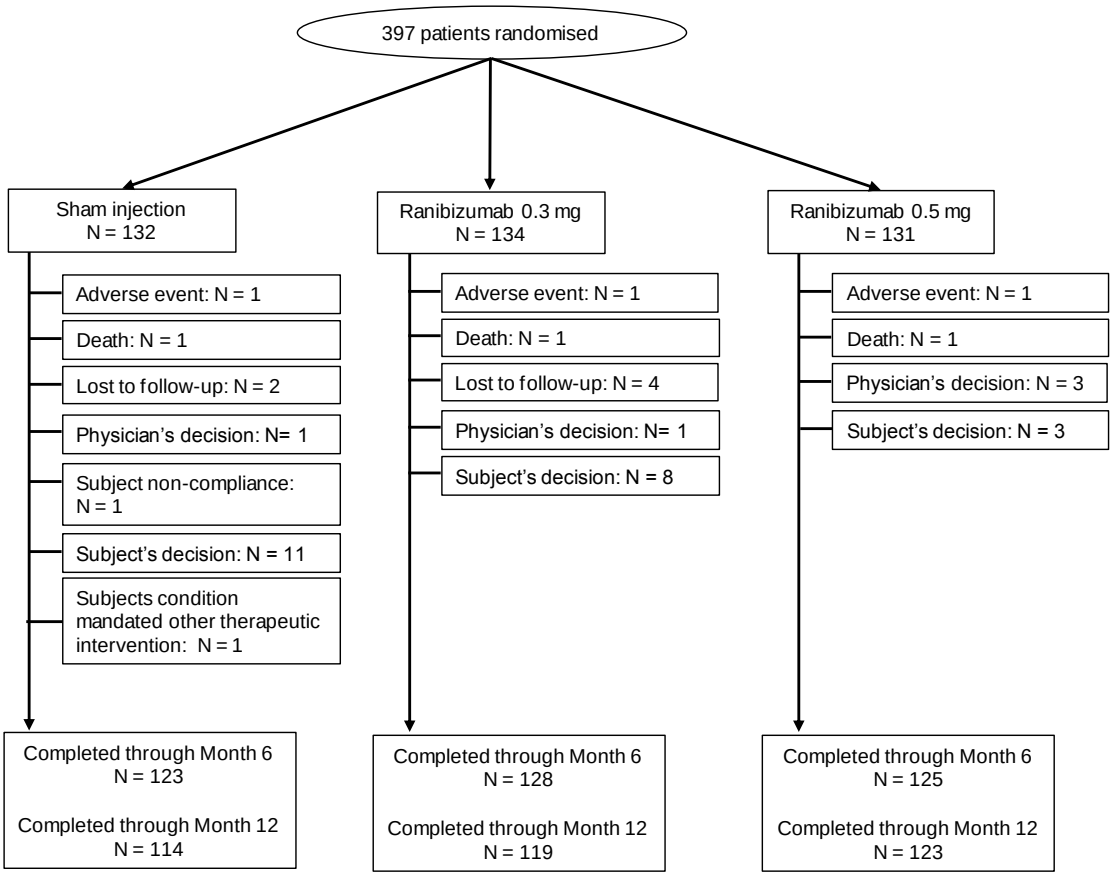
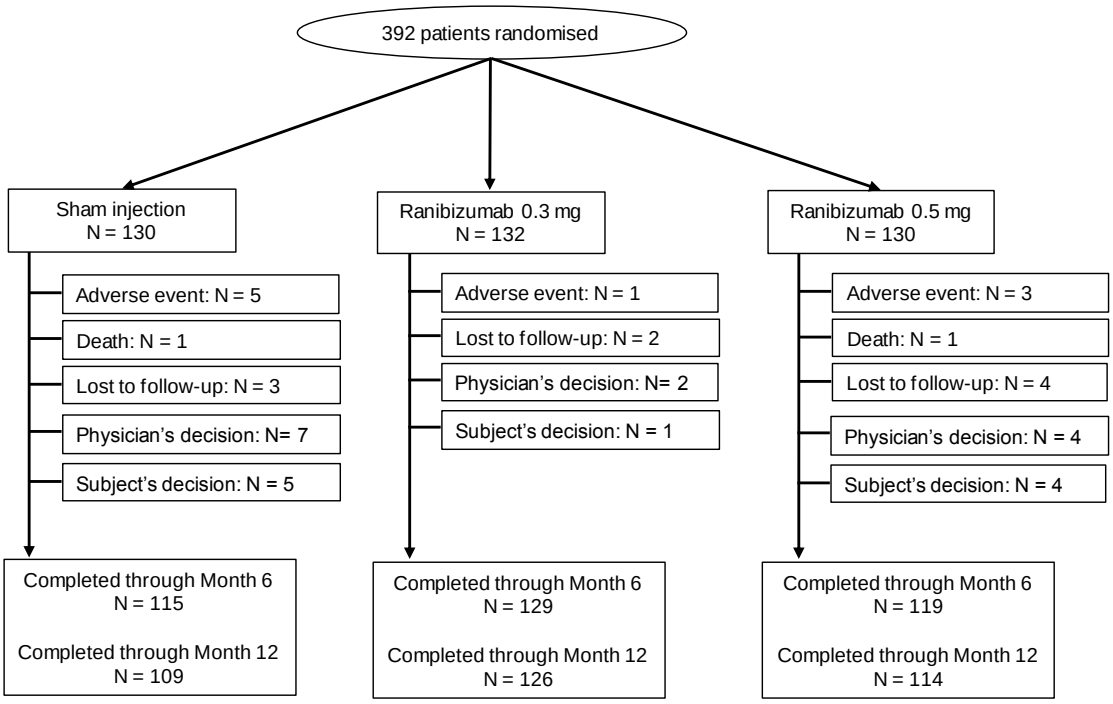


Figure B5 CRUISE CONSORT flow diagram for participant flow



Patients who completed the 12-month BRAVO and CRUISE trials could enter the open label extension study HORIZON (Cohort 2). [3] 304 patients that were initially enrolled in and completed BRAVO, and 304 patients that were initially enrolled in and completed CRUISE, were enrolled in HORIZON (Cohort 2); totalling 608 patients. Of these, 205 (67%) BRAVO and 181 (60%) CRUISE patients completed month 12 of HORIZON. Table B14 details the numbers of patients who were enrolled in and completed month 12 of HORIZON (Cohort 2), by the initial treatment group to which patients were randomised in the BRAVO and CRUISE trials. [redacted]

HORIZON was primarily designed to assess safety therefore robust conclusions on efficacy are limited.

Table B14 The retention of patients and average duration of patient follow-up in HORIZON (Cohort 2) open label extension study, by initial treatment groups of BRAVO and CRUISE

	Initial Trial					
	BRAVO			CRUISE		
	Sham/ 0.5 mg (n=97)	Ran 0.3 mg (n=103)	Ran 0.5 mg (n=104)	Sham/ 0.5 mg (n=98)	Ran 0.3 mg (n=107)	Ran 0.5 mg (n=99)
Completed HORIZON Month 12, n (%)	66 (68.0)	66 (64.1)	73 (70.2)	60 (61.2)	70 (65.4)	51 (51.5)
[redacted]						

Abbreviations used in table: Ran, ranibizumab

5.4 Critical appraisal of relevant RCTs

Summary of critical appraisal of relevant RCTs

- Both BRAVO and CRUISE had adequate randomisation, allocation concealment and blinding throughout. The treatment groups were similar at baseline, and patient numbers across groups remained balanced for the study duration. Intention-to-treat analysis was conducted on all efficacy data, and missing data was accounted for using last-observation-carried-forward methods.

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

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

5.4.2 Please provide as an appendix a complete quality assessment for each RCT. See section 9.3, appendix 3 for a suggested format.

See Section 9.3, appendix 3 for full details of quality assessment for BRAVO and CRUISE.

5.4.3 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.

The quality of HORIZON (Cohort 2) has not been assessed in this section as it was an open-label extension study of BRAVO and CRUISE. The main noteworthy point for HORIZON is that early termination of the study limited the results beyond 12 months from HORIZON baseline.

Table B15 Quality assessment results for RCTs

Trial no. (acronym)	BRAVO[25]	CRUISE[51]
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?	Yes Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using the last observation carried-forward method.	Yes Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using the last observation carried-forward method.

5.5 Results of the relevant RCTs

Summary of the results from relevant RCTs

- The large and high-quality BRAVO and CRUISE trials demonstrated that compared with sham injections, intraocular injections with ranibizumab 0.5 mg provided rapid and significant improvements in visual acuity over 6 months in patients with MO secondary to BRVO and CRVO, respectively. The observed improvement in visual acuity with ranibizumab treatment was associated with meaningful improvements in patient-reported vision-related function in both BRAVO and CRUISE.
- The 6-month observational periods of BRAVO and CRUISE demonstrate that the continuation of ranibizumab treatment on a PRN basis maintains the positive visual acuity and vision-related functional outcomes that were observed at the 6 month time point.
- In both BRAVO and CRUISE, the group differences observed for improvement of visual acuity from baseline were maintained when results were analysed by subgroups based on baseline BCVA, CFT and time from RVO diagnosis to screening for trial entry.

5.5.1 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.**

The following summary of the principal findings from the clinical evidence will consider only treatment with the higher 0.5 mg ranibizumab dose, because this is the dose of ranibizumab that is currently available and used in other ocular indications, and is the dose for which ranibizumab is expected to receive EMA approval for the treatment of MO secondary to RVO. Furthermore, the evidence from the key clinical trials of BRAVO and CRUISE generally indicate a trend towards more favourable clinical outcomes with the 0.5 mg dose, which do not appear to be associated with any additional safety concerns.

Treatment outcomes

With the design of the BRAVO and CRUISE trials in mind (described in section 5.3.2), Table B16 provides information on the completion rates and details of the treatment received by subjects in the different phases of BRAVO and CRUISE trials, as well as during the open-label extension HORIZON (Cohort 2) study.

In BRAVO, rescue laser was permitted based upon the precedent of the BVO Study (see Section 5.3.2). Laser was used in 57.6% of patients randomised to the group with sham injections, during the first 6 months of the study. The approach to laser treatment as given during BRAVO also meets the RCO Guidelines for management of BRVO.[8, 23]

In the BRAVO study only 21.4% of patients in the ranibizumab 0.5 mg arm were treated with laser during the first 6 months of the study. The RCO Guidelines for management of BRVO do not recommend concomitant use of laser and pharmacotherapy and the use of ranibizumab with laser is not expected to occur frequently in clinical practice once ranibizumab is introduced.[7] It should also be noted that a post-hoc analysis of the BRAVO trial results has demonstrated that the receipt of laser therapy did not improve the efficacy results for ranibizumab (see Appendix 19, Section 10.7 for full details). [50]

Table B16 also provides details on the proportion of patients in BRAVO who received laser treatment in the controlled treatment and uncontrolled observational periods of the study. The highest rates of laser therapy were observed during the first 6 month treatment phase of BRAVO in the group randomised to receive sham injection, where over half (57.6%) of the patients received treatment with laser therapy. In contrast, only 21.4% of patients in the 0.5 mg ranibizumab treatment arm received laser therapy in the 6-month treatment phase of BRAVO. Over the 12 month study period, 34.4% of patients in the 0.5 mg ranibizumab group received rescue laser treatment, compared to 61.4% of patients in the sham/0.5 mg ranibizumab group.

Table B16 Patient treatment received throughout BRAVO[25, 61], CRUISE[51, 61] and HORIZON[62]

	BRAVO		CRUISE	
	Sham (Sham/0.5 mg) (n = 132)	**Ranibizumab 0.5 mg (n = 131)**	**Sham (Sham/0.5 mg) (n = 130)**	**Ranibizumab 0.5 mg (n = 130)**
Received treatment at any time to Month 12 of BRAVO/CRUISE, n (%)	131 (99.2)	130 (99.2)	129 (99.2)	129 (99.2)
Received ranibizumab injection at month 6 of BRAVO/CRUISE, n (%)	104 (78.8)	50 (38.2)	100 (76.9)	64 (49.2)
Received PRN treatment during observation period (month 6 to 12 of BRAVO/CRUISE), n (%)	115 (87.1)	100 (76.3)	110 (84.6)	111 (85.4)
Mean [redacted] number of injections per patient in BRAVO/CRUISE*				
6-month treatment period†	5.6 [redacted]	5.7 [redacted]	5.5 [redacted]	5.6 [redacted]
6-month observation period	3.6 [redacted]	2.7 [redacted]	3.7 [redacted]	3.3 [redacted]
Received laser treatment in BRAVO, n (%)[50]				
6-month treatment period†	76 (57.6)	28 (21.4)		
6-month observation period†	31 (23.5)	31 (23.7)	-	-
[redacted]	[redacted]	[redacted]	-	-
			-	-
[redacted]	[redacted]	[redacted]	-	-
[redacted]	[redacted]	[redacted]	-	-
[redacted]	[redacted]	[redacted]	-	-
Enrolled in HORIZON, n	97	104	98	99
Received ranibizumab treatment during HORIZON, n (%)	[redacted]	[redacted]	[redacted]	[redacted]
Mean (range) number of injections per patient during 12-month HORIZON study	2.3 (0-9)	2.4 (0-12)	3.3 (0-13)	3.9 (0-12)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

* During the 6-month treatment period, the sham group received sham injections (day 0, months 1-5), during the 6 month observation period, the sham group received PRN 0.5 ranibizumab if they met requirement criteria (eligible months 6-11); †Received laser treatment at any time during the specified time period. All counts are based on results in the final database;
Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branched retinal vein occlusion; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata* (as needed); SD, standard deviation

Efficacy Outcomes

The efficacy outcome measures of BRAVO and CRUISE (and subsequently HORIZON) that were deemed to be relevant to the outcome decision are those pertaining to visual acuity and health-related quality of life:

- The primary efficacy outcome of mean change from baseline BCVA (in ETDRS letters) at 6 months
- The secondary efficacy outcomes:
    - Mean change from baseline in BCVA over time up to 6 and 12 months
    - Proportion of subjects who gained ≥ 15 letters in BCVA at 6 and 12 months compared with baseline
    - Proportion of subjects who lost < 15 letters in BCVA at 6 and 12 months compared with baseline
    - Mean change from baseline in the NEI VFQ-25 near activities subscale over time up to 6 months and at 12 months
    - Mean change from baseline in the NEI VFQ-25 distance activities subscale over time up to 6 months and at 12 months
- The exploratory efficacy outcomes:
    - Percentage of patients with Snellen equivalent BCVA ≥ 20/40 at month 6 and 12 months
    - Percentage of patients with Snellen equivalent BCVA ≤ 20/200 at month 6 and 12 months
    - Mean change from baseline in the NEI VFQ-25 composite score (of near and distance activities subscales) over time up to 6 months and at 12 months
    - Proportion of subjects who gained ≥ 10 letters in BCVA at 6 months compared with baseline. (Although an exploratory outcome, this outcome is presented below alongside the secondary outcome of proportion of subjects who gained ≥ 15 letters from baseline)
    - Proportion of subjects who lost ≥ 10 letters in BCVA at 6 months compared with baseline. (Although an exploratory outcome, this outcome is presented below alongside the secondary outcome of proportion of subjects who lost ≥ 15 letters from baseline)
    - Mean change from baseline in the number of correctly read words per minute on the reading speed test over time up to 6 months
    - Mean change from baseline in the number of correctly read words per minute on the reading speed test over time up to 12 months

The anatomical outcomes measured in BRAVO and CRUISE are not considered pertinent to the decision problem, and so the results for these outcomes are not discussed in the following section. However, it is noted that the rapid and sustained improvements in BCVA observed in both trials were accompanied by rapid and sustained reduction in central retinal thickness (see Appendix 15, Section 10.2).

The results up to the 6-month time point of BRAVO (Table B17, Figure B6 and Figure B7) and CRUISE (Table B18, Figure B8 and Figure B9) were published in Campochiaro et al. (2010)[25] and Brown et al (2010)[24], respectively. The results from the subgroup analysis at 6 months are presented in Table B22 and Table B23 for the BRAVO trial and in Table B24 and Table B25 for the CRUISE trial. Twelve-month outcomes of both BRAVO (Table B19) and CRUISE (Table B20) trials were presented together in a poster presentation by Ho et al. at the ARVO Annual Meeting, held in the USA in May 2010.[63]

Table B21 presents the visual acuity outcomes from the long-term follow-up, open label extension HORIZON (Cohort 2) study, that were presented as a poster presentation by Campochiaro et al. at the Macular Society 34th Annual Meeting in March 2011.

BRAVO

The BRAVO study met its primary end point and all of the secondary endpoints at 6 months, except the endpoint of loss of < 15 letters in visual acuity score from baseline for the 0.5 mg ranibizumab, for which the percentage was very high in all treatment groups (Table B17). When compared with sham injection, treatment with ranibizumab for 6 months significantly improved BCVA in patients with MO secondary to BRVO. At the 6-month time point, patients in the 0.5 mg ranibizumab groups had gained a mean (95% CI) of 18.3 (16.0 – 20.6) letters from baseline BCVA score, compared with a mean gain of only 7.3 (5.1 – 9.5) letters in the sham group ($P<0.0001$ for ranibizumab vs. sham). Furthermore, the significantly greater gains in visual acuity were apparent as early in the trial as Day 7 (Table B17, Figure B6). The mean improvement of between 15 and 20 letters of vision (between 3 and 4 lines) after 6 months of treatment with ranibizumab compared with 7 letters (1.5 lines) in the sham injection group is large and clinically meaningful.

Although less than 10% of patients were affected in their better-seeing eye, the impact on a patient's reported outcome based on visual function, measured by the NEI VFQ-25 score change from baseline, indicated that the visual acuity results achieved in the study eye translated into meaningful visual function results for the patient. After 6 months of treatment, the mean change from baseline in visual acuity of the fellow eye was reported to be 1.6 in the sham and 3.0 in the 0.5 mg ranibizumab group. As this was not a significant improvement from baseline we can conclude that improvements in physical functioning were due to improvements in visual acuity of the affected eye.

With ranibizumab treatment, around twice as much improvement in vision-related functioning had occurred at month 6 than with sham injection (Table B17). The observed improvement (mean improvement [95% CI]) at month 6 from baseline in the NEI VFQ-25 composite score was significantly greater in patients treated with ranibizumab 0.5 mg (10.4 [8.3 – 12.4] points) than in patients treated with sham injection (5.4 [3.6 – 7.3] points, P<0.005 for 0.5 mg ranibizumab vs. sham). Ranibizumab treated subjects also demonstrated a notable improvement in reading speed, with a mean change from baseline of 31.3 words per minute for the 0.5 mg ranibizumab group, compared with 15.0 words per minute in the sham group. Ranibizumab therapy provided significantly greater improvements from baseline at 6 months on the near and distance activities subscales compared with those achieved by patients receiving sham injection (P<0.05 0.5 mg ranibizumab vs. sham, for both subscales). The significant increase in near and distance vision subscale scores indicates improvements in the ability of patients receiving ranibizumab to perform daily activities such as reading normal newsprint (near vision subscale), going down stairs at night and watching films and plays (distance vision subscale).

Overall, the results demonstrate a clinically meaningful and statistically significant effect of ranibizumab on visual acuity and patient-reported outcomes based on the NEI VFQ-25 at 6 months.

Following the 6-month observation period of BRAVO, the results for outcomes measured at 12-months (Table B19) show that the significant improvements in visual acuity and vision-related functional outcomes achieved in the ranibizumab groups at Month 6 were maintained, on average, through to Month 12 with PRN treatment. At Month 12, the 0.5 mg ranibizumab group reported a mean (95% CI) gain in BCVA score from baseline of 18.3 (15.8 – 20.9) letters, compared with the sham/0.5 mg group who had gained a mean of only 12.1 (9.6 – 14.6) letters by month 12.

For subjects initially randomised to sham treatment (who could receive 0.5 mg ranibizumab from months 6 to 12), improvements in visual acuity and patient-reported outcomes were observed, on average, during the 6-month observation period. However on average, patients in the sham/0.5 mg group gained fewer letters from baseline by Month 12 than those patients who received ranibizumab in the treatment period of the study.

CRUISE

The CRUISE study met its primary end point and all of the secondary endpoints at 6 months (Table B18). Ranibizumab-treated patients in CRUISE had a dramatic improvement in visual acuity that was demonstrated as early as day 7 (Figure B8, Table B18), with continued improvements in vision to the primary endpoint at Month 6, when patients in the 0.5 mg groups gained, on average, approximately 15 letters (3 lines) of BCVA (at month 6, patients achieved a mean [95% CI] gain in BCVA score from baseline of 14.9 [12.6 – 17.2] and 0.8 [-2 to 3.6] ETDRS letters in the 0.5 mg ranibizumab and sham injection treatment groups, respectively [P<0.0001 for ranibizumab vs. sham]). Also by month 6, a significantly greater proportion of patients in both ranibizumab treatment groups gained at least 15 letters from baseline in BCVA score when compared with patients in the sham group. Consistent with the improvements in visual acuity observed with ranibizumab treatment, patients in both ranibizumab arms demonstrated significantly greater improvements in vision-related functioning, as measured by the NEI VFQ-25, than patients treated with sham injection (Table B18). An improvement from baseline in the mean NEI VFQ-25 composite score was observed as early as month 1 in ranibizumab treated patients. Ranibizumab therapy provided significantly greater improvements from baseline at 6 months on the near and distance activities subscales compared with those achieved by patients receiving sham injection (P<0.05 for 0.5 mg ranibizumab vs. sham, for both subscales). Ranibizumab treated subjects also demonstrated an improvement in reading speed, with a mean change from baseline of 20.5 words per minute for the 0.5 mg ranibizumab group, compared with 8.1 words per minute in the sham group. At the 6 month time point, the mean change from baseline in visual acuity of the fellow eye was reported to be 0.1 in both the sham injection and 0.5 mg ranibizumab groups. This demonstrates that as there was no improvement in visual acuity in the fellow eye, we can assume that all improvements in physical functioning were due to improvements in visual acuity of the study eye.

Overall, the results demonstrate a clinically meaningful and statistically significant positive effect of ranibizumab on visual acuity and patient-reported outcomes.

Following the 6-month observation period, the outcomes reported at 12 months (Table B20) found that the significant improvements in visual acuity and vision-related functional outcomes observed in the ranibizumab treatment group at Month 6 in CRUISE were generally maintained, on average, through to Month 12 with PRN treatment. At Month 12, the 0.5 mg ranibizumab group reported mean (95% CI) gains in BCVA score from baseline of 13.9 (11.5 – 16.4) letters, compared with the sham/0.5 mg group who had gained a mean (95% CI) of only 7.3 (4.5 – 10.0) letters by month 12.

For the sham injection treatment group that could receive 0.5 mg ranibizumab during the observation period, improvements in visual acuity and patient-reported outcomes were observed during the 6-month observation period. However on average, the sham/0.5 mg patients gained fewer letters by Month 12 than those patients who received ranibizumab in the treatment period of the study.

Subgroup analysis

The group differences in mean change in BCVA from baseline observed between treatment and control arms of the study at 6 months were maintained when analysed by subgroups based on baseline BCVA score, CFT and time from RVO diagnosis to screening. Although some of the subgroups were small (size ranged from 9 to 83 patients in subgroups within one arm), the analysis of subgroups in BRAVO found that the mean improvement in BCVA at month 6 was greater for patients with worse BCVA (≤ 34 letters) and CFT ≥ 450 μm at baseline (Table B22). Additionally, for all treatment groups, the mean improvement in BCVA letter score was greater for patients who were diagnosed with BRVO < 3 months before study screening compared with those diagnosed ≥ 3 months before screening. Again, although some of the subgroups were small, the analysis of subgroups in CRUISE (Table B24) found that the mean change in BCVA at month 6 was greater for patients with worse BCVA and CFT ≥ 450 μm at baseline. Thus as expected, those patients with worse BCVA at baseline have greater capacity for improvement in visual acuity.

HORIZON

Finally, the results from the first 12 months of HORIZON (Cohort 2) study (Table B21) indicate that the improvement in BCVA from BRAVO and CRUISE baseline seen in the ranibizumab treatment groups is sustained to 24 months. From BRAVO baseline, BRVO patients receiving sham/0.5 mg and 0.5 mg ranibizumab achieved mean changes in BCVA of +15.6 and +17.5 letters, respectively. From CRUISE baseline, CRVO patients receiving sham/0.5 mg and 0.5 mg ranibizumab achieved mean changes in BCVA of +7.6 and +12.0 letters, respectively.

The HORIZON results suggest that PRN dosing was adequate to maintain the strong clinical benefits to visual acuity observed after 12 months of ranibizumab treatment in those patients with MO secondary to BRVO, as BCVA scores remained relatively stable over the first 12 months of HORIZON. Unfortunately, the trial was not designed to compare efficacy outcomes of early versus "delayed 6 month" treatment with ranibizumab so it is difficult to make extensive conclusions on the results.

The PRN dosing criteria in HORIZON may not have been sufficient for patients with MO secondary to CRVO, as a slight decrease in BCVA score from HORIZON baseline was observed in these patients. The reason for these results was likely to be due to the quarterly follow-up protocol applied in HORIZON, as the design of HORIZON was not appropriate to assess the frequency of follow up with respect to CRVO.

Table B17 6 month primary and secondary outcomes of BRAVO[25]

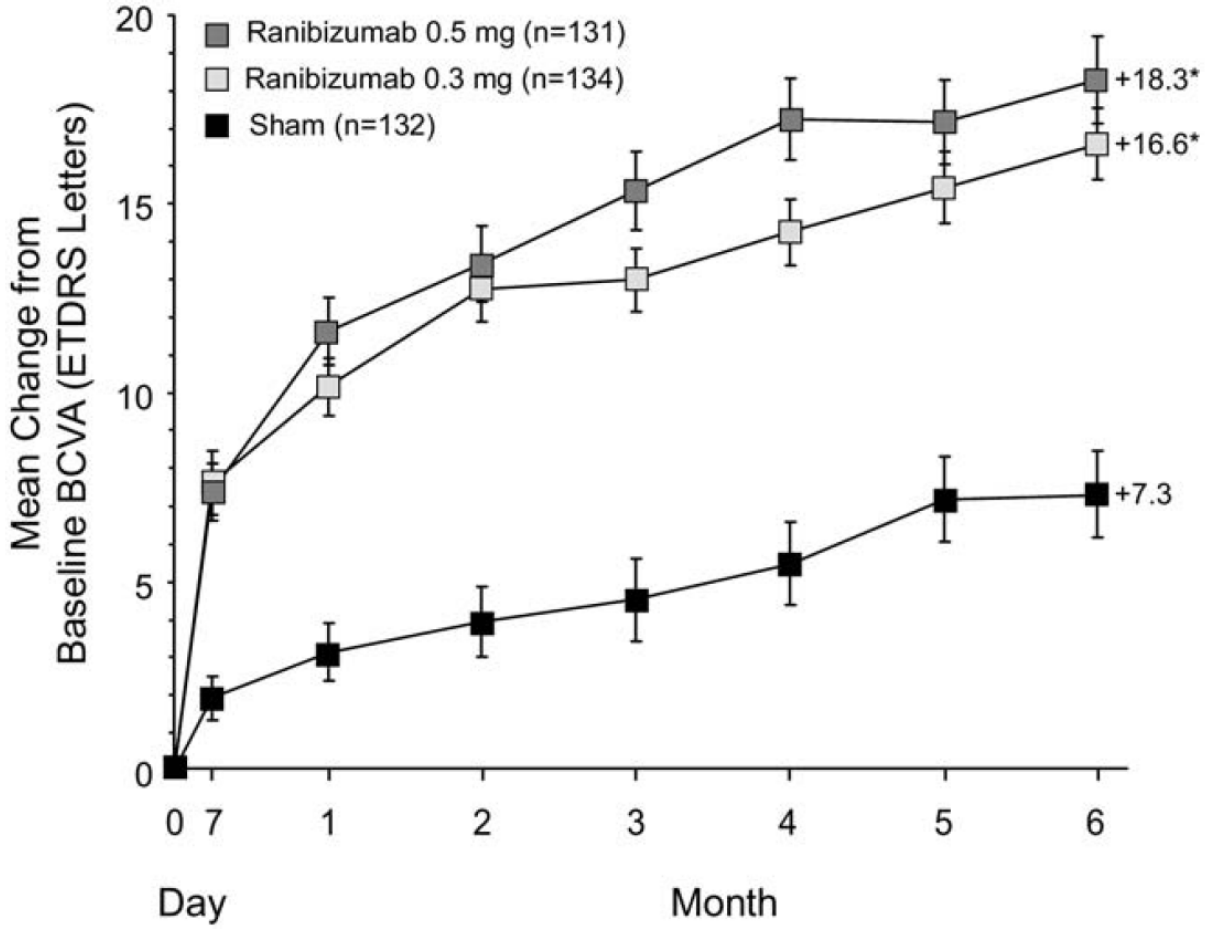
BRAVO[25] (n=397) **NCT00486018**	**Sham injection** **(n = 132)**	**Ranibizumab 0.5 mg** **(n = 131)**	**Significance**
Primary Outcome			
Mean (SD) change from baseline in BCVA score at month 6, ETDRS letters	7.3 (13.0)	18.3 (13.2)	
(95% CI for mean)*	(5.1 – 9.5)	(16.0 – 20.6)	P<0.0001 for ranibizumab vs. sham, based on pairwise ANOVA models adjusted for baseline ETDRS letter score (≤ 34 vs. 35–54 vs. ≥ 55).
Difference in means (vs. sham)	-	11.0	
(95% CI for difference)	-	(7.8 – 14.2)	
(See Figure B6)			
Secondary Outcomes			
Proportion of patients who gained ≥ 15 ETDRS letters at Month 6, n (%, see Figure B10)	[redacted](28.8%)	[redacted](61.1%)	P<0.0001 ranibizumab vs. sham (pre-specified secondary endpoint) for, from Cochran−Mantel−Haenszel χ^2 tests adjusted for baseline ETDRS letter score (≤ 34 vs. 35–54 vs. ≥ 55).
Percentage of patients who gained ≥ 15 ETDRS letters at:			P<0.005 (post hoc analysis) for ranibizumab vs. sham at each time point
Day 7	3.8%	14.5%	
Month 1	8.3%	32.8%	
Month 2	16.7%	39.7%	
Month 3	17.4%	50.4%	

Proportion of patients who lost < 15 ETDRS letters at Month 6, n (%)	126 (95.5%)	129 (98.5%)	(not significant) for ranibizumab vs. sham

Exploratory Outcomes			
Proportion of patients with Snellen equivalent BCVA ≥ 20/40 at month 6x (%)	(41.7%)	(64.9%)	P<0.0001 for ranibizumab vs. sham,
Proportion of patients with Snellen equivalent BCVA ≤ 20/200 at month 6 (%)	(9.1%)	(0.8%)	P<0.01 for ranibizumab vs. sham,
Mean change from baseline NEI VFQ-25 Composite Score at 6 months (95% CI for mean)* (Sham n=129; 0.5 mg ranibizumab n =130)	5.4 (3.6 – 7.3)	10.4 (8.3 – 12.4)	P<0.005 for ranibizumab vs. sham

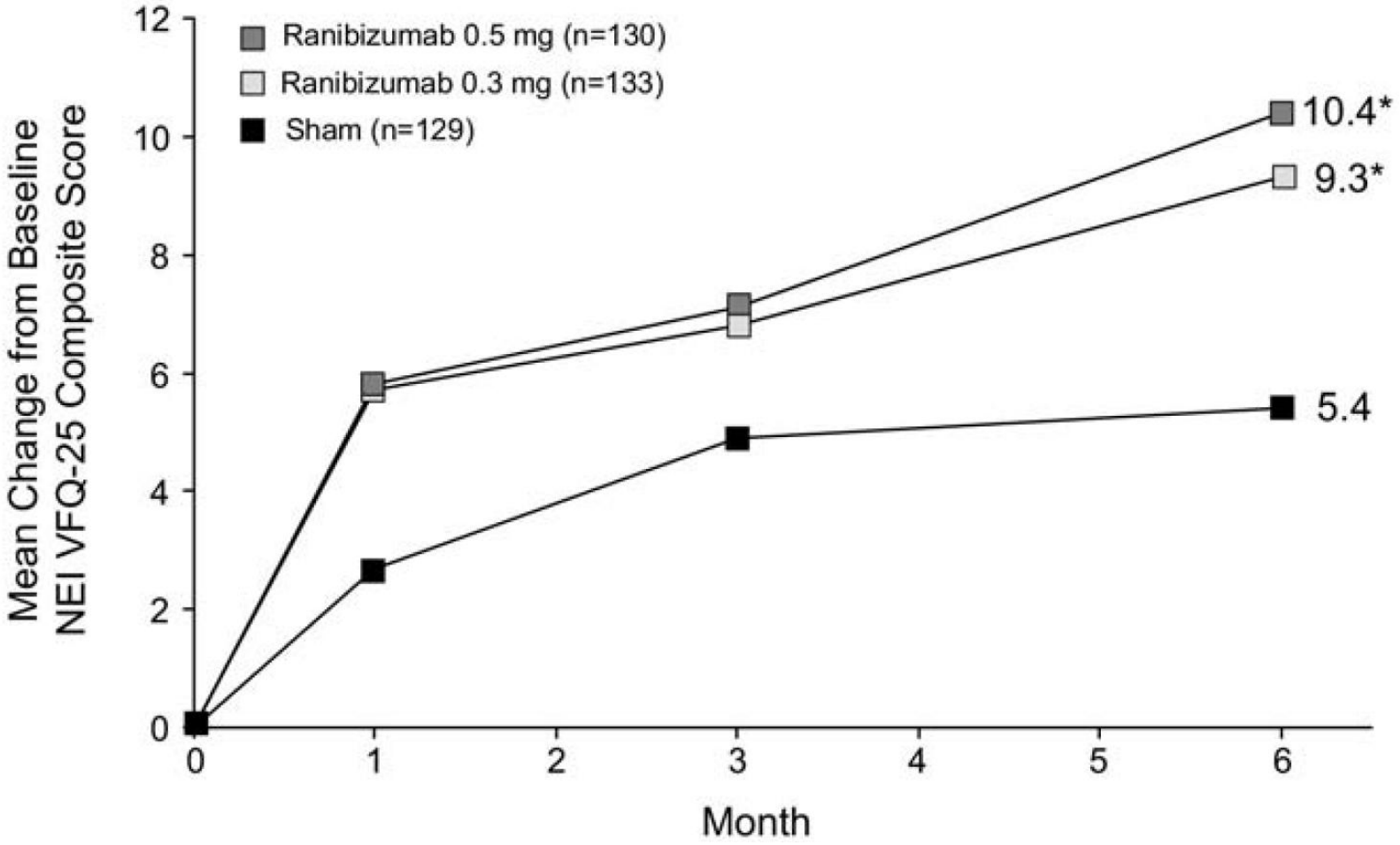
(See Figure B7)			
[redacted]	[redacted]	[redacted]	
[redacted]	[redacted]	[redacted]	
* Derived from the t-distributions, ** By normal approximation, [redacted] The last-observation-carried-forward method was used to impute missing data.			

Figure B6 Mean change from study eye baseline BCVA over time to month 6 in patients with MO secondary to BRVO. *P<0.0001 versus sham.



Earliest statistically significant group difference (P<0.0001 vs. sham) was at day 7. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward method was used to impute missing data. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

Figure B7 Mean change from baseline NEI VFQ-25 composite score over time to month 6 in patients with MO secondary to BRVO. *P<0.01 versus sham (pre-specified exploratory end point).



The last-observation-carried-forward method was used to impute missing data. NEI VFQ-25 ,National Eye Institute Visual Functioning Questionnaire-25.

Table B18 6 month primary and secondary outcomes of CRUISE[51]

CRUISE[51] (n = 392) **NCT00485836**	**Sham injection (n=130)**	**Ranibizumab 0.5 mg (n=130)**	**Significance**
Primary Outcome			
Mean (SD) change from baseline in BCVA score at month 6, ETDRS letters	0.8 (16.2)	14.9 (13.2)	
(95% CI for mean)*	(-2.0 to 3.6)	(12.6 – 17.2)	P<0.0001 for ranibizumab vs. sham, based on pairwise ANOVA models adjusting for baseline ETDRS letter score (≤ 34 vs. 35–54 vs. ≥ 55).
Difference in means (vs. sham)	-	14.1	
(95% CI for difference)	-	(10.5 – 17.7)	
(See Figure B8)			
Secondary Outcomes			
Proportion of patients who gained ≥ 15 ETDRS letters at Month 6, n (%, see Figure B10)	22 (16.9%)	62 (47.7%)	P<0.0001 for ranibizumab vs. sham (pre-specified secondary endpoint), from Cochran−Mantel−Haenszel χ^2 tests adjusted for baseline ETDRS letter score (≤ 34 vs. 35–54 vs. ≥ 55).
Percentage of patients who gained ≥ 15 ETDRS letters at:			P< 0.0001 (post hoc analysis) for ranibizumab vs. sham at each time point
Day 7	3.8%	26.9%	
Month 1	5.4%	25.4%	
Month 2	5.4%	37.7%	
Month 3	8.5%	36.9%	

CRUISE[51] (n = 392) **NCT00485836**	**Sham injection** **(n=130)**	**Ranibizumab 0.5 mg** **(n=130)**	**Significance**
[redacted]	[redacted]	[redacted]	
Proportion of patients who lost < 15 ETDRS letters at Month 6, n (%) [redacted]	[redacted] (84.6%) [redacted]	[redacted] (98.5%) [redacted]	P<0.005 for ranibizumab vs. sham from Cochran−Mantel−Haenszel χ^2 tests adjusted for baseline ETDRS letter score (≤ 34 vs. 35–54 vs. ≥ 55).
[redacted]	[redacted]	[redacted]	[redacted]

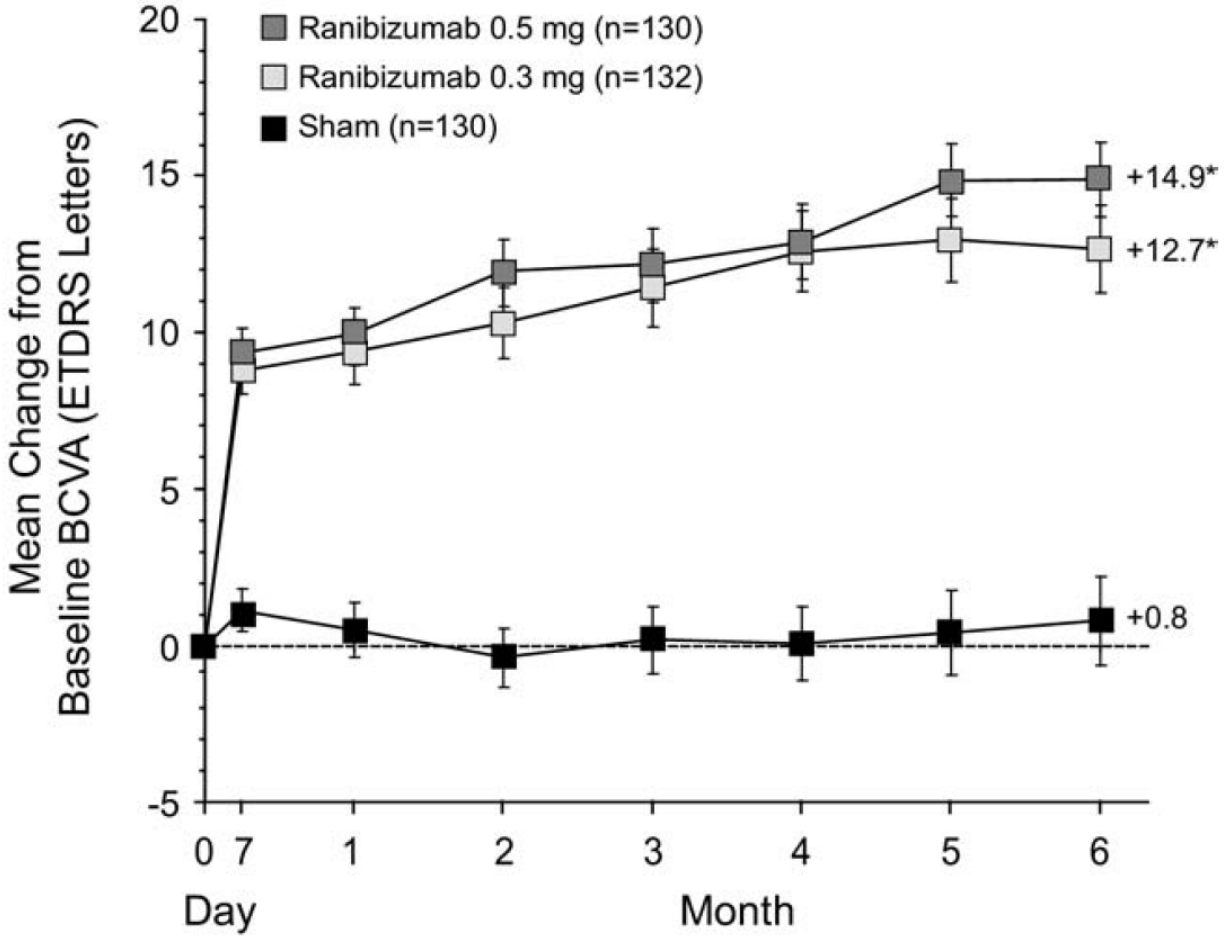
CRUISE[51] (n = 392) **NCT00485836**	**Sham injection** **(n=130)**	**Ranibizumab 0.5 mg** **(n=130)**	**Significance**
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Exploratory Outcomes			
Percentage of patients with Snellen equivalent BCVA ≥ 20/40 at month 6, n (%)	27 (20.8%)	61 (46.9%)	P<0.0001 for ranibizumab vs. sham
[redacted]	[redacted]	[redacted]	[redacted]

CRUISE[51] (n = 392) **NCT00485836**	**Sham injection (n=130)**	**Ranibizumab 0.5 mg (n=130)**	**Significance**
Proportion of patients with Snellen equivalent BCVA ≤ 20/200 at month 6, n (%)	36 (27.7%)	15 (11.5%)	P<0.005 for ranibizumab vs. sham, from Cochran−Mantel−Haenszel χ^2 tests adjusted for baseline ETDRS letter score (≤ 34 vs. 35–54 vs. ≥ 55).
Mean change from baseline NEI VFQ-25 Composite Score at 6 months (95% CI for mean)* (Sham n=127; 0.5 mg ranibizumab n =128) (See Figure B9)	2.8 (0.8 - 4.7)	6.2 (4.3 - 8.0)	P<0.05 for ranibizumab vs. sham

* Derived from the t-distributions, ** By normal approximation, † Weighted estimates adjusted for baseline visual acuity score (≤ 34, 35−54, ≥ 55 letters) using Cochran−Mantel−Haenszel weights

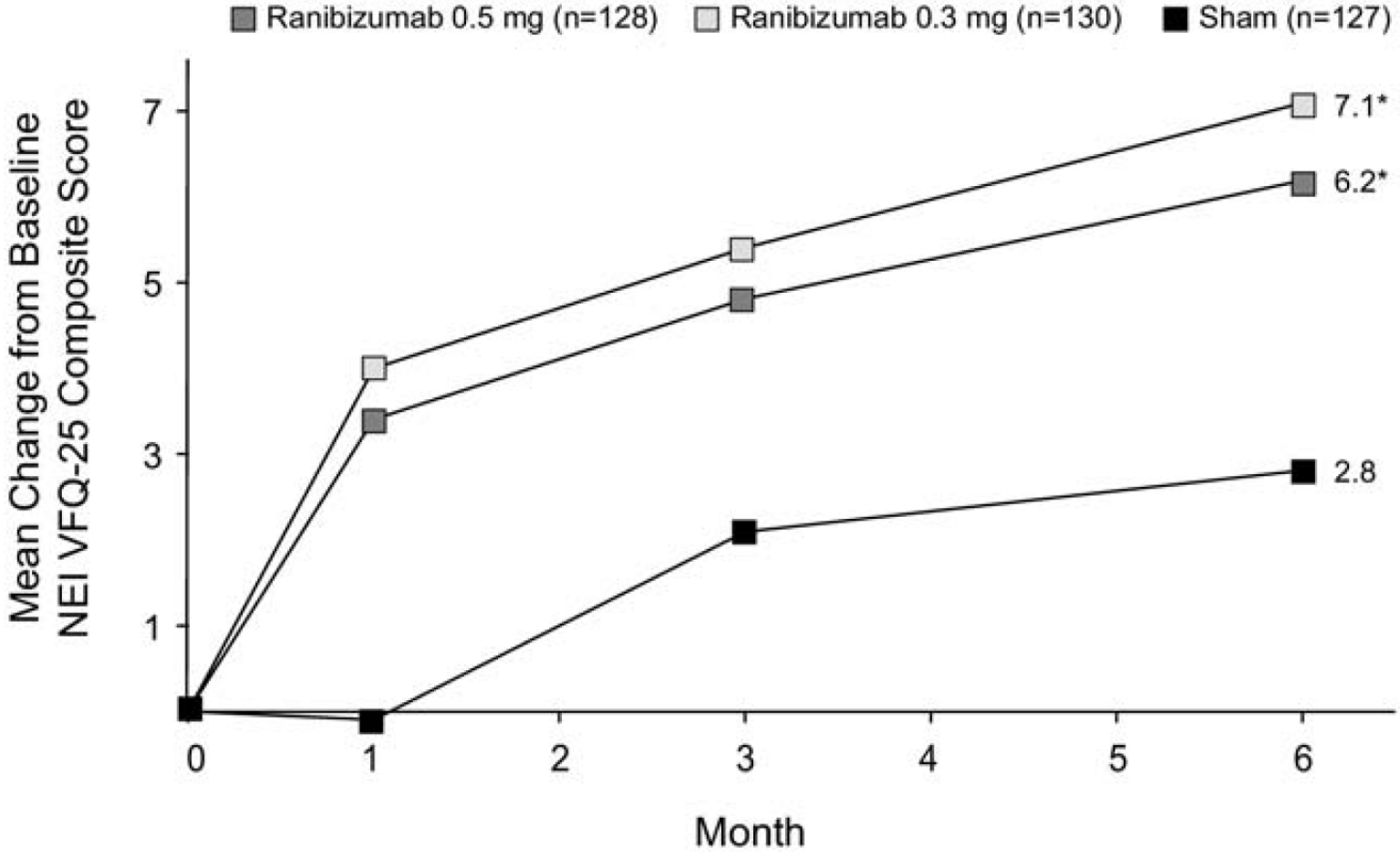
The last-observation-carried-forward method was used to impute missing data.

Figure B8 Mean change from study eye baseline BCVA over time to month 6 in patients with MO secondary to CRVO. *P<0.0001 versus sham.



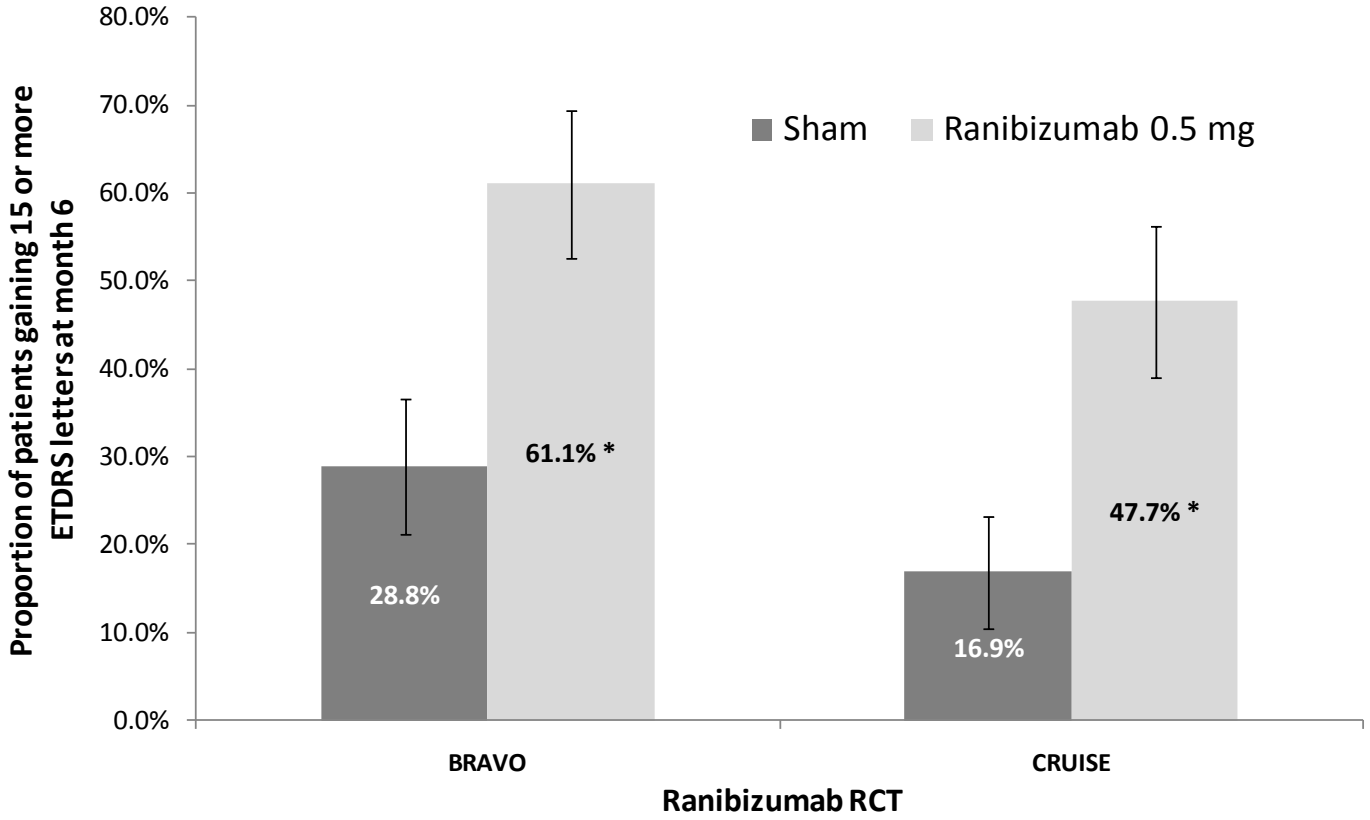
Earliest statistically significant group difference (P<0.0001 vs. sham) was at day 7. Vertical bars are ±1 standard error of the mean. The last-observation-carried-forward method was used to impute missing data. BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

Figure B9 Mean change from baseline NEI VFQ composite score over time to month 6 in patients with MO secondary to CRVO. *P<0.01 vs. sham (pre-specified exploratory end point)



The last-observation-carried-forward method was used to impute missing data. NEI VFQ-25 ,National Eye Institute Visual Functioning Questionnaire-25.

Figure B10 Proportion of patients gaining ≥ 15 ETDRS letters at month 6 in BRAVO and CRUISE



* P<0.0001 ranibizumab 0.5 mg vs. Sham. Vertical bars indicate 95% confidence interval for percentage. ETDRS, Early Treatment Diabetic Retinopathy Study.

Table B19 12 month secondary efficacy outcomes of BRAVO[61]

BRAVO (n=397) **NCT00486018**	**Sham injection/0.5 mg** **(n = 132)**	**Ranibizumab 0.5 mg** **(n = 131)**
Secondary Outcomes		
Mean (SD) change from baseline BCVA at 12 months (ETDRS letters) (95% CI for mean)**	12.1 (14.4) (9.6 - 14.6)	18.3 (14.6) (15.8 – 20.9)
[redacted]	[redacted]	[redacted]
Proportion of patients who gained ≥ 15 ETDRS letters from baseline BCVA at 12 months, n (%)	58 (43.9%)	79 (60.3%)
Proportion of patients who lost <15 ETDRS letters from baseline BCVA at 12 months, n (%) (95% CI for percentage)††	124 (93.9%)	128 (97.7%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Exploratory Outcomes		
Proportion of patients with Snellen equivalent BCVA ≥ 20/40 at 12 months, n (%)	75 (56.8%)	87 (66.4%)
Proportion of patients with Snellen equivalent BCVA < 20/200 at 12months, n (%)	9 (6.8%)	5 (3.8%)
Mean (SD) change from baseline NEI VFQ-25 Composite Score at 12 months	7.4 [redacted]	10.2 [redacted]
[redacted]	[redacted]	[redacted]

* During the 6-month treatment period, the sham group received sham injections (day 0, months 1-5), during the 6 month observation period, the sham group received PRN 0.5 ranibizumab if they met requirement criteria (eligible months 6-11); † Based on the month 6 database; ** Derived from t-distributions; ‡ By normal approximation; †† Exact CI based on the Blyth-Still-Casella method.
Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branched retinal vein occlusion; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata*

Table B20 12 month secondary efficacy outcomes of CRUISE[61]

CRUISE (n = 392) NCT00485836	Sham injection/0.5 mg (n=130)	Ranibizumab 0.5 mg (n=130)
Secondary Outcomes		
Mean (SD) change from baseline BCVA at 12 months (ETDRS letters) (95% CI for mean)**	7.3 (15.9) (4.5 – 10.0)	13.9 (14.2) (11.5 – 16.4)
[redacted]	[redacted]	[redacted]
Proportion of patients who gained ≥ 15 letters from baseline BCVA, n (%)	43 (33.1%)	66 (50.8%)
[redacted]	[redacted]	[redacted]
Proportion of patients who lost <15 ETDRS letters from baseline BCVA at 12 months, n (%)	117 (90.0%)	127 (97.7%)
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
Exploratory Outcomes		
Proportion of patients with Snellen equivalent BCVA ≥ 20/70 at 12 month, n (%)	68 (52.3%)	86 (66.2%)
[redacted]	[redacted]	[redacted]
Proportion of patients with Snellen equivalent BCVA < 20/200 at 12 month, n (%)	26 (20.0%)	16 (12.3%)
[redacted]	[redacted]	[redacted]
Mean (SD) change from baseline NEI VFQ-25 Composite Score at 12 months	5.0 [redacted]	6.6 [redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

P values for 0.5 mg groups vs. sham/0.5 mg at month 12 were not calculated or reported

* During the 6-month treatment period, the sham group received sham injections (day 0, months 1-5), during the 6 month observation period, the sham group received PRN 0.5 ranibizumab if they met requirement criteria (eligible months 6-11); † Based on the month 6 database; ** Derived from t-distributions; ‡ By normal approximation

Abbreviations used in table: BCVA, best-corrected visual acuity; CRVO, central retinal vein occlusion; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study; PRN, *pro re nata* (as needed)

Table B21 Primary efficacy outcomes for patients initially randomised in BRAVO and CRUISE trials, who then entered HORIZON (Cohort 2) extension study [3]

	Initial Trial			
	BRAVO		CRUISE	
	Sham/0.5 mg	Ranibizumab 0.5 mg	Sham/0.5 mg	Ranibizumab 0.5 mg
Mean (SD) change in BCVA score* from BRAVO or CRUISE baseline				
Month 12 of HORIZON (24 months from BRAVO/CRUISE baseline) [Number of patients with a VA score at Month 12]	15.6 [66]	17.5 [73]	7.6 [60]	12.0 [51]
Mean (SD) change in BCVA score* from HORIZON (Cohort 2) baseline				
Month 6 [Number of patients with a VA score at Month 6]	-0.1 (8.1) [88]	-1.3 (7.1) [98]	-3.2 (10.4) [90]	-3.2 (9.7) [91]
Month 9 [Number of patients with a VA score at Month 9]	0.6 (9.5) [84]	-1.8 (7.6) [92]	-4.9 (12.3) [76]	-3.9 (10.9) [75]
Month 12 [Number of patients with a VA score at Month 12]	0.9 (6.9) [66]	-0.7 (7.3) [73]	-4.2 (11.3) [58]	-4.1 (12.9) [50]
* Summaries based on the observed data; number of patients with observed data varies at each time point and includes patients with data available at that time point and initial study baseline Abbreviations used in the table: BCVA, best-corrected visual acuity; SD, standard deviation.				

Table B22 Mean change from baseline BCVA in ETDRS letters by subgroup at 6 months, in patients with MO secondary to BRVO, BRAVO[25]

Subgroup	Number of patients Sham (0.5 mg) / 0.5 mg	Mean change from baseline BCVA in ETDRS letters at 6 months		
		Sham/0.5 mg	Ranibizumab 0.5 mg	
		Mean (SD) [95% CI for mean]	Mean (SD) [95% CI for mean]	Difference in mean change vs. Sham/0.5 mg (95% CI for difference) [p-value vs. sham]
Baseline BCVA, ETDRS letter score				
≤ 34	9 / 13	13.6 [redacted] [2.3 – 24.9]	30.7 [redacted] [25.9 – 35.5]	[redacted]
35 – 54	50 / 49	8.9 [redacted] [5.0 – 12.9]	21.8 [redacted] [17.8 – 25.8]	[redacted]
≥ 55	73 / 69	5.4 [redacted] [2.6 – 8.2]	13.4 [redacted] [10.8 – 16.1]	[redacted]
Baseline CFT, µm				
< 450	61 / 48	8.0 [redacted] [5.4 – 10.5]	13.8 [redacted] [10.2 – 17.5]	[redacted]
≥ 450	71 / 83	6.8 [redacted] [3.2 – 10.4]	20.9 [redacted] [18.0 – 23.7]	[redacted]
Time from BRVO diagnosis to screening (months)				
< 3	71 / 75	8.2 [5.0 – 11.4]	19.9 [16.9 – 23.0]	[redacted]
≥ 3	61 / 56	6.3 [3.1 – 9.4]	16.1 [12.6 – 19.5]	[redacted]

[redacted]The last-observation-carried-forward method was used to impute missing data.

Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study

Table B23 Proportion of patients with MO secondary to CRVO who gained ≥ 15 ETDRS letters, in patients with MO secondary to BRVO, BRAVO[25, 64]

Subgroup	Number of patients Sham (0.5 mg) / 0.5 mg	Proportion of patients who gained ≥ 15 ETDRS letters at 6 months		
		Sham/0.5 mg	Ranibizumab 0.5 mg	
		n (%) [95% CI for %]	n (%) [95% CI for %]	Difference in % vs. Sham/0.5 mg (95% CI for difference) [p-value vs. sham]
Baseline BCVA, ETDRS letter score				
≤ 34	9 / 13	[redacted] (33.3%) [redacted]	[redacted] (100%) [redacted]	[redacted]
35 – 54	50 / 49	[redacted] (36.0%) [redacted]	[redacted] (63.3%) [redacted]	[redacted]
≥ 55	73 / 69	[redacted] (23.3%) [redacted]	[redacted] (52.2%) [redacted]	[redacted]
Baseline CFT, µm				
< 450	61 / 48	[redacted] (24.6%) [redacted]	[redacted] (47.9%) [redacted]	[redacted]
≥ 450	71 / 83	[redacted] (32.4%) [redacted]	[redacted] (68.7%) [redacted]	[redacted]
Time from BRVO diagnosis to screening (months)				
< 3	71 / 75	(32.4%)	(69.3%)	[redacted]
≥ 3	61 / 56	(24.6%)	(50.0%)	[redacted]
[redacted]				

The last-observation-carried-forward method was used to impute missing data.
Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study

Table B24 Mean change from baseline BCVA in ETDRS letters by subgroup at 6 months, in patients with MO secondary to CRVO, CRUISE[51, 64]

Subgroup	Number of patients Sham (0.5 mg) / 0.5 mg	Mean change from baseline BCVA in ETDRS letters at 6 months		
		Sham/0.5 mg	Ranibizumab 0.5 mg	
		Mean (SD) [95% CI for mean]	Mean (SD) [95% CI for mean]	Difference in mean change vs. Sham/0.5 mg (95% CI for difference) [p-value vs. sham]
Baseline BCVA, ETDRS letter score				
≤ 34	26 / 30	5.7 [redacted] [0.3 – 11.2]	18.4 [redacted] [12.4 – 24.4]	[redacted]
35 – 54	49 / 50	2.4 [redacted] [-2.2 to 7.1]	15.7 [redacted] [12.1 – 19.4]	[redacted]
≥ 55	55 / 50	-3.0 [redacted] [-7.5 to 1.5]	11.9 [redacted] [8.7 – 15.1]	[redacted]
Baseline CFT, µm				
< 450	20 / 19	-1.7 [redacted] [-12.5 to 9.1]	10.2 [redacted] [5.3 – 15.0]	[redacted]
≥ 450	109 / 111	1.2 [redacted] [-1.6 to 4.0]	15.7 [redacted] [13.2 – 18.2]	[redacted]
Time from CRVO diagnosis to screening (months)				
< 3	80 / 74	1.1 [-2.9 to 5.1]	14.3 [11.1 – 17.5]	[redacted]
≥ 3	50 / 56	0.4 [-3.4 to 4.1]	15.7 [12.4 – 18.9]	[redacted]

[redacted]The last-observation-carried-forward method was used to impute missing data.

Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study

Table B25 Proportion of patients with MO secondary to CRVO who gained ≥ 15 ETDRS letters, by subgroups at 6 months, CRUISE[51, 64]

Subgroup	Number of patients Sham (0.5 mg) / 0.5 mg	Proportion of patients who gained ≥ 15 ETDRS letters at 6 months		
		Sham/0.5 mg	Ranibizumab 0.5 mg	
		n (%) [95% CI for %]	n (%) [95% CI for %]	Difference in % vs. Sham/0.5 mg (95% CI for difference) [p-value vs. sham]
Baseline BCVA, ETDRS letter score				
≤ 34	26 / 30	[redacted] (19.2%)	[redacted] (53.3%)	[redacted]
35 – 54	49 / 50	[redacted] (28.6%)	[redacted] (50.0%)	[redacted]
≥ 55	55 / 50	[redacted] (5.5%)	[redacted] (42.0%)	[redacted]
Baseline CFT, µm				
< 450	20 / 19	[redacted] (25.0%)	[redacted] (31.6%)	[redacted]
≥ 450	109 / 111	[redacted] (15.6%)	[redacted] (50.5%)	[redacted]
Time from BRVO diagnosis to screening (months)				
< 3	80 / 74	(18.8%)	(51.4%)	[redacted]
≥ 3	50 / 56	(14.0%)	(42.9%)	[redacted]

[redacted] The last-observation-carried-forward method was used to impute missing data.
Abbreviations used in table: BCVA, best-corrected visual acuity; BRVO, branch retinal vein occlusion; CFT, central foveal thickness; CI, confidence interval; ETDRS, Early Treatment Diabetic Retinopathy Study

5.6 Meta-analysis

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

Summary of Meta-analysis

- CRUISE and ROCC patient populations could be pooled in a meta-analysis, but due to the much smaller nature of the ROCC study (N=32) compared to CRUISE (N=392), the meta-analysis results added no value to those previously reported for the CRUISE study.

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

- Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
- Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
- Provide an adequate description of the methods of statistical combination and justify their choice.
- Undertake sensitivity analysis when appropriate.
- Tabulate and/or graphically display the individual and combined results (such as through the use of forest plots).

CRUISE and ROCC both investigated ranibizumab treatment in patients with visual impairment due to MO secondary to CRVO. Additionally, they both had randomized, sham-controlled designs. Thus their study characteristics were considered similar to a great enough extent to allow pooling of the results.

Due to the small size of the ROCC study (N=32) compared to CRUISE (N=392), the meta-analysis does not provide any additional value than is given by the results of the CRUISE study, which are presented in Section 5.5. For transparency, the methodology and results of the meta-analysis, displayed as forest plots, are presented in Section 10.3, appendix 16.

5.6.2 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.

Not applicable

5.6.3 If any of the relevant RCTs listed in response to section 5.2.4 (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

5.7 Indirect and mixed treatment comparisons

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

Summary of Indirect Comparison Analysis

- An indirect comparison between ranibizumab and dexamethasone intravitreal implant was not feasible due to differences in the patient populations used in the clinical trials.
- Due to fundamental differences in trial design, ranibizumab could not be compared indirectly to laser photocoagulation therapy.
- Ranibizumab could not be compared indirectly to bevacizumab due to the lack of appropriate reliable data.

5.7.1 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 9.4, appendix 4.

A systematic review was undertaken to identify RCTs involving potential comparators for ranibizumab in the treatment of MO secondary to RVO.

Bevacizumab and IVTA are not considered appropriate comparators for ranibizumab in this submission because their use in the NHS is not routine nor best practice. Therefore these unlicensed interventions do not meet the definition of a comparator according to the NICE methods guide (see Section A 2.6).[43] Nonetheless in the interests of transparency the extent of their RCT evidence was also investigated in this systematic review. Evidence for IVTA is not presented here, as this comparator

was removed from the final scope produced by NICE following confirmation by stakeholders that it was not a relevant comparator for interventions in this therapy area.

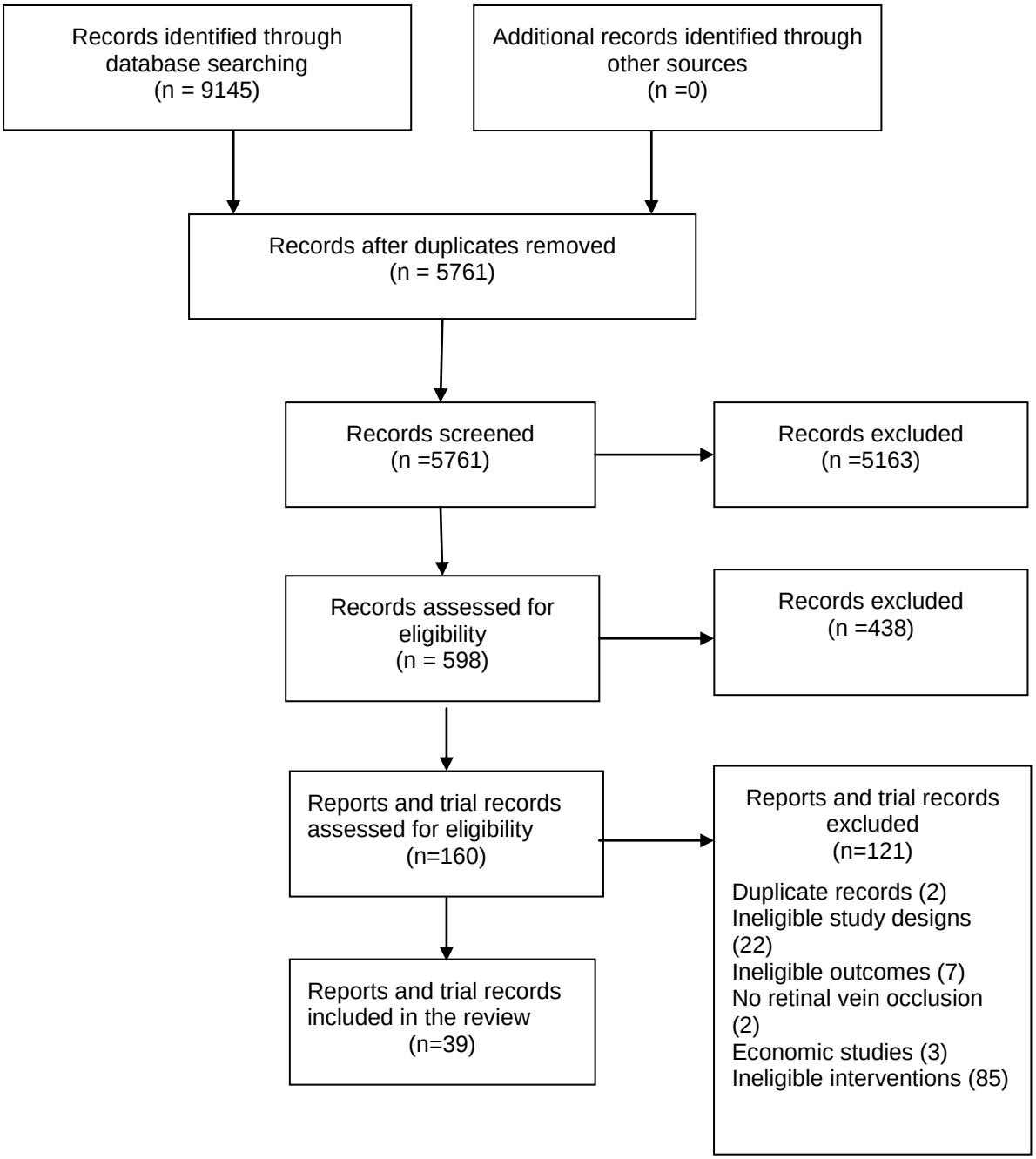
The methodology used to identify this literature is identical to that used to search for ranibizumab RCTs, as the searches and the review of articles for the comparators were run parallel to those for ranibizumab. Thus the description of the search strategy can be found in Section 5.1.1 and the full details in Section 9.2, appendix 2.

5.7.2 Please follow the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, quality assessment and the presentation of results. Provide in section 9.5, appendix 5, a complete quality assessment for each comparator RCT identified.

The inclusion and exclusion criteria used to select appropriate comparator trials differs from those presented in Table B2 in Section 5.2.1 only in that trials that investigated dexamethasone biodegradable implant (Ozurdex), laser photocoagulation, bevacizumab or IVTA were included.

Figure B11 below shows the study identification process.

Figure B11 Flow diagram showing study identification process for comparator RCTs



The 39 articles identified by the review correspond to 11 trials (see Table B26 for details). The characteristics of these trials were then reviewed in order to assess whether indirect comparison to ranibizumab data was feasible. The full critical appraisal of these studies is presented in Appendix 5 in Section 9.5.

Table B26 List of identified comparator RCTs

Trial no. (acronym)	Intervention	Comparator	Population	Primary study ref.
NCT00000162 (BVOS)	Laser	Observation	Patients with MO secondary to BRVO (of at least 3 months duration) and decreased VA	BVO Study Group 1984[23]
NCT00000131 (CVOS)	Laser	Observation	Patients with MO secondary to CRVO (of at least 3 months duration) and decreased VA	CVO Study Group 1993[22]
Battaglia 1999	Laser	Observation	Patients with BRVO of less than 15 days duration with MO and visual impairment	Battaglia 1999[65]
Laatikainen 1977	Laser	Observation	Patients with CRVO	Laatikainen 1977[66]
May 1976	Laser	Observation	Patients with CRVO and reduced VA	May 1976[67]
Haller 2003	Dexamethasone implant	Observation	Patients with MO due to BRVO or CRVO and with visual impairment	Haller 2003[68]
NCT00168298 and NCT00168324 (Haller 2010)	Dexamethasone implant	Sham	Patients with visual impairment due to MO secondary to either CRVO or BRVO of at least 6 weeks duration	Haller 2010[69]
NCT00035906 (Kupperman 2007)	Dexamethasone implant	Observation	Patients with persistent MO secondary to BRVO, CRVO or DMO	Kupperman 2007[70]
Faghihii 2008	Bevacizumab	Sham	Patients with visual impairment due	Faghihii 2008[71]

			to MO secondary to ischaemic or non-ischaemic CRVO of less than 6 months duration	
NCT0037085 (Moradian 2007)	Bevacizumab	Sham	Patients with acute BRVO and visual impairment	Moradian 2007[72]
Russo 2009	Bevacizumab	Laser	Patients with MO due to non-ischaemic BRVO of at least 3 months duration	Russo 2009[73]

Abbreviations: BVOS, Branch Vein Occlusion Study; CVOS, Central Vein Occlusion Study; VA, visual acuity

Assessment of Feasibility for Indirect Comparison

The suitability of trials for inclusion in indirect and mixed treatment comparisons is determined by considering whether studies are sufficiently homogeneous. Indirect comparisons of multiple treatments can provide an indirect estimate of the benefit of one treatment (A) over another (B) by comparing trials of treatment A v placebo with trials of treatment B v placebo. This method requires that treatment A can only be compared with treatment B when they share a mutual comparator (eg. placebo). There is currently no UK guidance on best practice for indirect and mixed treatment comparisons.[74-76]

The feasibility of using the trials listed in Table B26 for indirect comparison to ranibizumab was assessed using the following criteria: quality or methodology of randomised trials, confounding factors in relation to participant populations, confounding factors in relation to circumstances, treatments and comparators, outcome measures and methods of statistical analysis. The assessment considered options for CRVO and BRVO separately.

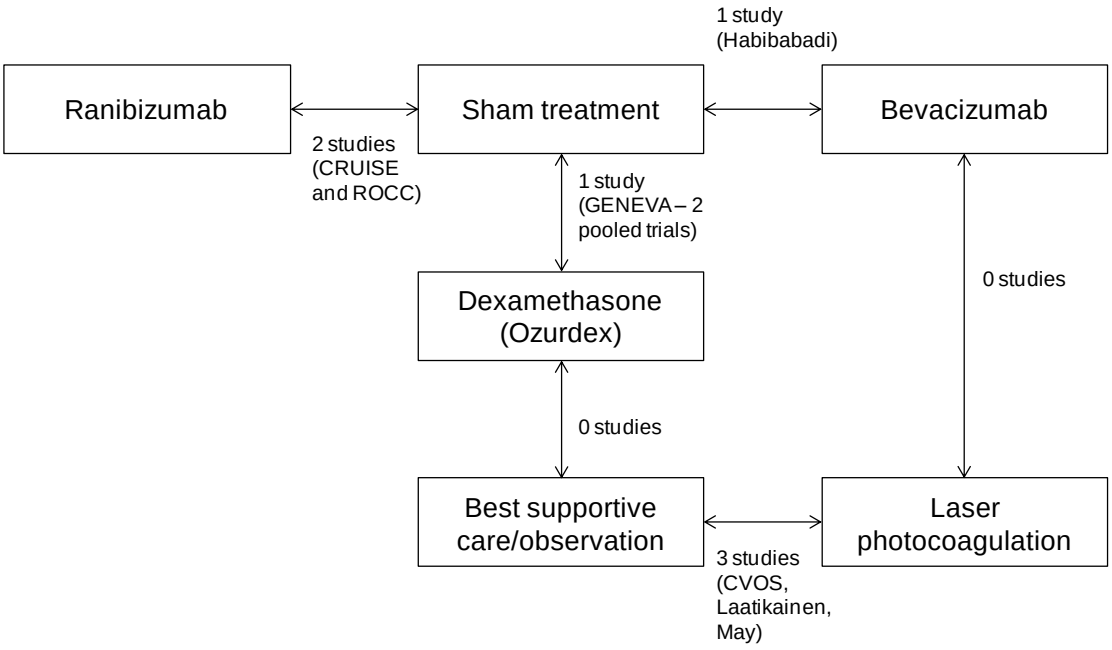
Haller 2003 is only an abstract that does not report any results and Kupperman 2007 does not distinguish between the underlying causes of MO. Therefore neither of these studies can be used for indirect comparison of ranibizumab to dexamethasone.

CRVO

The feasibility of the following comparisons for CRVO was assessed:

- Ranibizumab vs. dexamethasone intravitreal implant via sham treatment
- Ranibizumab vs. bevacizumab via sham treatment
- For completeness, laser studies were included in the network to assess whether an extended network meta-analysis may be possible. As Figure B12 illustrates, this was not possible and the studies of laser in CRVO are therefore not discussed further in this submission.

Figure B12 Potential network of evidence for ranibizumab compared to other therapies for CRVO



Ranibizumab vs. Dexamethasone Intravitreal (IVT) Implant for CRVO

The feasibility of comparing the CRUISE and ROCC studies for ranibizumab to the CRVO subgroup of the twin dexamethasone IVT implant trials (pooled in the GENEVA trial) was assessed. The key characteristics of the trials are presented in Table B27.

Although the study designs are similar, in that they are all randomised, double-blind, sham-controlled trials, there are a number of significant differences between the patient inclusion criteria for the CRUISE and GENEVA trials (also see Table B27):

- CRUISE (ranibizumab) allowed a longer period of MO prior to entry into the study than the GENEVA studies (within 12 months for CRUISE, within 6 to 9 months in GENEVA; Table B27).
- Both the baseline range of BCVA acceptable for inclusion and the eligible value for retinal thickness were different in the CRUISE and GENEVA studies (baseline BCVA acceptable in CRUISE: 20/40-20/320, compared to 20/200-20/50 letters in GENEVA; baseline eligible CFT in CRUISE: ≥250 µm, compared to ≥300 µm in GENEVA; Table B27).
- CRUISE excluded patients who had received photocoagulation within the previous 4 months prior to baseline, whereas this was not an exclusion criterion in the GENEVA trial.
- Patients intolerant of steroids were excluded from the GENEVA trial, but not from the CRUISE trial. This is estimated to comprise approximately 5-10% of the general population, but their ocular characteristics with regards to RVO are unknown.

In terms of the baseline characteristics of the patient populations enrolled, again there is substantial variation between the ranibizumab and the dexamethasone IVT implant studies (also see Table B27):

- The duration of MO was longer in GENEVA where only a minority of patients (17%) had MO duration of <90 days at baseline (CRVO and BRVO patients together) compared to CRUISE where the majority of patients had MO duration at baseline of ≤3 months. A greater mean duration of RVO tends to result in a poorer response to treatment.[69, 77]
- The mean central foveal thickness was lower in GENEVA (550 µm; both CRVO and BRVO patients) than in CRUISE (685 µm). This is an important difference because a greater CFT at baseline may correlate to greater reductions and better visual acuity outcomes during the trial.[77]

Furthermore, there are several problems with the dexamethasone IVT implant data that is publically reported:

- The patient demographic data for the CRVO subgroup are not reported separately to the BRVO subgroup for either of the twin studies nor for the pooled GENEVA study. It is therefore not possible to ascertain whether there are other characteristics of the populations studied that may have important differences.

- The data on CRVO is derived from three tables in the study report (Haller 2010[69]) and data in the manufacturer's submission to NICE.[78] This data is provided for the two trials together and not disaggregated into the individual studies. This may mask some variation in patient populations between the two twin trials.

In light of the differences between the ranibizumab and dexamethasone IVT implant trial populations, an indirect comparison between these two agents is not appropriate for CRVO, as baseline characteristics, and in particular duration of MO, are considered to be predictors of outcomes in MO secondary to RVO.[69, 77] The additional reporting problems with the dexamethasone IVT implant data add to the infeasibility of the comparison.

Table B27 Key study features of ranibizumab and dexamethasone intravitreal implant studies for the treatment of CRVO

	CRUISE (Brown[24]) 0.5mg (n=362)	**ROCC (Kinge[49]) 0.5mg Ranibizumab vs. sham (n=32)**	**GENEVA CRVO subset (Haller [69]) n=136 dexamethasone implant 0.7mg licensed indication in the UK n=147 Sham**
Study design	Randomised double-blind sham (placebo) controlled trial	Randomised double-blind (placebo) controlled trial	Two identical blinded, randomised sham-controlled clinical trials
Population	Mean age 0.5 mg: 67.6 Mean age sham: 65.4 Males 0.5 mg: 61.5% Males sham: 72% Baseline mean BCVA: 48.3 letters (20/100) Baseline mean CFT: 685 µm Baseline mean duration: 3.3 months	Mean age 72 Sex: no details Baseline mean BCVA:.43 letters (20/138) Baseline mean CFT: 625 µm Baseline mean duration: 78 days	Mean age (CRVO and BRVO): 64.7 (33–90) 63.9 (31–91) Sex (CRVO and BRVO): 217 (50.8%) 240 (56.3%) Baseline mean BCVA (CRVO and BRVO): 54 letters (20/80) Baseline mean CFT (CRVO and BRVO): 550 µm Baseline mean duration (CRVO and BRVO): approx. 156 days Very little information provided for CRVO patients alone
Duration	6 months (followed by 6 months observation)	6 months	180 days (6 months)
Endpoints	Visual acuity improvement from baseline Percentage of eyes achieving 15 letters of improvement from baseline BCVA	Visual acuity improved using data for improvement of 2 lines or more	Percentage of eyes achieving 10 letters and 15 letters of improvement from baseline BCVA (figures presented) Mean change from baseline BCVA (graph) Many adverse outcomes
Inclusion criteria	≥18 years of age Foveal centre-involved MO secondary to CRVO diagnosed within 12 months before study initiation; BCVA 20/40 - 20/320 Snellen equivalent using the ETDRS charts; Mean central subfield thickness ≥250µm from 2 OCT measurements; Underwent a physical examination and a complete eye examination (including measurement of BCVA), OCT and laboratory tests.	MO secondary to CRVO in 1 eye, previously untreated. Symptom duration ≤6 months, age ≥50 years, BCVA using ETDRS between ≤73 and ≥6 letters	>= 18 years old Decreased VA as a result of clinically detectable MO associated with CRVO. Time since initial diagnosis of MO between 6 weeks and 9 months. A 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 measured by OCT2 or OCT 3 had to be ≥300um in the study eye

	CRUISE (Brown[24]) 0.5mg (n=362)	**ROCC (Kinge[49]) 0.5mg Ranibizumab vs. sham (n=32)**	**GENEVA CRVO subset (Haller [69]) n=136 dexamethasone implant 0.7mg licensed indication in the UK n=147 Sham**
Exclusion criteria	Prior episode of RVO; Brisk afferent pupillary defect (i.e. obvious and unequivocal); >10 letter improvement in BCVA between screening and day 0; History of radial optic neurotomy or sheathotomy; Intraocular corticosteroid use in study eye within 3 months before day 0; History or presence of wet or dry AMD; Panretinal scatter photocoagulation or sector laser photocoagulation within 3 months before day 0 or anticipated within 4 months after day 0; Laser photocoagulation for macular edema within 4 months before day 0 (for patients who had previously received grid laser photocoagulation, the area of leakage at day 0 must have extended into the fovea (i.e. prior laser treatment was inadequate), and there could be no evidence of laser damage to the fovea; Evidence on examination of any diabetic retinopathy; CVA or MI within 3 months before day 0; Prior anti-VEGF treatment in study or fellow eye within 3 months before day 0 or systemic anti-VEGF or pro VEGF-treatment within 6 months before day 0.	Any concomitant ocular disease that could compromise ocular assessments in the study eye or induce complications such as active extra ocular intraocular infection or inflammation, prior treatment of macular disease, history of uncontrolled glaucoma, filtration surgery, or corneal transplantation, 3 months prior to baseline aphakia, cataract, diabetic retinopathy in rapid progression, vitreous haemorrhage, previous rhegmatogenous retinal detachment, pregnancy, current treatment for active systematic infection, receiving other investigational drugs, or had received medication known to be toxic to the eye, history of hypersensitivity or allergy to fluorescein, inability to obtain fundus photographs or fluorescein angiograms.	Clinically significant epiretinal membrane active retinal membrane active retinal or optic neovascularisation, active or history of choroidal neovascularisation, presence of rubeosis iridis any active infection aphakia or anterior chamber intraocular lens, clinically significant media opacit, glaucoma, or current ocular, hypertension requiring more than 1 medication to control IOP in the study eye or a history of steroid induced IOP in the study eye. Diabetic retinopathy in either eye any uncontrolled systemic disease, the use of systematic steroids, or anticoagulants or any ocular condition that in the opinion of the investigator would prevent a 15-letter improvement in VA.

Ranibizumab vs. bevacizumab for CRVO

Faghihii (2008) is reported only in a poster and an abstract.[71, 79] It presents BCVA change in a graph for only 63 of the 101 randomised patients across 3 treatment arms:

- 1.25 mg bevacizumab (n = 22)
- 1.25 mg bevacizumab + 2 mg triamcinolone (n = 29 and not relevant to this decision problem), and
- sham injections (n = 14).

Injections were given at baseline and then twice further at 6 weekly intervals; data reported are interim at 18 weeks but no subsequently published data for this study could be identified. Neither the abstract nor poster report standard deviations so the data from the study were not suitable for use in an indirect comparison.

There is inadequate information available with regards to the baseline characteristics of the randomised population or the missing patients to make an assessment on its suitability for indirect comparison with ranibizumab studies via a sham comparator

Therefore there is inadequate RCT data to conduct an indirect comparison between ranibizumab and bevacizumab for CRVO.

BRVO

The feasibility of making comparisons to other drug therapies via the control arm of BRAVO is complicated by the use of laser in the majority of the sham treated patients. In order to fully explore all potential opportunities for indirect comparisons, the feasibility assessment was undertaken assuming that the BRAVO control arm was equivalent to sham alone and to laser alone. The following potential is suggested by the network diagrams:

- Ranibizumab vs. dexamethasone intravitreal implant via sham treatment
- Ranibizumab vs. bevacizumab via sham treatment
- Ranibizumab vs bevacizumab via laser.

In order to establish whether a mixed treatment comparison including laser might be feasible, the potential to compare ranibizumab to laser via sham treatment was also considered.

Figure B13 Potential network of evidence for ranibizumab compared to other therapies for BRVO – BRAVO control arm equivalent to sham alone

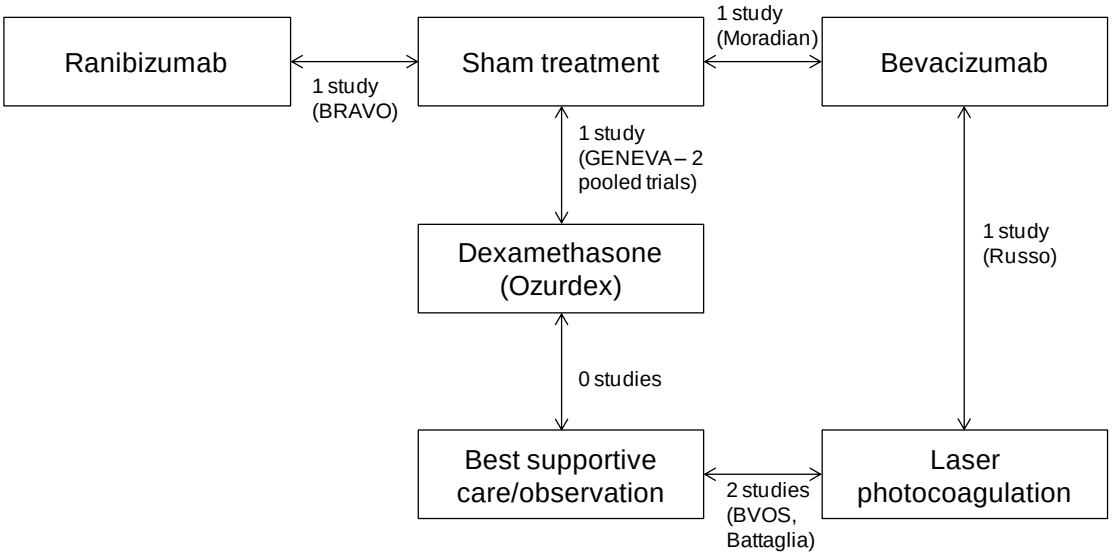
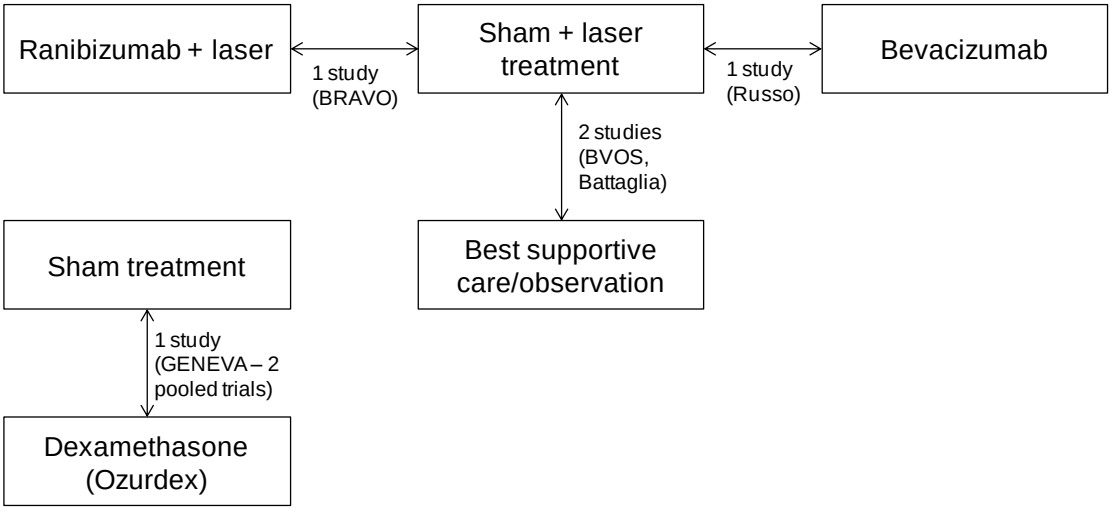


Figure B14 Potential network of evidence for ranibizumab compared to other therapies for BRVO - BRAVO control arm equivalent to laser alone



Ranibizumab vs. dexamethasone IVT Implant for BRVO

The feasibility of comparing the BRAVO studies for ranibizumab to the BRVO subgroup of the twin dexamethasone IVT implant trials (pooled in the GENEVA trial) was assessed. Similar concerns as for the CRVO indication apply and are described below.

Although the study designs are similar, in that they are all randomised, double-blind, sham-controlled trials, there are a number of significant differences between the patient inclusion criteria for the BRAVO and GENEVA trials:

- BRAVO (ranibizumab) allowed a longer period of MO prior to entry into the study than the GENEVA studies
- Both the baseline range of BCVA acceptable for inclusion and the eligible value for retinal thickness were different in the BRAVO and GENEVA studies.
- BRAVO excluded patients who had received photocoagulation within the previous 3 months.
- Patients intolerant of steroids were excluded from the GENEVA trial, but not from the BRAVO trial. This is estimated to comprise approximately 5-10% of the general population, but their ocular characteristics with regards to RVO are unknown.

In terms of the actual characteristics of the patient populations enrolled, again there is some noteworthy variation between the ranibizumab and the dexamethasone IVT implant studies:

- The duration of MO was longer in GENEVA where only a minority of patients (17%) had MO duration of <90 days at baseline (CRVO and BRVO patients together) compared to BRAVO where the majority of patients had MO duration at baseline of ≤3 months. A greater mean duration of RVO tends to result in a poorer response to treatment.[69, 77]

Furthermore, there are several problems with the reporting of the dexamethasone IVT implant data:

- The patient demographic data for the BRVO subgroup are not reported separately to the CRVO subgroup for either of the twin studies nor for the pooled GENEVA study.
- The data on BRVO are derived from three tables in the study report (Haller 2010[69]) and data in the manufacturer's submission to NICE[78]. This data is

provided for the two trials together and not disaggregated into the individual studies. This may mask some variation in patient populations between the two twin trials.

In light of the differences between the ranibizumab and dexamethasone IVT implant trial populations, an indirect comparison between these two agents is not appropriate for BRVO, as baseline characteristics are known to be predictors of outcomes in MO secondary to RVO.[69, 77] The additional reporting problems with the dexamethasone IVT implant data add to the infeasibility of the comparison. The same conclusion was reached by other investigators.[80]

Table B28 Key study features of ranibizumab and dexamethasone IVT implant studies for the treatment of BRVO

	BRAVO (Campochiaro[25]) **0.5 mg ranibizumab vs. sham** **(n=397)**	**GENEVA BRVO subset (Haller[69])** **n=291 dexamethasone IVT implant 0.7mg licensed indication in the UK.** **n= 279 sham**
Population	Mean age: 67.5 (0.5mg) Mean age: 65.2 (sham) 54/2% male(0.5mg) 56.1% male (sham) Baseline mean BCVA: 54.6 letters (20/80) Baseline mean CFT: 520.5 µm Baseline mean duration: 3.5 months	Mean age(CRVO and BRVO): 64.7 (0.7 mg), 63.9 (sham) Male sex (CRVO and BRVO): 217 (50.8%; 0.7 mg), 240 (56.3%; sham) Baseline mean BCVA (CRVO and BRVO): 54 letters (20/80) Baseline mean CFT (CRVO and BRVO): 550 µm Baseline mean duration (CRVO and BRVO): approx. 156 days Over 50% of patients entered the trials with a history of cataracts (CRVO and BRVO) Very little information provided for BRVO patients alone
Study design	Randomised placebo controlled double blind trial	Two identical blinded, randomised sham-controlled clinical trials
Duration	6 months (followed by 6 months observation)	180 days (6 months)
Endpoints	BCVA change from baseline at 6, 12 months. BCVA gaining > 15 letters at 6, 12 months	Percentage of eyes achieving more than 10 and more than 15 letters of improvement from baseline BCVA Mean change from baseline BCVA Data from paper, and manufacturer's submission.
Inclusion criteria	≥ 18 years of age foveal centre–involved macular edema secondary to BRVO. BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts of 20/40 to 20/400 (Snellen equivalent) and a mean central subfield thickness ≥ 250 µm on two optical coherence tomography (OCT) measurements (at screening and Day 0) in the study eye.	>=18 years old Deceased VA as a result of clinically detectable ME associated with BRVO. Time since initial diagnosis of ME between 6 weeks and 12 months. A 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 measured by OCT2 or OCT 3 had to be ≥300um in the study eye.
Exclusion criteria	History of cerebral vascular accident or myocardial infarction within 3 months prior to Day 0; History of any anti−VEGF treatment in fellow eye within 3 months prior to Day 0; uncontrolled blood pressure; pregnancy; For study eye: prior episode of RVO in study eye; a detailed list of other ocular diseases and treatments received; history of any anti-VEGF treatment	The presence of a clinically significant epiretinal membrane active retinal membrane active retinal or optic neovascularisation, active or history of choroidal neovascularisation, presence of rubeosis iridis any active infection aphakia or anterior chamber intraocular lens, clinically significant media opacit, glaucoma, or current ocular, hypertension requiring more than 1 medication to control IOP in the study eye or a history of steroid induced IOP in the study eye. Diabetic retinopathy in either eye, any uncontrolled systemic disease, use of systematic steroids, or anticoagulants or any ocular condition that might prevent a 15-letter improvement in VA.

Ranibizumab vs. laser for BRVO

Given that laser therapy was permitted in the ranibizumab arms of the BRAVO trial, a direct comparison of ranibizumab alone for all patients and laser therapy for all patients is not obtainable from this trial. Therefore, the two laser studies in patients with BRVO identified by the systematic review (Battaglia 1999[65] and BVOS 1984[23]) were assessed for the potential for inclusion in a mixed treatment comparison or indirect comparison to ranibizumab.

The most significant difference between BRAVO and these trials of laser photocoagulation is that BRAVO is sham-injection-controlled and the “laser trials” are not; using observation (no treatment) as the control arm. Thus, in the BRAVO study patients, investigators and assessors were blinded to treatment whereas participants in the laser trials were aware of treatment allocation. Additionally, as already noted, patients in BRAVO could be treated with laser during Months 3 to 6 of the double blind period, which gives a further reason why the sham-injection arm in BRAVO is not directly comparable to the observation arms of the laser trials.

All the trials seem to be of high quality with the exception of Battaglia which reports little detail. Battaglia and colleagues note that their study was not large enough to draw definite conclusions.

BRAVO, Battaglia and BVOS have similar patient profiles. Patients recruited to Battaglia had to have a recent occurrence of BRVO within 15 days whereas BVOS required patients to have had BRVO for at least 3 months and up to 18 months previously. Battaglia specifically excluded patients who had had previous laser or surgical treatment, whereas BVOS did not state whether patients had had prior therapy. The laser trials have longer follow-up periods than BRAVO: BVOS in particular reports detailed data for the 3 year follow-up (rather than the 12 months of BRAVO).

In conclusion, the study designs are fundamentally different and therefore indirect or mixed treatment comparisons between ranibizumab and laser for BRVO would be difficult to justify. Specifically combining data from double-blind sham controlled trials with data from open label (at best single blind) trials where the control arm had received no placebo treatment would be to ignore fundamental trial design differences.

Table B29 Key study features of ranibizumab and laser studies for the treatment of BRVO

	BRAVO (Campochiaro[25]) 0.5mg	**Battaglia[65] (n=77)**	**BVOS[23] (n=139 eyes)**
Population	Mean age: 67.5 (0.5mg) Mean age: 65.2 (sham) 54/2% male(0.5mg) 56.1% male (sham)	Mean age 69.5±6.8 60.3% male Baseline BCVA:	Median age: 60-69 years (treatment) Median age : 60-69 (no treatment) 49% male (treatment) 52% male (no treatment)
Study design	Randomised placebo controlled double blind trial of ranibizumab vs. sham. All patients could receive rescue laser therapy during months 3-6.	Randomised controlled trial of laser photocoagulation versus no treatment. Few details reported on study methods but it does not seem to report an ITT analysis. The authors note that their study was not large enough to draw definite conclusions.	Randomised controlled trial of laser photocoagulation versus no treatment
Duration	6 months (followed by 6 months observation)	24 months	36 months (average follow-up)
Endpoints	BCVA change from baseline at 6, 12 months. BCVA gaining > 15 letters at 6, 12 months.	Improvement of BCVA for 2 lines Visual acuity decrease	Improvement of BCVA of 2 lines
Inclusion criteria	≥ 18 years of age foveal centre–involved macular oedema secondary to BRVO. BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts of 20/40 to 20/400 (Snellen equivalent) and a mean central subfield thickness ≥ 250 µm on two optical coherence tomography (OCT) measurements (at screening and Day 0) in the study eye.	Recent occurrence of BRVO within 15 days, significant macular oedema and visual acuity less than 0.6	Documented branch vein occlusion for at least 3 months Visual acuity was 20/40 or less Macular oedema identified by fluorescein angiography.
Exclusion criteria	History of cerebral vascular accident or myocardial infarction within 3 months prior to Day 0; History of any anti−VEGF treatment in fellow eye within 3 months prior to Day 0; uncontrolled blood pressure; pregnancy; For study eye: prior episode of RVO in study eye; a detailed list of other ocular diseases and treatments received; history of any anti-VEGF treatment	Media opacities, previous laser treatment, previous surgical therapy, other retinal pathology	

Ranibizumab vs. bevacizumab for BRVO

An assessment was made as to whether the ranibizumab BRAVO study[25] could be compared to the Moradian study[72, 81] of bevacizumab via sham treatment.

In terms of study design the studies are similar as they are randomised, double-blind sham-controlled studies. However, the Moradian study is much smaller than BRAVO (81 participants compared to 397), the mean age of the patients differs (67.5 and 65.2 years in BRAVO compared to 57.6 in Moradian) and the mean duration of MO was far less. Moradian and colleagues randomised patients with acute BRVO (less than 3 months duration) resulting in a mean duration of symptoms of 7.5 (SD 4.8) *weeks* in bevacizumab patients and 4.9 (SD 3.2) *weeks* in the sham group (compared to a mean duration of 3.3 months (SD 3.1) and 3.7 months (SD 3.7) in BRAVO). Patients with shorter duration of MO are expected to experience better outcomes to treatment. Also of note, more than 20% of patients included in the Moradian study presented with foveal ischaemia. Less than 1% of patients in BRAVO were ischaemic.

Therefore the published data for bevacizumab and ranibizumab in BRVO are not sufficiently homogenous with respect to the included patients in order to conduct an unbiased indirect comparison.

Importantly, the Moradian study is much shorter than the BRAVO study (12 weeks compared to 12 months).[72] Patients enrolled in this study received only 2 injections of bevacizumab, 6 weeks apart. It is unclear whether the study will report any results for a greater duration of treatment or follow up than 12 weeks, as the results at 12 weeks were not significantly different between groups. The longer term safety and efficacy of repeated bevacizumab injections cannot therefore be determined from this trial. .

Finally, Moradian and colleagues do not state whether an intention to treat analysis was performed and the number of withdrawals was not stated (Section 9.5, Appendix 5). This generates potential for bias in the study with implications for bias in any indirect comparison to ranibizumab.

The BRAVO study was also compared to the Russo study of bevacizumab, for a potential indirect comparison via laser treatment (Table B30). In terms of study design the studies are rather different: BRAVO is a randomized, double-blind controlled study whereas Russo is a quasi-randomised unblinded study and there is the potential for bias in patient allocation. Furthermore, the Russo study is much smaller than BRAVO (30 participants compared to 397). Given the small size of the

Russo study it is likely that the trial was underpowered meaning that the significant results could be due to chance

It is also important to note that mean CFT at baseline was higher in the Russo study, compared to BRAVO (690 µm vs. 552 µm, in the bevacizumab and ranibizumab arms respectively). Mean BCVA at baseline was also lower in the Russo population; 0.87 logMAR which is equivalent to approximately 45 ETDRS letters. Mean BCVA at baseline in the ranibizumab-treated patients was 53 letters. These data suggest important clinical heterogeneity between the two populations that would influence outcome.

The studies have the same follow-up period (12 months). Patients in the bevacizumab study could receive a 1.25 mg intravitreal injection of bevacizumab at baseline, repeated at months 0, 1, 3, 6 and 12 if macular oedema was unresolved (based on OCT measurement only). However, this differs to the BRAVO study, and moreover to expectations of management of BRVO patients in UK clinical practice, where patients will receive continued treatment driven primarily by BCVA outcomes.

Table B30 Key study features of ranibizumab and bevacizumab studies for the treatment of BRVO

	BRAVO (Campochiaro[25]) 0.5mg (n=397)	**Moradian[72, 81] (n=81)**	**Russo[73] (n=30)**
Population	Mean age: 67.5 (0.5mg) Mean age: 65.2 (sham) 54/2% male(0.5mg) 56.1% male (sham)	Mean age 57.6 ±9.8 (34-81) 42% male 13 patients had diabetes, 35 had hypertension and 25 had hyperlipidaemia. Patients in the treatment group had experienced symptoms for mean 7.5 weeks (2-12) and 4.9 weeks for sham group (1-12)	65.2 (laser) 64.6 (bevacizumab) 73% male (laser) 80% male (bevacizumab)
Study design	Randomised placebo controlled double blind trial	Randomised placebo controlled double blind trial	Quasi-randomized controlled trial. Not blinded.
Duration	12 months	3 months	12 months
Endpoints	BCVA follow up @ 6, 12 months. BCVA losing <15 letters @ 6, 12 months. BCVA gaining > 15 letters @ 6, 12 months. In the economics model=2 lines (10 letters)	Improvement in logMAR (presented in a conference poster)	BCVA: Improvement in logMAR BCVA gaining more than 15 letters Change in macular thickness Treatment complications
Inclusion criteria	≥ 18 years of age foveal centre–involved macular oedema secondary to BRVO. BCVA using Early Treatment Diabetic Retinopathy Study (ETDRS) charts of 20/40 to 20/400 (Snellen equivalent) and a mean central subfield thickness ≥ 250 µm on two optical coherence tomography (OCT) measurements (at screening and Day 0) in the study eye.	Patients with acute BRVO (<3 month duration) and BCVA =<20/50	Patients with BRVO (at least 3 months duration), macular leakage and logMAR EDTRS BCVA =<0.4; BCVA =<20/50. CMT at least 300µm
Exclusion criteria	History of cerebral vascular accident or myocardial infarction within 3 months prior to Day 0; History of any anti−VEGF treatment in fellow eye within 3 months prior to Day 0; uncontrolled blood pressure; pregnancy; For study eye: prior episode of RVO in study eye; a detailed list of other ocular diseases and treatments received; history of any anti-VEGF treatment	Patients with one eye, surgical candidate eyes, intraocular surgery in past 6 months, macular thickening less than 250 µ by OCT, BCVA >= 20/40, ocular media haziness precluding evaluation by OCT and funduscopy, any new vessel formation, accompanying arterial obstruction, signs of chronicity (vascular shunts), other macular diseases affecting central vision, pregnancy, incompliance, uncontrolled hypertension or any recent history of MI or CVA within the past 6 months	Diabetic retinopathy; age-related macular degeneration; previous cataract surgery

Non-RCTs for bevacizumab

Due to the lack of appropriate RCT data for bevacizumab, a systematic review was performed to identify non-RCT evidence which may offer evidence of relative effectiveness (See Appendix 20, Section 10.8 for further details of the review methodology). Although 18 non-RCT studies were identified that investigated bevacizumab in the treatment of MO secondary to RVO (either CRVO or BRVO), the quality of all the studies was low (**Error! Reference source not found.** in Appendix 20). The major limitations identified were that all studies were of a very small sample size (range 8 to 61 eyes), giving low power, and none were controlled (9 were uncontrolled before-and-after studies and 9 were uncontrolled case series, although study designs were often unclear). Two studies (Funk 2009[82] and Park 2009[83]) contained control participants who only provided reference samples for analysis and were not monitored for clinical effects such as visual function; these studies were therefore not considered to be controlled trials with respect to the decision problem. Furthermore, the majority of studies (12 studies, 67%) evaluated single injections, with some reporting re-injections for patients meeting specific retreatment criteria; others studied two or three injections given at 6-week intervals. Follow-up time was generally short in the identified studies, with only 1 study reporting follow-up of longer than 12 months. Thus the studies do not offer evidence of the efficacy or effectiveness of one defined dosing regimen, likely to reflect clinical practice, or evidence of longer term outcomes. Importantly, adverse event measurement was generally not pre-specified, systematic or fully reported. It is therefore difficult to draw conclusions with respect to safety or efficacy of bevacizumab from these studies, and unfeasible to determine relative effectiveness versus ranibizumab.

The non-RCT systematic review purposefully excluded retrospective studies, as these are considered to be unreliable forms of observational evidence. This approach is consistent with the systematic review protocol developed by the Southampton Health Technology Appraisal Centre for their exploration of evidence for bevacizumab across eye conditions.[84] However, the PACORES retrospective dose comparison study for bevacizumab in CRVO and BRVO was highlighted by the Evidence Review Group during a different appraisal for this indication. Retrospective studies are flawed with regards to the evidence that they provide for comparative efficacy because of the limitations arising from sampling bias and dependency on accurate historical reporting. The PACORES study was uncontrolled, was not highly powered (86 CRVO eyes, of which only 44 received 1.25 mg bevacizumab) and

selection bias may have occurred due to the inclusion criteria of a minimum of 24 months follow up .[85] The PACORES study also has limited applicability to the UK, as retreatment criteria were based solely on CFT rather than VA outcomes, and the as-needed dosing schedule used throughout the study may have resulted in under-treatment.[85] Therefore, the PACORES study was not deemed to provide adequate evidence for the efficacy of bevacizumab to be informative to the decision problem in the absence of good RCT evidence.

5.8 Non-RCT evidence

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

Summary of Non-RCT Evidence

- One pivotal non-RCT (Campochiaro 2008/2010) of medium quality provided data on two year experience with ranibizumab in RVO.
- Ranibizumab treatment was found to provide long-term benefits to patients with MO secondary to RVO, particular for patients with MO secondary to BRVO:
    - For BRVO patients (N=17) the mean improvement in BCVA from baseline at month 24 was 17.8 letters (compared with 15.6 letters at month 3).
    - For CRVO patients (N=14) the mean improvement in BCVA from baseline at month 24 was 8.5 letters (compared with 12.0 letters at month 3).

5.8.1 If non-RCT evidence is considered (see section 5.2.7), please repeat the instructions specified in sections 5.1 to 5.5 for the identification, selection and methodology of the trials, and the presentation of results. For the quality assessments of non-RCTs, use an appropriate and validated quality assessment instrument. Key aspects of quality to be considered can be found in 'Systematic reviews: CRD's guidance for undertaking reviews in health care' (www.york.ac.uk/inst/crd). Exact details of the search strategy used and a complete quality assessment for each trial should be provided in sections 9.6 and 9.7, appendices 6 and 7.

Search strategy

The search strategy used to identify RCTs outlined in Section 5.1.1 and 9.2 (appendix 2) did not include search terms that limited the search results to RCTs only. This was to ensure that all studies that reported adverse events were identified. Therefore non-RCTs for ranibizumab in the treatment of visual impairment due to MO secondary to RVO were collected during the review of the search results.

Review and selection of non-RCTs

A full list, along with a description, of all the non-RCTs identified for ranibizumab in the indication under consideration can be found in Section 10.4, appendix 16. Pivotal non-RCTs to include in this submission were selected if they were deemed to add any valuable and additional evidence to what has been reported in ranibizumab RCTs. Such evidence would include long-term data (more than 1 year experience with ranibizumab) or data from a large cohort of patients (more than 500 patients).

These criteria selected one pivotal non-RCT: Campochiaro 2008/2010 (randomised, non-controlled, dose comparison Phase II study with 2 year data).[47, 48] The methodology, baseline characteristics and quality assessment for this non-RCT are described in Section 10.5, Appendix 17.

Results of the relevant non-RCT (Campochiaro 2008/2010[47, 48])

3 month primary endpoint (Campochiaro 2008)

BRVO patients (N=20)

- At 3 months, the percentage of patients with an improvement of 15 ETDRS letters or more was 40% in the 0.3 mg ranibizumab group and 70% in the 0.5 mg ranibizumab group.
- At 3 months, the median improvement from baseline in BCVA was 10 in the 0.3 mg ranibizumab group and 18 in the 0.5 mg ranibizumab group.

CRVO patients (N=20)

- At 3 months, the percentage of patients with an improvement of 15 ETDRS letters or more was 70% in the 0.3 mg ranibizumab group and 40% in the 0.5 mg ranibizumab group.

- At 3 months, the median improvement from baseline in BCVA was 17 in the 0.3 mg ranibizumab group and 14 in the 0.5 mg ranibizumab group.

24 month long-term results (Campochiaro 2010)

Ranibizumab treatment was found to provide long-term benefits to patients with MO secondary to RVO, particular for patients with MO secondary to BRVO. Although patient level data is presented in the publication (Campochiaro 2010), no comparison is made between the two ranibizumab doses.

BRVO patients (N=17)

- For the 17 BRVO patients who completed 24 months follow-up, the mean improvement from baseline in BCVA at month 24 was 17.8 (±2.8) letters (compared with 15.6 letters at month 3). Using an ITT analysis, the mean improvement in BCVA at month 24 was also 17.8 letters.
- Improvement by at least 6, 3 or 2 lines by 24 months was achieved by 18%, 59% and 76% of patients, respectively.
- The Snellen equivalent BCVA at month 24 was 20/40 or better in 10 of 17 patients.
- BRVO patients had an average of 2 injections each in year 2 of the study.

CRVO patients (N=14)

- For the 14 CRVO patients who completed 24 months follow-up, the mean improvement from baseline in BCVA at month 24 was 8.5 (±14.8) letters (compared with 12.0 (±9.8) letters at month 3). Using an ITT analysis, the mean improvement in BCVA at month 24 was 9 letters.
- Of the 14 CRVO patients who completed 24 months follow-up, improvement by at least 6, 3 or 2 lines by 24 months was achieved by 14.4%, 28.6% and 42.9% of patients, respectively.
- The Snellen equivalent BCVA at month 24 was 20/40 or better in 4 of 14 patients.
- CRVO patients had an average of 3.5 injections each in year 2 of the study.

5.9 Adverse Events

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

Summary of Adverse Events

- Ranibizumab has been found to be safe and well tolerated in 765 patients with MO secondary to RVO in randomised clinical trials.
- The favourable safety profile for ranibizumab in patients with visual impairment due to MO secondary to RVO is similar to that previously seen in patients with wet AMD and DMO; the cumulative exposure from its launch in 2006 to 31 June 2010 is 751,000 patient-years
- In BRAVO, the incidence of ocular adverse events in the first 6-months was lower in the treatment groups than in the sham group (11 events (8.2%) in the 0.3 mg ranibizumab group and 7 events (5.4%) in the 0.5 mg ranibizumab group compared to 17 (13%) in the sham group).
- In CRUISE, the incidence of ocular adverse events in the first 6-months was also lower in the treatment groups than in the sham group (12 events (9.0%) and 12 events (9.3%) in the 0.3 mg and 0.5 mg ranibizumab groups, respectively, compared to 25 (19.4%) in the sham group).
- There was a low rate of raised intraocular pressure at the 6 month time point and low incidence of cataracts in both BRAVO and CRUISE and the extension studies.
- Serious thromboembolic events occurred in 1 patient in the 0.5 mg ranibizumab group and in 1 patient in the sham group in the first 6 months of the BRAVO trial. In CRUISE, one serious thromboembolic event occurred in each group in the first 6 months of the trial.
- Results from the 1-year open label extension study HORIZON reported a low incidence of serious adverse events (SAEs). The incidence of study eye SAEs and SAEs potentially related to systemic VEGF inhibition across treatment arms was 2%-9% and 1%-6%, respectively.

5.9.1 If any of the main trials are designed primarily to assess safety outcomes (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse event), please repeat the instructions specified in sections 5.1 to 5.5 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 9.8 and 9.9, appendices 8 and 9.

None of the main RCTs were designed primarily to assess safety outcomes.

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

BRAVO and CRUISE

Table B31 and Table B32 show the frequency of adverse events recorded in the BRAVO RCT (NCT00486018) at 6-months[25] and 12-months[61]. Table B33 and Table B34 show the frequency of adverse events recorded in the CRUISE RCT (NCT00485836) at 6-months[51] and 12-months[61].

In both studies adverse events were defined as any new sign, symptom, illness or worsening of any pre-existing medical condition recorded at each study visit. An adverse event was classified as serious if it led to death, was life threatening, required prolonged hospitalization, resulted in persistent or significant disability, resulted in a congenital anomaly/birth defect, or was considered a significant medical event by the investigator. The safety population was defined as those patients who had received at least one injection of ranibizumab or sham injection during the 6-month treatment period (BRAVO sham = 129, 0.3 mg = 132, 0.5 mg = 129) (CRUISE sham = 131, 0.3 mg = 134, 0.5 mg = 130), with treatment groups defined according to the treatment actually received. Patients who discontinued the study before the

12 month visit were encouraged to return for an early termination visit 30 days after their last injection or study visit to record adverse events (AEs) and serious adverse events (SAEs) that had occurred since.

Table B31 Frequency of adverse events at 6-months (BRAVO)

NCT00486018 BRAVO [25]	**Frequency of adverse events at 6-months, n (%) *(Relative risk [95% CI], risk difference)***		
	Sham (n = 131)	**0.3mg ranibizumab (n = 134)**	**0.5mg ranibizumab (n=130)**
Key Study Eye Ocular Adverse Events			
[redacted]	[redacted]	[redacted]	[redacted]
Any Intraocular Inflammation Event	4 (3.1)	2 (1.5)	0
Iridocyclitis	0	1 (0.7)	0
Iritis	4 (3.1)	1 (0.7)	0
Vitritis	0	0	0
Endophthalmitis	0	0	1 (0.8)[a]
Lens Damage	0	0	0
Cataract	4 (3.1)	1 (0.7)	4 (3.1)
Iris Neovascularisation	3 (2.3)	0	0
Neovascular glaucoma	0	0	0
Rhegmatogenous retinal detachment	0	1 (0.7)[a,b]	0
Retinal Tear	0	1 (0.7)[a,b]	0
Vitreous haemorrhage	6 (4.6)	6 (4.5)	2 (1.5)
Non-ocular serious adverse events potentially related to VEGF inhibition[9]			
Haemorrhagic stroke	1 (0.8)	0	1 (0.8)[c]
Ischaemic stroke	0	0	0
Acute myocardial infarction	0	0	1 (0.8)
Unstable angina	0	0	1 (0.8)
Hypertension	0	2 (1.5)	0
Nonocular haemorrhage, other	0	2 (1.5)[d]	1 (0.8)[e]
Intestinal perforation	0	0	1 (0.8)
Proteinuria	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events (Serious adverse events)			
Vascular death	0	0	1 (0.8)[f]
Nonfatal myocardial infarction	0	0	1 (0.8)
Nonfatal haemorrhagic stroke	1 (0.8)	0	0
Nonfatal ischaemic stroke	0	0	0

[a] Event was reported as serious
[b] The same patient had thegmatogenous retinal detachment and retinal tear which were both classified as serious
[c] There was one patient death in the 0.5 mg ranibizumab group from haemorrhagic cerebral stroke
[d] In the 0.3mg ranibizumab group there was one intra-abdominal haematoma and one rectal haemorrhage
[e] The non-ocular haemorrhage in the 0.5 mg ranibizumab group was dye to post procedural (colonoscopy) haemorrhage
[f] The incident of vascular death in the 0.5 mg ranibizumab group was also reported as haemorrhagic stroke potentially related to VEGF inhibition
[g] All non-ocular adverse events that were potentially related to VEGF inhibition were classified as serious

Table B32 Frequency of adverse events at 12 months (BRAVO)

NCT00486018 BRAVO[61]	Frequency of adverse events at one year, n (%)			
	Sham[a] (n = 131)	Sham/0.5mg[b] (n=115)	0.3mg ranibizumab (n = 134)	0.5mg ranibizumab (n=130)
Key Study Eye Ocular Adverse Events				
Any intraocular inflammation event (iridocyclitis, iritis, vitritis)	4 (3.1)	1 (0.9)	3 (2.2)	0
Endophthalmitis	0	0	0	1 (0.8)[c]
Cataract	4 (3.1)	3 (2.6)	6 (4.5)	8 (6.2)
Iris Neovascularisation	3 (2.3)	0	1 (0.7)	1 (0.8)
Neovascular glaucoma	0	0	0	0
Rhegmatogenous retinal detachment	0	0	1 (0.7)[c,d]	0
Retinal Tear	0	0	1 (0.7)[c,d]	0
Vitreous haemorrhage	6 (4.6)	1 (0.9)	7 (5.2)	2 (1.5)
Non-ocular serious adverse events potentially related to VEGF inhibition[g]				
Haemorrhagic stroke	-	1 (0.8)[e]	0	1 (0.8)
Ischaemic stroke	-	0	1 (0.7)	0
Transient ischaemic attack	-	0	0	0
Acute myocardial infarction	-	1 (0.9)	0	1 (0.8)
Angina pectoris	-	0	0	1 (0.8)[f]
Retinal artery embolism/occlusion	-	0	0	0
Hypertension	-	1 (0.9)	3 (2.2)	1 (0.8)
Nonocular haemorrhage	-	0	2 (1.5)	1 (0.8)
Intestinal perforation	-	0	0	1 (0.8)
Proteinuria	-	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events (Serious adverse events)				
Vascular death	-	0	0	0
Nonfatal myocardial infarction	-	1 (0.9)	0	1 (0.8)
Nonfatal haemorrhagic stroke	-	1 (0.8)[e]	0	1 (0.8)
Nonfatal ischaemic stroke	-	0	1 (0.7)	0

[a] Outcomes during 6-month treatment period for safety evaluable sham-group patients (i.e. received at least one sham injection during the treatment period)
[b] Outcomes during 6-month observation period for safety evaluable sham/0.5mg group patients (i.e. received at least one dose 0.5mg ranibizumab PRN during the observation period)
[c] Event was reported as serious
[d] The same patient had rhegmatogenous retinal detachment and retinal tear which were both classified as serious
[e] Event occurred during 6-month treatment period (sham n=131)
[f] Event was reported as unstable angina
[g] All non-ocular adverse events that were potentially related to VEGF inhibition were classified as serious

Table B33 Frequency of adverse events at 6 months (CRUISE)

NCT00485836 CRUISE [51]	Frequency of adverse events at 6-months, n (%) *(Relative risk [95% CI], risk difference)*		
	Sham (n=129)	**0.3mg ranibizumab (n=132)**	**0.5mg ranibizumab (n=129)**
Ocular Adverse Events			
[redacted]	[redacted]	[redacted]	[redacted]
Iridocyclitis	0	0	0
Iritis	3 (2.3)	2 (1.5)	2 (1.6)[c]
Vitritis	2 (1.6)	1 (0.8)	1 (0.8)[c]
Endophthalmitis	0	0	0
Lens Damage	0	0	0
Cataract	0	2 (1.5)	2 (1.6)
Iris Neovascularisation	9 (7.0)	2 (1.5)	1 (0.8)[a]
Neovascular glaucoma	2 (1.6)	0	0
Rhegmatogenous retinal detachment	0	0	0
Retinal Tear	0	0	0
Vitreous haemorrhage	9 (7.0)[b]	5 (3.8) (0.54 [0.19-1.58], 0.032)	7 (5.4) (0.78 [0.30-2.03], 0.016)
Non-ocular serious adverse events potentially related to VEGF inhibition[e]			
Haemorrhagic stroke	0	0	0
Ischaemic stroke	0	0	0
Transient ischaemic attack	0	0	1 (0.8)[d]
Myocardial infarction	1 (0.8)	1 (0.8)	1 (0.8)
Angina pectoris	0	0	1 (0.8)[d]
Hypertension	1 (0.8)	0	0
Nonocular haemorrhage, other	0	0	0
Proteinuria	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events			
Vascular death	0	0	0
Nonfatal myocardial infarction	1 (0.8)	1 (0.8)	1 (0.8)
Nonfatal haemorrhagic stroke	0	0	0
Nonfatal ischaemic stroke	0	0	0

[a] Event was reported as serious

[b] One vitreous haemorrhage was reported as serious in the sham group

[c] The same patient in the 0.5 mg ranibizumab group had both iritis and vitritis

[d] The same patient in the 0.5 mg ranibizumab group had both transient ischaemic attack and angina pectoris

[e] All non-ocular adverse events that were potentially related to VEGF inhibition were classified as serious

Table B34 Frequency of adverse events at 12 months (CRUISE)

NCT00485836 CRUISE[61]	Frequency of adverse events at one year, n (%)			
	Sham[a] (n=129)	Sham/0.5mg[b] (n=110)	0.3mg ranibizumab (n=132)	0.5mg ranibizumab (n=129)
Ocular Adverse Events				
Any intraocular inflammation event (iridocyclitis, iritis, vitritis)	5 (3.9)	2 (1.8)	3 (2.3)	2 (1.6)
Endophthalmitis	0	0	0	0
Cataract	0	2 (1.8)[c]	5 (3.8)	9 (7.0)
Iris Neovascularisation	9 (7.0)	2 (1.8)	2 (1.5)	5 (3.9)[c]
Neovascular glaucoma	2 (1.6)	0	0	1 (0.8)
Rhegmatogenous retinal detachment	0	0	0	0
Retinal Tear	0	2 (1.8)[c]	0	2 (1.6)
Vitreous haemorrhage	9 (7.0)[c]	2 (1.8)[c]	7 (5.3)	7 (5.4)
Non-ocular serious adverse events potentially related to VEGF inhibition				
Haemorrhagic stroke	-	0	0	0
Ischaemic stroke	-	0	0	1 (0.8)
Transient ischaemic attack	-	0	1 (0.8)	1 (0.8)[d]
Acute myocardial infarction	-	1 (0.8)[e]	1 (0.8)	1 (0.8)
Angina pectoris	-	0	0	1 (0.8)[d]
Retinal artery embolism/occlusion	-	0	1 (0.8)	0
Hypertension	-	1 (0.8)[e]	0	0
Nonocular haemorrhage	-	0	0	0
Intestinal perforation	-	0	0	0
Proteinuria	-	0	0	0
Antiplatelet Trialists' Collaboration arterial thromboembolic events				
Vascular death	-	0	0	0
Death of unknown cause		0	0	1 (0.8)
Nonfatal myocardial infarction	-	1 (0.8)[e]	1 (0.8)	1 (0.8)
Nonfatal haemorrhagic stroke	-	0	0	0
Nonfatal ischaemic stroke	-	0	0	1 (0.8)

[a] Outcomes during the 6-month treatment period for safety evaluable sham-group patients (i.e. received at least one sham injection during the treatment period)

[b] Outcomes during the 6-month observation period for safety evaluable sham/0.5mg group patients (i.e. received at least one dose 0.5mg ranibizumab PRN during the observation period)

[c] Iris neovascularisation was reported as serious in one patient in the 0.5 mg ranibizumab group

[d] The same patient in the 0.5 mg ranibizumab group had both transient ischaemic attack and angina pectoris

[e] Occurred during the 6-month treatment period (sham n=129)

HORIZON open-label extension study

Table B35 and Table B36 show the frequency of adverse events in the BRAVO and CRUISE arms of the HORIZON one year extension study.

Table B35 Frequency of adverse events in HORIZON one year extension study (BRVO patients from BRAVO)

NCT00379795 **HORIZON**	**Frequency of adverse events in one year follow-up of BRAVO, n (%)**		
	Sham/0.5mg (n=93)	**0.3mg ranibizumab (n=103)**	**0.5mg ranibizumab (n=104)**
Serious Ocular Adverse Events			
Any adverse event	2 (2.2%)	4 (3.9%)	6 (5.8%)
Amaurosis fugax	0	1 (1.0%)	0
IOP increased	0	1 (1.0%)	1 (1.0%)
Macular edema	0	0	2 (1.9%)
Macular ischaemia	0	1 (1.0%)	0
Ischaemic optic neuropathy	0	0	1 (1.0%)
Retinal vein occlusion	0	1 (1.0%)	1 (1.0%)
Visual acuity reduced	1 (1.1%)	0	1 (1.0%)
Vitreous haemorrhage	1 (1.1%)	1 (1.0%)	0
Ocular Adverse Events			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
Non-ocular Serious Adverse Events Potentially related to VEGF inhibition			
Any adverse event	1 (1.1%)	5 (4.9%)	6 (5.8%)
Hypertension	0	1 (1.0%)	1 (1.0%)
Acute coronary syndrome	0	0	0
Acute myocardial infarction	0	0	0
Amaurosis fugax	0	1 (1.0%)	0
Angina pectoris	1 (1.1%)	0	0
Cerebral haemorrhage	0	0	0
Cerebrovascular accident	0	0	1 (1.0%)
Intestinal ischaemia	0	0	0
Myocardial infarction	0	1 (1.0%)	1 (1.0%)
Transient ischaemic attack	0	3 (2.9%)	0
Non-ocular haemorrhage	0	0	3 (2.9%)[a]
Other potentially associated events	0	0	1 (1.0%)
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

Table B36 Frequency of adverse events in HORIZON one year extension study (CRVO patients from CRUISE)

NCT00379795 **HORIZON**	**Frequency of adverse events in one year follow-up of CRUISE, n (%)**		
	Sham/0.5mg (n=96)	**0.3mg ranibizumab (n=107)**	**0.5mg ranibizumab (n=99)**
Serious Ocular Adverse Events			
Any adverse event	5 (5.2%)	10 (9.3%)	3 (3.0%)
Cataract	0	1 (0.9%)	0
Cystoid macular edema	0	1 (0.9%)	0
Endophthalmitis	0	2 (1.9%)	0
IOP increased	0	1 (0.9%)	0
Macular oedema	1 (1.0%)	2 (1.9%)	2 (2.0%)
Ischaemic optic neuropathy	0	1 (0.9%)	0
Visual acuity reduced	3 (3.1%)	2 (1.9%)	1 (1.0%)
Visual acuity reduced transiently	0	1 (0.9%)	0
Vitreous haemorrhage	1 (1.0%)	0	0
Ocular Adverse Events			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
[redacted]			
Non-ocular serious adverse events potentially related to VEGF inhibition			
Any adverse event	3 (3.1%)	2 (1.9%)	6 (6.1%)
Hypertension	0	0	0
Acute coronary syndrome	0	0	1 (1.0%)
Acute myocardial infarction	0	1 (0.9%)	0
Amaurosis fugax	0	0	0
Angina pectoris	0	0	0
Cerebral haemorrhage	1 (1.0%)	0	0
Cerebrovascular accident	0	0	1 (1.0%)
Intestinal ischaemia	1 (1.0%)	0	0
Ischaemic stroke	0	0	1 (1.0%)
Transient ischaemic attack	0	1 (0.9%)	0
Non-ocular haemorrhage	2 (2.1%)[b]	0	2 (2.0%)[c]
Other potentially associated events	0	0	1 (1.0%)
[redacted]			
[redacted]			
[redacted]			
[redacted]			

[redacted]

ROCC

During the ROCC trial, in the ranibizumab group (n=15), 64 intravitreal injections were administered. One patient experienced a retinal artery thrombosis shortly after the first injection, and two patients experienced a small haemorrhage in the vitreous cavity attributable to vitreous traction, which resolved without further complications. In the sham group (n=14) one patient had a retinal tear and received laser photocoagulation, and one patient developed neovascular disease and received panretinal photocoagulation.

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

Ranibizumab has a favourable safety profile based on clinical data from several trials including patients with MO secondary to RVO, and also from its licensed use in treating wet AMD and DMO. The safety of ranibizumab has been demonstrated previously in a programme of clinical studies in patients with wet AMD (4562 treated patients in total) and DMO (795 treated patients in total), and through its licensed use worldwide in patients with wet AMD (cumulative exposure from its launch in 2006 to 31 June 2010, 751,000 patient-years) .[86, 87]

Systemic safety

In several large retrospective studies, ranibizumab has also been demonstrated to show a significantly improved safety profile compared to bevacizumab in the treatment of wet AMD.[44, 45, 88] Table B37 provides an overview of the methods of the studies and the adverse event rates, and particularly arterial thromboembolic events (ATEs).

The largest of these analyses, by Curtis and colleagues, indicates that compared to pegaptanib and photodynamic therapy, ranibizumab was not associated with increased risks of mortality, stroke, MI or bleeding. The outcome of a secondary analysis by Curtis et al., comparing ranibizumab with unlicensed intravitreal bevacizumab, showed a difference in the safety profiles between the two drugs with a significantly lower risk of both stroke and all-cause mortality with ranibizumab when compared to bevacizumab (Hazard Ratio (HR) 0.78; 99% CI, 0.64-0.96 and HR, 0.86; 99% CI, 0.75-0.98, respectively).

A recent study by Gower et al also found a significant increase in haemorrhagic stroke and all cause mortality rate when patients are treated with bevacizumab compared to ranibizumab (HR 1.57; 99% CI, 1.04 – 2.37 and HR 1.11; 99% CI 1.01 – 1.23).[88] Furthermore, a new safety signal has arisen from the recently published CATT trial indicating a significantly higher rate of hospitalizations due to serious adverse events in patients treated with bevacizumab (24.1%) compared to ranibizumab (19.0%) (RR 1.29, 95% CI 1.01

– 1.66).[89] These safety signals are consistent with the different systemic effects seen with ranibizumab and bevacizumab. Bevacizumab has been shown to suppress systemic plasma VEGF for at least a month after treatment (p=0.0002), while this has been demonstrated to not be the case with ranibizumab.[90] The plasma VEGF levels at 4 months following treatment differed significantly between patients treated with ranibizumab and bevacizumab (p=0.005), with the bevacizumab group showing a significant decrease compared to baseline. This indicates the higher systemic activity of bevacizumab compared to ranibizumab, which goes some way in explaining the higher risk of systemic adverse events with bevacizumab.

Importantly, the proportion of patients with diabetes at baseline was similar between the retrospective studies and the BRAVO and CRUISE studies. As would be expected given that AMD manifests in later life than RVO, the age of patients in BRAVO and CRUISE was lower than in the AMD studies. A comparison of other potential cardiovascular risk factors is difficult due to differences in definitions and reporting.

Table B37 Overview of retrospective studies comparing ranibizumab to bevacizumab in wet AMD

	Carneiro 2011[44]	**Curtis 2010[43]**	**Gower 2011[79] (Abstract only)**
Methods	Retrospective chart review of 378 patients diagnosed with a treated for neovascular AMD in a Portuguese hospital December 2006 to January 2010	Retrospective cohort study of 149,942 Medicare beneficiaries aged ≥ 65 years with a claim for AMD and treated with anti-VEGF therapy or photodynamic therapy (PDT) July 2006 to December 2006[a]	Retrospective study of 77 886 Medicare beneficiaries with 1+ neovascular AMD 2005 to 2009
Results[bc]	ATEs: Bevacizumab – 12.4% (12/97) Ranibizumab – 1.4% (3/219) Odds Ratio – 10.16 (2.80 – 36.93); P < 0.0001	**Primary analysis (adjusted)[a]** All cause mortality Hazard ratio – 0.85 (0.75-0.95) Incident myocardial infarction Hazard ratio – 0.73 (0.58-0.92) Bleeding Hazard ratio – 0.97 (0.88-1.07) Stroke Hazard ratio – 0.83 (0.69-0.99) Hazard ratio ranibizumab vs. PDT **Secondary analysis[a]** All cause mortality Bevacizumab – 4.7% (833/21,815) Ranibizumab – 4.1% (647/19,026) Hazard Ratio – 0.86 (0.75 – 0.98); P < 0.05 Incident myocardial infarction Bevacizumab – 1.3% (1793/21,815) Ranibizumab – 1.1% (1390/19,026) Hazard Ratio – 0.83 (0.64 – 1.08) Bleeding Bevacizumab – 5.6% (2403/21,815) Ranibizumab – 5.8% (2025/19,026) Hazard Ratio – 1.03 (0.92 – 1.16)	Overall mortality Hazard Ratio – 1.11 (1.01 – 1.23) Risk of haemorrhagic cerebrovascular accident Hazard Ratio – 1.57 (1.04 – 2.37) No statistically significant differences for myocardial infarction or ischaemic cerebrovascular accident Hazard Ratio bevacizumab vs. ranibizumab

		Incident stroke Bevacizumab – 2.2% (1893/21,815) Ranibizumab – 1.8% (1471/19,026) Hazard Ratio – 0.78 (0.64 – 0.96); P < 0.05 Hazard Ratio ranibizumab vs. bevacizumab	

[a] In primary analysis patients with higher socioeconomic status may have been more likely to receive these ranibizumab and bevacizumab therapies and therefore the primary analysis may have been subject to selection bias. The primary analysis did not identify a statistically significant relationship between treatment group and bleeding events or stroke. The secondary analysis of full study population (n=40,841) limited to newly treated patients who receive ranibizumab or bevacizumab.

[b] Underlining indicates a statistically significantly lower risk of the specific AE with ranibizumab vs. bevacizumab

[c] Hazard ratios and odds ratios presented with 95% confidence intervals for Carneiro 2011 and Curtis 2010. Hazard ratio for Gower 2011 presented with 99% confidence interval

The safety of ranibizumab has been studied in 765 patients with MO secondary to RVO in the BRAVO, CRUISE and ROCC trials. These trials supported a favourable safety profile for ranibizumab in patients with visual impairment due to MO secondary to RVO, indicating a similar safety profile to that in patients with wet AMD and DMO.

In BRAVO, the incidence of ocular adverse events was low in the ranibizumab groups, with 11 events (8.2%) in the 0.3 mg group and 7 events (5.4%) in the 0.5 mg group in the first 6-months, compared to 17 (13%) in the sham group.

- A retinal detachment and retinal tear occurred in the same patient in the 0.3 mg ranibizumab group.
- One patient in the 0.5 mg group discontinued the study after developing endophthalmitis, a recognized complication of intraocular injections.
- Cataract was reported in 4 patients in the sham injection group, 1 patient in the 0.3 mg ranibizumab group, and 4 patients in the 0.5 mg ranibizumab group.

There was a low incidence of raised intraocular pressure, reported in 2 patients in the sham injection group, 7 patients in the 0.3 mg ranibizumab group, and 7 patients in the 0.5 mg ranibizumab group.

The incidence of non-ocular serious adverse events potentially related to VEGF inhibition was low in all groups, with 1 (0.8%) in the sham group, 4 (3%) in the 0.3 mg group and 5 (3.8%) in the 0.5 mg group.

- One patient in the sham group had a haemorrhagic stroke.
- In the 0.3 mg ranibizumab group, 2 patients had hypertension, and 2 patients had nonocular haemorrhages: 1 intra-abdominal hematoma and 1 rectal haemorrhage.
- In the 0.5 mg ranibizumab group, there was 1 fatal cerebral haemorrhage, 1 nonfatal myocardial infarction, 1 unstable angina, 1 haemorrhage after colonoscopy, and 1 intestinal perforation in a patient with intestinal obstruction from adhesions.

Of these events, three qualified as serious thromboembolic events based on Antiplatelet Trialists' Collaboration criteria; a non fatal haemorrhagic stroke in the sham group and a fatal haemorrhagic stroke and nonfatal myocardial infarction in the 0.5 mg group.

The safety profiles of the 0.3 mg and 0.5 mg ranibizumab groups in the BRAVO trial over 12 months were consistent with previous phase III ranibizumab trials. There was a low incidence of serious adverse events reported in the 6-month observation period.

- There was one incidence of nonfatal myocardial infarction in the sham/0.5 mg group, 1 incidence of ischaemic stroke in the 0.3 mg group and 1 incidence of haemorrhagic stroke in the 0.5 mg group.
- There was 1 case of hypertension reported in each group

In CRUISE , the incidence of ocular adverse events was low in the ranibizumab groups, with 12 events (9%) in the 0.3 mg group and 12 events (9.3%) in the 0.5 mg group in the first 6-months, compared to 25 (19.4%) in the sham group. There were no events of endophthalmitis, retinal tear, or retinal detachment during the 6-month treatment period.

- Two serious adverse events were reported, one vitreous haemorrhage in the sham group and one iris neovascularisation in the 0.5 mg group
- Iris neovascularisation and neovascular glaucoma were more common in the sham group compared to the ranibizumab groups.
- Cataracts were reported in 2 patients in the 0.3 mg group and 2 patients in the 0.5 mg group.

There was a low incidence of raised intraocular pressure, reported in 4 patients (3.1%) in the sham injection group, 11 patients (8.3%) in the 0.3 mg ranibizumab group, and 10 patients (7.8%) in the 0.5 mg ranibizumab group.

The incidence of non-ocular serious adverse events potentially related to VEGF inhibition was low in all groups, with 2 (1.6%) in the sham group, 1 (0.9%) in the 0.3 mg group and 3 (2.3%) in the 0.5 mg group. One non fatal myocardial infarction occurred in each group, which were defined as serious arterial thromboembolic events as defined by the Antiplatelet Trialists' Collaboration criteria.

The safety profiles of the 0.3 mg and 0.5 mg ranibizumab groups in the CRUISE trial over 12 months were consistent with previous phase III ranibizumab trials. The incidence of serious adverse events was low in the 6-month observation period.

- There was 1 death of unknown cause and 1 nonfatal ischaemic stroke in the 0.5 mg ranibizumab group.

Results from the 1-year open label extension study HORIZON study reported a low incidence of serious adverse events (SAEs). The incidence of study eye SAEs across all treatment groups ranged from 2% to 9%, and the incidence of SAEs potentially related to systemic VEGF inhibition across all treatment groups ranged from 1% to 6%.

[redacted]

5.10 Interpretation of clinical evidence

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

The efficacy and safety of ranibizumab in the treatment of visual impairment due to MO secondary to BRVO or CRVO has been established by two large, high quality RCTs, BRAVO and CRUISE. In BRAVO, laser was allowed based upon the precedent of the BVO Study (see Section 5.3.2) and in line with the RCO Guidelines for management of BRVO.[8, 23] Thus, the comparator arm in BRAVO is equivalent to UK standard of care incorporating laser therapy. In the absence of alternative drug therapy that is licensed and routinely available in the NHS, best supportive care (observation) is the standard of care for patients with CRVO with or without ischaemia. Thus, the comparator arm of CRUISE is also equivalent to UK standard of care.

Ranibizumab provides rapid, significant and clinically meaningful improvements in BCVA in patients with MO secondary to BRVO and CRVO compared to the control arm across a range of patients with varying baseline ocular characteristics.

- In the BRAVO study at Month 6, patients in the 0.5 mg ranibizumab group had gained a mean (95% CI) 18.3 (16.0 – 20.6) letters from baseline BCVA score, compared with a gain of only 7.3 (5.1 – 9.5) letters in the sham group (P<0.0001 for 0.5 mg ranibizumab vs. sham).
- Significantly greater improvements from baseline in mean BCVA letter score were observed with ranibizumab treatment as early as Day 7 (P<0.0001 vs. sham). Patients treated with ranibizumab experienced benefits in VA earlier than those in the sham group (whose treatment equates to standard care), which highlights the benefit of early treatment.
- An analysis of the usage of laser in the BRAVO trial demonstrated that the ranibizumab treated patients who used laser therapy during the 6-month treatment period (approximately 20% of patients) did not attain the same level of BCVA gains as those who did not need or receive laser treatment (see Appendix 19, Section 10.7 for full details).[48]
- In the CRUISE study at month 6, patients in the 0.5 mg ranibizumab treatment group had gained a mean of 14.9 (95% CI: 12.6 – 17.2) letters from baseline BCVA score, compared with the sham treatment group, where no statistically significant change in mean BCVA was observed at 6 months, 0.8 (-2 to 3.6) (P<0.0001 for 0.5 mg ranibizumab vs. Sham injection).

- A gain of ≥ 10 letters in BCVA score is considered a clinically meaningful improvement in visual acuity.[91] In BRAVO, a significantly greater proportion of patients receiving 0.5 mg ranibizumab (76.3%) experienced a gain in BCVA of 10 letters or more during the 6-month treatment phase of the study compared with only 38.6% of patients who were randomised to receive sham-injection. In CRUISE, a significantly greater proportion of patients receiving 0.5 mg ranibizumab (70.8%) experienced a gain in BCVA of 10 letters or more during the 6-month treatment phase of the study compared with only 25.4% of patients who were randomised to receive sham-injection (P<0.00001 for 0.5 mg ranibizumab vs. sham).
- Many of the patients receiving ranibizumab achieved clinical stability with good BCVA before the 6 month time point (45% in CRUISE 0.5 mg arm and 51% in BRAVO 0.5 mg arm).[64] The RCTs may therefore overestimate the amount of treatment necessary to achieve a stable (over 3 months) clinical outcome.

Ranibizumab significantly improves patient vision-related functioning, as assessed by the NEI VFQ-25 (a validated test that measures the impact of visual function on activities of daily life) compared to sham injection in patients with MO secondary to BRVO and CRVO. Improvements in functioning were reported despite treatment being predominantly in the worse seeing eye in these studies.

- In BRAVO, treatment with ranibizumab was associated with nearly twice as much improvement at month 6 on the NEI VFQ-25 than that observed in the sham injection-treated group.
- In CRUISE the observed improvement (mean improvement [95% CI]) at month 6 from baseline in the NEI VFQ-25 composite score was significantly greater in patients treated with ranibizumab 0.5 mg (6.2 [4.3 – 8.0] points) than in patients treated with sham injection (2.8 [0.8 – 4.7] points, P<0.05 for 0.5 mg ranibizumab vs. sham).

The extension study to both of these trials, HORIZON (Cohort 2), has demonstrated that the clinical benefits of ranibizumab can be maintained through 2 years when it is administered on an as-needed basis. The effect of treatment was sustained despite a lower frequency of injections in the second year of treatment

- The BRAVO and CRUISE studies consisted of a 6-month controlled treatment phase, followed by a 6-month uncontrolled observation phase during which all study participants could receive ranibizumab PRN. Improvements in visual acuity achieved in the ranibizumab groups at Month 6 were maintained, on average, through Month

12. For subjects initially randomised to sham treatment (who could receive 0.5 mg ranibizumab from months 6 to 12), improvements in visual acuity and patient-reported outcomes were observed, on average, during the 6-month observation period. However on average, patients in the sham/0.5 mg group gained fewer letters from baseline by Month 12 than those patients in the ranibizumab treatment groups indicating that early treatment with ranibizumab is preferable.

- The HORIZON (Cohort 2) trial was an open label follow up to BRAVO and CRUISE. The results from the first 12-months of this study suggest that the PRN dosing and quarterly follow-up used during the trial were adequate to maintain visual gains in those patients with MO secondary to BRVO, as BCVA scores remained relatively stable (within approximately ± 2 letters of baseline) over the 12 months. After the first 12 months of the HORIZON study, a slight decrease in BCVA score was seen from HORIZON baseline in patients who had previously participated in CRUISE. This could indicate that different frequency of assessment for PRN dosing are required by CRVO patients to maintain the marked clinical benefits in visual acuity observed after 12 months of ranibizumab treatment.

Ranibizumab has been found to be safe and well tolerated in over 750 patients with MO secondary to RVO in clinical trials:

- Ocular adverse events occurred at a lower frequency in the ranibizumab treatment arms of the BRAVO and CRUISE studies than in the sham arm during the 6 month treatment period.
- The incidence of cataract, elevated IOP and glaucoma was low in the BRAVO and CRUISE studies.
- Serious thromboembolic events occurred in 1 patient in the 0.5 mg ranibizumab group and in 1 patient in the sham group in the first 6 months of the BRAVO trial. In CRUISE, one serious thromboembolic event occurred in each group in the first 6 months of the trial.

The favourable safety profile for ranibizumab in patients with visual impairment due to MO secondary to RVO is similar to that seen previously in patients with wet AMD and DMO.

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

Strengths of the clinical-evidence base

The major strength of the clinical evidence base for ranibizumab in the indication under consideration in this submission is that there is a high quality RCT for both BRVO and CRVO subgroups of patient. The BRAVO trial (N=397) was a large, adequately randomised, sham controlled trial in BRVO patients with MO, which had little risk of bias and thus reliable results.[25] Furthermore, BRAVO protocol permitted patients to receive laser therapy if necessary and thus reflects standard of care in clinical practice. The CRUISE study (N=392) enrolled patients with MO secondary to CRVO, but had the same study design as BRAVO (apart from the fact that laser treatment was not permitted).[24] It is of paramount importance that BRVO and CRVO patients are considered separately, as the two indications have differing severities and prognoses.[27, 28]

Additionally, there is long term data available that supports the use of ranibizumab for the treatment of visual impairment due to MO secondary to RVO into year 2, for those patients who still require treatment. The HORIZON study was the extension of both BRAVO and CRUISE, and reported 12 month visual outcomes data (24 months from BRAVO/CRUISE baseline) by the original randomisation groups in BRAVO and CRUISE.[3] Campochiaro 2008/2010 was a much smaller blinded Phase II study, which randomised patients to 0.3 mg or 0.5 mg ranibizumab, but did not have a control arm.[48] Nonetheless, the 24 month results from this study are still valuable to the decision problem.

Subgroup data was available for three of the categories specified in the original scope (type of RVO, baseline visual acuity and duration of MO). Although some of the sub groups were quite small for baseline visual acuity and duration of MO, the differences in visual acuity outcomes between the ranibizumab groups and the sham group were still obvious.

Limitations of the clinical-evidence base

The main clinical-evidence base is limited to only one large RCT for both BRVO and CRVO indications. The ROCC study (N=32), which included only CRVO patients with MO, was small compared to CRUISE.

Regarding long term data, there is no evidence available yet of ranibizumab treatment beyond 2 years for visual impairment due to MO secondary to RVO. This data is currently being collected in the second 12 months of the HORIZON study (although few patients are

likely to be followed for the full 24 months) and in the RETAIN study (NCT01198327), which takes patients after they have completed the HORIZON study.

The existing 2 year data for ranibizumab in the treatment of visual impairment due to MO secondary RVO may have some risk of bias for the following reasons:

- The HORIZON extension study only enrolled patients who had completed 12 months of BRAVO and CRUISE. Thus patients who withdrew from BRAVO and CRUISE were not represented in the long term results. Considering the reasons why patients withdrew from BRAVO and CRUISE (see Section 5.3.8), it is unclear what characteristics these patients had in terms of VA and prognosis. If they withdrew because their condition had stabilised, then the efficacy of ranibizumab in the long term follow up study HORIZON may have been underestimated. However, if the patients withdrew due to lack of efficacy, HORIZON would be likely to overestimate the true efficacy if ranibizumab in a general population.

- The HORIZON study was primarily a safety study and therefore limitations in the trial methodology mean that robust conclusions on efficacy are limited.

- The Phase II study that provided 2 year results, Campochiaro 2008/2010, was very small compared to HORIZON and was also uncontrolled in the initial stages. Thus it is hard to reliably attribute the improvement in VA over 2 years to the intervention, as the underlying course of the disease of the patients in the study in unknown.

In terms of subgroup analysis, there was no data available for the following subgroups: ischaemic vs. non ischaemic patients, perfusion at the back of the eye and damage to the central fovea. The common definition of ischaemia used in RVO is based on perfusion: a case of greater than 10 fluorescein angiography disc areas of capillary non-perfusion is classed as ischaemia.[22] Although this characteristic was measured at baseline in BRAVO and CRUISE, very few patients actually fulfilled this definition of ischaemia (0 in BRAVO and 2 in CRUISE). This is likely due to the fact that patients with brisk afferent pupillary defect, which equates to severe ischaemia, were excluded from the trials.

There is no direct evidence for ranibizumab versus other drug therapies. Additionally, differences in the inclusion criteria, patient characteristics, and fundamental aspects of study design between trials prohibited indirect comparison of ranibizumab to any comparator (see Section 5.7).

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

The clinical-evidence base, provided mainly by the BRAVO and CRUISE trials in BRVO and CRVO patients respectively, reports the outcomes that are highly relevant to patients in clinical practice and thus are relevant to the decision problem. Visual acuity outcomes are the most relevant to patients in clinical practice, as it is the visual impairment associated with the condition that is the most debilitating symptom. The measurement of functioning associated with vision in the clinical trials demonstrates the real impact that improved vision has on patients lives. This is a good indicator of the quality of the patient's life.

The only outcome that was specified in the original scope but was not measured in the pivotal RCTs was visual acuity of the whole person. The BCVA of a whole person with one very good better-seeing eye (BSE) and one very poor worse-seeing eye (WSE) would be very different from a person where both BSE and WSE are similar. Therefore, the unilateral BCVA measures used in these RCTs would not be representative of the BCVA of the whole person. However, the measurement of vision-related functioning (using the NEI VFQ-25, for example) is an indirect measure of the level of overall vision experienced by a person and represents a good surrogate for the benefits to the patient in terms of the 'whole person'.

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

Conduct of the trials

Both the BRAVO and CRUISE studies investigated the licensed dose of ranibizumab (0.5 mg). They also investigated a lower dose of 0.3 mg and thus half of the evidence base is for the dose of ranibizumab given in the SPC.

The dosing schedule used in the pivotal RCTs was not exactly as is set out in the draft SPC, which states that monthly dosing should continue until VA is stable for 3 consecutive months

(see SPC, Section 9.1, appendix 1). For the RCTs, it was important that all patients were dosed exactly the same for 6 months. However, considering that many of the patients achieved clinical stability with good BCVA before the 6 month time point (45% in CRUISE 0.5 mg arm and 51% in BRAVO 0.5 mg arm)[64], the RCTs may overestimate the necessary amount of treatment. In clinical practice, based on clinical opinion, it would be expected that those patients who reach clinical stability before 6 months would interrupt ranibizumab treatment. Observational studies can be used to determine the efficacy of the recommended dosing pattern, which is tailored to the individual patient right from the start of ranibizumab treatment.

The BRAVO trial protocol included the important aspect of allowing laser photocoagulation therapy for those patients who required it. In the control arm, this reflects the decisions that would be made in clinical practice for such patients and thus means that BRAVO had good external validity in terms of study conduct. Subsequent analysis of the BRAVO trial results has demonstrated that the receipt of laser therapy by approximately 20% of patients in the ranibizumab arms did not inflate the efficacy results for ranibizumab, as these patients experienced lower BCVA gains on average than those who did not receive laser therapy (see Appendix 19, Section 10.7 for full details).[50] In UK clinical practice, it may be expected that the patients who responded poorly to ranibizumab cease treatment at 3 months (in line with the expected posology). Furthermore, in UK clinical practice, as ranibizumab and laser therapy are not currently recommended as combination therapies by the RCO this regimen is unlikely to be employed.[6] Laser photocoagulation is not recommended for CRVO patients with MO and thus the protocol of CRUISE did not allow laser therapy, in keeping with clinical practice.

Inclusion and exclusion criteria

The following inclusion and exclusion criteria utilised in both BRAVO and CRUISE were necessary in order for the RCTs to enrol a homogenous population in which treatment effects could be observed. However they may have reduced the external validity of the trial population:

- The RCTs only included patients with a diagnosis of CRVO or BRVO within the 12 months prior to study initiation. Patients with very chronic MO due to CRVO or BRVO, of more than 12 months duration, were therefore excluded. However, this type of patient will become increasingly rare in clinical practice due to the new paradigm to treat the condition early with pharmacological agents, thus preventing chronic MO due to RVO developing.[6] In addition, irreversible vision loss may have

occurred in a proportion of patients who had MO for more than 12 months MO, and these patients would therefore be ineligible for treatment.[6]

- Patients who had experienced a prior episode of RVO were excluded from the BRAVO and CRUISE. There is no experience of ranibizumab treatment in these patients. Recurrence of RVO is a very rare event and therefore this is not likely to have a major impact on the interpretation of the results.

- BRAVO and CRUISE excluded patients with brisk APD, which equates to severe ischaemia. Although these patients may be seen in clinical practice, the recent RCO guidelines do not recommend pharmacological treatment for patients with ischaemic CRVO or BRVO, and thus the patients excluded from the RCTs would probably not receive treatment if seen in clinical practice.

- Patients who had experienced previous treatment for RVO in the months leading up to study initiation (corticosteroid treatment with 3 months prior to day 0, panretinal scatter photocoagulation within 3 months prior to day 0, laser photocoagulation for MO within 4 months prior to day 0, prior anti-VEGF treatment in study eye within 3 months prior to day 0 or systemic anti-VEGF within 4 months prior to day 0) were excluded. Such patients would be eligible to receive ranibizumab treatment in clinical practice.

6 Cost effectiveness

Summary of cost effectiveness

- The cost effectiveness of ranibizumab in MO secondary to BRVO and CRVO was based on a Markov model with patients moving between eight different health states of BCVA and a ninth state of death.
- In BRVO the cost effectiveness of ranibizumab was compared to laser therapy, which represents standard of care in this patient population.
- In CRVO the cost effectiveness of ranibizumab was compared to observation, which represents standard of care in this patient population.
- Utilities were applied to each visual acuity state in order to generate quality-adjusted life years. The base case analysis uses utility data drawn from utilities for the better-seeing eye from Brown 1999.[1] The utilities for the worse-seeing eye from this paper were illogical and therefore the WSE utilities could not be modelled.
- The adverse events of cataracts, IOP and stroke were incorporated into the model. The rates of cataract and IOP were taken from the pivotal clinical trials and the rate of stoke was assumed to be equivalent for all treatments. For ranibizumab the cost of adverse events for 1000 RVO patients over a 15 year time horizon was £61, compared to £5 for laser, £5 for observation and £152 for dexamethasone implant.
- For BRVO, the base case ICER for ranibizumab compared to standard care (laser) was £24,610 per QALY gained. For CRVO, the base case ICER for ranibizumab compared to standard care (observation) in CRVO was £11,428 per QALY gained.
- The base case ICERs for ranibizumab compared to dexamethasone implant were £10,883 (giving extended dominance) for BRVO and £12,027 for CRVO, but these must be interpreted with caution as the sensitivity analysis showed that these results were highly sensitive to changes in efficacy of either agent.
- For BRVO, the probability of ranibizumab being cost-effective compared to standard of care (including laser therapy) at a willingness to pay (WTP) threshold of £20,000 was 42.0%, and at a WTP threshold of £30,000 was 56.6%. For CRVO, the probability of ranibizumab being cost-effective compared to best supportive care at a WTP threshold of £20,000 was 60.9%, and at a WTP threshold of £30,000 was 80.0%.
- The direction of the deterministic sensitivity analysis results follows prior expectation: decreasing the effectiveness of ranibizumab, increasing natural deterioration of vision, decreasing the cost of blindness or increasing the frequency of ranibizumab injections increases the ICER.

6.1 Published cost-effectiveness evaluations

Identification of studies

6.1.1 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 9.10, appendix 10.

A systematic review was performed to identify published economic literature in the treatment of visual impairment due to MO secondary to RVO. The electronic databases searched in November 2010 were: MEDLINE, MEDLINE In-Process, EMBASE, NHS Economic Evaluation Database (NHS EED), Health Economic Evaluation Database (HEED), EconLit, Research Papers in Economics (RePEc) and clinicaltrials.gov.

The search strategy combined search terms for 'macular oedema/retinal vein occlusion' with terms for the relevant interventions (see Table B38for interventions). This strategy was used to identify a range of evidence and was not limited by using a methodological search filter. The search was limited to English language studies, and no date limits were applied. Full details of the search strategies are provided in Section 9.10, Appendix 10.

The search results were then assessed against the inclusion and exclusion criteria (Table B38 below) independently by two reviewers and any disagreements were resolved through reconciliation or arbitration.

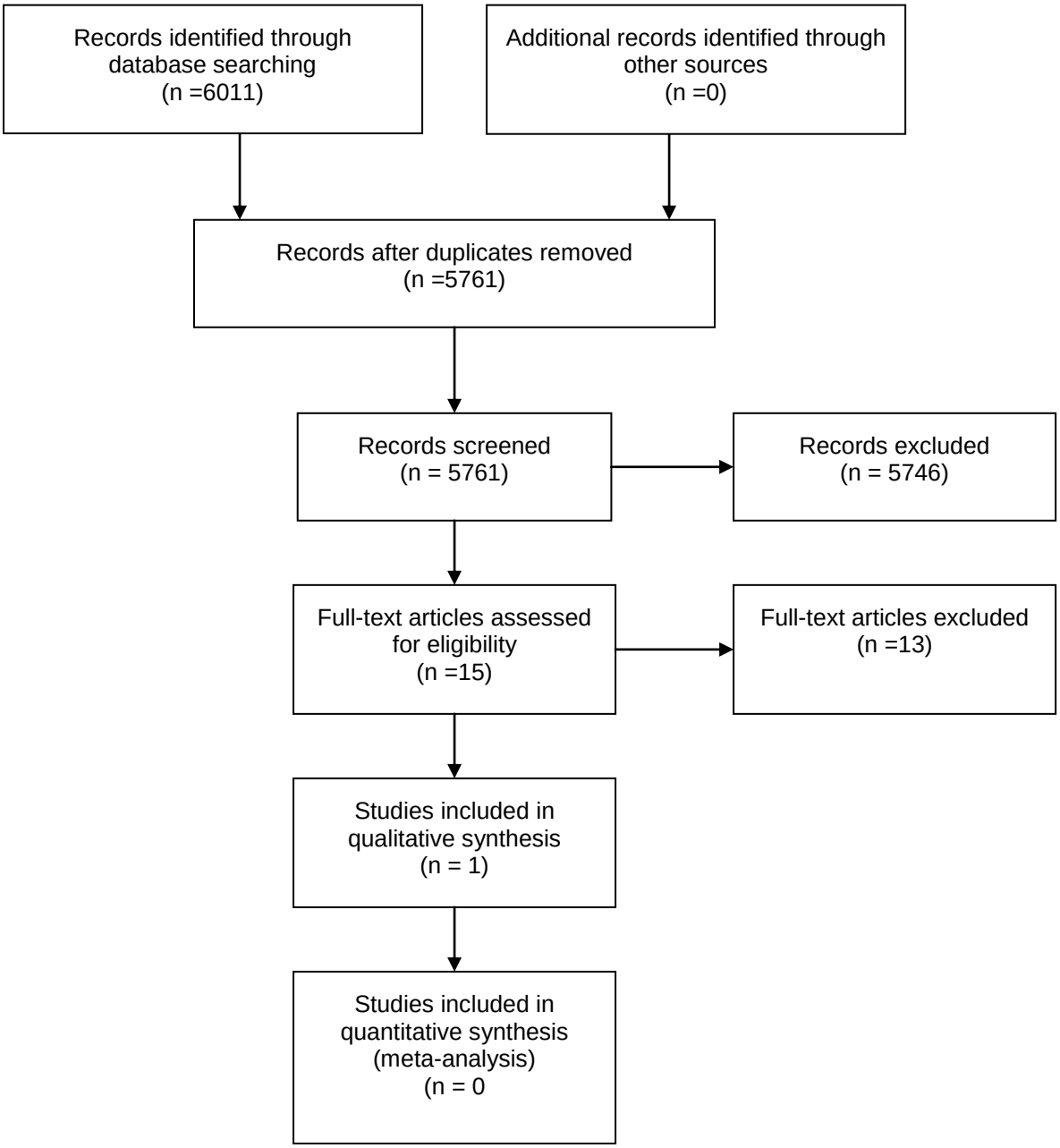
Table B38 Inclusion and exclusion criteria used to identify relevant cost-effectiveness studies

Inclusion Criteria	Exclusion Criteria
• Studies must be an economic evaluation (cost-minimisation, cost-effectiveness, cost-utility or cost-benefit analysis) • Studies must assess either ranibizumab (Review 1) or laser, dexamethasone IVT implant, IVTA or bevacizumab (Review 2) for the treatment of MO secondary to RVO	• Studies where none of the interventions listed in the inclusion criteria are assessed

The review identified 6011 search results, of which 5761 remained after deduplication (Figure B15). Fifteen articles were identified as potentially relevant based on their titles and abstracts and their full texts were assessed. Only one cost-effectiveness study (Brown et al. 2002[92]) was identified, which was a cost-utility analysis that compared the incremental cost-effectiveness of laser therapy versus no treatment for vision loss associated with BRVO.

No cost-effectiveness studies or cost-utility models that include ranibizumab as a study drug were identified. It can be concluded, therefore, that there is not yet any published literature on the cost-effectiveness of ranibizumab in the treatment of visual impairment due to MO secondary to RVO and thus no studies on the cost-effectiveness of ranibizumab are presented in the following Sections 6.1.2 and 6.1.3.

Figure B15 Article flow for cost-effectiveness systematic review



Description of identified studies

6.1.2 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.

One cost-utility study was identified: Brown et al. (2002).[92] Brown was undertaken by health economics units based in the USA and Canada. No UK specific analyses were identified.

The purpose of the study was to ascertain the incremental cost-effectiveness of therapeutic interventions for improving visual loss associated with BRVO. The cost-utility analysis compared the incremental cost-effectiveness of laser therapy versus no treatment, for MO occurring secondary to BRVO. The authors did not state the perspective of the analysis, but it is likely to be from the health care payer perspective. A Markov model was constructed using patient-based quality-adjusted life year (QALY) values obtained using the time trade off (TTO) method as the outcome and US Dollars (2000) as costs. The cost-effectiveness results were expressed as $/QALY. The model took into account the visual acuity in the 'better seeing' eye (BSE) and the recurrent risk for visual loss in the contralateral eye. The main source of the effectiveness and utility data were the BVOS Group.[23] Direct costs were included in the analysis. However, only costs of laser photocoagulation and fluorescein angiography were included whilst other important direct costs that contributed to the incremental costs during follow-up were omitted (such as outpatient visits, General Practitioner (GP) visits, nurse home visits). The abstract stated that laser therapy for MO secondary to BRVO was associated with an incremental cost of $6,118 (US dollars in the year 2000). However, the results section and the discussion section of the paper reported inconsistent incremental cost-effectiveness ratios compared to the abstract ($4,439/QALY and $6,843/QALY respectively). Despite the inconsistencies in the report, laser therapy was stated to be a cost-effective intervention for improving visual loss associated with MO secondary to BRVO. The study is summarised in Table B39 and rated as acceptable in quality (Table B40).

Despite this quality assessment, this study is of limited applicability to the UK and is therefore of low relevance to decision making in England and Wales:

- This US-based study cannot be easily generalised to the UK setting, given the differences in healthcare system and unit costs.
- The perspective, although unclear, appears to be more restrictive than required of the NICE reference case, in that the total cost of health and social care have been omitted from the analysis. The analysis assumes that patients in the comparator arm – those observed – use no resources over and above those of patients in the laser arm. This is based on the BVO Study rather than on clinical practice.
- Utility valuation was not reflective of the NICE reference case, having been based on patient or author values rather than those of the general public.
- Sensitivity analysis was limited to 2 parameters, making it difficult to ascertain the full uncertainty in the results.

Table B39 Summary details of Brown et al. 2002[92]

Study name	Brown 2002
Country of study	USA (Although the analysis was performed by USA and Canada jointly).
Type of evaluation and synthesis	Cost-utility analysis
Interventions	Laser therapy versus no treatment.
Study population	Patients with macular oedema secondary to BRVO. The source of the effects data was the BRVO study. Mean age: 66 years. Mean follow-up: 3.1 years. Mean life expectancy: 16.5 years. Initial vision in the affected eye: 20/70 (mean, Snellen). Initial utility: 0.74 (mean).
Duration	Life time (16.5 years) and beyond 3 years, extrapolation was applied.
Type of model	Markov model built using TreeAge software that accounts for the recurrent risk of developing a retinal vein occlusion in the second eyes of patients over their lifetimes (mean 16.5 years). No cycle length was stated.
Perspective	The authors did not state the perspective. However, no facility costs, direct non-medical costs or indirect or intangible costs were included in the analysis. Therefore, a health care payer perspective is implied.
Model assumptions	**1.** Treatment for BRVO has no effect on mortality; **2.** The mortality rate in patients with BRVO is the same as for an age-matched US general population; **3.** 7% of patients have worse vision in the fellow eye than in the treated eye at the time of treatment;

	4. Approximately 3% of patients per year with BRVO will develop a retinal venous obstruction in the fellow eye after the initial diagnosis; **5.** Those patients who develop a retinal venous occlusion in the fellow eye will have vision in the fellow eye equal to or poorer than that in the initial eye; **6.** The beneficial effect of laser therapy for improving vision, which was shown to last over 3 years in the BRVO study, is presumed to last for the remainder of a treated patient's life; **7.** The following utility values were assigned according to visual acuity in the better seeing eye for untreated and laser treated patients: 20/20=0.92; 20/45=0.785; 20/70=0.74; **8.** Patients with a unilateral BRVO and better vision in the eye without the vein obstruction are assumed to have 20/20 vision in the better seeing eye, giving a utility value of 0.92; **9.** The maximum visual benefit from laser therapy begins at a mean time (including weighted retreatment data) of 6 months after initial treatment.
Cost items	Only direct costs were included. Laser therapy (destruction of localized lesion of retina by photocoagulation) cost $638/per patient. The average number of treatments per eye was 1.45. Therefore, the cost of laser therapy per patient was $925.10 (1.45 x $638). The cost of an initial consultation was not included as it did not represent incremental costs. 0.45 repeat fluorescein angiograms per patient would be needed during follow-up amounting to $42.30/per patient (0.45 x $94). The total cost per patient was $967.40.
Source of cost data	2000 US Dollars using the average 2000 Medicare Fee Schedule without geographical adjustment.
Resource use	An average of 1.45 treatments per eye.
Source of resource use data	Data from the BVO study group.[23]
Currency and currency year	$ (USD) 2000
Discount rate for costs	3%
Efficacy data	Mean initial vision in affected eye: 20/70. Mean vision after laser treatment: 20/45.
Source of efficacy data	Data from the BRVO study group.
Health outcomes/utility	QALYs using patient based preferences obtained from TTO analysis. Mean initial utility value (20.70): 0.74. Mean final utility value after treatment (20/45): 0.785. Mean utility value for a 20/20 better seeing eye: 0.92.
Source of health outcome data	For 20/70 and 20/45: BVOS study. For 20/20 utility: Brown 1999 (cited in the paper).

Discount rate for health	3%
Cost of laser therapy	$638
Total costs	0.45 repeat fluorescein angiograms per patient would be needed during follow-up: $42.30 (0.45 x $94). 1.45 x $638=$925.10 Total cost= $925.10+$42.30=$967.40 Discounted costs:$1056.50
Total incremental costs	These were not reported by the authors because 'no treatment' costs were stated.
Total outcomes	Not clear. Authors stated that "...assuming a 3% recurrent annual risk of contralateral vascular obstruction, the mean number of QALYs gained from laser therapy, versus no treatment, in eyes with BRVO was 0.230. The routine decision analysis tree for the 7% of patients with poor initial vision in both eyes accounted for discounted QALYs, while the Markov model in the remaining 93% of the cohort added an additional of 0.166 QALYs. When the discounted costs, using a yearly discount rate of 3%, associated with laser therapy were incorporated with the number of discounted QALYs (0.198) gained from treatment."
Total incremental outcomes	Not clear.
Cost-effectiveness ratio	$4,439/QALY.
Sensitivity analysis method	Two-way sensitivity analysis was undertaken. Discount rate for costs and annual recurrent risk of developing a RVO in the contralateral eye parameter inputs are being altered simultaneously.
Sensitivity analysis results	The authors explained that the change of yearly recurrent risk of developing retinal vein occlusion in the contralateral eye resulted in: 0.153 discounted QALYs gained for a 1% yearly incidence of contralateral venous obstruction; 0.193 QALYs; gained for a 2% incidence; 0.295 QALYs gained for a 5% incidence. The discounted total costs were: $1061 using a 0% discount rate; $1060 using a 1% discount rate; $1053 using a 5% discount rate; $1046 using a 10% discount rate. (Table 2.5 in the paper shows the results of sensitivity analysis)
Conclusion	Laser therapy appears to be a cost-effective intervention for improving visual loss associated with macular oedema secondary to BRVO. Note that the authors state different cost/QALY values for base case results in the results section and in their discussion section ($4439/QALYs vs. $6843/QALYs). In addition, it is not possible to replicate the same results by dividing the costs by QALYs presented.
Do the authors have an industry affiliation	None.

6.1.3 Please provide a complete quality assessment for each cost-effectiveness study identified. Use an appropriate and validated instrument, such as those of Drummond and Jefferson (1996)[1] or Philips et al. (2004)[2]. For a suggested format based on Drummond and Jefferson (1996), please see section 9.11, appendix 11.

Table B40 Quality assessment of Brown et al. 2002[92]

Quality assessment parameter	Comment
Was the research question clearly stated?	Yes
Was the choice of comparator explicitly justified?	No
Was the comparator chosen to represent current practice in the country's setting?	Not reported
Was the sample representative of the population?	Yes
Was the perspective of the analysis stated?	No
Was the cost-effectiveness methodology applied in the study clearly described?	Acceptable
Was the model structure/technique adequately described?	Yes
Did the authors identify the source of the effects data used to inform the cost-effectiveness study?	Yes
Did the study methodology for deriving the effects data show an adequate level of internal validity (if it was a study)?	Yes (randomised controlled trial)
If utilities were used, was the valuation method specified?	Yes
Did the authors identify the source of data for the costs used to inform the cost-effectiveness study?	Yes
Did the authors identify the source of data for resource use used to inform the cost-effectiveness study?	Yes
Did authors justify of their choice of parameters estimates to inform the model?	No
Did the authors provide details of the subjects from whom costs were obtained?	No
Were resources reported separately from their unit costs?	Yes
Were methods for the estimates of quantities of resource use described?	Yes (from an RCT)
Were methods for the estimates of the unit costs of direct costs described?	Yes
Were methods for the estimation of productivity costs clearly described?	Not applicable (no productivity costs were included).
Were the currency and year/month of price data recorded?	Yes
Were details of currency of price adjustments for inflation or currency conversion given?	Not applicable
Was a time horizon for costs provided?	Yes
Was the choice of discount rate justified?	No

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

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

Quality assessment parameter	Comment
Were costs presented in a disaggregated manner?	Yes
Did all the relevant cost elements appear to have been included?	No
If some costs are omitted, are these the relatively less important costs that do not drive the results?	No
Did the authors make appropriate comparisons of their results with the findings from other studies?	No
Was the issue of generalisability to other settings addressed?	No
Did the authors present their results selectively?	Unclear
Did authors' conclusions reflect the scope of the analysis?	Yes
Are the authors' conclusions supported by the results of the study?	Yes
Did the authors report any further limitations of their study?	No
Final comment of the assessor	Acceptable quality. There are inconsistencies in the results reported and the sensitivity analysis is unclear. Some of the methods are not explicitly justified.

6.2 De novo analysis

Patients

6.2.1 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 1.4 and 5.3.3, 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 economic model includes a cohort of patients with MO secondary to RVO. The included patients are reflective of those included within the BRAVO and CRUISE trials as described in Section 5.2. The included patients are also in line with the anticipated licensed indication for ranibizumab as described in Section 1.5 (visual impairment due to MO secondary to RVO).

The two major patient subgroups of RVO, BRVO and CRVO are treated separately within the model as the treatment alternatives and the natural disease progression differs between them.

Model structure

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

The economic evaluation is a Markov model developed in Microsoft® Excel. The diagrammatical representation of the model is provided in Figure B15 below.

Patients move between nine different health states at monthly cycles. The health states are based on eight different intervals of BCVA and a ninth absorbing state, 'death'. Health states were defined as bands of 10 EDTRS letters (2 lines) based on the assumption that 2 line changes are clinically significant. The ETDRS is used to measure the severity of a patient's visual impairment as this is the most commonly used scale in clinical trials. The approximate equivalent Snellen values are also provided in the figure below.

The model follows a cohort of 1,000 hypothetical generated patients, of whom each patient may experience a different health pathway over the course of the model. The model predicts changes in each patient's quality of life, resource use and costs.

In the primary analysis of the model for both MO secondary to BRVO and MO secondary to CRVO ranibizumab was compared to the standard of care in this group of patients. For BRVO, ranibizumab was compared to laser therapy and data for the comparator group was based on the BRAVO trial in which 57.6% of patients in the control standard care arm received rescue laser treatment in the first 6 months of treatment. For CRVO ranibizumab was compared to observation as per the CRUISE trial, which represents standard of care in this population.

Modelled eye

In BRAVO and CRUISE trials the majority of patients were treated in their worst seeing eye (WSE) (Table B7 and Table B8). In BRAVO and CRUISE there was considerable HRQL gain (assessed using the NEI-VFQ 25 questionnaire) associated with treating eyes that were predominantly worse seeing (Table B17 and Table B18). However, it has not yet been possible to translate these HRQL gains into utilities for use in a cost-utility analysis. Examples of areas that are likely to benefit from treatment of the WSE include reading speed, reading accuracy, stereopsis, and contrast sensitivity. Furthermore, there is a general paucity of data on costs and utility of changing vision in the WSE in MO secondary to RVO, or indeed in other ocular conditions. The model therefore assumes treatment in the better seeing eye (BSE) for the base case analysis.

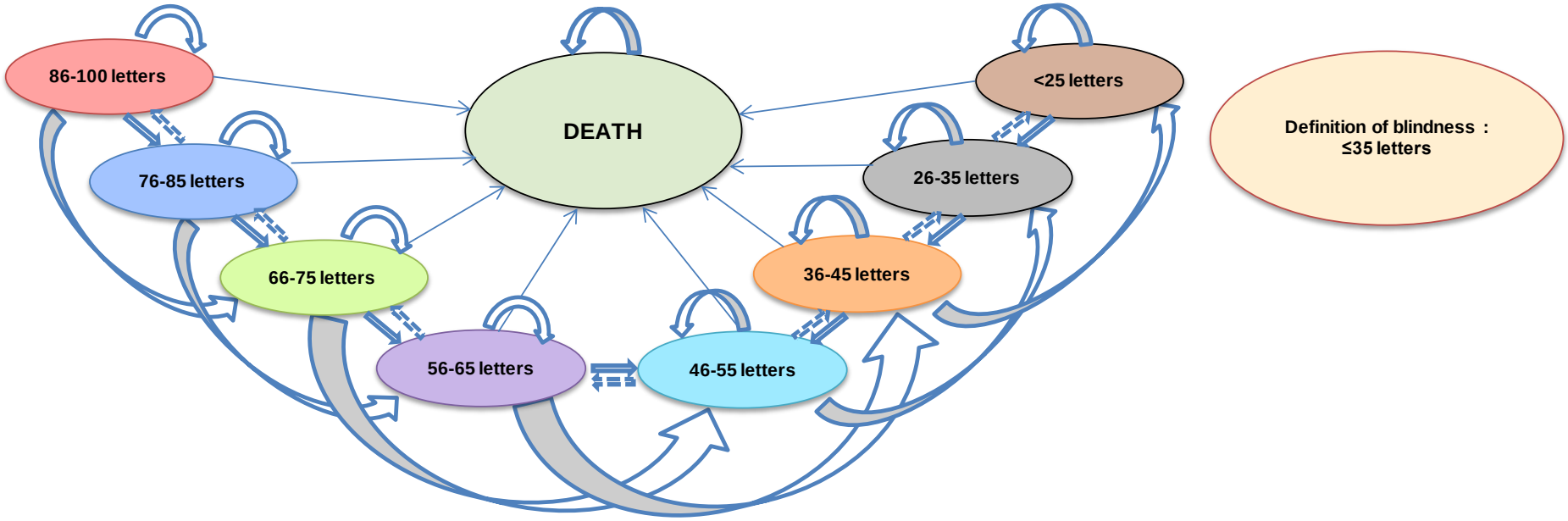
This approach follows that of previous technology appraisals in wet AMD (NICE TA155 and TA 018), in which an approach to modelling treatment of only the BSE was taken to provide a framework for decision making.[93] During TA155, the manufacturers and the Evidence Review Group (ERG) presented cost-effectiveness analyses of anti-VEGFs on the basis of the treatment of one eye. In TA155 the BSE was modelled, although in the pivotal trials predominantly the WSE was treated. The Committee also concluded that 'assuming a strategy of treating the first-affected eye would not be cost-effective', that is to say, it is harder to demonstrate cost-effectiveness of treating the WSE. However, given the views of consultees, the TA155 Committee agreed that 'it would be unacceptable and clinically inappropriate not to treat the first eye to come to clinical attention'. Thus the TA155 Committee noted that it's 'considerations of cost-effectiveness should relate to starting treatment

with the first eye to present clinically'. Thus, although cost effectiveness estimates of the BSE were presented and discussed, recommendations also related to the WSE to avoid an unethical scenario where patients were allowed to go blind in one eye before becoming eligible for ranibizumab treatment.

In RVO, the rate of bilateral involvement is substantially lower than in wet AMD. However there remains a possibility that a patient affected with RVO in one eye may develop a different ocular condition in the fellow eye at a later time. There are several risk factors common to RVO and other eye conditions, particularly given the advanced age of the RVO population, and a large majority of patients with RVO are diabetics, at risk of sight related diabetic complications. Glaucoma has also been associated with a raised risk of RVO. Denial of treatment of one eye, if vision in the other is less or unaffected, solely on the grounds of potential poor cost effectiveness would be as unethical and inappropriate for patients with RVO as it was determined to be for patients with wet AMD.

Therefore, the base case analysis of treatment of the BSE is presented. Similarly to TA 155 it is understood that the results will be applied to the affected eye.

Figure B16 Model structure



Note: Approximate Snellen-equivalents

VA: 20/16-20/10=86-100 letters

VA: 20/32-20/20=76-85 letters

VA: 20/64-20/40=66-75 letters

VA: 20/80-20/50=56-65 letters

VA: 20/125-20/80=46-55 letters

VA: 20/200-20/125=36-45 letters

VA: 20/320-20/200=26-35 letters

VA < 20/320=<25 letters

6.2.3 Please justify the chosen structure in line with the clinical pathway of care identified in section 2.4.

The aim of treatment is to reduce MO and improve or prevent further deterioration in VA. The model structure therefore fits the care pathway as the effectiveness of interventions is determined by their ability to improve and stabilise VA.

The Markov approach used here has been employed in other economic models of interventions used to treat conditions with a deterioration of VA, and the model therefore represents an appropriate approach to modelling the impact on costs and quality of life of VA over time.[93, 94]

The structure is based on 10 letter changes in BCVA on the ETDRS eye chart as a loss of 10 letters (2 lines) is considered to be clinically significant. In a study of vision loss in patients with diabetic retinopathy, a decrease in vision of 10 letters was associated with a substantial decline in HRQL (e.g. inability to drive, increased dependency, role limitations, impaired mental health), and was correlated with a significant change in vision related quality of life as measured with the NEI VFQ-25.[91]

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

The health states in the model are based on the VA in the treated eye (under the assumption that the treated eye is the better seeing). This therefore directly captures the disease progression over time. Given that VA is closely related to HRQL and the symptoms of MO due to RVO that most affect the patient, the health states capture the impact of the condition, and its treatment, on a patient's health related quality of life.

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

The main aspect of the condition is vision loss – the reduction of visual acuity. This is captured directly as described in sections 6.2.3 and 6.2.4. A change in visual acuity

has implications for HRQL as well as the type and frequency of healthcare provided. In years 1 and 2 of the model, disease progression reflects the treated populations of the ranibizumab pivotal trials (BRAVO, CRUISE and HORIZON). Thereafter, the underlying disease progression in the model reflects observational study data describing changes in visual acuity over the longer-term (section 6.3). The pathophysiology of the disease, as described in section 2.1, is reflected in the model through observed changes in visual acuity.

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

Table B41 Key features of analysis

Factor	Chosen values	Justification	Reference
Time horizon	15 years	Patients have an average age of 66 years at model entry. 15 years is considered a sufficient period to reflect the time to reach, or avoid, severe visual impairment and blindness and for the impact on costs and quality of life to be assessed.	NICE methods guide
Cycle length	1 month	This allows sufficient granularity to capture movement between health states on a regular bases, and allows for the regular treatment and follow up frequency in this condition	BRAVO and CRUISE
Half-cycle correction	Yes	NICE reference case	NICE methods guide
Were health effects measured in QALYs; if not, what was used?	Yes, QALYs	NICE reference case	NICE methods guide
Discount of 3.5% for utilities and costs	3.5%	NICE reference case	NICE methods guide
Perspective (NHS/PSS)	NHS and PSS	NICE reference case	NICE methods guide
NHS, National Health Service; PSS, Personal Social Services; QALYs, quality-adjusted life years			

Technology

6.2.7 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?

In the model for both BRVO and CRVO ranibizumab is administered in line with the marketing authorisation. In BRVO the use of rescue laser is also administered in line with UK standard of care. This is described further in section 6.2.8 below. The dexamethasone implant is administered every 6 months in the model for both BRVO and CRVO, as indicated as the minimum time between doses in the SPC.[95]

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

- The costs and health consequences of factors as a result of implementing the continuation rule (for example, any additional monitoring required).
- The robustness and plausibility of the endpoint on which the rule is based.
- Whether the 'response' criteria defined in the rule can be reasonably achieved.
- The appropriateness and robustness of the time at which response is measured.
- Whether the rule can be incorporated into routine clinical practice.

- Whether the rule is likely to predict those patients for whom the technology is particularly cost effective.
- Issues with respect to withdrawal of treatment from non-responders and other equity considerations.

Based on the SPC ranibizumab is administered monthly and continued until maximum VA is achieved, confirmed by stable VA for three consecutive monthly assessments performed while on ranibizumab treatment. Thereafter patients should be monitored monthly for VA. Treatment is resumed with monthly injections when monitoring indicates a loss of VA due to MO secondary to RVO and continued until stable VA is reached again for three consecutive monthly assessments. As described in section 1.13, these criteria require regular patient monitoring and additional associated resources. However, a continuation rule based primarily on VA can be readily incorporated into clinical practice and is a robust and plausible endpoint.

The use of ranibizumab within the model is based on data from the BRAVO, CRUISE and HORIZON studies. In these studies predefined treatment criteria determined the retreatment rules for ranibizumab in MO secondary to BRVO and CRVO and these are in line with the proposed SPC (Table B5). In the model for BRVO, data on laser therapy is taken from the BRAVO study, with laser allowed according to pre specified criteria. This is reflective of UK standard of care.

In the model a mean number of ranibizumab injections or laser treatments (for BRVO) administered to patients in each treatment group is included based on data from BRAVO, CRUISE and HORIZON. This is described further in section 6.5.5. Thus, variation in disease activity and subsequent treatment suspension and re-initiation is captured.

Table B42 Frequency of treatment and follow up (BRVO)

	Year 1		Year 2		Year 3+	
Treatment	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**
Ranibizumab	8.0[a]	4.0[b]	2.5[c]	3.5[d]	0.0[e]	2.0[f]
Grid laser (standard care)	1.5[g]	2.5[f]	1.0[g]	3.0[f]	0.0[e]	2.0[f]
Dexamethasone	2.0[h]	6.0[i]	2.0[h]	6.0[i]	0.0[e]	2.0[f]

a BRAVO (data on file)
b Assumption; SPC (based on a total of 12 visits of any type per year)
c HORIZON (data on file)
d Assumption; HORIZON, expert opinion (based on a total of 6 visits of any type per year)
e Assumption; expert opinion

f Assumption; expert opinion (based on a total of 4 visits of any type per year)
g SCORE study[32]
h NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.
i. Assumption (based on a total of 8 visits of any type per year)

Table B43 Frequency of treatment and follow up (CRVO)

	Year 1		Year 2		Year 3+	
Treatment	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**
Ranibizumab	9.0[a]	3.0[b]	3.8[c]	6.2[d]	0.0[e]	4.0[f]
Standard care	0.0[e]	6.0[g]	0.0[e]	4.0[f]	0.0[e]	4.0[f]
Dexamethasone	2.0[h]	6.0[i]	2.0[h]	6.0[i]	0.0[e]	4.0[f]

a CRUISE (data on file)
b Assumption; SPC (based on a total of 12 visits of any type per year)
c HORIZON (data on file)
d Assumption; HORIZON, expert opinion (based on a total of 10 visits of any type per year)
e Assumption
f Assumption; expert opinion (based on a total of 4 visits of any type per year)
g Assumption; expert opinion (based on a total of 6 visits of any type per year)
h. NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.
i. Assumption (based on a total of 8 visits of any type per year)

6.3 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 5). 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.

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

The effectiveness of the treatments in the model is expressed as the probability of moving between health states based on the change in BCVA scores measured in the treated eye. Patient level data from the BRAVO and CRUISE datasets were used for BRVO and CRVO respectively. The effectiveness data was analysed using the study eye data from the datasets excluding the fellow eye data in cases where the fellow

eye was treated during the trials. The number of patients treated in the fellow eye was negligible, and only laser was administered. Effectiveness data were available at monthly follow up visits, for the full 12 months of each trial.

In the base case analysis, the year 1 transition probabilities were calculated assuming that the probability of moving health state was the same, irrespective of the patient's current VA. An alternative approach was attempted whereby the probability of change was dependent upon the patient's current VA (i.e. the patient's VA at $Month_N$ determines their likelihood of change by $Month_{N+1}$). Each approach closely reflected the observed mean VA in the clinical trials, although the former approach slightly underestimated trial outcomes. However, when dependence on starting health state was assumed the small size of the datasets, particularly at health states reflecting extremes of visual acuity, generated some transition probabilities unlikely to reflect observed outcomes. These transition probabilities were also unsuitable for analyses of subgroups where sample sizes were insufficient, and for comparisons against dexamethasone, where effectiveness data are not available by current VA level. Thus, the simple approach was preferred for the base case analysis.

Transition probabilities were calculated for three different time periods:

- Baseline to Month 1;
- Month 2 to Month 6;
- Month 7 to Month 12.

It should be noted that in the BRAVO and CRUISE trials all patients could receive ranibizumab after six months, and there are no data for the standard of care comparators beyond month 6.

- For CRVO, the month 2 to 6 transition probabilities are reapplied to months 7 to 12.
- For BRVO data were pooled across both treatment arms for months 7 to 12 to generate month 7 to 12 transition probabilities. To reapply the probabilities based on data from month 2 to 6 was considered inappropriate as it would ignore the benefits obtained from laser treatment; a conservative assumption was made that the effectiveness in the laser group during months 7 to 12 would be identical to that of ranibizumab.

6.3.2 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.

To calculate the transition probabilities for the model, the following method was used:

i. All VA scores for the study eye were assigned to one of the VA groups specified in the model structure;
ii. For each patient at each time point, the change in health state was determined;
iii. The probability (by treatment) of moving between groups was then determined for each month;
iv. Where probabilities were calculated over longer periods (i.e. Month 2 to 6), the probability of changing each month was used to derive the overall probabilities, as opposed to the probability of having changed between months 2 and 6 only. For example, if a patient started in Group 3, moved to Group 2 after one month, and then moved back to Group 3, this would impact on the probability of gaining and losing a group during that time period
v. The probabilities were then calculated for the following outcomes:
    a. Probability of gaining at least 4 lines;
    b. Probability of gaining between 2 and 4 lines;
    c. Probability of no change;
    d. Probability of losing between 2 and 4 lines;
    e. Probability of losing at least 4 lines.

Patients therefore faced six ‘probabilities’ in each cycle: (a) they could improve by two health states, (b) they were allowed to improve to the adjacent health state (c) they were allowed to stay in their current health state, (d) they could worsen by one health state, (e) they could worsen by two health states, or they could die. The probability of death was estimated using annual rates based on life tables for England and Wales as described in more detail below.

The probabilities were calculated assuming that the probability of change is constant and irrespective of the patient’s current VA level. These transition probabilities are shown in Table B44 and Table B45 below, for BRVO and CRVO respectively. The

transition probability matrices developed are available in the model, and can be provided in Microsoft® Word format on request.

Table B44 Collapsed transition probabilities: BRVO

Effectiveness progression rates	Ranibizumab	Standard care
Month 1		
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]
No change	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]
Months 2 to 6		
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]
No change	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]
Months 7 to 12		
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]
No change	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]

Table B45 Collapsed transition probabilities: CRVO

Effectiveness progression rates	Ranibizumab	Standard care
Month 1		
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]
No change	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]
Months 2 to 6		
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]
No change	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]
Months 7 to 12		
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]

No change Lose between 2 and 4 lines Lose at least 4 lines	[redacted]	[redacted]

Dexamethasone clinical data

As described in Section 5.7 a systematic review was undertaken and found that there was insufficient data available in order to undertake a formal indirect comparison of ranibizumab with dexamethasone. Crucially, the populations studied in GENEVA trials compared to those of BRAVO and CRUISE were considered too heterogeneous to provide an appropriate comparison. This is described in full in Section 5.7.

Despite these limitations of the data, a comparison to dexamethasone is clearly of interest and attempts are made to incorporate the available data in the model. It is acknowledged that there are severe limitations to this approach, and the results should be considered exploratory and uncertain.

Risk ratios were identified for dexamethasone from the Haller 2010 study and assigned to the probabilities observed in the control groups of BRAVO and CRUISE.[69] Detailed calculations are available on request. Unfortunately, risk ratios were available at specific time points only and the ratios were reported as change from baseline rather than for that specific period (i.e. between 2 and 6 months). As such, it would not be appropriate to assign two risk ratios to each of the model periods. For instance, if the risk ratio for improvement of 2 lines was 2.0 at one month, and 2.0 at six months, this would imply that all of the 'benefit' was observed in the first month, and that the benefit had simply been retained for the remainder. Applying the ratio of 2.0 to subsequent months in the model would lead to double-counting of those benefits. As such, only one risk ratio was applied in the model, and this was applied in the first month (due to insufficient data suggesting otherwise). If ratios were available at different time points, the largest risk ratio was taken in order to undertake a conservative approach from the perspective of ranibizumab. The risk ratios used in the model are shown below in Table B46.

Table B46 Relative risk gaining and losing lines with dexamethasone vs. no treatment

	BRVO	CRVO
	RR (Dexamethasone vs. no treatment)	RR (Dexamethasone vs. no treatment)
Gain at least 4 lines	[redacted]	[redacted]
Gain between 2 and 4 lines	[redacted]	[redacted]
No change	[redacted]	[redacted]
Lose between 2 and 4 lines	[redacted]	[redacted]
Lose at least 4 lines	[redacted]	[redacted]

Long-term disease progression

During year two of the model (i.e. between months 13 and 24), it was assumed that the transition probabilities would be equivalent to the rates observed between months 7 and 12. From year 3 and beyond, natural worsening of BCVA was integrated to the model using the data sourced from the Beaver Dam Eye study.[96] That study reported that the number of patients reporting 'mild' VA symptoms increased from 2% in patients between the ages of 43 and 54 to 9.4% between the ages of 65 and 74. The increase from 'no problems' to 'mild' is equivalent to around 2 lines. Therefore, it may be expected to see 7.4% of patients worsening by this magnitude over a period of 20 years. As such, it is possible to convert that progression rate into a monthly probability for inclusion in the model which translated to 0.031% for the probability of losing between 2 and 4 lines. The following formula was used for the above-mentioned conversion.

$$Monthly\,rate = 1 - \exp\left[\ln\left(\frac{7.4\%}{20 * 12}\right)\right]$$

Blindness

In the model, blindness was defined as a BCVA score of ≤35 letters in the BSE.

Mortality

All cause mortality was included in the model, using annual rates based on life tables for England and Wales (England & Wales Life Tables 2007-09, Government's Actuary Department).[97] The rates for males and females were calculated as an average, and were converted to monthly rates using the following formula:

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

No excess mortality risk due to RVO was applied to the model in the base case analysis. This is based on the low mortality rates observed in BRAVO and CRUISE, and several studies which showed that there was no significant difference in risk of mortality between patients with RVO and the general population.45, 98 This approach is consistent with previous submissions to NICE in RVO.

Studies have demonstrated a relationship between VA and risk of mortality.[99, 100] Whilst these studies were not specific to RVO, it seems reasonable that the worsening of VA in RVO may also lead to similar increases in mortality when the BSE is affected. The risk ratio applied to each VA band is shown in Table B47. The data from the Christ 2008 study is utilised for ETDRS bands <25, 26-35, 36 to 45 and 46-55. For the other bands there is no data available and therefore the relative risk is assumed to be 1.

Table B47 Risk ratio for mortality, by VA status

ETDRS	Relative risk of mortality
86-100	1.00
76-85	1.00
66-75	1.00
56-65	1.00
46-55	1.23
36-45	1.23
26-35	1.54
<25	1.54

It should be highlighted that the above risk ratios are applicable for the VA level in the patient's BSE. That is, the increase in mortality is dependent only upon the patient's BSE.

Adverse events

A number of adverse events were included in the model as described in Table B48. The rationale for inclusion of each adverse event was based on a combination of the relative prevalence and severity of each event. That is, infrequent and non-severe events were not included.

For ranibizumab the event rate for cataracts and IOP (treated with drug and treated with surgery) was taken from a pooled analysis of the BRAVO and CRUISE trials. In

BRVO, for laser, no data were identified on the incidence rate of these adverse events and therefore a zero rate was assumed. In CRVO the incidence of these adverse events with observation only was also assumed to be zero.

The rates of cataracts and IOP for dexamethasone came from a pooled analysis of the two GENEVA trials. The rates were presented in the dexamethasone implant STA manufacturer's submission for a period of 180 days.[78] For this analysis, these values were multiplied by two to estimate the yearly rate.

A recent publication has reported an increased risk of ischaemic or haemorrhagic stroke in the RVO population compared to a control population, with a relative risk of 1.72.[101] Anti-VEGF therapy has a theoretical risk of arteriothrombolic events. Stroke is therefore included in the model. The baseline incidence of stroke in the model was calculated by applying this relative risk of 1.72 to the annual haemorrhagic stroke rate in England. The annual haemorrhagic stroke rate in England was calculated from the incidence of acute stroke in England and Wales (0.214%)[102] adjusted to reflect haemorrhagic strokes only, estimated to account for 13% of all strokes based on data from the American Stroke Association.[103] The incidence of stroke is assumed to be constant for all interventions. No increased risk of stroke for ranibizumab-treated patients is included, given the evidence from large retrospective studies that there is no increased rate of stroke compared to other interventions (see section 5.9).

Table B48 Adverse events included in the model

Events per patient (%)	Ranibizumab	BRVO - Rescue laser- Standard care	CRVO – Observation – Standard care	Dex. implant
Cataracts	6.60%	0.00%	0.00%	14.80%
IOP increased (treated with drug)	10.00%	0.00%	0.00%	50.40%
IOP increased (treated with surgery)	0.00%	0.00%	0.00%	1.40%
Stroke	0.05%	0.05%	0.05%	0.05%

The justification for the exclusion of a number of adverse events from the model is provided. The incidence of endophthalmitis and retinal tear were very low in BRAVO and CRUISE (Table B31 to Table B34). Although these studies were not designed to primarily assess safety outcomes, evidence from ranibizumab use in other indications also suggests very low rates of endophthalmitis. As such these adverse events were not included in the model. The incidence of vitreous haemorrhage was lower in the ranibizumab arm than in the laser or control arms of BRAVO and CRUISE respectively. It is possible that this is a result of the anti-VEGF mechanism

of action of ranibizumab reducing the chance of progression of patients to proliferative retinopathy. Vitreous haemorrhage was not included in the model and this represents a conservative approach, biased against ranibizumab.

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

The transition probabilities between health states are based on three different time points up to two years as described above. The natural progression rate for decrease in BCVA due to other eye diseases or aging is integrated from year 3 onwards in the model.

6.3.4 Were intermediate outcome measures linked to final outcomes (for example, was a change in a surrogate outcome linked to a final clinical outcome)? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

No, BCVA changes, the final outcome used in the model, were measured directly in the clinical trials.

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

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated

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

- declaration of potential conflict(s) of interest from each expert or medical speciality 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).

Three clinical experts were selected and invited to participate in a telephone interview to discuss clinical assumptions applied to the economic model. Each were consultant ophthalmologists currently practising in NHS general (2) and teaching (1) hospitals in England. Background reading and an outline of the discussion points was provided in advance and is presented in Section 10.9, appendix 21. Summarised notes of the telephone discussions are also presented in Section 10.9, appendix 21. The opinion of the clinical advisers guided decisions as to the acceptability of key assumptions in the model from a clinical practice.

Summary of selected values

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

Variables not yet presented in previous sections are included in the tables below.

Table B49 Summary of variables applied in the economic model – BRVO

Variable	Value	CI (distribution)	Reference to section in submission
Baseline Age	66.43	Not applicable	Table B7
Baseline health state distribution (BCVA letter score)			
86-100	0.0%	Not applicable	Table B7
76-85	0.4%	Not applicable	
66-75	17.2%	Not applicable	
56-65	33.6%	Not applicable	
46-55	26.0%	Not applicable	
36-45	13.7%	Not applicable	
26-35	7.3%	Not applicable	
<25	1.9%	Not applicable	

Table B50 Summary of variables applied in the economic model – CRVO

Variable	Value	CI (distribution)	Reference to section in submission
Baseline Age	67.61	Not applicable	Table B8
Baseline health state distribution (BCVA letter score)			
86-100	0.0%	Not applicable	Table B8
76-85	0.0%	Not applicable	
66-75	13.5%	Not applicable	
56-65	26.9%	Not applicable	
46-55	21.2%	Not applicable	
36-45	16.2%	Not applicable	
26-35	15.0%	Not applicable	
<25	7.3%	Not applicable	

6.3.7 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.

The costs and clinical outcomes have been extrapolated to a time horizon of 15 years, based on assumptions described in section 6.3.2. This time period was

chosen in order to capture the long term benefits of improved vision. From year 3 and onwards, natural worsening of BCVA was integrated to the model.

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

Table B51 Assumptions within the model

Parameter	Assumptions	Justification
Time horizon	15 years	Time is sufficient period to reflect the clinical benefits of therapy for this chronic condition.
Health states	Defined by two lines	Clinical meaningfulness, supported by data
BCVA at Baseline	Distribution as in the BRAVO and CRUISE trials	This reflected the baseline health states of the population from the key trials used in the model.
Treated eye	BSE is treated Observed VA changes of treating the WSE are equivalent to the BSE	Robust utility values are available for BSE but not for WSE. Previous economic models have applied VA gains of the WSE to the BSE, and drawn conclusions regarding the treatment of WSE based on cost-effectiveness of treatment in the BSE
Progression in year 1	In BRAVO, the data was pooled across both treatment arms for months 7 to 12 to generate month 7 to 12 transition probabilities. In CRUISE, the month 2-6 transition probabilities were reapplied for months 7-12.	In BRAVO, to reapply the probabilities based on data from month 2 to 6 was considered inappropriate given that the comparator arm included active laser treatment, and the probabilities from months 2 to 6 would ignore the benefits achieved with treatment.

	The year 1 transition probabilities were calculated assuming that the probability of moving health state was the same, irrespective of the patient's current VA. This is as opposed to the assumption that probability of moving health state is dependent on the health state at baseline.	When the probability of moving health state was linked to dependence on starting health state the small size of the datasets, particularly at health states reflecting extremes of visual acuity, generated some transition probabilities unlikely to reflect observed outcomes. These transition probabilities were also unsuitable for analyses of subgroups where sample sizes were insufficient, and for comparisons against dexamethasone, where effectiveness data are not available by current VA level. Thus, the simple approach was preferred for the base case analysis.
Withdrawals	Patients were assumed to stay on treatment for 2 years; discontinuations were not modelled in the Markov model.	Rate of discontinuation was low and therefore would have minimal impact on the results.[63]
Utilities	Utilities have not been adjusted downwards over time to account for reduced HRQL experienced by older people, independent of impact of VA.	The impact of this adjustment is expected to be negligible.
Mortality	Decrease in VA was associated with an increased mortality risk. No excess overall mortality risk due to RVO was applied.	Several studies have demonstrated no significant difference in risk of overall mortality between patients with RVO and the general population.[45, 98] However, decrease in VA is associated with reduced mortality, with blindness (≤35 ETDRS letters) linked to a relative risk of mortality of 1.54 compared to the general population.[99]
Adverse events	Cataract, intraocular pressure increase and stroke were modelled.	Mild, transient and adverse events not actively managed were excluded as they were not expected to have an important impact on costs or utility. The incidence of endophthalmitis and retinal tear were very low in BRAVO and CRUISE and their incidence of vitreous haemorrhage was lower in the ranibizumab arm than in the laser or control arms, respectively. As such these adverse events were not included in the model.

6.4 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

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

MO due to RVO is characterised by a rapid loss of vision. Loss of VA is associated with increased difficulty in performing everyday tasks such as driving and reading, and it may impact on the patient's ability to work or participate in many sports and hobbies. This is associated with a considerable reduction in HRQL. [11, 14] It has specifically been reported that both CRVO and BRVO are associated with a decrease in vision-related QoL scores (as measured by the NEI VFQ-25) and this reduction in QoL was related to the degree of VA. [11, 12]

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

Although some patients can experience a spontaneous improvement in MO and thus VA, in general without treatment the MO persists and VA is reduced. Without treatment, a deterioration of visual acuity will occur, with progression to blindness in some cases. Delayed treatment, and therefore persistent oedema, results in irreversible vision impairment.[10] Visual impairment is accompanied by loss of HRQL, as described in section 6.4.1. Of particular relevance to RVO is the rapidity of vision loss. For many patients, visual acuity will decrease suddenly and even overnight,

causing distress and anxiety that is likely to marked impact on quality of life. Furthermore, for patients that cannot be treated there is likely to be additional anxiety and depression associated with the knowledge that the visual loss may eventually be irreversible. This is very apparent in population studies measuring quality of life in terms of VFQ score in RVO patients and compared to the general populations, irrespective of whether this affects the WSE or the BSE.[11, 12, 104, 105]

HRQL data derived from clinical trials

6.4.3 If HRQL data were collected in the clinical trials identified in section 5 (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 BRAVO and CRUISE trials HRQL data were collected using the NEI VFQ-25, a validated test that measures the impact of visual function on activities of daily life. The NEI VFQ-25 is a non-preference based, vision-specific QoL measure, which does not include a direct estimation of utility weights. These HRQL data are not consistent with the NICE reference case. HRQL outcomes are presented in section 5.5; in both trials the observed improvement at month 6 from baseline in the NEI VFQ-25 score was significantly greater in patients treated with ranibizumab 0.5 mg compared to sham.

Mapping

6.4.4 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.

There was no mapping undertaken for the de novo analysis.

HRQL studies

6.4.5 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 9.12, appendix 12.

The objective of the systematic review undertaken was to assess utility values reported in the literature for populations with visual impairment due to retinal disease. Priority was given to populations with MO secondary to CRVO or BRVO, either alone or in combination with other diseases, but consideration was also given to patients with DMO or AMD, if utilities for RVO could not be identified. The following types of study were eligible for selection for the review:

- Reports of utility elicitation exercises;
- Reports of utility validation exercises;
- Reports of economic evaluations using utility measures gathered during the studies.

Reviews of utility studies were also eligible for selection in order to scan the reports for relevant primary studies. Reviews might also provide comparative data against which to compare the results of this review. Data from unpublished studies were eligible for inclusion.

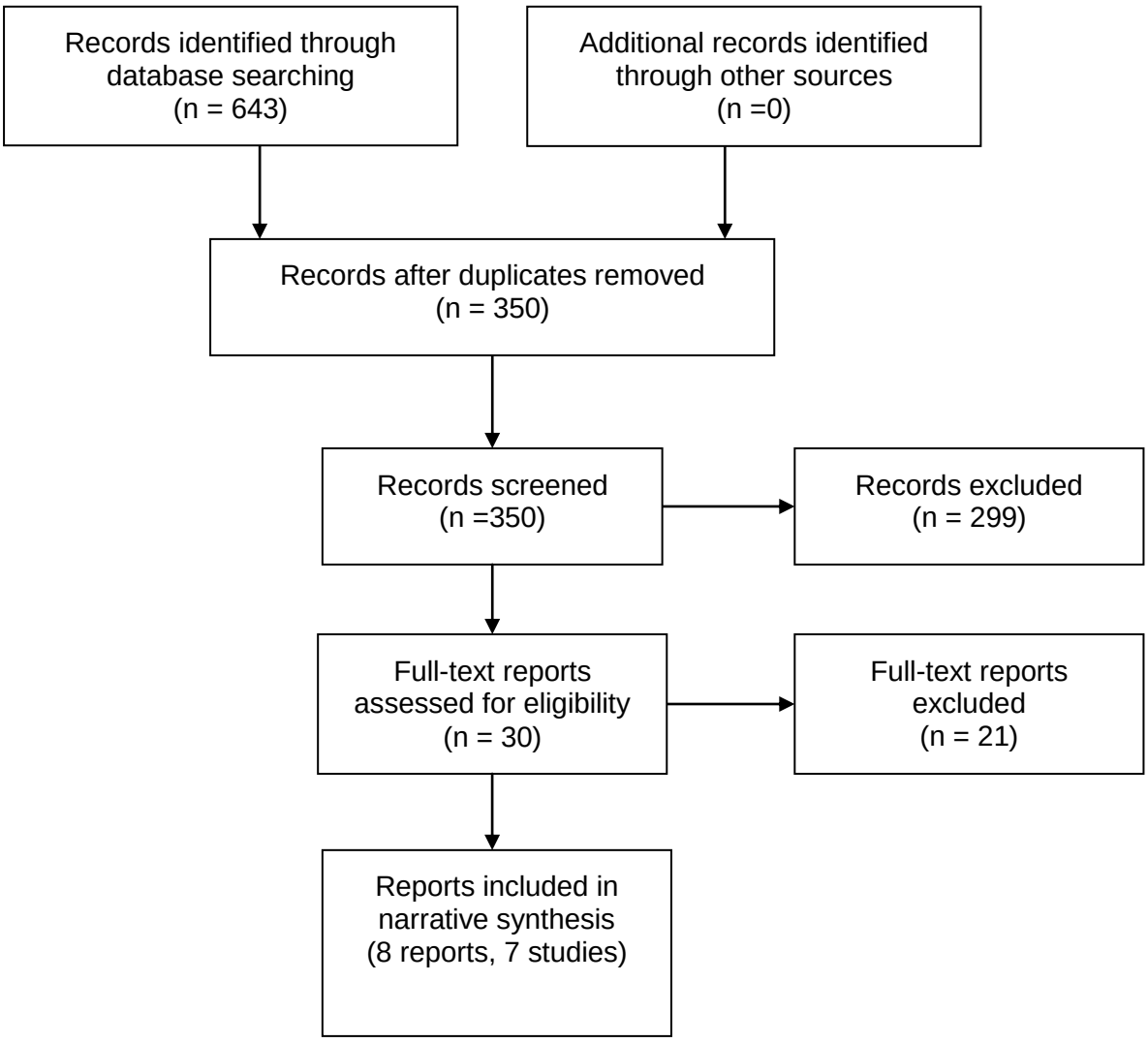
In addition, to be eligible for the review, a utility report must include:

- Reported mean or median utility values at different disease levels (if available);
- The country/perspective;
- A standard method of utility assessment (e.g. standard gamble, TTO, rating scale);
- A description of the health state valuation instrument (e.g. generic preference-based measures such as the EQ-5D or the valuation of health state descriptions).

The databases searched included MEDLINE, MEDLINE In-Process, EMBASE, NHS EED, HTA, HEED, EconLit, CEA Registry and PROQOLID. The search strategy combined population search terms with utilities terms. No date or language limits were applied. Full details of the search strategy utilised can be found in Section 9.12, appendix 12. The search results were downloaded and deduplicated. Initial record selection from the title and abstract was undertaken by one reviewer. During this initial selection, very obvious false positives were removed. For reports assessed as potentially relevant the full papers were obtained and assessed for relevance by one reviewer and checked by a second. Discrepancies were resolved through discussion or by consulting a third reviewer. Included studies were data extracted by a health economist and checked by a second researcher. Any disagreements were resolved by reference to a third researcher.

A total of 643 records were identified by the searches. After deduplication, 350 records remained for assessment from titles and abstracts. From these, 51 reports were assessed for relevance on the basis of full texts. The figure below shows how reports were removed during stages of the record assessment process.

Figure B17 Flow of studies in systematic review to identify health state utility values



6.4.6 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.

A total of eight reports (relating to seven studies) met the inclusion criteria (see Table B52); two of these reports use the same data.[1, 92] The studies included patients with macular oedema secondary to RVO and some included patients who had other vitreoretinal disorders as well as RVO. Of the seven studies:

- Three studies (in four reports) provided utility values;[1, 92, 106, 107]
- One study provided preference values which were not utilities;[108]
- Three studies provided disease-specific HRQL values (VFQ-25).[11, 58, 109]

All studies were published in English and were conducted in the USA except for one (Okamoto 2010) that was conducted in Japan.[109] Where insufficient data were reported, authors were contacted. One study reported generic utility values by using SF-36 and EuroQol-5D (EQ-5D) for the specific population of interest that is MO

secondary to RVO.[106] This study was published as a conference abstract which contained no quantitative values. The main author of the study was contacted to request the full results, but no reply was received. Two studies reported utility values that were obtained by time trade off (TTO)[1, 107] and one of them also reported utility values that were obtained by standard gamble (SG), which were single attribute direct utility elicitation methods in a population that included RVO patients.[1] All utilities or HRQL values were from the perspective of the patients included in the studies assessing their own health. A 'full health' or 'highest possible function' high anchor was used, rather than a 'free of symptom' high anchor.

Brazier and colleagues (2009)[110] noted that the quality of utility studies can be difficult to assess from the information provided in publications. Several quality issues were apparent in the studies. Only Rentz (2010) had a large sample size, although the utilities were collected alongside a randomised clinical trial which might impact the generalisability of the results to a wider population of patients.[106] The other studies had small patient sample sizes. The reporting of methods was limited and impacted upon quality assessment.

Table B52 Studies selected for inclusion in the utilities/HRQL review

Brown GC. Vision and Quality of Life. *Transactions of the American Ophthalmology Society* 1999;97:473-511.[1]	
Objective	To determine the relationship of visual acuity loss to quality of life.
Methods	325 patients with visual loss to a minimum of 20/40 or greater in at least one eye were interviewed in a standardized fashion using a modified VFQ-14, questionnaire. Utility values were also obtained using both the TTO and standard gamble methods of utility assessment.
Participants	Patients with various vitreoretinal diseases were included: 7% had RVO. Results were reported separately for the better seeing eye and the worse seeing eye. Although patients who had bilateral eye involvement were included to the study, the utilities were not reported separately for this subgroup. Consecutive patients with: 1 Visual loss to a level of 20/40 or worse in at least one eye; 2 Visual loss occurring predominantly secondary to the same cause in each eye when the visual loss was bilateral, were selected for entrance into the study group. The patients were mostly from a population with vitreoretinal diseases seen in a hospital outpatient setting as well as in peripheral offices. Since many of the patients had more than one cause for visual loss

	(e.g. cataract and age-related macular degeneration), only patients who had, in the judgment of the examiner, at least 80% of their visual loss in an eye occurring secondary to one specific ocular disease entity were included. Questionable cases were excluded. Where there was doubt due to concomitant cataract and a posterior segment abnormality, a potential acuity meter reading was obtained. If the vision could be improved by greater than 20% (e.g. from 20/100 to 20/80, a 25% improvement), the patient was excluded. A vision of 20/40 or less in at least one eye was set as an entrance criterion, because previous focus group data had revealed that patients who have essentially normal vision in each eye have a visual utility value approaching 1.0. Such patients are often unwilling to trade time or risk immediate death in return for essentially no improvement in vision. Out of 2000 patients screened, 325 were finally included in the study. 40% were male (men: 120, women: 205) and 96% were Caucasian (African American: 12). The mean age was 67.5 years and the median age was 70 (range: 28 - 87 years). Primary causes of vision loss in the 325 patients were: ● Age-related macular degeneration: 107 (33%); ● Diabetic retinopathy: 107 (33%); ● Retinal detachment: 27 (7%); ● **Retinal vein occlusion: 26 (7%);** ● Cataract: 23 (7%); ● Macular hole: 7 (2%); ● Amblyopia: 6 (2%); ● Macular oedema: 5 (2%); ● Glaucoma: 4 (1%); ● Macular pucker: 4 (1%); ● Endophthalmitis: 3 (1%); ● Parafoveal telangiectasis: 2 (1%); ● Anterior ischaemic optic neuropathy: 2 (1%); ● X-linked retinoschisis: 1 (1%); ● Trauma: 1 (1%). Study country: USA.
Treatment	Not reported.
HRQL/Utility measurement	Three methods were used to measure HRQL related to vision loss in both the better seeing eye and worse seeing eye in the study: *1) New version of VFQ-14 form:* An evaluation of quality of life measured by questions similar to those in the VFQ-14. VFQ-14 evaluates the ability of a patient with visual loss to function in the activities of daily life. In addition to standard VF-14 questions, the form included questions that evaluated the degree of disability caused by ocular pain, depression and frustration. An overall subjective evaluation of the degree to which visual loss has decreased quality of life was included. The form included 10 questions that evaluated primarily activities that could be readily performed with uniocular vision and 12 questions

	about activities thought to be best performed with binocular vision. Eleven questions focused on basic activities for daily functioning (for example reading and driving), five questions were about social issues (for example interacting with friends), three questions about emotional or psychosocial issues associated with visual loss, and three questions about issues associated with work activities. These classifications are arbitrary and there is overlap between them. *2)Direct utility elicitation by standard gamble method* *3)Direct utility elicitation using time trade off method* Best-corrected visual acuity was correlated with the visual function score on the modified VFQ-14 questionnaire, as well as with utility values obtained using both the TTO and standard gamble methods (Table B53 and Table B54 contain the utility values).
Results	The utility results for both the worse and better seeing eyes are presented and discussed below this table.
Appropriateness for cost-effectiveness analysis	In the absence of utility values calculated from the EQ-5D, TTO-derived utilities are acceptable. Therefore the utility values for the better-seeing eye from this study are highly appropriate for use in the cost-effectiveness model. Further discussion and justification for use of the utilities from this study are provided below this table.
Brown *et al.* Incremental cost-effectiveness of laser therapy for visual loss secondary to branch retinal vein occlusion. *Ophthalmic Epidemiology* 2002;9:1-10.[92]	
Note:	Brown 2002 ascertained the incremental cost-effectiveness of therapeutic interventions (laser photocoagulation vs. no treatment) for improving visual loss associated with branch retinal vein occlusion. The utility values for the defined health states were taken from Brown 1999 (reported above).
Rentz AM et al. Normative comparison of generic- and vision-targeted health-related quality of life (HRQL) outcomes in patients with vision loss due to macular oedema following retinal vein occlusion. ARVO Meeting Abstracts. 2010;51:4728.[106]	
Objective	To assess the HRQL and visual functioning in patients with worse-seeing eye vision loss due to macular oedema following BRVO and CRVO compared to USA population norms.
Methods	Two generic and one vision-targeted HRQL measures (SF-36 health survey, EQ-5D and VFQ-25) were administered at baseline in two multicenter, masked, randomized, sham-controlled trials of dexamethasone intravitreal implant (Ozurdex®). SF-36 and EQ-5D scores were compared to general USA population scores from the National Health Medical Survey (NHMS). Analyses were performed for all patients and for worse-seeing eye study patients.
Participants	Total: 1171 patients (BRVO n:753, CRVO n:418). Mean age 65 years; 54% were male; 78% were white; and study-eye baseline mean visual acuity was 54 letters (20/80). The study eye was worse-seeing eye for 97% of participants. Study country: Implied as USA.
Treatment	Not reported.

HRQL/Utility measurement	No quantitative values were reported for SF-36, EQ-5D or VFQ-25 surveys.
Results	All patients and worse-seeing eye patients had significantly lower SF-36 mental component scores ($P < .001$), role-physical ($P < .001$), role-emotional ($P < .001$), and mental health ($P < .001$) scores compared to the reference group. No difference was observed for EQ-5D score. Compared to the normal vision group, total and worse-seeing eye patients reported significantly more impaired scores on all VFQ-25 subscales ($P < .05$) and for 7 subscales, differences exceeded 10 points.
Appropriateness for cost-effectiveness analysis	No useful numerical values were reported.
Real *et al.* The effect of co morbidities upon ocular and systemic health-related quality of life *British Journal of Ophthalmology* 2008;92:6:770-774.[107]	
Objective	To assess whether, and to what degree, co-morbidities affect patient quality of life.
Methods	A cross-sectional, quality-of-life study of 170 consecutive vitreoretinal patients compared the utility associated with a participant's primary (most incapacitating) disease and the utility associated with a grouping of all of the participants' diseases. All study participants answered TTO utility analysis questions for ophthalmic conditions. Anchors of death (utility=0.00) and normal bilateral vision permanently (20/20 or better bilaterally was given a utility of 1.00) were used.
Participants	The study included 170 patients with various vitreoretinal disorders: • Diabetic retinopathy 74 (43.5%) • Macular degeneration 51 (30.0%) • Retinal detachment/tear 12 (7.1%) • Lattice degeneration/posterior vitreous detachment 11 (6.5%) • **Central/branch retinal vein occlusion 7 (4.1%)** • Uveitis 3 (1.8%) • Macular pucker 3 (1.8%) • Cystoid macular oedema 2 (1.2%) • Retinal/choroidal haemangioma 2 (1.2%) • Central retinal artery occlusion 1 (0.6%) • Central serous chorioretinopathy 1 (0.6%) • Coats disease 1 (0.6%) • Radiation retinopathy 1 (0.6%) • Trauma 1 (0.6%) It was not stated whether the RVO was unilateral nor whether the results were being reported for the worse/better seeing eye. The Snellen visual acuity in the better-seeing eye (N=170) ranged from 20/20 to light perception. The mean Snellen decimal vision in the better-seeing eye was 0.49 (approximately 20/40) and the median vision was 20/40. Therefore, it is implied that the results were reported for the better-seeing eye. Study participants included consecutive adult patients drawn from a

	vitreoretinal ophthalmic practice in Wills Eye Hospital. 104 (61%) were women. 150 participants were Caucasian (88%) and 20 were non-Caucasian (12%). Participants' mean age was 68.6 (SD 12.5) years, with a median of 71 years. Participants had a mean 1.8 (0.7) co-morbidities. Study country: USA.
Treatment	Not reported.
HRQL/Utility measurement	The TTO utility analysis questions were asked in a similar order for each health condition: • How long do you expect to live? • What is the maximum amount of your estimated remaining time of life, if any, would you be willing to theoretically trade in return for an intervention which immediately cures your health problem permanently? After answering TTO utility analysis questions concerning individual health conditions, participants were asked: • What is the maximum amount of your estimated remaining time of life, if any, would you be willing to theoretically trade in return for interventions which immediately and permanently cure all of your health problems? This question asked how much time a participant was willing to trade to eliminate a primary disease along with all co-morbidities. For the purpose of this study, the primary disease was defined as the health condition perceived by the participant to have the most adverse (or least desirable) effect upon their quality of life. The primary disease was thus associated with the lowest utility value reported for a single disease. Other health conditions accompanying the primary disease were considered to be co-morbidities. The number of disease-specific assessment forms completed by each participant was arbitrarily limited to five because of patient fatigue. Where the selection of particular health conditions and the exclusion of others was required, the screening researcher selected the diseases which the participants believed to most severely affect their quality of life.
Results	There was no significant difference between the mean utility reported for the primary health condition and the mean utility associated with the combination grouping of all health conditions (N=170; p=0.56). The mean lowest utility reported for a single disease was 0.82 (0.22), and the mean utility value associated with eliminating all studied diseases was 0.80 (0.24). Among the 96 (56% of total) participants who traded time of remaining life to eliminate at least one health problem, there was also no significant difference between the mean primary disease utility and the mean utility associated with being rid of all discussed health problems (primary disease and co morbidities) (p=0.40). The mean lowest utility reported in this subset of patients for the primary disease was 0.68 (0.20), and the mean utility associated with eliminating all studied diseases was 0.65 (0.22).
Appropriateness for cost-effectiveness analysis	The use of the utility values reported by this study in the economic model is limited for several reasons. Firstly, the study does not report whether the results are for the better or worse seeing eye. Secondly,

	utility values were not measured for different visual acuity levels.
Deramo VA *et al.* Vision-related quality of life in people with central retinal vein occlusion using the 25-item national eye institute visual function questionnaire. *Archives of Ophthalmology* 2003;121:1297-1302.[11]	
Objective	To study visual function and vision-related quality of life in persons with central retinal vein occlusion using the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25).
Methods	Interviewer-administered study of individuals with central retinal vein occlusion. Scores on the VFQ-25 were analysed and converted to a 100-point scale in which 100 represents the best possible score and 0 represents the worst. Subscale results were compared with previously published data, and a subgroup analysis was performed.
Participants	Only patients with CRVO in at least one eye were included. 63% were ischaemic CRVO. Although patients who had bilateral eye involvement were included in the study, the scores were not reported separately for this subgroup. Quantitative subscale responses obtained by VFQ-25 were reported for the involved worse seeing eye. All patients with a clinical diagnosis of central retinal vein occlusion (CRVO) were identified by a search of the computerised patient database of the Duke University Eye Centre (Durham, NC) from August 1998 to July 1999 inclusive. The single inclusion criterion was the presence of CRVO in at least one eye. Patients were excluded from the study if they were younger than 18 years of age or had no recorded examination by a retinal specialist at the institution to verify the diagnosis. The presence of macular oedema was not an inclusion criterion in this study. There were 51 participants with a mean age of 69.5 (±13.1) years. 27 (53%) were female. The median visual acuity of the affected eye was counting fingers. The median duration of symptoms was one year (range: 0.2 - 14), ischaemic CRVO was seen in 32 participants (63%). 10 (20%) participants were employed and 15 (29%) were living alone. The values obtained were compared with previously known data from a reference group without ocular disease, persons with diabetic retinopathy and individuals with low vision from a variety of causes. CRVO group contained 51 participants. The reference group comprised 122 participants (previously known) and the diabetic retinopathy group contained 123 patients (previously known). Study country: USA.
Treatment	Not reported.
HRQL/Utility measurement	Respondents completed 20-minute surveys during their routine clinic appointment or by interview, administered by one of the authors. The interviewer was not the patient's regular physician. The data of patients with bilateral and unilateral involvement were analyzed separately. The VFQ-25 comprises 25 items that require the patient to assess the levels of difficulty of particular visual symptoms or day-to-day

	activities. The VFQ-25 addresses 12 subscales: general health (one question), general vision (one question), near vision (three questions), distance vision (three questions), driving (two questions), peripheral vision (one question), colour vision (one question), ocular pain (two questions), role limitations (two questions), dependency (three questions), social function (two questions) and mental health (four questions). The subscales have 0 to 100 points, where 100 indicates the highest possible function or minimal subjective impairment. Each subscale represents the average of one or more questions. The VFQ-25 composite score is calculated as the unweighted average response to all items, excluding the questions on general health. 48 of the 51 patients in this study had unilateral involvement and five had bilateral involvement. Two patients were surveyed twice, initially with unilateral CRVO and again after developing bilateral CRVO.
Results	VFQ-25 scores were significantly lower ($p<0.001$) for all VFQ-25 subscales apart for ocular pain ($p=0.9$) in the CRVO group compared to the reference group. VFQ-25 scores (±SD) for the CRVO group ranged from 50±39 (driving) to 85±18 (ocular pain).
Appropriateness for cost-effectiveness analysis	No utility values were reported; therefore the study does not inform the economic model.
Chang MA *et al.* Patients' preferences in choosing therapy for retinal vein occlusions. Responsiveness of disease-specific and generic utility instruments in prostate cancer patients. *Retina* 2007;27;6:789-797.[108]	
Objective	To assess preference values for vein occlusions with macular oedema and to determine how this might affect patients' perceptions of potential treatments.
Methods	The Submacular Surgery Trials Vision Preference Value Scale and questions regarding enthusiasm for potential treatments were administered to 153 patients with retinal vein occlusion. Relationships between preference values and enthusiasm were assessed.
Participants	Patients were eligible if the RVO was recent onset (less than one year before presentation to the retina division) and if macular oedema was documented at presentation or during follow-up examination. If RVO was present in both eyes, the more recently affected eye was included in the study. 153 participants were included with a mean age at onset of 68.6 years (±12.3). 47.1% were male, 72 (54.9%) had BRVO and 69 (45.1%) had CRVO. 63.8% of participants had hypertension, 36.8% hyperlipidaemia, 14% heart disease, 13.2% diabetes and 10.5% bilateral RVO. 42.1% of participants had cataract, 20.5% had glaucoma and 9.2% had early or intermediate acute macular age-related degeneration (AMD). 153 participants, 69 with CRVO and 84 with BRVO. Study country: USA.
Treatment	Patients received the following treatments: observation only, laser

	photocoagulation or intravitreal triamcinolone.
HRQL/Utility measurement	The primary outcome variable was defined as the overall preference value assigned by study subjects with RVO to their visual state. Preference values were graded on a zero to one scale, from death to perfect health. Secondary outcomes included level of enthusiasm for potential treatments for RVO and how preference values were related to level of enthusiasm. Enthusiasm for each treatment was defined as the percentage of patients stating qualitative preference in four categories ranging from "Not enthusiastic" to "Very enthusiastic". Both preference values for BRVO/CRVO and enthusiasm rates for each intervention were not utilities.
Results	The mean preference value (± SD) was 0.65±0.20 for patients with BRVO and 0.65±0.19 for patients with CRVO. For patients with vein occlusions for one year or longer (n=128) the mean preference value was 0.64±0.20, whereas for patients who had had vein occlusions for a year or less the mean preference value was 0.72±0.15 (n=25) (p=0.04). The preference values were also significantly different for patients with vein occlusions for two years or less (n=80) and those with RVO for more than two years (n=73) (0.69±0.18 vs. 0.61±0.20, p=0.01). There were no significant differences in preference values among those with RVO for more than 3 years compared to those with RVO for three years or less, or when considering a four year cut-off. In multivariate regression models adjusting for potential confounders, the last recorded logMAR visual acuity in the study eye (p=0.02) appeared to be related to preference value.
Appropriateness for cost-effectiveness analysis	Although the values were between zero and one, they were not defined as utilities in the study. As such, they are not useful to inform economic models based on the NICE reference case.
Okamoto *et al.* Vision-related quality of life and visual function after vitrectomy for various vitreoretinal disorders. *Investigative Ophthalmology & Visual Science* 2010;51:2:744-751.[109]	
Objective	To investigate vision-related quality of life (VR-QOL) in patients undergoing vitrectomy for various vitreoretinal disorders and to evaluate the relationship between VR-QOL and visual function.
Methods	The 25-item National Eye Institute Visual Function Questionnaire (VFQ-25) was answered by the patients with vitreoretinal disorders. Clinical data were collected, including visual acuity, contrast sensitivity, and severity of metamorphopsia.
Participants	The study included 100 normal control subjects and 299 patients with various vitreoretinal disorders: • 99 with proliferative diabetic retinopathy (PDR); • 38 with diabetic macular oedema (DMO); • **20 with branch retinal vein occlusion (BRVO);** • **12 with central retinal vein occlusion (CRVO);** • with macular hole (MH); • 33 with epiretinal membrane (ERM); • 55 with rhegmatogenous retinal detachment (RD). The results were reported separately for the CRVO and BRVO patients. The report did not describe whether the disease was unilateral nor whether the results were reported for the better or

	worse-seeing eye. All patients underwent pars plana vitrectomy surgery at Tsukuba University Hospital between June 14, 2005, and April 20, 2007. The 12 CRVO patients had a mean age of 62.4 years and a male to female ratio of 9/3. For CRVO, 12 eyes were assessed. The 20 BRVO patients had a mean age of 64.1 years and the male to female ratio was 9/11. For BRVO, 20 eyes were assessed. Study country: Japan.
Treatment	Both groups (patients and controls) answered the VFQ-25 before and 3 months after surgery.
HRQL/Utility measurement	The patients answered the VFQ-25 before surgery and three months after surgery. In the patients with retinal detachment, preoperative evaluation by VFQ-25 was not performed, because of the rapid nature of its onset. The research staff explained the questionnaire to the patients, gave instructions verbally, and provided assistance when required. A description of the VFQ-25 can be found in Deramo 2003, above.
Results	VFQ-25 scores were significantly lower ($p<0.01$) for all VFQ-25 subscales apart for ocular pain in the CRVO and BRVO pre- and post-operative groups compared to the reference group. VFQ-25 subscale scores (±SD) for the pre-operative CRVO group ranged from 47.9±17.4 (general health) to 78.1±20.7 (ocular pain). VFQ-25 subscale scores for the pre-operative BRVO group ranged from 40.0±12.9 (general health) to 73.1±20.0 (ocular pain).
Appropriateness for cost-effectiveness analysis	No utility values were reported; therefore the study does not inform the economic model.
Awdeh RM *et al.* Vision-related quality of life in persons with unilateral branch retinal vein occlusion using the 25-item national eye institute visual function questionnaire. *British Journal of Ophthalmology* 2010;94:319-323.[58]	
Objective	To evaluate vision-related quality of life in persons with branch retinal vein occlusion (BRVO) using the 25-item National Eye Institute Visual Function Questionnaire (NEI VFQ-25).
Methods	Observational, cross-sectional, interviewer-administered study. 46 patients with unilateral BRVO were included. Scores on the VFQ-25 were analyzed and converted to scaled scores using NEI VFQ-25 algorithms. Clinical data including age, gender, employment status, living arrangements, visual acuity, number of systemic diseases and duration of BRVO were also recorded. Subscale results were compared with previously published data, and subgroup analyses were performed.
Participants	Only results of unilateral BRVO were reported. The first 50 consecutive patients to complete the above questionnaire participated in the study. Forty-six patients with unilateral BRVO were included in this analysis and four patients with bilateral BRVO were excluded. The average age of participants was

	67.8 years (range: 44 - 83). 23 (50%) were male. The median visual acuity (logMAR) in the affected eye at the time of study entry was 0.4771 (approximately 20/60). Thirty-three eyes had unilateral BRVO with a visual acuity of 20/25 or better in the fellow eye. The mean duration of the occlusion prior to administration of the VFQ-25 was 1.7 years (SD=1.6 years). Other groups that were known from previous reports: Reference group N: 22; Diabetic retinopathy N: 123; CRVO N:51; AMD N:108; LV N:90. Study country: USA.
Treatment	Not reported.
HRQL/Utility measurement	The VFQ-25 was used to measure HRQL values. A description of the VFQ-25 can be found in Deramo 2003, above. Guidelines published by the NEI were adhered to when calculating the scale conversions and subscale scores.
Results	The VFQ-25 subscale values reported for CRVO patients were those already reported by Deramo 203 (see above). VFQ-25 subscale scores for the BRVO group ranged from 61.4±20.9 (general health) to 96.7±12.5 (colour vision).
Appropriateness for cost-effectiveness analysis	No utility values were reported; therefore the study does not inform the economic model.

As described in the table above very few of the studies reported utility values. The only study that reports utility values by VA, and is therefore appropriate for use in cost effectiveness analysis, is Brown 1999.[1] This study presented utilities for both the WSE and the BSE as shown in Table B53 and Table B54 respectively. However, in this study, there was little discernible correlation between VA in the WSE and mean utility values of the five visual subgroups using either the TTO or standard gamble methods (Table B53). With the TTO method, the group with 20/40 to 20/50 vision in the WSE had a mean utility value of 0.86 (95% CI 0.78-0.94), while those with no light perception in the WSE had a mean utility value of 0.81 (95% CI, 0.67-0.95). The difference between these two subgroups was not significant (p=0.70) with the heteroscedastic, two-tailed Student's t test. The difference between the extreme standard gamble subgroups was also not significant (p=0.65) (Table B53).

This lack of correlation between VA in the WSE and utility reported by Brown and colleagues is not corroborated by studies that report on the quality of life. Deramo 2003 found that for the majority of VFQ-25 subscales, the HRQL scores were significantly lower in the CRVO group, where the affected eyes were the WSEs, than in the reference group, indicating that loss of vision in the WSE does have a negative

impact upon HRQL.[11] Awdeh 2010 found that HRQL scores for BRVO patients were associated with the level of VA in the affected eye, even if the other eye had good vision.[58] These findings are corroborated by the BRAVO and CRUISE studies for ranibizumab, where approximately 90% of the patients were affected in the WSE. In these studies treatment with ranibizumab was associated with a significantly greater improvement at month 6 on the VFQ-25 than that observed in the sham injection-treated group for both BRVO and CRVO patients.[24, 25] Therefore the WSE utilities from Brown 1999 do not seem to be representative of the true quality of life loss caused by vision impairment in the worse-seeing eye due to RVO.

For the BSE, using the TTO method, the mean utility values from Brown 1999 ranged from 0.92 with 20/20 vision to 0.35 when the vision was in the 'hand motions to no light perception' range in the better eye (Table B54).[1] As the visual acuity in the better eye decreased, the corresponding TTO utility value concomitantly decreased at every visual stratification level. The most dramatic decreases in mean utility values occurred when the vision changed from 20/70 to 20/100 (-0.07 utility change), from 20/300 to 20/400 (-0.09 utility change), and from 'counting fingers' to 'hand motions/light perception' (-0.17 utility change). Utility values obtained with the standard gamble method also generally decreased as the vision in the better-seeing eye worsened, but the decrease was not as direct and consistent as with the TTO method. At the 20/20 level the mean utility value was 0.96, while at the 'hand motions to counting fingers' range it dropped to 0.49 (Table B54).

Table B53 Utility values for the worst-seeing eye (Brown 1999)[1]

	Utility values associated with visual acuity in the worse-seeing eye		
Visual acuity	**Number of patients**	**Time trade-off**	**Standard gamble**
All patients in the study	78		
20/40-20/50	18	0.86 (SD=0.18)	0.93 (SD=0.13)
20/70-20/100	12	0.90 (SD=0.16)	0.96 (SD=0.05)
20/200-20/400	13	0.95 (SD=0.12)	0.94 (SD=0.13)
Counting fingers-light perception	28	0.88 (SD=0.18)	0.92 (SD=0.14)
No light perception	7	0.81 (SD=0.19)	0.95 (SD=0.08)

Note: This is a subgroup of patients out of a total of 325 patients. 78 patients had good vision (20/20 to 20/25) in 1 eye. These 78 patients were subdivided, according to the visual acuity in the eye with the worst vision.

Table B54 Utility values for the better-seeing eye (Brown 1999)[1]

	Utility values associated with visual acuity in the better-seeing eye			
Visual acuity	**Number**	**Time trade-off**	**Standard**	**P value**

	of patients		gamble	
All patients in the study	325	0.77 (SD=0.23)	0.85 (SD=0.21)	<.001
20/20	32	0.92 (SD=0.13)	0.96 (SD=0.06)	0.02
20/25	50	0.87 (SD=0.19)	0.92 (SD=0.15)	0.01
20/30	44	0.84 (SD=0.19)	0.91 (SD=0.18)	0.03
20/40	54	0.80 (SD=0.22)	0.89 (SD=0.17)	0.003
20/50	31	0.77 (SD=0.20)	0.83 (SD=0.15)	0.15
20/70	40	0.74 (SD=0.21)	0.80 (SD=0.25)	0.12
20/100	18	0.67 (SD=0.21)	0.82 (SD=0.22)	0.002
20/200	16	0.66 (SD=0.23)	0.80 (SD=0.21)	0.004
20/300	13	0.63 (SD=0.16)	0.78 (SD=0.21)	0.01
20/400	9	0.54 (SD=0.17)	0.59 (SD=0.19)	0.4
Counting fingers	12	0.52 (SD=0.29)	0.65 (SD=0.26)	0.02
Hand motions-no light perception	6	0.35 (SD=0.29)	0.49 (SD=0.37)	0.43

When the mean utility values for the TTO and SG methods were compared using the paired, two-tailed Student's t test, the difference between the means was highly significant ($p<0.001$). Brown suggested that participants understood the TTO concepts substantially better than the SG concept, so TTO results are likely to be more reliable.[1] Additionally, as was likely to be the case in this study, evidence has accumulated that the SG method overestimates risk aversion.

Based on this review of the HRQL and the appraisal of identified studies the TTO results for the BSE as reported in Brown 1999 were utilised in the model. Whilst the use of TTO utilities is consistent with the NICE's stated preference for utility data, where EQ-5D data are not available, the use of a patient sample is not. It is generally believed that patients report higher values for health states than the general public.[111] However for conditions resulting in visual impairment, there is evidence that this paradox may be reversed, with the general public and health professionals reporting higher values for health states than patients.[112]

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

Not applicable.

Adverse events

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

Disutilities were applied to each patient experiencing an adverse event in the model. Rates were only available for the twelve-month trial period, without a detailed breakdown of the timing of the events and therefore the disutilities were calculated as one-off events, weighted by the expected duration of the quality of life impact. The disutilities of adverse events are shown in Table B55.

The disutility with cataracts was taken from a study in neovascular macular degeneration.[113] For increased IOP it was assumed that the disutility would be equal to utility for drug-treated ocular hypertension.[114] The duration of cataracts and IOP increased was based on expert clinical opinion.

For stroke the Schwander study reported that the utility level for people with stroke was 0.66.[115] If it is assumed that the highest utility level that patients with eye diseases that causes vision loss is 0.92 (reported by Brown 1999[1]), then the loss in utility (the disutility) that stroke would cause is 0.92-0.66=0.26. This disutility was multiplied by the remaining life expectancy in the model.

Table B55 Disutilities of adverse events

Adverse event	Disutility	Source	Duration (months)	Source
Cataracts	-0.14	Brown et al. 2007[113]	6.00	Assumption
IOP increased (treated with drug)	-0.01	Vaahtoranta-Lehtonen *et al*. (2007)[114]	0.03 (one day)	Assumption
IOP increased (treated with surgery)	-0.01	Vaahtoranta-Lehtonen *et al*. (2007)[114]	6.00	Assumption
Stroke	-0.26	Schwander *et al*. 2009[115]	Lifetime	Assumption

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

6.4.9 Please summarise the values you have chosen for your cost-effectiveness analysis in the following table, referencing values obtained in sections 6.4.3 to 6.4.8. Justify the choice of utility values, giving consideration to the reference case.

The literature review described in section 6.4.6 demonstrates that there is very limited evidence regarding utility data in RVO. There is a particular paucity of

evidence for utility change associated with the VA of the WSE. The study by Brown 1999 presents results that are most appropriate for inclusion in the economic model, as they most closely meet the requirements of the NICE reference case. [1] A limitation of this study is that it was a mixed patient population with 7% of patients having RVO in the BSE. However, the HRQL data from other conditions associated with a loss of VA is assumed to be appropriate for the RVO patient population.

As described previously in section 6.4.6 this study included results of quality of life scores related to the WSE but these results appear to be illogical (e.g. in some cases utilities increased as the vision deteriorated) due to the small sample size available per VA level. As such, the base case analysis uses utility data drawn from utilities for the BSE from Brown 1999. [1]

Utilities were applied to each health state in order to generate quality-adjusted life years.

Table B56 Summary of quality-of-life values for cost-effectiveness analysis

State	Utility value	Reference in submission	Justification
VA 86-100 letters	0.920	Brown 1999	As described in Section 6.4.6
VA 76-85 letters	0.880	Brown 1999	As described in Section 6.4.6
VA 66-75 letters	0.770	Brown 1999	As described in Section 6.4.6
VA 56-65 letters	0.755	Brown 1999	As described in Section 6.4.6
VA 46-55 letters	0.670	Brown 1999	As described in Section 6.4.6
VA 36-45 letters	0.665	Brown 1999	As described in Section 6.4.6
VA 26-35 letters	0.645	Brown 1999	As described in Section 6.4.6
VA<25 letters	0.510	Brown 1999	As described in Section 6.4.6
Death	0.000	Brown 1999	As described in Section 6.4.6
Cataracts	-0.14	Brown *et al*. 2007	As described in Section 6.4.8
IOP increased (treated with drug)	-0.01	Vaahtoranta-Lehtonen *et al*. (2007)	As described in Section 6.4.8
IOP increased (treated with surgery)	-0.01	Vaahtoranta-Lehtonen *et al*. (2007)	As described in Section 6.4.8
Stroke	-0.26	Schwander *et al*. 2009	As described in Section 6.4.8

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

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality 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).

The clinical experts who provided advice regarding resource use and clinical assumptions in the model were asked for their advice about the applicability of utilities derived from patients with visual impairment due to non-RVO diseases to patients with visual impairment due to MO secondary to RVO. The clinical experts concluded that age and extent of affected eyes were important in determining whether utilities were applicable across vision disorders. Furthermore, the rapid onset of vision loss with RVO was likely to have an important influence on quality of life, and utilities. The clinical experts also highlighted that the extent of loss of the visual field versus central vision loss is different between ocular diseases. These factors could be important in determining the patients' visual function and therefore impact of VA on their health related quality of life.

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

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

HRQL is expected to change according to the health state. The higher the level of VA observed in a patient, the better the HRQL experienced. Lower health states represent worsening VA and therefore, patients are expected to experience worse HRQL. HRQL was assumed to remain constant within each health state.

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

Some adverse events observed in the BRAVO and CRUISE trials were excluded from the analysis as they were considered transient and mild and therefore have a negligible impact on utility values attached to them. Only those adverse events known to require active management were included in the analysis; in the absence of utility data specific to these adverse events their impact on HRQL were excluded.

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

Not applicable.

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

HRQL is assumed to be constant over time and dependent on the health state based on VA.

In the model utilities are independent of age. This is appropriate as it assumes that older patients have the same capacity to benefit from improved vision as younger patients. It is also in line with the NICE methods guide which states in paragraph 5.12.2 that ‘an additional QALY is of equal value regardless of other characteristics of the individuals’. It is worth noting that any impact of changing utilities with age on the model results is expected to be negligible.

6.4.15 Have the values in sections 6.4.3 to 6.4.8 been amended? If so, please describe how and why they have been altered and the methodology.

Not applicable.

6.5 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

6.5.1 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.

Laser is the current standard of care for BRVO in the NHS. The HRG descriptions for laser (including administration) and administration of ranibizumab used for NHS costing are as follows:

Table B57 HRG codes

HRG code	HRG name
BZ22Z	Vitreous Retinal Procedures – category 2
BZ23Z	Vitreous Retinal Procedures – category 1

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

- Laser photocoagulation to lesion of the retina NEC (C82.6) – vitreous retinal (VR) banding of 1.
- Injection of therapeutic substance into posterior segment of eye NEC (C89.3) – VR banding of 2 (for ranibizumab)

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

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

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

The NHS Reference Costs are more appropriate because they represent the actual national average costs that have already been incurred as a result of delivering care. These costs take into account staff time, event-based time and standard equipment time. Thus, they include opportunity costs, whereas the PbR Tariffs are prices (or prospective costs) which are prone to adjustment in the future. Thus at point of use in the model, costs based on the PbR Tariff will not reflect opportunity costs of delivering care.

Resource identification, measurement and valuation studies

6.5.3 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 9.13, appendix 13. If the systematic search yields limited UK-specific data, the search strategy may be extended to capture data from non-UK sources. Please give the following details of included studies:

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

The systematic review to identify relevant resource use data for the UK was performed alongside the review to identify relevant cost-effectiveness studies and the same methodology and search strategy were used (see Section 6.1.1 and Section 9.10, Appendix 10).

No UK specific resource use data could be identified. Therefore papers reporting resource use for other countries were included. One abstract and one full paper were

identified.[13, 116] The abstract (Sahel 2009) reported the costs and resource use of BRVO and CRVO in Germany, France and Italy and the authors of this study were funded by Allergan to undertake this analysis. [116] As there were no numerical results reported and a full report could not be identified, this abstract was excluded from the review.

The full paper by Fekrat and colleagues (2010) reported a US study that evaluated resource use and costs of BRVO and CRVO in the elderly. The objective of the study was to examine the incidence, prevalence, resource use and costs associated with BRVO and CRVO in elderly patients.[13] The study had a retrospective cohort design using a nationally representative sample of Medicare beneficiaries from 2001 through to 2006. Costs and resource use were derived from a Medicare database (5% of the beneficiaries were sampled). Therefore, the perspective of the study was understood to be the health care payer. The authors identified patients with BRVO (n=10,682) and CRVO (n=6,236) and controls with hypertension (n=49,524), and glaucoma (n=49,569) but no RVO.

The costs results showed that after adjustment for baseline characteristics, incident BRVO was associated with 17% higher one-year costs and 13% higher three-year costs compared with hypertension and 18% higher one-year costs and 11% higher three-year costs compared with glaucoma. Incident CRVO was associated with 24% higher one-year costs and 16% higher three-year costs compared with hypertension and 24% higher one-year costs and 14% higher three-year costs compared with as glaucoma .

Table B58 presents the details of the resource use in the study. With the exception of optical coherence tomography, patients with BRVO and CRVO received more imaging and treatment services than controls ($p<0.05$ for all comparisons) (Table B58). Moreover, unadjusted mean one-year and three-year total direct medical costs were greater among all cases than controls at all time points. Inpatient costs accounted for approximately 40% of total Medicare payment. Inpatient, outpatient, and professional claims accounted for at least three quarters of total costs, and skilled nursing, home health, hospice, and durable medical equipment payments accounted for less than 25%. Costs in the year before incidence were nearly 30% lower for patients with BRVO ($7,211 vs. $10,153) and 24% lower for patients with CRVO ($8,851 vs. $11,587). Costs in the hypertension and glaucoma control groups during the year before the index date were 7% and 15% lower, respectively.

There were several limitations to the study. It was not generalisable to younger patients, or managed-care beneficiaries, and it did not include non-medical expenditures or outpatient prescriptions. There are potentially incomplete diagnosis and procedure costs. The authors could not account for clinical variables such as the amount of vision loss and it was not feasible to adjust for whether one or both eyes were affected or treated. A full quality assessment of the study is presented in Section 10.6, Appendix 18.

Table B58 One-year resource use reported in Fekrat et al 2010

Procedure	BRVO (n = 10,682)	CRVO (n = 6,236)	Hypertension (n = 49,524)	p-value for BRVO vs. hypertension	p-value for CRVO vs. hypertension	Glaucoma (n = 49,569)	p-value for BRVO vs. glaucoma	p-value for CRVO vs. glaucoma
Fluorescein angiography	45.0	38.9	2.2	<0.001	<0.001	3.2	<0.001	<0.001
Intravitreal injection	6.1	8.2	0.2	<0.001	<0.001	0.3	<0.001	<0.001
Laser photocoagulation	20.5	9.6	0.5	<0.001	<0.001	0.6	<0.001	<0.001
Optical coherence tomography	16.0	16.6	4.9	<0.001	<0.001	28.2	<0.001	<0.001
Pan-retinal laser photocoagulation	7.6	14.8	0.3	<0.001	<0.001	0.4	<0.001	<0.001
Vitrectomy	3.1	5.5	0.2	<0.001	<0.001	0.3	<0.001	<0.001

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

- the criteria for selecting the experts
- the number of experts approached
- the number of experts who participated
- declaration of potential conflict(s) of interest from each expert or medical speciality 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).

Three clinical experts were selected and invited to participate in a telephone interview to discuss clinical assumptions applied to the economic model. Each were consultant ophthalmologists currently practising in NHS general (2) and teaching (1) hospitals in England. The consultants were offered honoraria for their time spent in preparation and for the telephone call. Background reading and an outline of the discussion points was provided in advance and is presented in Section 10.9 appendix 21. Summarised notes of the telephone discussions are also presented in Section 10.9, appendix 21. The opinion of the clinical advisers guided decisions as to the acceptability of key assumptions in the model from a clinical practice.

Intervention and comparators' costs

6.5.5 Please summarise the cost of each treatment in the following table. Cross-reference to other sections of the submission; for example,

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

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 6.2.2.

Costs were obtained from published sources in order to calculate the cost per intervention for each of the treatments. These are summarised in Table B59.

For laser treatment there are no direct treatment costs. It could be argued that there would be a marginal depreciation cost each time the equipment is used and subsequently maintained, but no data are currently available. As such, only an administration cost was applied. The ranibizumab injection administration visit was also costed as an office based outpatient procedure (Vitreous Retinal Procedures - category 1).[117] For dexamethasone implant, based on clinical opinion and the manufacturer's submission to NICE, a weighted average cost of an outpatient procedure (75%) and day case procedure (25%) (Vitreous Retinal Procedures - category 1) was assumed in order to account for the greater complexity of the implant procedure.

The cost of OCT was estimated to be the same as an outpatient diagnostic procedure coded as an ultrasound scan of less than 20 minutes (RA23Z). Although the OCT procedure would be expected to be superseded by the administration visit with regards to determining NHS Reference costs in NHS practice, a more conservative approach was taken and the cost of OCT was applied separately. It is recognised that this may represent double counting, but any impact would be biased against ranibizumab.

Table B59 Unit costs associated with the technology in the economic model

	Ranibizumab	Section in submission	BRVO - Laser	Ref. in submission	CRVO - Observation	Ref. in submission	B&CRVO Dex	Ref in submission
Technology cost	£742.17	1.10	£0.00	NA	£0.00	NA	£870.00	NA
Administration cost	£192.00[a]	1.5	£192.00[b]	NA	£0.00	NA	£295.25[c]	NA
Follow up visit cost	£151.00	1.5	£151.00	NA	£151.00	NA	£151.00	NA

[a] Ranibizumab injection visit (£137) + optical coherence tomography (£55)
[b] Laser administration cost (£137) + optical coherence tomography (£55). 57% of patients incur laser costs as per control arm of BRAVO
[c] Dexamethasone implant visit (£240) + optical coherence tomography (£55)

In addition to the treatment and administration costs, patients with RVO also require follow up visits in order to monitor their disease status. In many cases, such follow up visits can be combined with a treatment visit and, as such, would not incur any additional costs. However, there will be some occasions whereby a patient requires follow up without treatment and these costs are included in the model. The cost of a follow up visit (irrespective of the treatment being received at other times) is shown in Table B60. The staffing cost was for a consultant led multi-professional face to face follow up visit for ophthalmology. As before the cost of OCT was estimated to be the same as an outpatient procedure coded as an ultrasound scan of less than 20 minutes (RA23Z).

Table B60 Follow up visit costs

Treatment	Cost per visit
Staffing (ophthalmologist)	£96.00
OCT	£55.00
Total	**£151.00**

Treatment follow up and frequency

The costs described above were multiplied by the frequency of treatment visits and follow up visits in order to calculate total costs. The frequency of treatment differed between BRVO and CRVO, and the details are shown below.

The frequencies of injection visits in year 1 and 2 of the model for ranibizumab were taken from the BRAVO, CRUISE and HORIZON studies as described in Table B16. The number of laser treatments in year 1 and year 2 are taken from the SCORE study which compared laser with IVT in patients with MO secondary to BRVO.[32]

In the BRAVO trial, 57.6% of patients in the control standard care arm received laser treatment. Therefore, the cost of administration was applied to 57.6% of patients in the laser standard care arm of the BRVO model. In the SCORE trials almost 80% of patients received laser in the first year, therefore this is a conservative estimate.[77] Costs of laser were not included in the base case analysis for 21.6 % of patients in the ranibizumab 0.5 mg arm of BRAVO, given that laser did not appear to add benefit to these patients and this treatment approach is unlikely to reflect NHS clinical practice.

Table B61 Frequency of treatment and follow up (BRVO)

	Year 1		Year 2		Year 3+	
Treatment	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**
Ranibizumab	8.0[a]	4.0[b]	2.5[c]	3.5[d]	0.0[e]	2.0[f]
Grid laser (standard care)	1.5[g]	2.5[f]	1.0[g]	3.0[f]	0.0[e]	2.0[f]
Dexamethasone	2.0[h]	6.0[i]	2.0[h]	6.0[i]	0.0[e]	2.0[f]

a BRAVO (data on file)
b Assumption; SPC (based on a total of 12 visits of any type per year)
c HORIZON (data on file)
d Assumption; HORIZON, expert opinion (based on a total of 6 visits of any type per year)
e Assumption; expert opinion
f Assumption; expert opinion (based on a total of 4 visits of any type per year)
g SCORE study[32]
h NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.
i. Assumption (based on a total of 8 visits of any type per year)

Table B62 Frequency of treatment and follow up (CRVO)

	Year 1		Year 2		Year 3+	
Treatment	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**	**Injection visits**	**Follow up visits**
Ranibizumab	9.0[a]	3.0[b]	3.8[c]	6.2[d]	0.0[e]	4.0[f]
Standard care	0.0[e]	6.0[g]	0.0[e]	4.0[f]	0.0[e]	4.0[f]
Dexamethasone	2.0[h]	6.0[i]	2.0[h]	6.0[i]	0.0[e]	4.0[f]

a CRUISE (data on file)
b Assumption; SPC (based on a total of 12 visits of any type per year)
c HORIZON (data on file)
d Assumption; HORIZON, expert opinion (based on a total of 10 visits of any type per year)
e Assumption
f Assumption; expert opinion (based on a total of 4 visits of any type per year)
g Assumption; expert opinion (based on a total of 6 visits of any type per year)
h. NICE Dexamethasone intravitreal implant (Ozurdex®) for the treatment of macular oedema caused by retinal vein occlusion STA. September 2010.
i. Assumption (based on a total of 8 visits of any type per year)

Health-state costs

6.5.6 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 6.2.4.

Based on a systematic review no data were found to link disease severity with resource use in RVO. However, patients considered to be blind (i.e. those patients whose VA is below 35 letters) have been demonstrated to incur significant lifetime costs. The costs were drawn from the same reference source used in previous appraisal of interventions for ocular conditions, using the same approach as the ERG applied in the single technology appraisal for dexamethasone in the treatment of MO due to RVO. Costs were uprated to 2010 using the Personal and Social Services Research Unit (PSSRU) Health and Social Care Services (HSCS) index.[118, 119] These costs are shown below in Table B63.

This analysis assumes that low vision aids and low vision rehabilitation (in addition to blind registration) are costs that are experienced once only in the first year of blindness and these are not included in the subsequent year costs. This is in line with other evaluations conducted in RVO and this assumption has been retained for consistency. However, it should be noted that in their response to technology appraisal TA155 the Royal National Institute of Blind People (RNIB) indicated that the costs of low vision aids and low vision rehabilitation would in fact be biannual. As such the subsequent annual costs of blindness in the model may represent a slight underestimate.

Table B63 Costs of blindness

Blindness resource use (per case)	Cost	% of patients
Residential care	£16,999	30%
Community care	£7,658	6%
Depression	£504	39%
Hip replacement	£6,287	5%
Low vision aids	£175	33%
Low vision rehabilitation	£303	11%
Blind registration	£134	95%
First year cost	**£6,286.10**	
Subsequent annual costs	**£6,067.93**	

It should be noted that the above costs are applicable for blindness in the patient's BSE, rather than in either eye.

Adverse-event costs

6.5.7 Please summarise the costs for each adverse event listed in section 5.9 (Adverse events). These should include the costs of therapies identified in section 2.7. 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 6.2.2.

Patients experiencing adverse events were assumed to incur the cost of managing those events as summarised in Table B64.

Table B64 List of adverse events and summary of costs included in the economic model

Adverse events	Items	Value	Reference in submission
Cataract	Technology	£800	NHS reference cost[a]
IOP increased (treated with drug)	Technology	£31.67	Table B65
IOP increased (treated with surgery)	Technology	£872.63	Table B66
Stroke	Technology	£10,281	Schwander 2009 *et al*.[b]

a BZ02Z: NHS Trusts Day Cases HRG Data= £800 (Phacoemulsification Cataract Extraction & Lens Implant).

b Inflated to 2010 from 2009. The original cost was £10,111 in 2009 prices.

The calculations for the costs for IOP (requiring treatment with drug or with surgery) are shown in Table B65 and Table B66 below. The figures were derived from the manufacturer's submission for the NICE STA for Dexamethasone intravitreal implant (Ozurdex®) for the treatment of MO caused by RVO (September 2010). Specifically, the calculation are an average of the cost per patient experiencing the adverse events reported for the first 6 months and for the second 6 months reported on page 169 of this reference.[78]

Table B65 Cost of IOP treated with drug

Drug	% of use	Unit cost	Units	Total cost	Weight[b]	Total
Beta-blockers	14%	£1.55	4.5	£6.98	30%	£2.07
Prostaglandins	9%	£12.48	4.5	£56.16	18%	£10.23
CA inhibitors	5%	£6.56	3.5	£22.96	10%	£2.38
Combination	10%	£10.05	5	£50.25	21%	£10.61
Brimonidine	10%	£6.85	4.5	£30.83	21%	£6.38
Total	48%[a]					**£31.67**

Abbreviations: CA, Carbonic anhydrase

a Rate of use was reported for all patients (regardless of adverse event rate), so total does not necessarily sum to 100%

b The contribution of each drug to total cost, given % use.

Table B66 Cost of IOP treated with surgery

Intervention	% of use	Unit cost	Units	Total cost	Weight	Total
Trabeculoplasty	0.415%	£571.00	1	£571.00	40%	£227.85
Sclerectomy	0.120%	£1,278.00	1	£1,278.00	12%	£147.46
Aqueous shunt	0.120%	£1,278.00	1	£1,278.00	12%	£147.46
Cryotherapy	0.120%	£1,061.00	1	£1,061.00	12%	£122.42
Iridectomy	0.145%	£1,061.00	1	£1,061.00	14%	£147.93
Scleral reinforcement	0.120%	£689.00	1	£689.00	12%	£79.50
	1.040%[a]					**£872.63**

a Rate of use was reported for all patients (regardless of adverse event rate), so total does not necessarily sum to 100%

b The contribution of each intervention to total cost, given % use.

Miscellaneous costs

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

None.

6.6 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.

6.6.1 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.

Scenario analysis, including assessment of uncertainty around appropriate data sources and structure of the model, was explored using deterministic and probabilistic methods of analysis (section 6.6.2 and 6.6.3).

6.6.2 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 6.3.6 (Summary of selected values) were omitted from sensitivity analysis, please provide the rationale.

A number of sensitivity analyses were undertaken as described in Table B67. These analyses were selected as each of these variables was considered of key importance in the model, in that they would be expected to influence costs and/or outcomes. Variables were varied based on expert opinion (resource use) or otherwise plausible ranges, given the absence of evidence and the model structure.

Scenario or sensitivity analyses around maintenance of treatment effect of ranibizumab after treatment cessation, versus comparators, were not undertaken. Based on the natural history of MO due to RVO, and clinical expectation, there is no basis on which to assume that once MO is resolved VA would return to pre-treatment VA levels. For patients with MO that does not resolve in response to treatment, the clinical expectation is that MO would resolve over a longer duration of time but result in irreversible visual impairment. The duration of treatment effect over the longer term is therefore not relevant to this condition and is not expected to differ between treatments.

Given the data limitations of the ranibizumab and dexamethasone and the need for the assumptions described in section 5.7.2, this analysis must be considered with caution. Several inputs to this analysis were tested to further understand the relative impact of these variables (Table B87, Table B88, Figure B41 to Figure B52).

Table B67 Sensitivity analyses to be presented (ranibizumab vs. standard care)

Variable	Base case	Scenario
Model structure		
Time horizon	15 years	1 to 25 years
Discount rate costs	3.5%	0% costs and QALYs, 6% costs and QALYs
Discount rate benefits	3.5%	0% costs and 3.5% QALYs
Treatment duration and administration frequency		
Duration of treatment	2 years	1 to 5 years
Frequency of treatment in year 1	BRVO – 8 injections CRVO – 9 injections	BRVO – 4 to 12 injections CRVO – 6 to 12 injections
Frequency of treatment in year 2	BRVO – 2.5 injections CRVO –3.8 injections	0 to 6 injections
Continued treatment in year 3	BRVO – 0 injections CRVO – 0 injection	BRVO – 1 injection CRVO - 1 injection
Frequency of ranibizumab visits in year 2	BRVO - 6 CRVO - 10	BRVO – 4 to 8 CRVO – 6 to 12
Frequency of ranibizumab visits in year 3+	BRVO – 2 CRVO – 4	BRVO – 0-4 CRVO – 2-6
Costs		
Administration costs	£192	£96 to £288
Follow up costs	£151	£76 to £227
Cost of blindness (subsequent annual costs)	£6068	£3034 to £12 136
Effectiveness of treatment		
Ranibizumab effectiveness multiplier Month 0 to 6	1	0 to 2.0
Ranibizumab effectiveness multiplier Month 7 to 12	1	0 to 2.0
Ranibizumab effectiveness multiplier Month 12 to 24	1	0 to 2.0
Comparator effectiveness multiplier Month 0 to 6	1	0 to 2.0
Comparator effectiveness multiplier Month 7 to 12	1	0 to 2.0
Other		
Monthly rate of VA deterioration in years 3 and beyond (loss of 2 lines)	0.031%	0 to 0.4%
Risk of mortality compared to general population	1.0	1.0 to 3.0
Scenario analyses		
% of patients stopping after 3 months due to insufficient response	BRAVO – 10% CRUISE – 6%	0% to 20%
Utilities for BSE	Brown utilities	Sharma utilities
% BSE at baseline and 12 months	100% at both baseline and 12 months	Trial based: 5.2% at baseline, 7.1% at 12 months Expected in clinical practice :10% at baseline, 20% at 12 months

Table B68 Sensitivity analyses to be presented (ranibizumab vs. dexamethasone implant)

Variable	Base case	Scenario
Treatment duration and administration frequency		
Frequency of ranibizumab treatment in year 1	BRVO – 8 injections CRVO – 9 injections	BRVO – 4 to 12 injections CRVO – 6 to 12 injections
Frequency of ranibizumab treatment in year 2	BRVO – 2.5 injections CRVO –3.8 injections	0 to 6 injections
Frequency of ranibizumab visits in year 2	BRVO - 6 CRVO – 10	BRVO – 4 to 8 CRVO – 6 to 12
Frequency of dexamethasone treatment in year 1	BRVO – 2 CRVO – 2	BRVO – 1 CRVO – 1
Frequency of dexamethasone treatment in year 2	BRVO – 2 CRVO – 2	BRVO – 0 CRVO – 0
Frequency of dexamethasone visits in year 2	BRVO – 8 CRVO - 8	BRVO – 4 to 10 CRVO – 4 to 10
Costs		
Administration costs (ranibizumab)	£192	£96 to £288
Administration costs (dexamethasone)	£295.25	£147.63 to £590.52
Effectiveness of treatment		
Ranibizumab effectiveness multiplier Month 0 to 6	1	0 to 2.0
Ranibizumab effectiveness multiplier Month 7 to 12	1	0 to 2.0
Dexamethasone effectiveness multiplier Month 0 to 6	1	0 to 2.0
Dexamethasone effectiveness multiplier Month 7 to 12	1	0 to 2.0

6.6.3 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 6.3.6, 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).

In addition to the deterministic model described above, a probabilistic approach was also undertaken. To do so, distributions were fitted to key parameters within the model. For probabilities, beta distributions were used, whilst cost parameters were fitted with gamma distributions (beta distributions are bound between the values of zero and one, whereas gamma distributions produce only non-negative values). Normal distributions were assumed for parameters such as age, where non-negative values were very unlikely, and lognormal distributions were used for risk ratios.

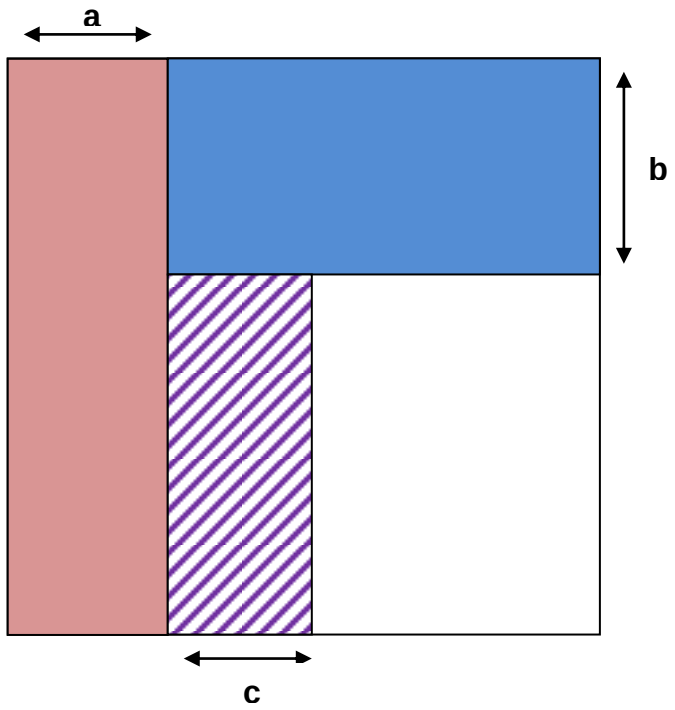
For parameters such as the transition probability rates, the beta distribution was determined by the trial results. Specifically, the 'alpha' input for each probability was

represented by the number of patients who moved health state, whilst the ‘beta’ value was determined by the number who did not move to that state.

This allowed the level of uncertainty to be accurately quantified by way of a mean and standard deviation input. For cost data, no estimates of the magnitude of uncertainty were available, and so the standard deviation was assumed to be equivalent to 20% of the total cost.

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

Figure B18 Probability manipulation



For example, the first probability (‘a’) is drawn from a pre-determined distribution (see above). Note that the selected probability may be larger or smaller than the base case assumption. After ‘a’ has been determined, the value for ‘b’ will also be drawn from a (different) distribution, and adjusted as a proportion of the remaining ‘probability’. The same process is then applied to ‘c’, ‘d’ and any other probabilities until all parameters have been selected, leaving a residual probability (in this case, ‘e’). A full list of probabilistic inputs are shown below, in Table B69

Table B69 Probabilistic parameters

Parameter	Mean	Variation	Type	Alpha	Beta	Notes
General						
Starting age – BRVO	66.4	5	Normal	n/a	n/a	Assumption
Starting age - CRVO	67.6	5	Normal	n/a	n/a	
% BSE at baseline	100%	n/a	Beta	522	0	Assumption
% BSE at 12m	100%	n/a	Beta	522	0	Assumption
Effectiveness						
Treatment effectiveness probs - M1	1	0.1	Lognormal	n/a	n/a	Multiplier/assumption
Treatment effectiveness probs - M2 to M6	1	0.1	Lognormal	n/a	n/a	Multiplier/assumption
Treatment effectiveness probs - M7 to 12	1	0.1	Lognormal	n/a	n/a	Multiplier/assumption
Comp effectiveness probs - M1	1	0.1	Lognormal	n/a	n/a	Multiplier/assumption
Comp effectiveness probs – M2 to 6	1	0.1	Lognormal	n/a	n/a	Multiplier/assumption
Comp effectiveness probs - M7 to 12	1	0.1	Lognormal	n/a	n/a	Multiplier/assumption
Monthly rate of VA deterioration in years 3 and beyond (loss of 2 lines)	0.031%	n/a	Beta	3.1	9996.9	Assumes n = 10,000
Mortality RR (moderate)	1.23	0.1	Lognormal	n/a	n/a	Assumption
Mortality RR (severe)	1.54	0.1	Lognormal	n/a	n/a	Assumption
Quality of life						
Utilities (all)	1	0.05	Normal	n/a	n/a	Assumption
Disutility for cataract	-0.14	0.0284	Normal	n/a	n/a	Assumption (±20%)
Disutility for IOP (drug)	-0.01	0.0026	Normal	n/a	n/a	Assumption (±20%)
Disutility for IOP (surgery)	-0.01	0.002	Normal	n/a	n/a	Assumption (±20%)
Disutility for stroke	-0.26	0.052	Normal	n/a	n/a	Assumption (±20%)
Costs						
Administration costs (all other treatments)	1.000	0.200	Gamma	25	0.04	Assumption (±20%)
Follow up costs (all treatments)	1.000	0.200	Gamma	25	0.04	Assumption (±20%)
Treatment visits year 1 (ranibizumab) BRVO	8	0.8	Gamma	100	0.08	Assumption (±10%)
Treatment visits year 2 (ranibizumab) BRVO	2.5	0.25	Gamma	100	0.025	Assumption (±10%)
Treatment visits year 1 (laser)	2	0.2	Gamma	100	0.02	Assumption (±10%)
Treatment visits year 2 (laser)	1	0.1	Gamma	100	0.01	Assumption (±10%)
Treatment visits year 1 (ranibizumab) CRVO	9	0.9	Gamma	100	0.09	Assumption (±10%)
Treatment visits year 2 (ranibizumab) CRVO	3.8	0.38	Gamma	100	0.038	Assumption (±10%)
Cost of cataract	£800	160	Gamma	25	32	Assumption (±20%)
Cost of IOP (drug)	£32	6.3335424	Gamma	25	1.267	Assumption (±20%)
Cost of IOP (surgery)	£873	174.525	Gamma	25	34.905	Assumption (±20%)
Cost of stroke	£10,281	2056.282	Gamma	25	411.3	Assumption (±20%)
Cost of blindness	1.000	0.200	Gamma	25	0.04	Assumption (±20%)

Adverse event rates						
Cataracts	6.60%	n/a	Beta	34	488	BRAVO & CRUISE
IOP drug	10.00 %	n/a	Beta	52	470	BRAVO & CRUISE

6.7 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

6.7.1 For the outcomes highlighted in the decision problem (see section 4), 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.

The mean BCVA at baseline, month 6, 1 year and 2 years from the BRAVO, CRUISE and HORIZON trials are compared with the data from the model for BRVO and CRVO in Table B70 and Table B71 below. The data from the model closely matches the data from the clinical trials, with differences explained by the fact that all patients receive PRN ranibizumab from month 6, and the slight difference in baseline BCVA in the trials compared to the model. The progression of VA over the model time horizon is presented in Figure B19 and Figure B20. The model demonstrates that

visual acuity tends to have an immediate improvement, due to treatment. Thereafter, the level of acuity appears to remain relatively constant over time. In fact, there is a small decrease in mean VA, due to a natural worsening of VA over time. There is, however, a countering factor in that, because VA severity is related to mortality, the cohort is self-selecting to some degree and, as such, the patients with improved VA are slightly more likely to survive each cycle in the model. Therefore, over time, the model's cohort survivors are more likely to be those with better VA, thus increasing the average VA of the group to some extent.

Table B70 Summary of model results compared with clinical data - BRVO

Outcome	Clinical trial result	Model result
Visual acuity at baseline - ranibizumab	54.7	58.57
Visual acuity at baseline –laser	53.0	54.87
Visual acuity at 6 months - ranibizumab	70.8	68.53
Visual acuity at 6 months –laser	62.0	60.28
Visual acuity at 12 months - ranibizumab	71.3	68.32
Visual acuity at 12 months – rescue laser	66.8	61.59
Visual acuity at 24 months - ranibizumab	70.6	70.9
Visual acuity at 24 months – rescue laser	67.7	63.21

Table B71 Summary of model results compared with clinical data - CRVO

Outcome	Clinical trial result (0.5 mg ranibizumab added to observation after month 6)	Model result (ranibizumab not added to observation)
Visual acuity at baseline – ranibizumab	48.1	52.52
Visual acuity at baseline – observation	49.2	48.43
Visual acuity at 6 months - ranibizumab	63.0	61.79
Visual acuity at 6 months – observation	50.0	50.55
Visual acuity at 12 months - ranibizumab	62.0	62.40
Visual acuity at 12 months observation	56.5	52.11
Visual acuity at 24 months – ranibizumab	57.9	62.98
Visual acuity at 24 months observation	52.3	54.24

Figure B19 Modelled VA over time (BRVO)

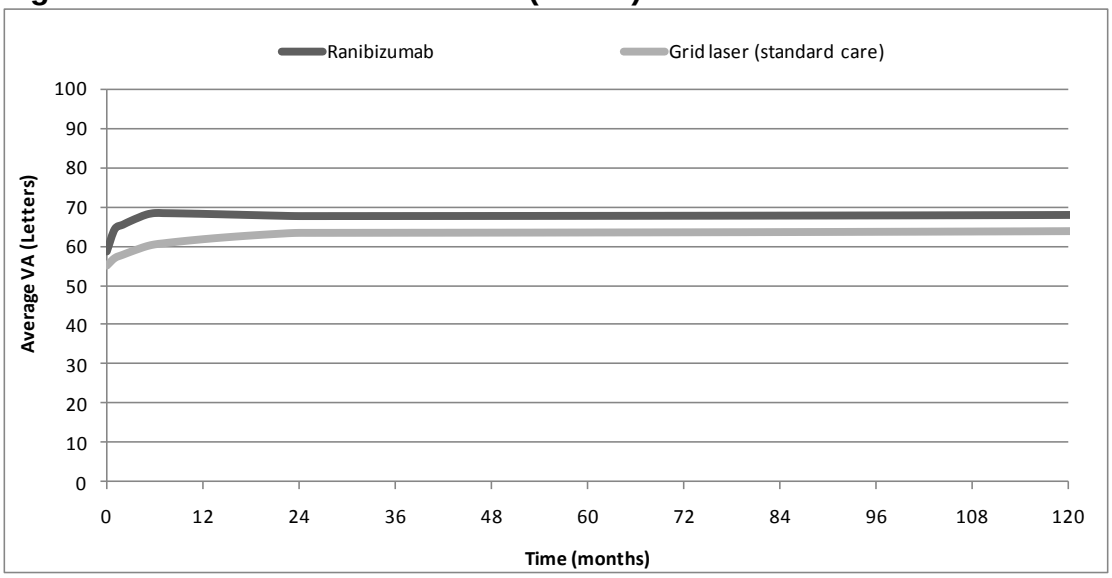
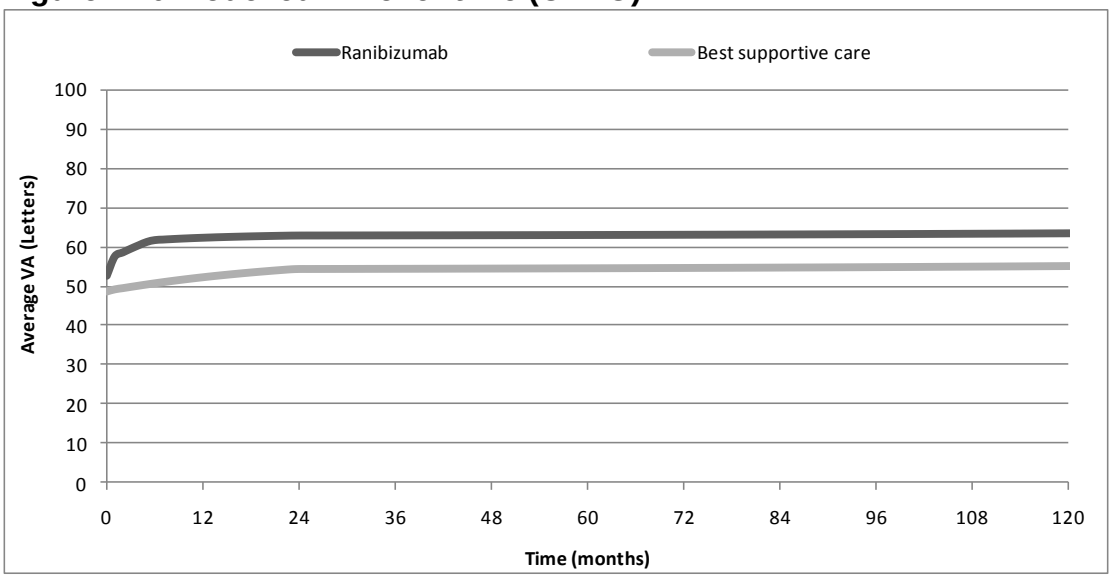


Figure B20 Modelled VA over time (CRVO)



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

The Markov traces for each comparator in the model up to 24 months are provided in the tables below.

Table B72 Markov trace of ranibizumab - BRVO

Month	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25	Dead	Total
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000

Table B73 Markov trace of rescue laser – BRVO

Month	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25	Dead	Total
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000

Table B74 Markov trace of ranibizumab - CRVO

Month	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25	Dead	Total
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000

Table B75 Markov trace of observation - CRVO

Month	86-100	76-85	66-75	56-65	46-55	36-45	26-35	<25	Dead	Total
0	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
1	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
2	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
3	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
4	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
5	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
6	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
7	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
8	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
9	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
10	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
11	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
12	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
13	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
14	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
15	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
16	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
17	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
18	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
19	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
20	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
21	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
22	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
23	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000
24	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	1,000

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

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

6.7.4 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.

The table below disaggregates costs and outcomes according to a cut-off point where VA ≤ 35 letters in the BSE would be regarded as legally partial sighted or severely visually impaired (blind).

Table B76 Model outputs by clinical outcomes

Outcome	QALY	Cost (£)
Ranibizumab - BRVO		
Visual acuity > 35 letters	7.442	£13,026
Visual acuity <=35 letters	0.544	£5,691
Loss due to AEs	-0.007	-
Total	7.978	£18,717
Laser - BRVO		
Visual acuity > 35 letters	6.898	£3,487
Visual acuity <=35 letters	0.808	£8,503
Loss due to AEs	-0.002	-
Total	7.705	£11,990
Ranibizumab - CRVO		
Visual acuity > 35 letters	6.729	£17,564
Visual acuity <=35 letters	0.829	£8,763
Loss due to AEs	-0.007	-
Total	7.551	£26,327
Observation - CRVO		
Visual acuity > 35 letters	5.69	£6,132
Visual acuity <=35 letters	1.374	£14,595
Loss due to AEs	-0.002	-
Total	7.061	£20,727
QALY, quality-adjusted life year		

6.7.5 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.

Table B77 Summary of QALY gain by health state – BRVO

Health state	QALY intervention (ranibizumab)	QALY comparator (rescue laser)	Increment	Absolute increment	% absolute increment
86-100	2.350	1.865	0.484	0.484	33.85%
76-85	1.681	1.411	0.270	0.270	18.86%
66-75	1.256	1.158	0.098	0.098	6.85%
56-65	1.000	1.039	-0.039	0.039	2.74%
46-55	0.667	0.783	-0.116	0.116	8.13%
36-45	0.488	0.642	-0.154	0.154	10.75%
26-35	0.332	0.481	-0.149	0.149	10.42%
<25	0.212	0.327	-0.116	0.116	8.08%
Loss due to AEs	-0.007	-0.002	-0.005	0.005	0.33%
Total	7.978	7.705	0.273	1.431	100.00%

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 B78 Summary of QALY gain by health state - CRVO

Health state	QALY intervention (ranibizumab)	QALY comparator (observation)	Increment	Absolute increment	% absolute increment
86-100	1.910	1.114	0.796	0.796	34.77%
76-85	1.364	0.969	0.395	0.395	17.24%
66-75	1.123	0.931	0.193	0.193	8.41%
56-65	0.979	0.973	0.006	0.006	0.28%
46-55	0.735	0.860	-0.125	0.125	5.45%
36-45	0.618	0.843	-0.225	0.225	9.81%
26-35	0.474	0.758	-0.284	0.284	12.40%
<25	0.355	0.616	-0.262	0.262	11.43%
Loss due to AEs	-0.007	-0.002	-0.005	0.005	0.20%
Total	7.551	7.061	0.490	2.290	100.00%

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 B79 Summary of predicted resource use by category of cost – BRVO

Item	Costs intervention (ranibizumab)	Costs comparator (laser)	Increment	Absolute increment	% absolute increment
Treatment costs	£7,501	£0	£7,501	£7,501	60.74%
Admin costs	£1,941	£264	£1,677	£1,677	13.58%
Follow-up	£3,522	£3,218	£304	£304	2.47%
Cost of AEs	£61	£5	£56	£56	0.45%
Cost of blindness	£5,691	£8,503	-£2,811	£2,811	22.77%
Total	£18,717	£11,990	£6,727	£12,350	100.00%
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 B80 Summary of predicted resource use by category of cost – CRVO

Item	Costs intervention (ranibizumab)	Costs comparator (laser)	Increment	Absolute increment	% absolute increment
Treatment costs	£9,098	£0	£9,098	£9,098	52.24%
Admin costs	£2,354	£0	£2,354	£2,354	13.51%
Follow-up	£6,052	£6,128	-£76	£76	0.44%
Cost of AEs	£61	£5	£56	£56	0.32%
Cost of blindness	£8,763	£14,595	-£5,832	£5,832	33.48%
Total	£26,327	£20,727	£5,600	£17,416	100.00%
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					

Base-case analysis

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

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

Table B81 Base-case results – BRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Laser	£11,990	12.561	7.705				
Ranibizumab	£18,717	12.625	7.978	£6,727	0.064	0.273	**£24,610**
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Table B82 Base-case results – CRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) incremental (QALYs)
Observation	£20,727	12.149	7.061	-	-	-	-
Ranibizumab	£26,327	12.283	7.551	£5,600	0.134	0.490	**£11,428**
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years							

Despite the limitations of the cost effectiveness analysis of ranibizumab versus dexamethasone implant, the base case results including dexamethasone are presented below. These should be interpreted with caution for the reasons described previously (see section 6.6.2).

Table B83 Base-case results including dexamethasone implant – BRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)	Notes
Laser	£11,990	12.56	7.705	-	-	-	-	-	
Dexamethasone implant	£16,448	12.58	7.769	£4,458	0.018	0.065	£68,742	£68,742	
Ranibizumab	£18,717	12.63	7.978	£2,269	0.046	0.208	£24,610	£10,883	Extended dominance over Dex. implant
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years									

Table B84 Base-case results including dexamethasone implant - CRVO

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£) versus baseline (QALYs)	ICER (£) incremental (QALYs)
Observation	£20,727	12.149	7.061	-	-	-	-	
Dexamethasone implant	£22,945	12.209	7.270	£2,218	0.060	0.209	£10,622	£10,622
Ranibizumab	£26,327	12.283	7.551	£3,382	0.074	0.281	£11,428	£12,027
ICER, incremental cost-effectiveness ratio; LYG, life years gained; QALYs, quality-adjusted life years								

Sensitivity analyses

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

BRAVO

Table B85 Deterministic sensitivity analysis – BRVO

Parameter	Incremental costs	Incremental QALYs	Incremental cost per QALY
Base case	£6,727	0.273	£24,610
Frequency of ranibizumab treatment in year 1, 3 injections	£2,914	0.273	£10,660
Frequency of ranibizumab treatment in year 1, 12 injections	£9,777	0.273	£25,770
Frequency of ranibizumab treatment in year 2, 3 injections	£4,912	0.273	£17,971
Frequency of ranibizumab treatment in year 2, 6 injections	£9,268	0.273	£33,905
Continued ranibizumab treatment in year 3, 1 injection	£7,593	0.273	£27,778
Administration costs, £96	£5,757	0.273	£21,060
Administration costs, £288	£7,697	0.273	£28,160
Follow up costs, £76	£4,977	0.273	£18,209
Follow up costs, £227	£8,500	0.273	£31,096
Frequency of ranibizumab visits in year 2, 4	£6,447	0.273	£23,586
Frequency of ranibizumab visits in year 2, 8	£7,007	0.273	£25,634
Frequency of ranibizumab visits in year 3+, 0	£4,282	0.273	£15,667
Frequency of ranibizumab visits in year 3+, 4	£9,171	0.273	£33,553
Discount rate costs 0% and discount rate benefits 0%	£6,332	0.344	£18,409
Discount rate costs 6% and discount rate benefits 6%	£6,903	0.236	£29,235
Discount rates cost 3.5% and discount rates benefits 0%	£6,272	0.344	£19,557

Figure B21 Deterministic sensitivity analysis – BRVO – Time horizon

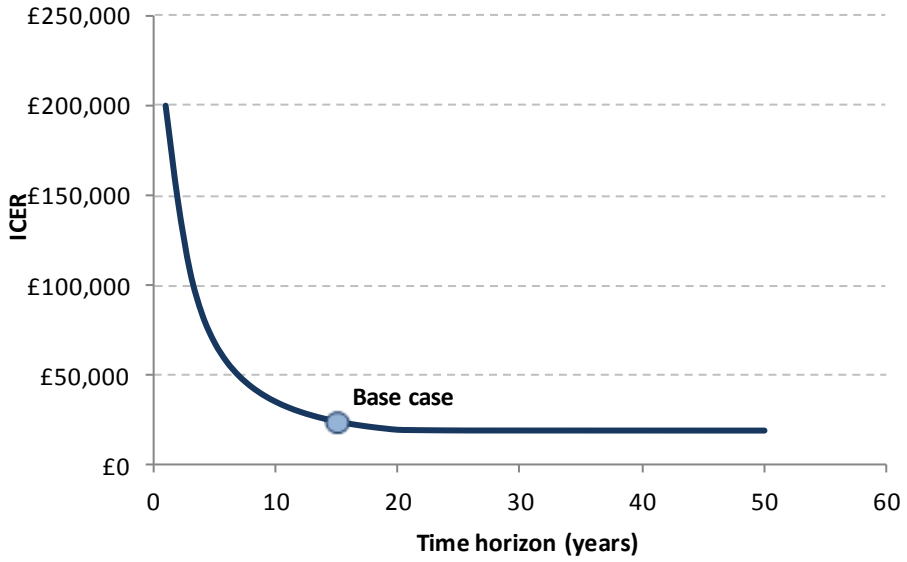


Figure B22 Deterministic sensitivity analysis – BRVO – Ranibizumab effectiveness multiplier (month 1)

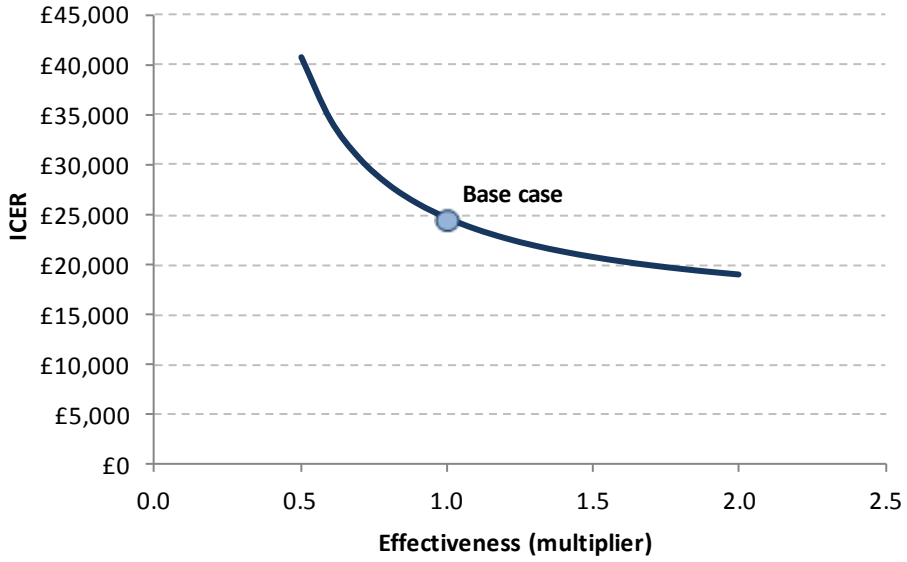


Figure B23 Deterministic sensitivity analysis – BRVO – Ranibizumab effectiveness multiplier (months 2 – 6)

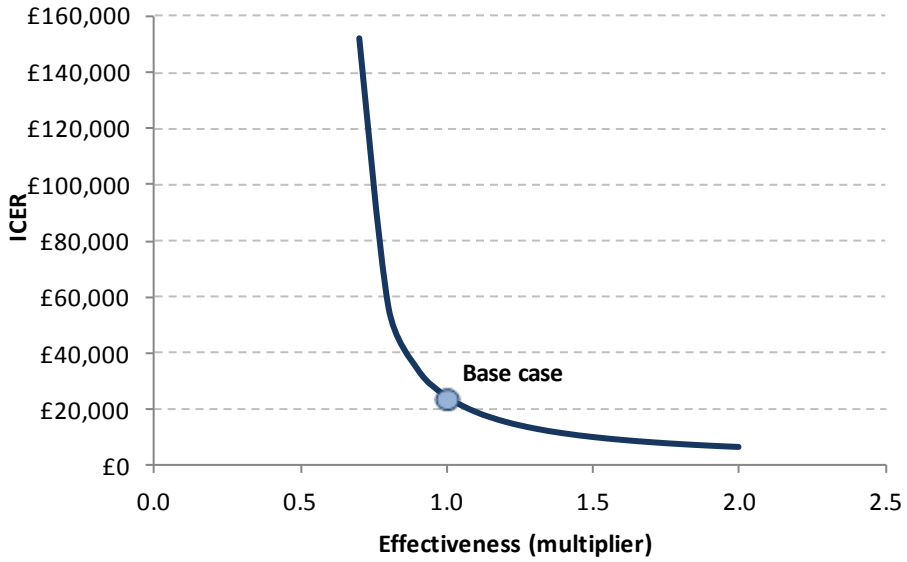


Figure B24 Deterministic sensitivity analysis – BRVO – Ranibizumab effectiveness multiplier (months 7 – 12)

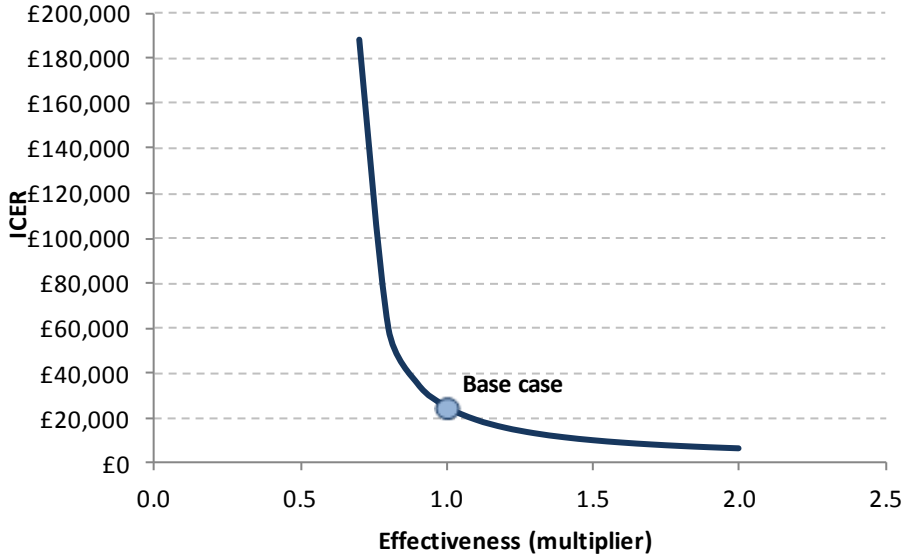


Figure B25 Deterministic sensitivity analysis – BRVO – comparator effectiveness multiplier (month 1)

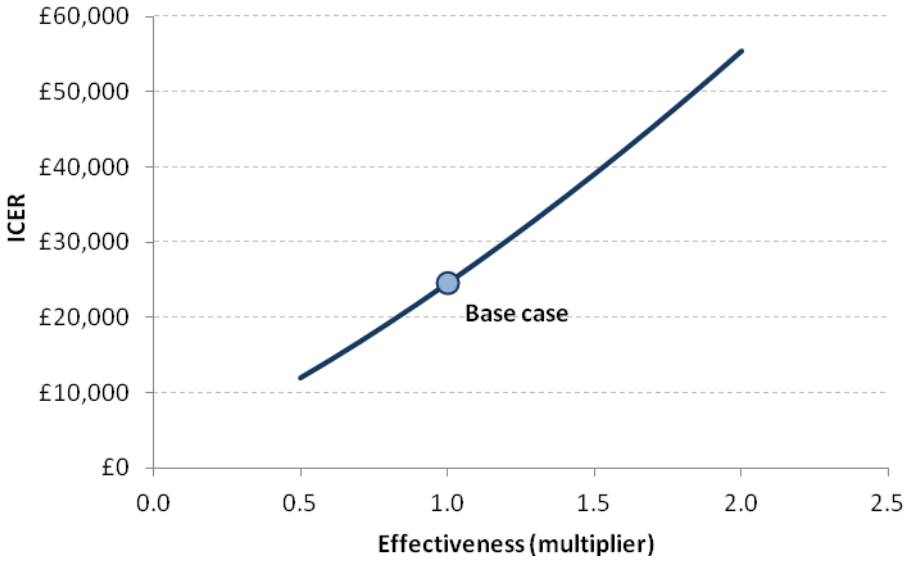


Figure B26 Deterministic sensitivity analysis – BRVO – comparator effectiveness multiplier (months 2 – 6)

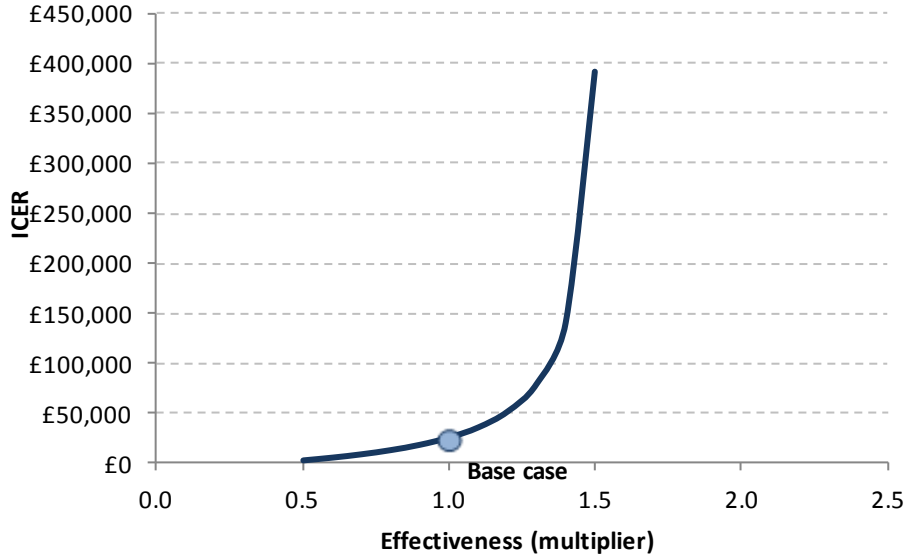


Figure B27 Deterministic sensitivity analysis – BRVO – comparator effectiveness multiplier (months 7 – 12)

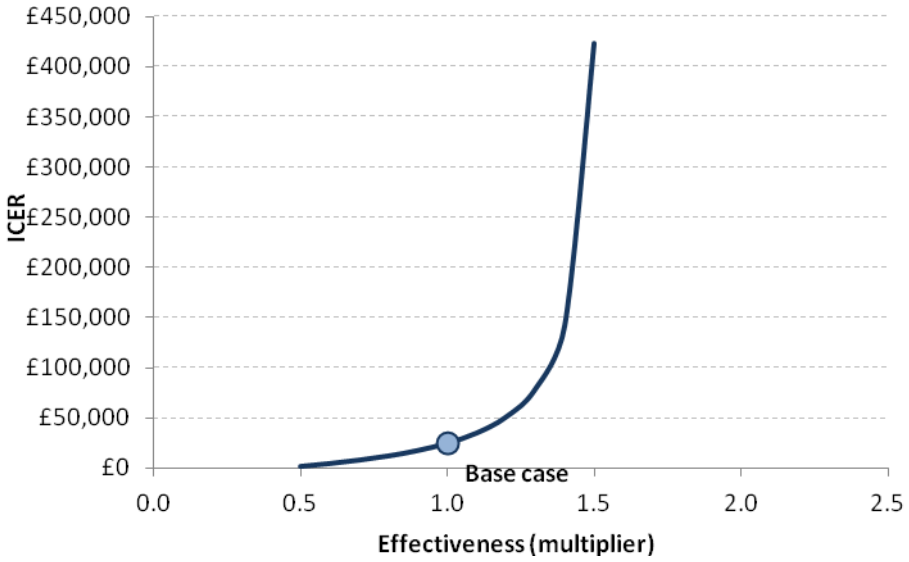


Figure B28: Deterministic sensitivity analysis – BRVO – Monthly rate of VA deterioration in 3 years (loss of 2 lines)

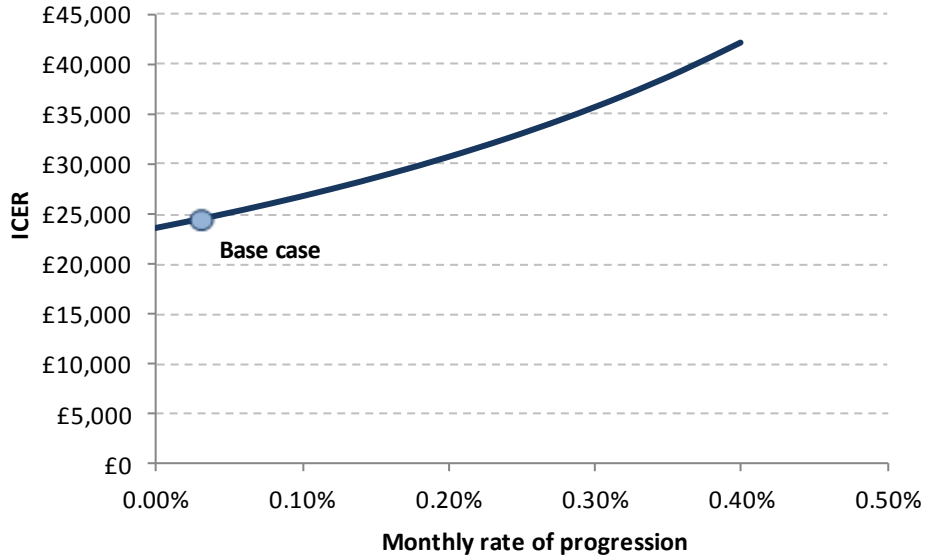


Figure B29 Deterministic sensitivity analysis – BRVO – Risk of mortality compared to general population

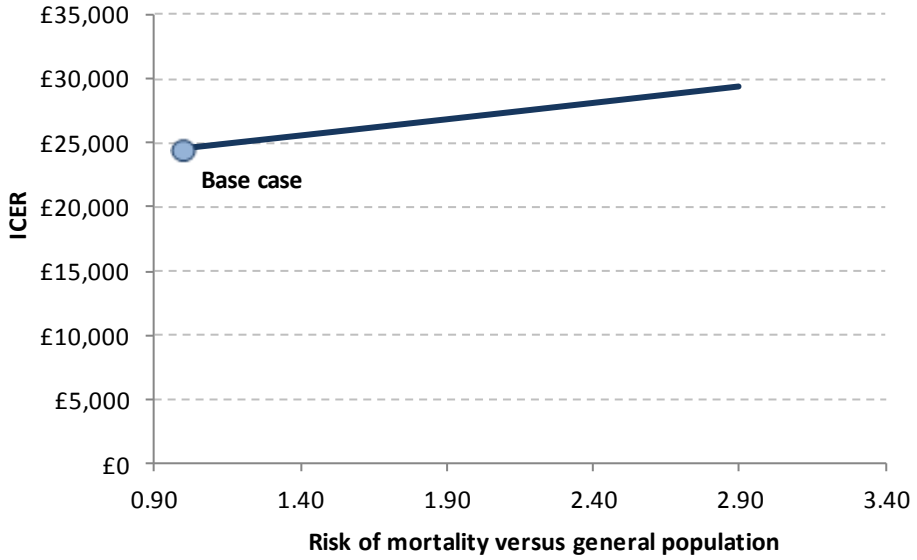
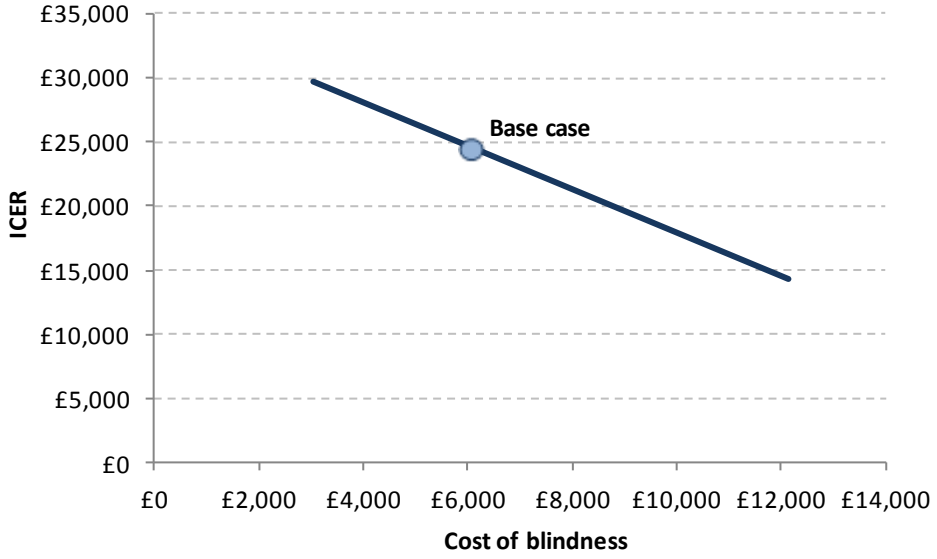


Figure B30 Deterministic sensitivity analysis – BRVO – Cost of blindness



CRUISE

Table B86 Deterministic sensitivity analysis – CRVO

Variable	Incremental Costs	Incremental QALYs	Cost per QALY
Base case	**£5,600**	**0.490**	**£11,428**
Frequency of ranibizumab treatment in year 1, 3	£1,031	0.490	£2,104
Frequency of ranibizumab treatment in year 1, 12	£7,884	0.490	£16,091
Frequency of ranibizumab treatment in year 2, 0	£2,853	0.490	£5,822
Frequency of ranibizumab treatment in year 2, 6	£7,190	0.490	£14,674
Continued treatment in year 3, 1 injection	£6,462	0.490	£13,188
Administration costs, £96	£4,423	0.490	£9,027
Administration costs, £288	£6,777	0.490	£13,830
Follow up costs, £76	£2,594	0.490	£5,294
Follow up costs, £227	£8,646	0.490	£17,644
Frequency of ranibizumab visits in year 2, 6	£5,042	0.490	£10,291
Frequency of ranibizumab visits in year 2, 12	£5,879	0.490	£11,997
Frequency of ranibizumab visits in year 3+, 2	£3,226	0.490	£6,585
Frequency of ranibizumab visits in year 3+, 6	£7,973	0.490	£16,272
Discount rate costs 0% and discount rate benefits 0%	£4,598	0.622	£7,393
Discount rate costs 6% and discount rate benefits 6%	£6,092	0.421	£14,484
Discount rates cost 3.5% and discount rates benefits 0%	£5,600	0.622	£9,005

Figure B31 Deterministic sensitivity analysis – CRVO Time horizon

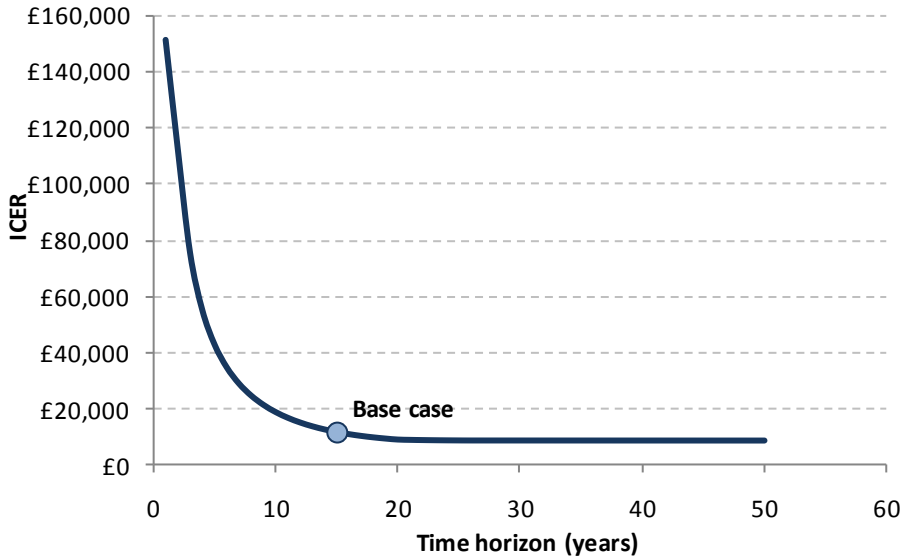


Figure B32 Deterministic sensitivity analysis – CRVO Ranibizumab effectiveness multiplier Month 1

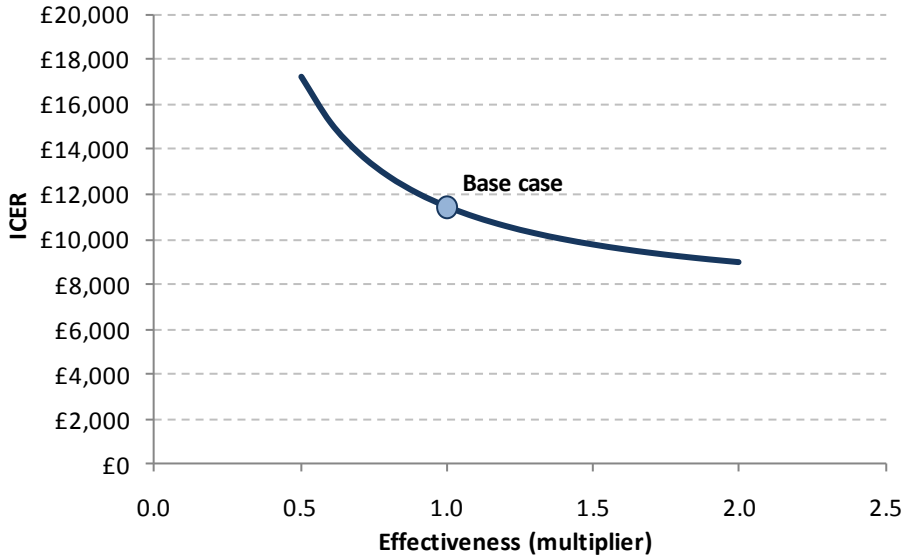


Figure B33 Deterministic sensitivity analysis – CRVO Ranibizumab effectiveness multiplier Month 2-6

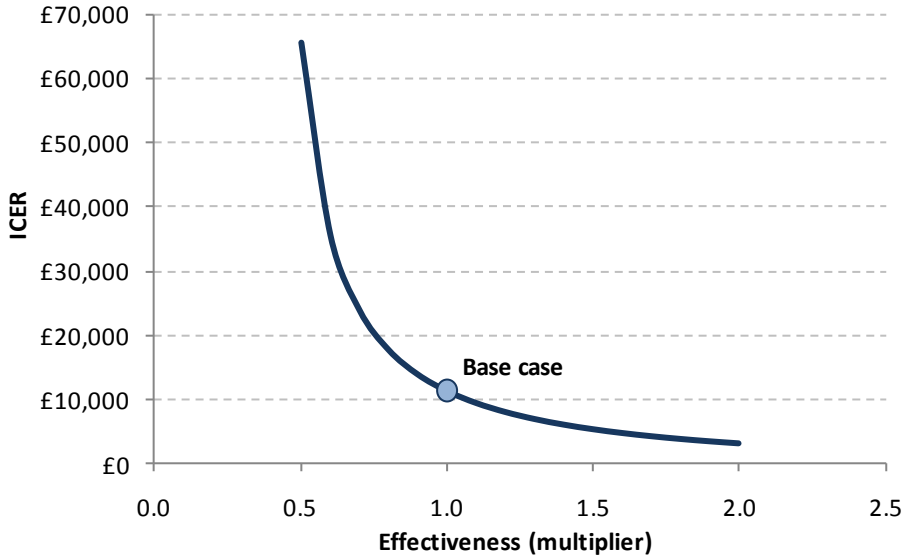


Figure B34 Deterministic sensitivity analysis – CRVO Ranibizumab effectiveness multiplier Month 7-12

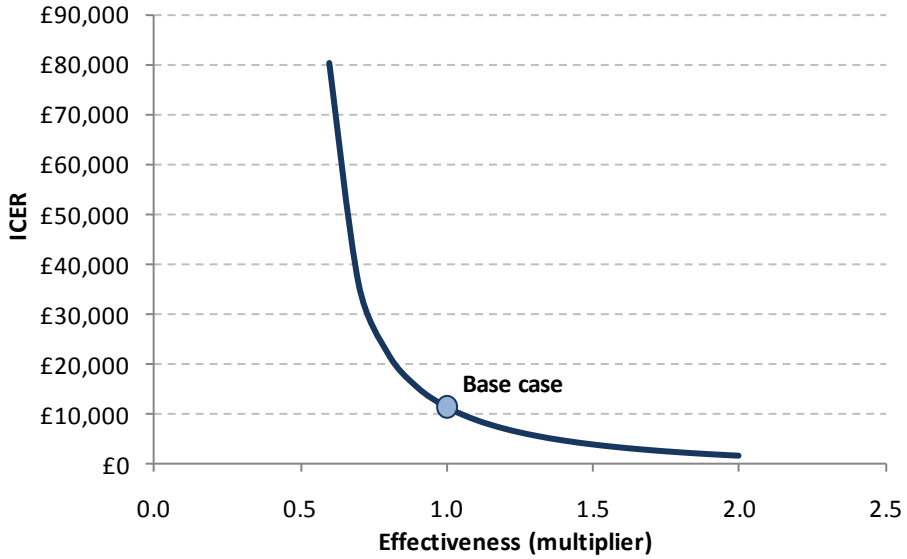


Figure B35 Deterministic sensitivity analysis – CRVO Comparator effectiveness multiplier Month 1

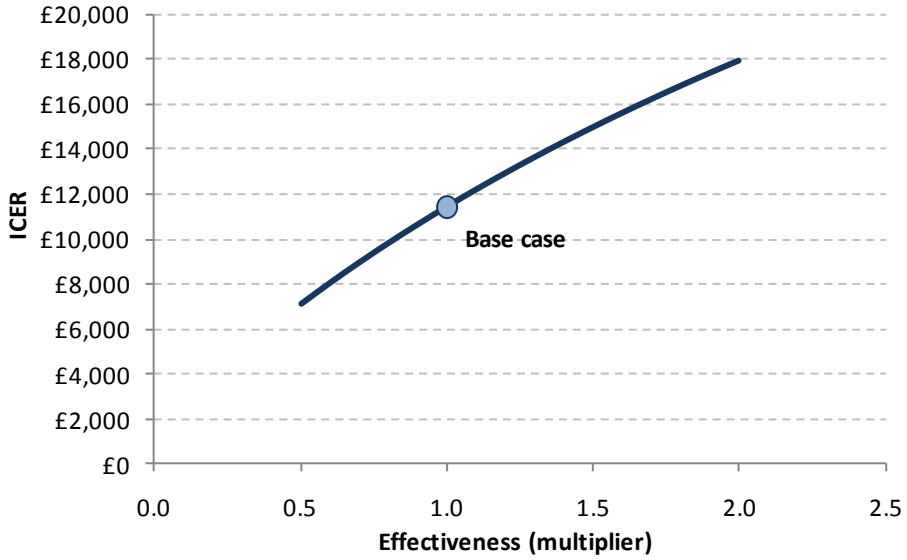


Figure B36 Deterministic sensitivity analysis – CRVO Comparator effectiveness multiplier Month 2-6

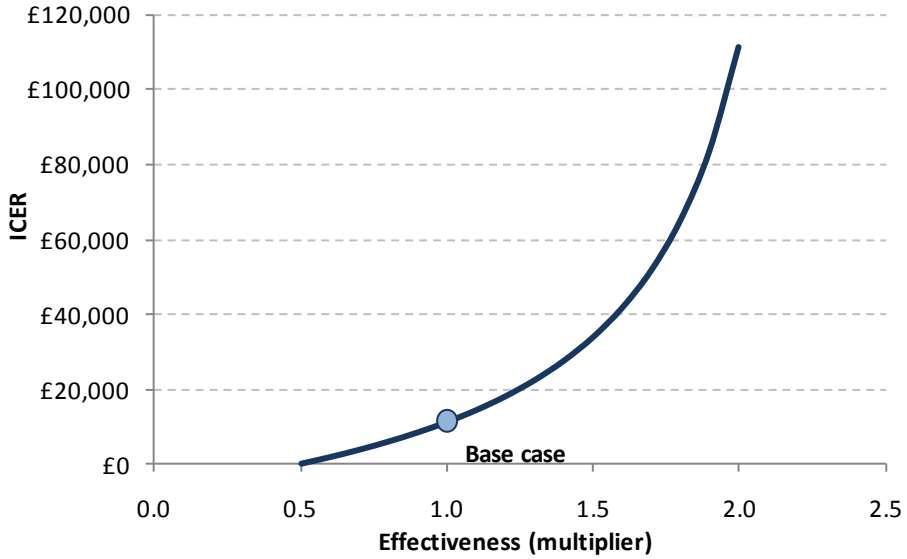


Figure B37 Deterministic sensitivity analysis – CRVO Comparator effectiveness multiplier Month 7-12

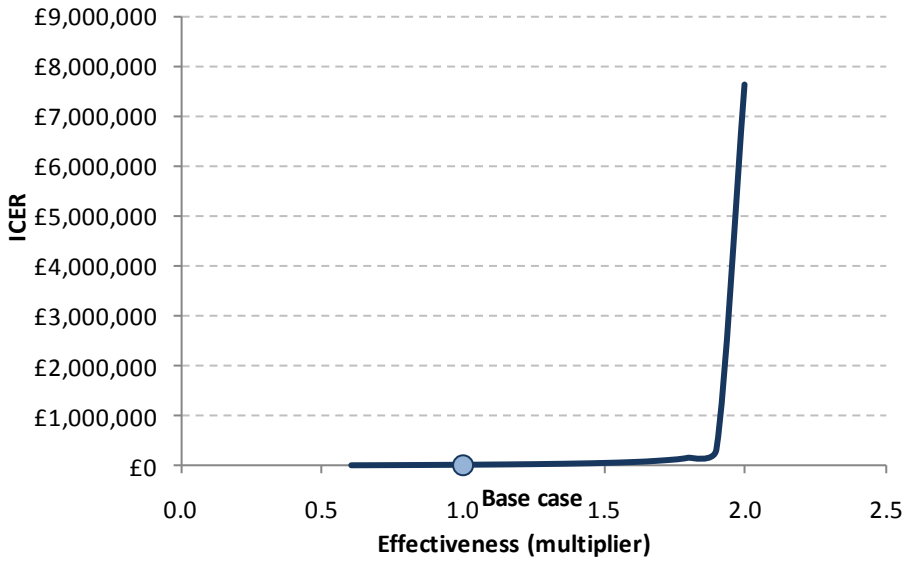


Figure B38 Deterministic sensitivity analysis – CRVO Monthly rate of VA deterioration in years 3+ (loss of 2 lines)

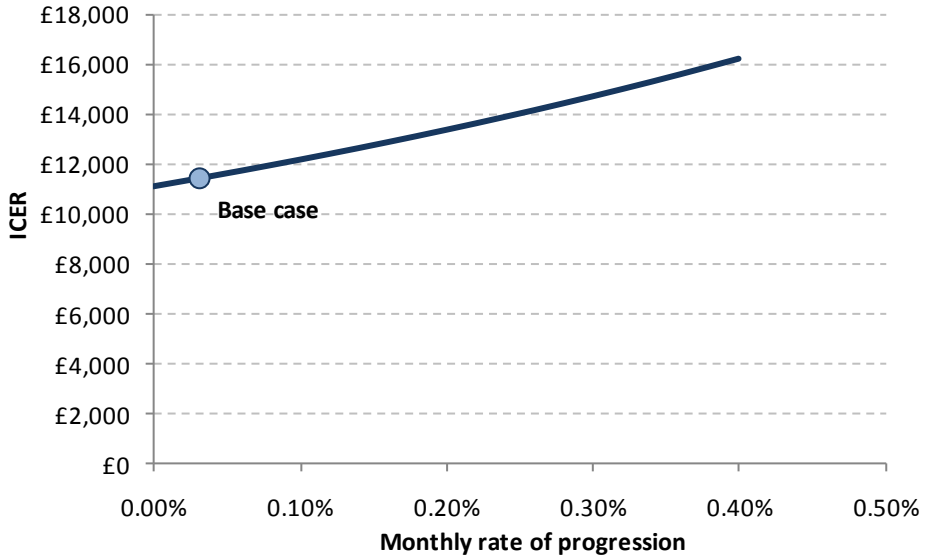


Figure B39 Deterministic sensitivity analysis – CRVO Risk of mortality compared to general population

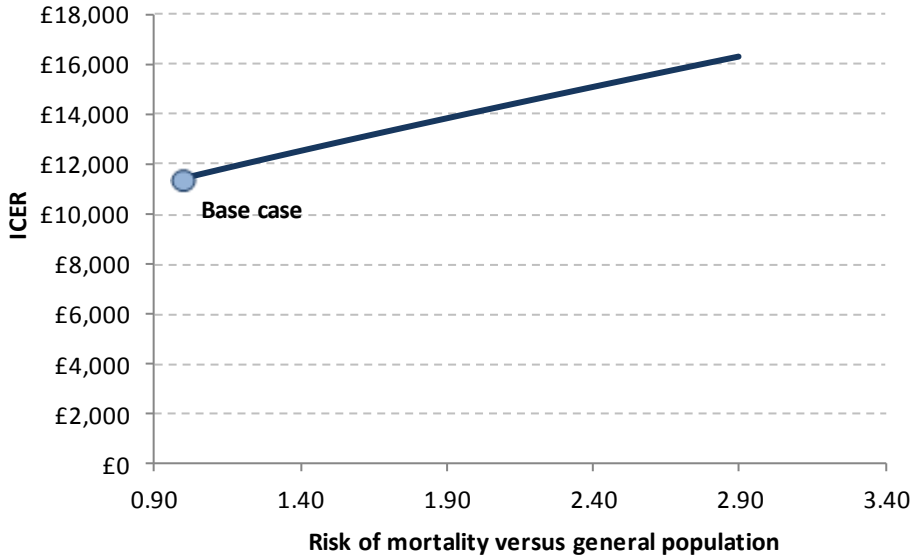
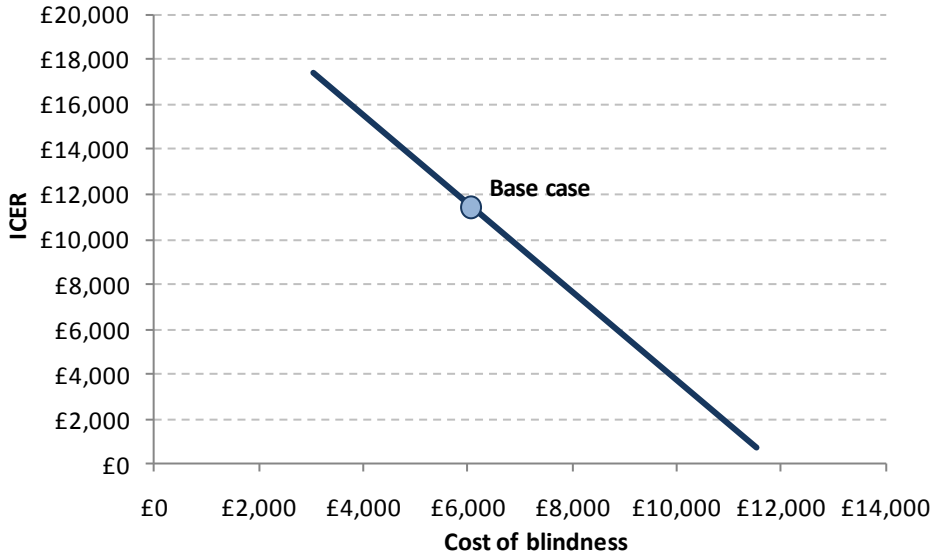


Figure B40 Deterministic sensitivity analysis – CRVO Cost of blindness



Deterministic sensitivity analysis of dexamethasone implant comparison

Table B87 Deterministic sensitivity analysis (ranibizumab vs. dexamethasone implant) BRVO

Variable	Incremental Costs	Incremental QALYs	Cost per QALY
Base case	£2,269	0.208	£10,883
Treatment duration and administration frequency			
Frequency of ranibizumab treatment in year 1: 4 injections	-£1,370	0.208	Dominant
Frequency of ranibizumab treatment in year 1: 12 injections	£5,908	0.208	£28,336
Frequency of ranibizumab treatment in year 2: 0	£104	0.208	£501
Frequency of ranibizumab treatment in year 2: 6	£5,300	0.208	£25,419
Frequency of ranibizumab visits in year 2: 4	£1,989	0.208	£9,541
Frequency of ranibizumab visits in year 2: 8	£2,549	0.208	£12,226
Frequency of dexamethasone treatment in year 1: 1	£3,403	0.208	£16,324
Frequency of dexamethasone treatment in year 2: 0	£4,428	0.208	£21,237
Frequency of dexamethasone visits in year 2: 4	£2,829	0.208	£13,567
Frequency of dexamethasone visits in year 2: 10	£1,989	0.208	£9,542
Costs			
Administration costs (ranibizumab)	£1,299	0.208	£6,229
Administration costs (dexamethasone)	£3,239	0.208	£15,537

Figure B41 Ranibizumab effectiveness probabilities for BRVO – month 1

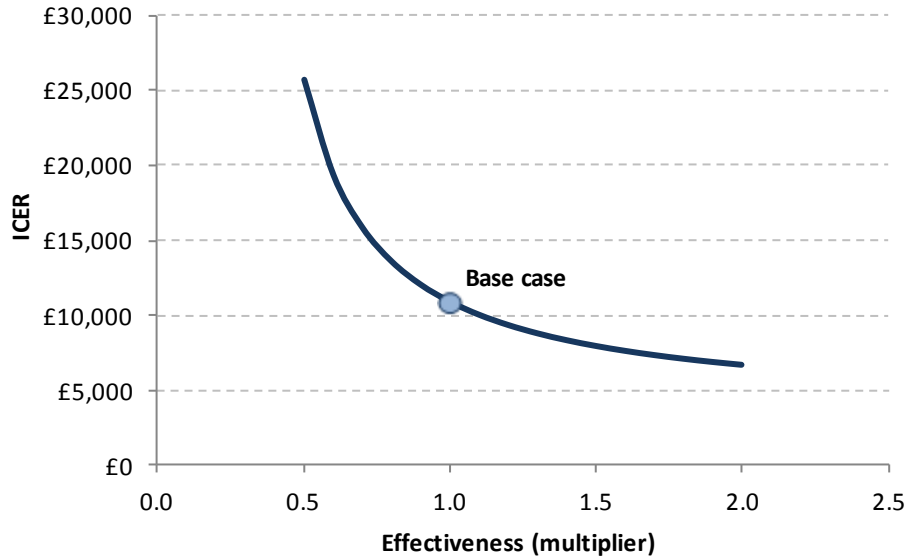


Figure B42 Ranibizumab effectiveness probabilities for BRVO – months 2 to 6

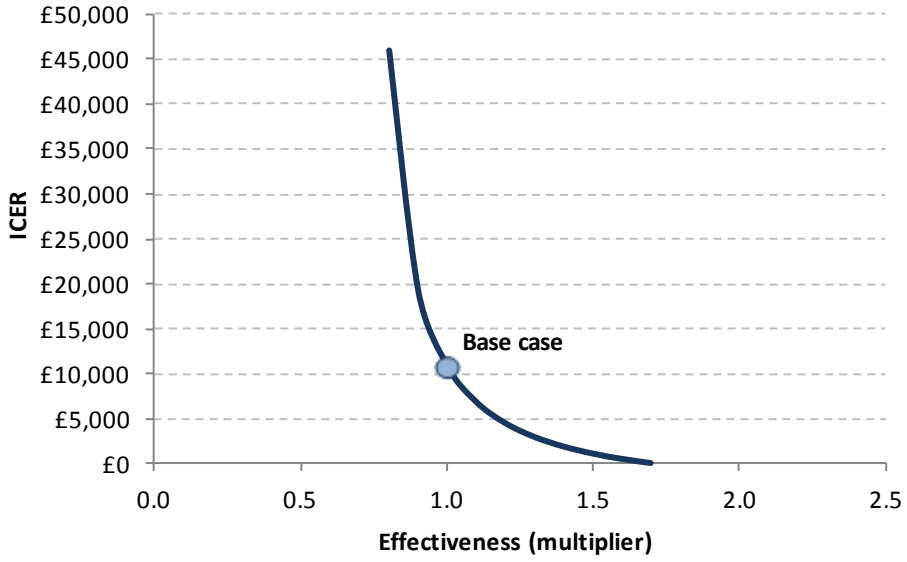


Figure B43 Ranibizumab effectiveness probabilities for BRVO – months 7 to 12

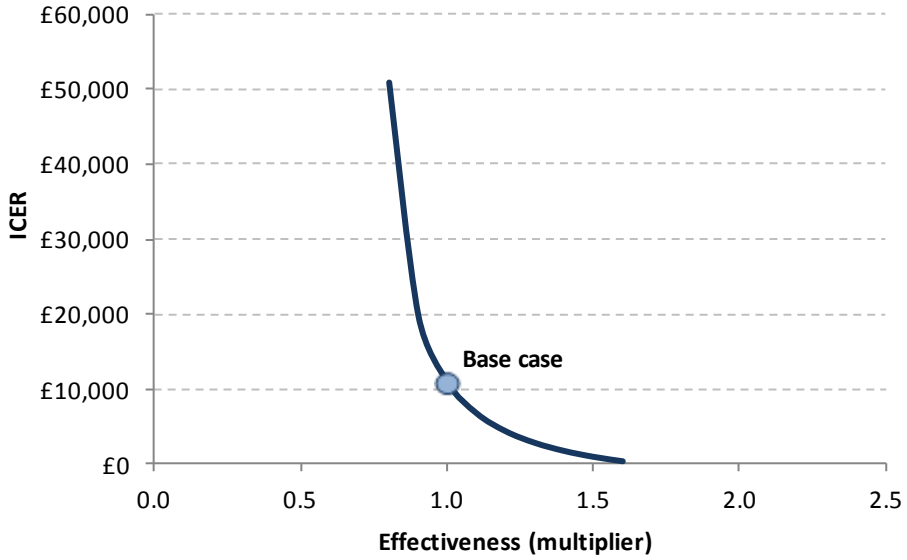


Figure B44 Dexamethasone implant effectiveness probabilities for BRVO – month 1

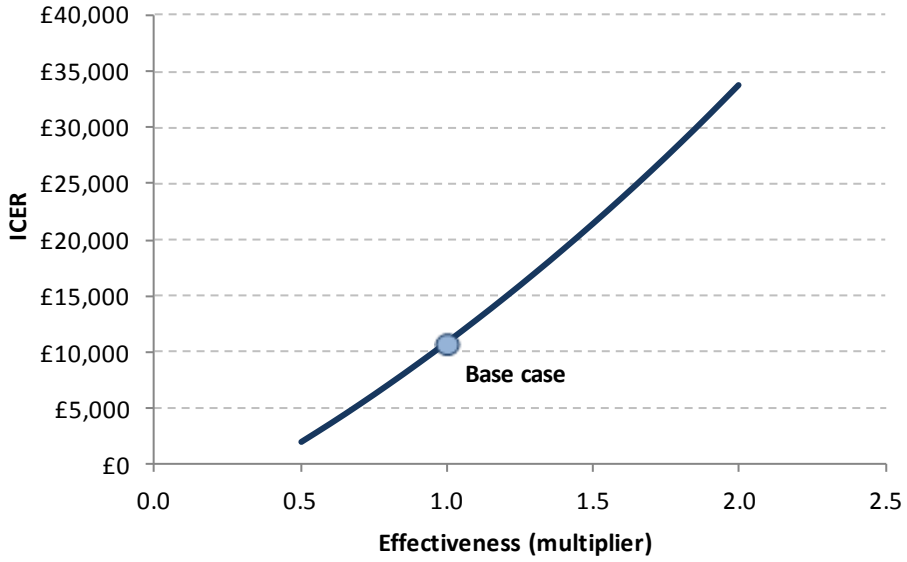


Figure B45 Dexamethasone implant effectiveness probabilities for BRVO – months 2 to 6

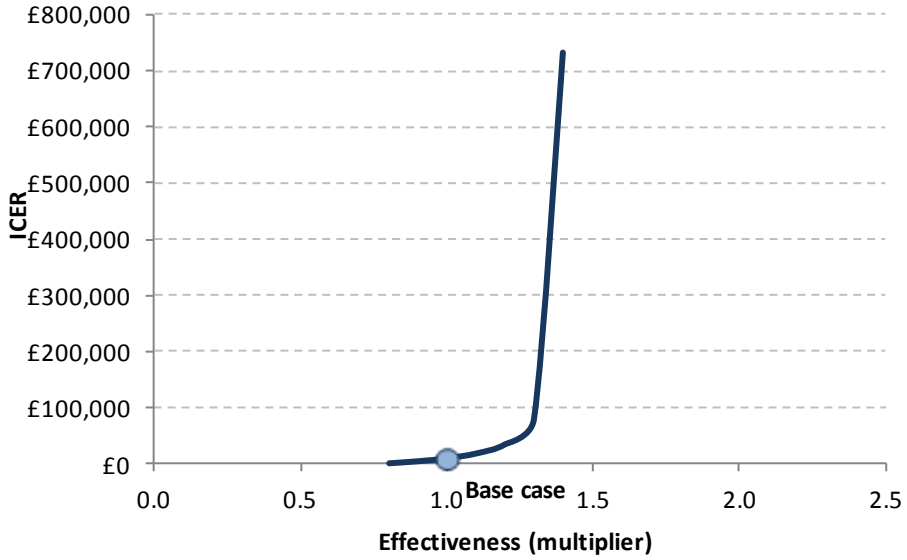


Figure B46 Dexamethasone implant effectiveness probabilities for BRVO – months 7 to 12

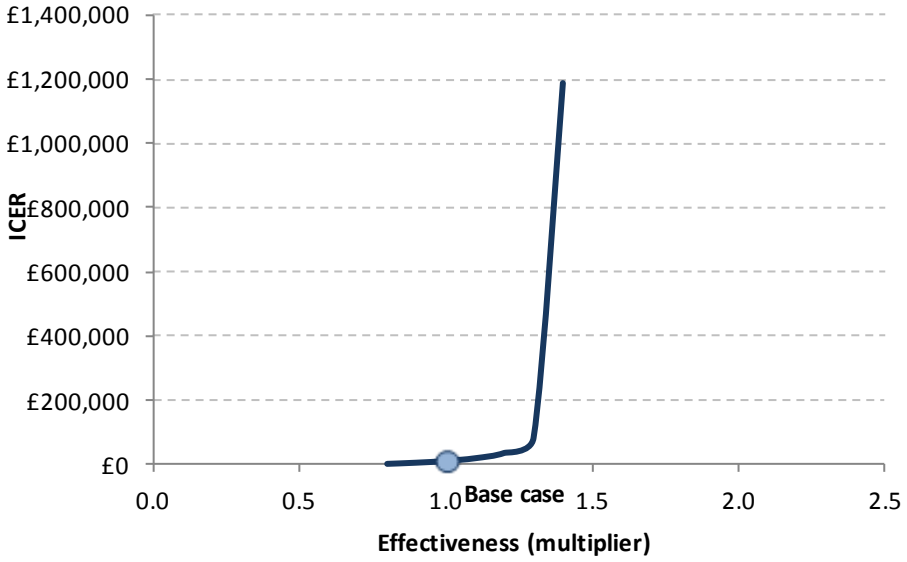


Table B88 Deterministic sensitivity analysis (ranibizumab vs. dexamethasone implant) CRVO

Variable	Incremental Costs	Incremental QALYs	Cost per QALY
Base case	£3,382	0.281	£12,027
Treatment duration and administration frequency			
Frequency of ranibizumab treatment in year 1: 6 injections	£657	0.281	£2,337
Frequency of ranibizumab treatment in year 1: 12 injections	£6,107	0.281	£21,716
Frequency of ranibizumab treatment in year 2: 0	£105	0.281	£375
Frequency of ranibizumab treatment in year 2: 6	£5,279	0.281	£18,773
Frequency of ranibizumab visits in year 2: 6	£2,825	0.281	£10,044
Frequency of ranibizumab visits in year 2: 12	£3,661	0.281	£13,018
Frequency of dexamethasone treatment in year 1: 1	£4,515	0.281	£16,054
Frequency of dexamethasone treatment in year 1: 4	£1,117	0.281	£3,973
Frequency of dexamethasone treatment in year 2: 0	£5,531	0.281	£19,666
Frequency of dexamethasone treatment in year 2: 4	£1,234	0.281	£4,388
Frequency of dexamethasone visits in year 2: 4	£3,939	0.281	£14,007
Frequency of dexamethasone visits in year 2: 10	£3,104	0.281	£11,037
Costs			
Administration costs (ranibizumab)	£3,941	0.281	£14,015
Administration costs (dexamethasone)	£2,264	0.281	£8,050

Figure B47 Ranibizumab effectiveness probabilities for CRVO – month 1

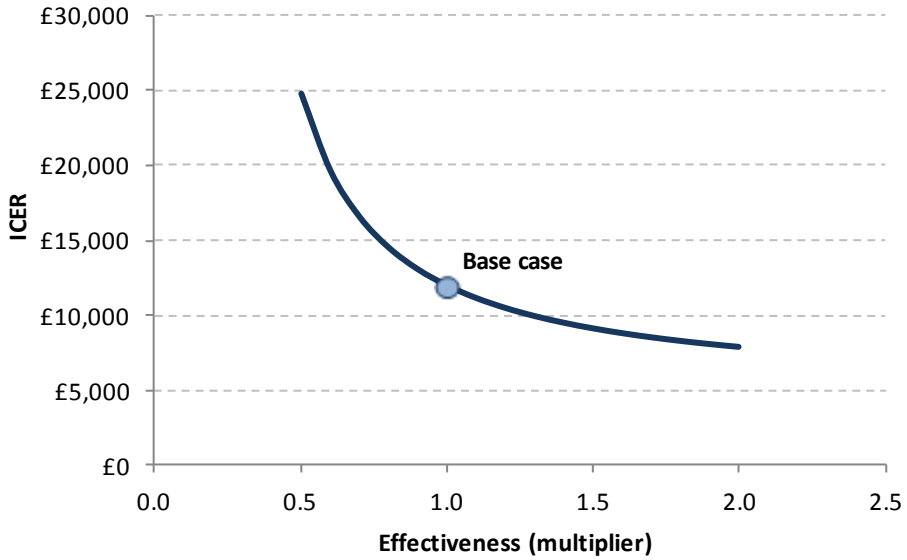


Figure B48 Ranibizumab effectiveness probabilities for CRVO – months 2 to 6

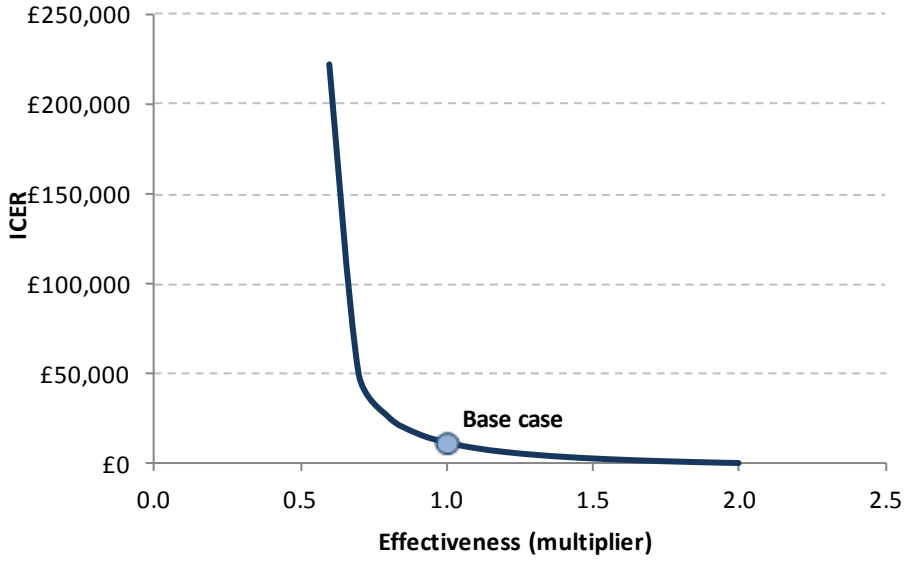


Figure B49 Ranibizumab effectiveness probabilities for CRVO – months 7 to 12

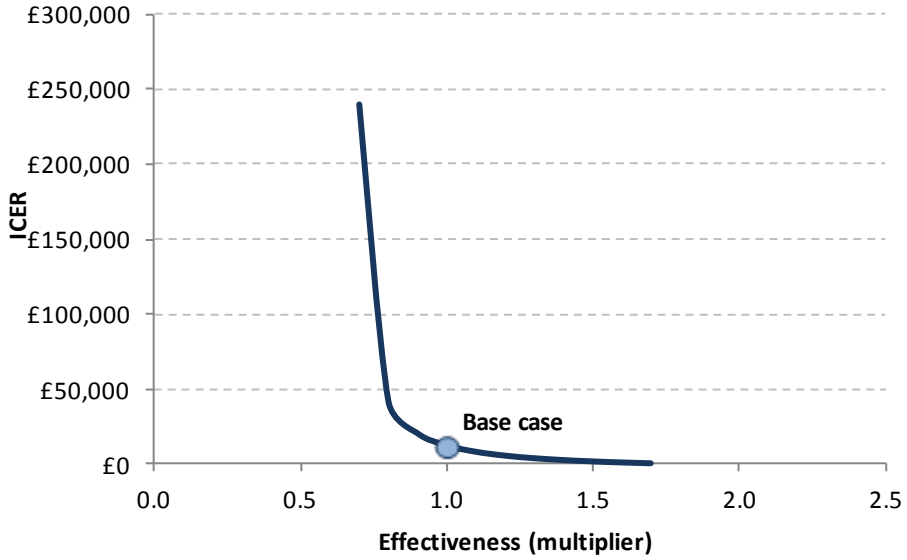


Figure B50 Dexamethasone implant effectiveness probabilities for CRVO – month 1

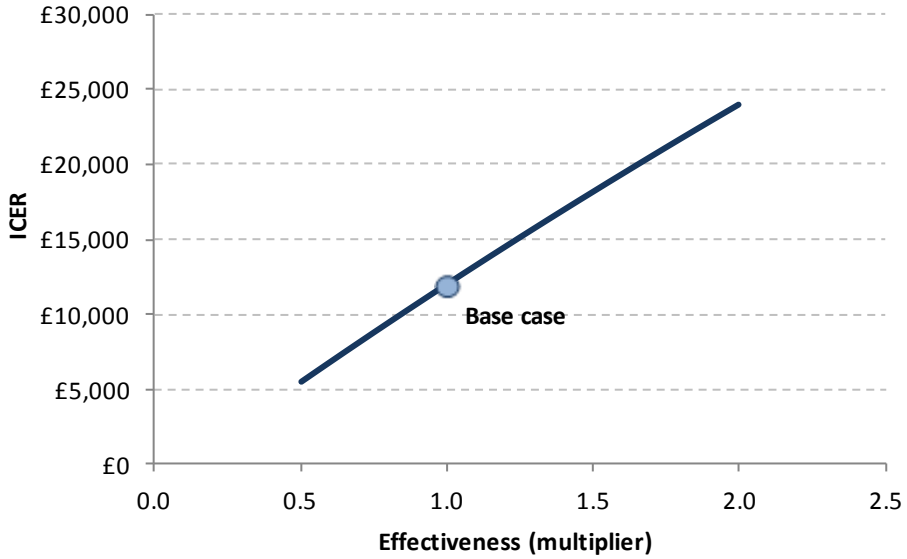


Figure B51 Dexamethasone implant effectiveness probabilities for CRVO – months 2 to 6

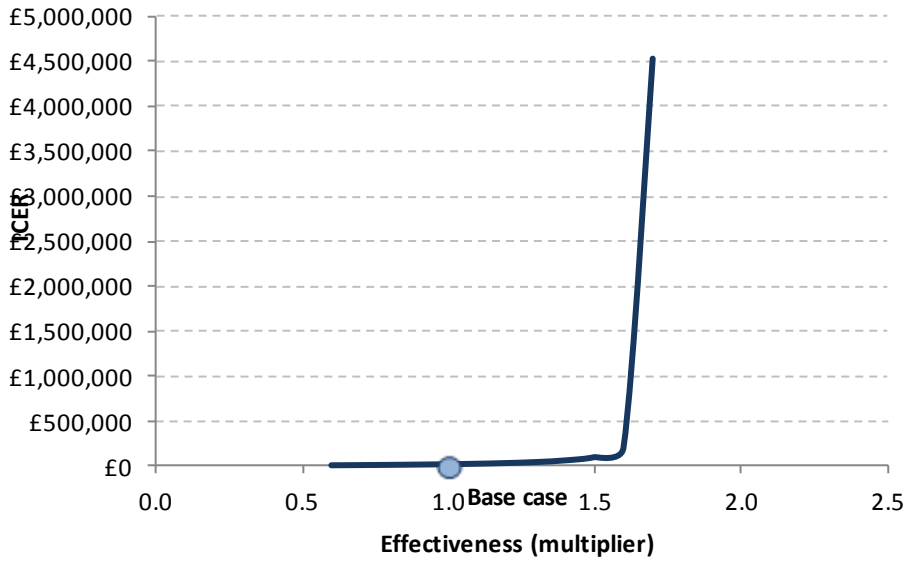
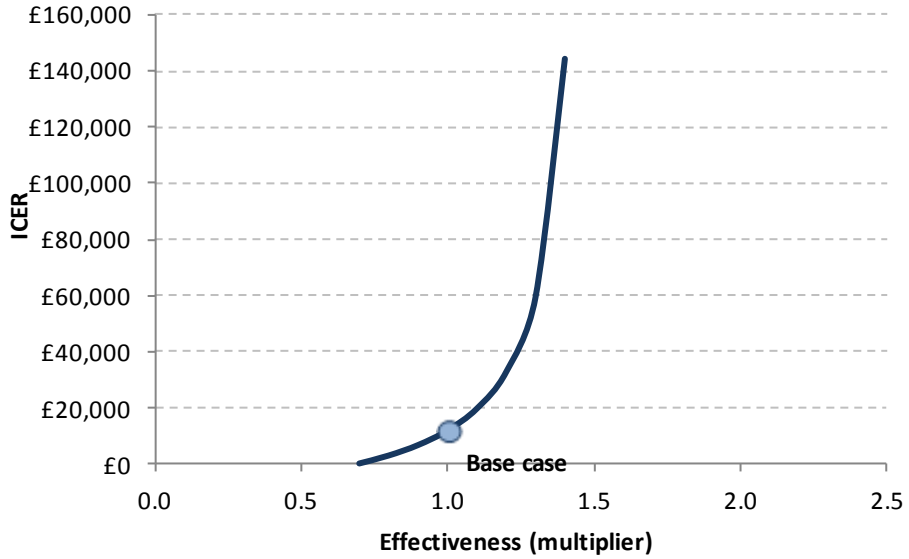


Figure B52 Dexamethasone implant effectiveness probabilities for CRVO – months 7 to 12



6.7.8 Please present the results of a PSA, and include scatter plots and cost-effectiveness acceptability curves.

Incremental QALY, cost and cost-effectiveness ratios were presented as base case results in section 6.7.6. Scatter plots and acceptability curves are shown below. Table B89 shows the probability of ranibizumab being cost-effective.

The probability that ranibizumab is cost-effective when compared to laser is 42.0% at a willingness-to-pay (WTP) threshold of £20,000 and 56.6% with at a WTP threshold of £30,000. For ranibizumab the probability of being cost-effective compared to observation in CRVO is 60.9% and 80.0% at WTP thresholds of £20,000 and £30,000 respectively.

Table B89 Probability of cost-effectiveness

	Probability of being cost-effective		
	WTP= £0	**WTP= £20,000**	**WTP= £30,000**
Ranibizumab vs. laser - BRVO	1.5%	42.0%	56.6%
Ranibizumab vs. observation - CRVO	4.5%	60.9%	80.0%

Figure B53 Scatter plot of incremental cost and incremental QALY, ranibizumab vs. laser in BRVO 1000 iterations

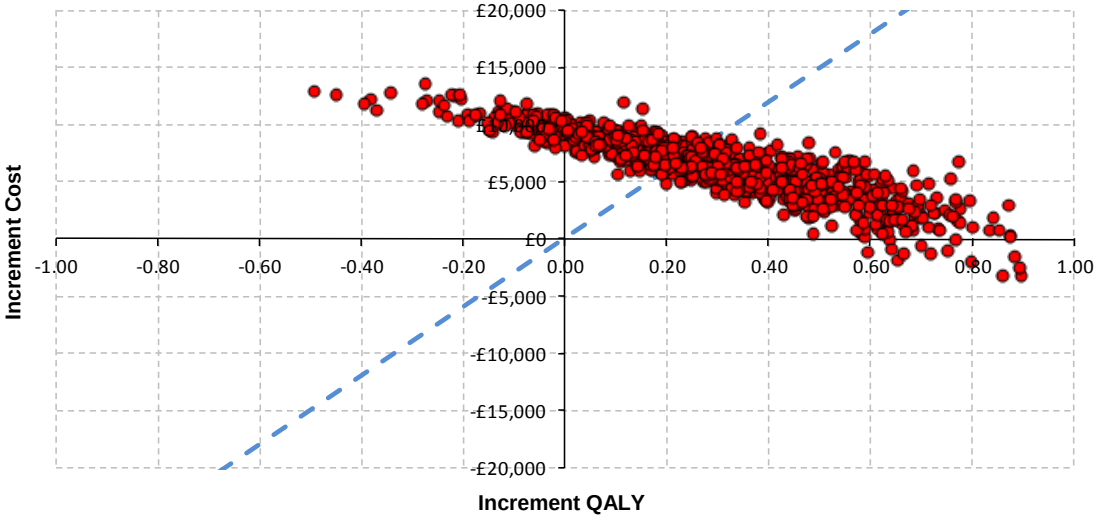


Figure B54 Cost-Effectiveness Acceptability Curve (CEAC) ranibizumab vs. laser – BRVO

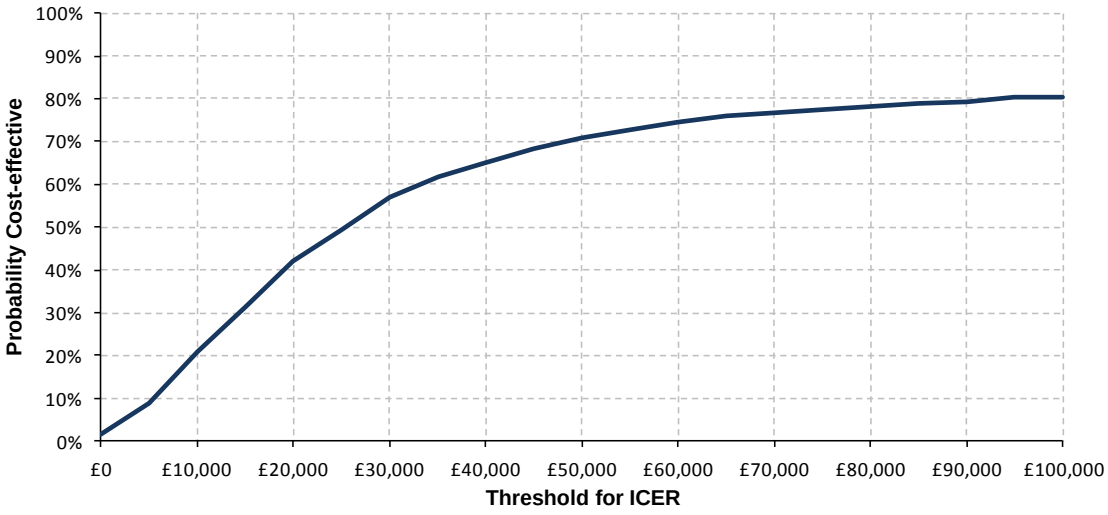


Figure B55Scatter plot of incremental cost and incremental QALY, ranibizumab vs. observation in CRVO 1000 iterations

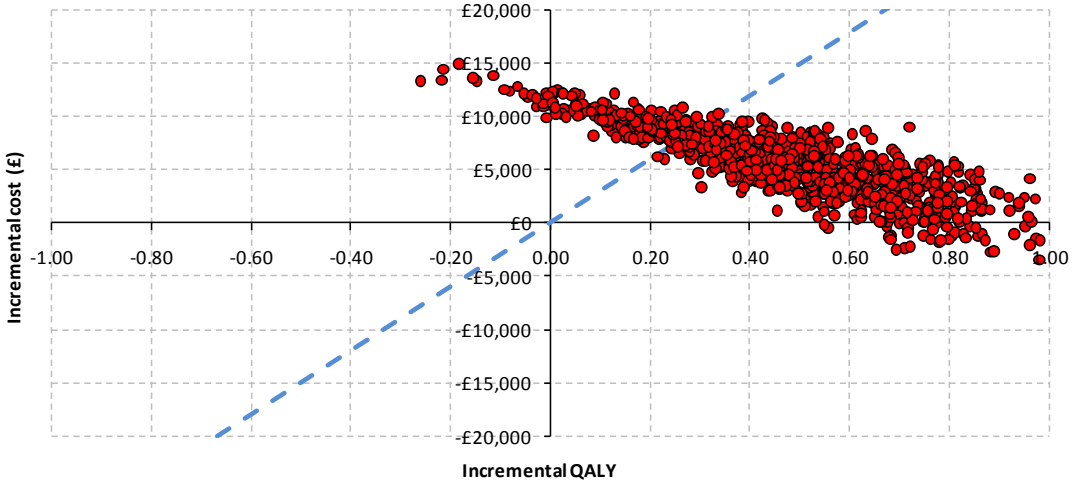
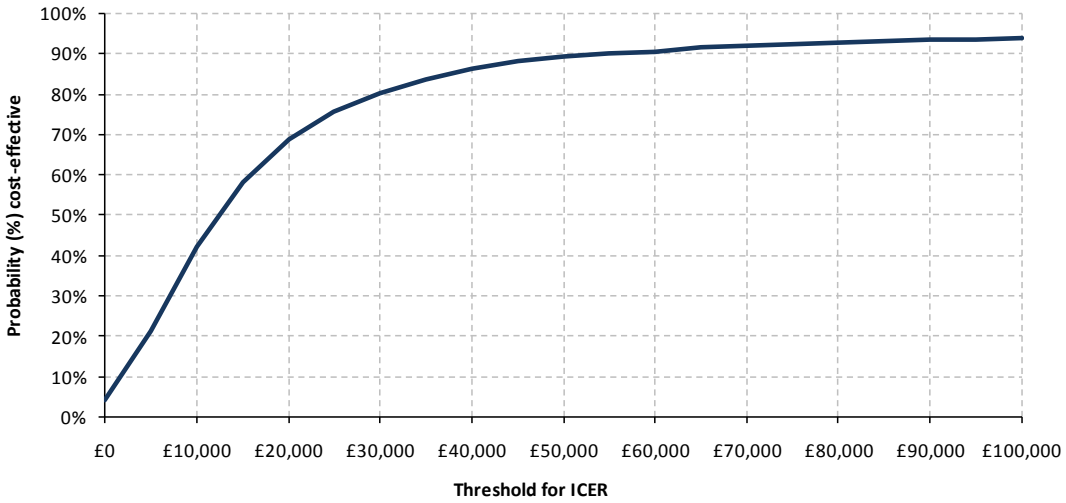


Figure B56 CEAC ranibizumab vs. observation in CRVO



6.7.9 Please present the results of scenario analysis. Include details of structural sensitivity analysis.

Source of Utilities

Table B90 Deterministic scenario analysis – source of utilities

Parameter	Incremental costs	Incremental QALYs	Incremental cost per QALY
BRVO			
Base case	**£6,727**	**0.273**	**£24,610**
Utilities for BSE, Sharma 2000 utilities (univariate)	£6,727	0.339	£19,841
Utilities for BSE, Sharma 2000 utilities (bivariate)	£6,727	0.355	£18,923
CRVO			
Base case	**£5,600**	**0.490**	**£11,428**
Utilities for BSE, Sharma 2000 utilities (univariate)	£5,600	0.576	£9,723
Utilities for BSE, Sharma 2000 utilities (bivariate)	£5,600	0.601	£9,322

Potential stopping rule

In line with the posology, a post-hoc analysis was undertaken to identify a subgroup of patients that exhibited a poor response to ranibizumab treatment at month 3. This demonstrated that:

- BRAVO: 26/265 (10%) of patients (0.3/0.5 mg) showed no increase of more than 5 letters over the initial 3 month period
- CRUISE: 17/262 (6%) of patients (0.3/0.5 mg) showed no increase of more than 3 letters over the initial 3 month period.

A description of the analysis is presented in the appendix (Section 10.10, appendix 22), illustrating that this subgroup of patients showed a poor response at 12 months. A scenario analysis was conducted where these poor responders were excluded after month 3. Applying this stopping rule improves cost-effectiveness for the BRVO and CRVO cohorts, to £22,404 and £9,909 respectively. Figure B57 and Figure B58 show the impact of uncertainty in the proportion of BRVO and CRVO patients in whom ranibizumab is stopped at month 3.

Figure B57 Deterministic sensitivity analysis – BRVO - % of patients stopping after 3 months due to insufficient response

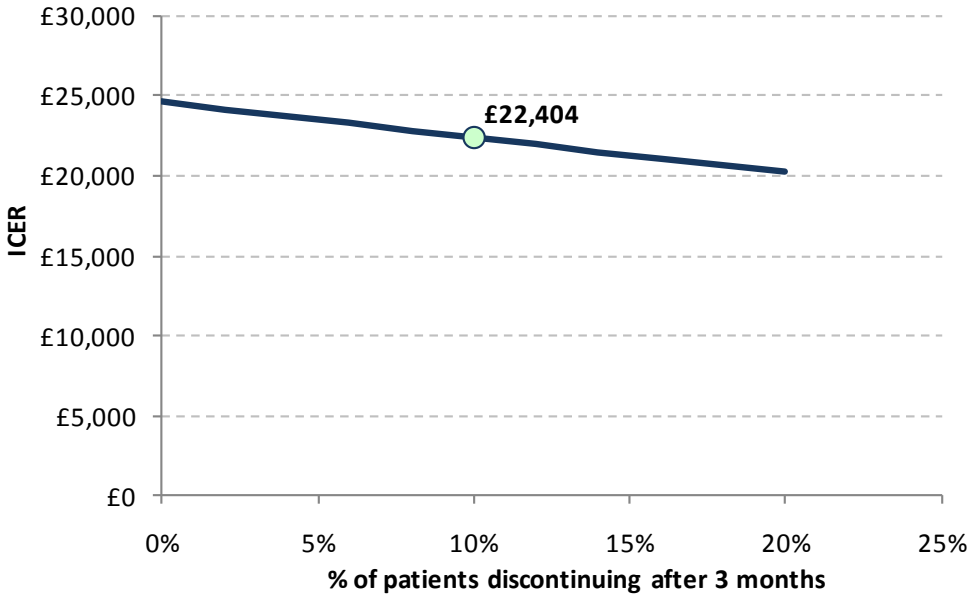
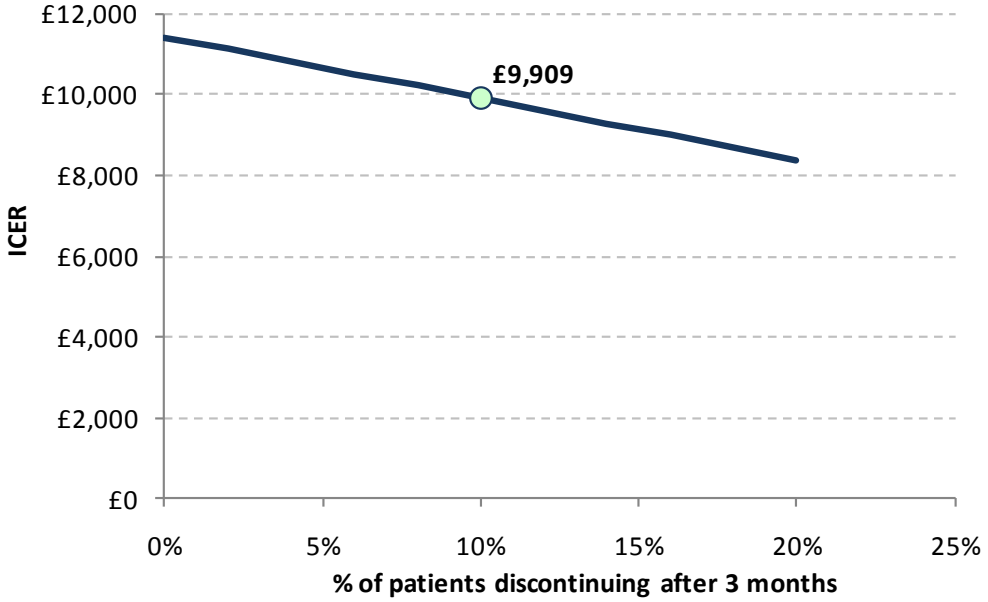


Figure B58 Deterministic sensitivity analysis – CRVO - % of patients stopping after 3 months due to insufficient response



Involvement of WSE

The Markov model used assumes treatment with ranibizumab in the BSE for the base case analysis, as there exist no robust utility values for WSE. However, in BRAVO and CRUISE trials the majority of patients were treated in their WSE. Utility curves for BRVO and CRVO are presented below for the following scenarios of WSE involvement:

- Trial based
  5.2% BSE at baseline, 7.1% BSE at 12 months
- Expected in clinical practice (assumption)
  10% BSE at baseline, 20% BSE at 12 months.

It is assumed that in clinical practice, the proportion of patients treated with visual impairment due to MO secondary to RVO in the BSE is higher than observed in the trials. One reason for this is the prevalence of glaucoma. This is a condition which affects the peripheral visual field, not only central visual acuity, and particularly so at the earlier stages of disease. Thus, using only a measure of VA to determine blindness would not capture those patients with VA that would not render them legally partially signted or severely sight impaired, but whose loss of peripheral visual field would.

Figure B59 Deterministic sensitivity analysis – BRVO - Slope of utility curve (trial based)

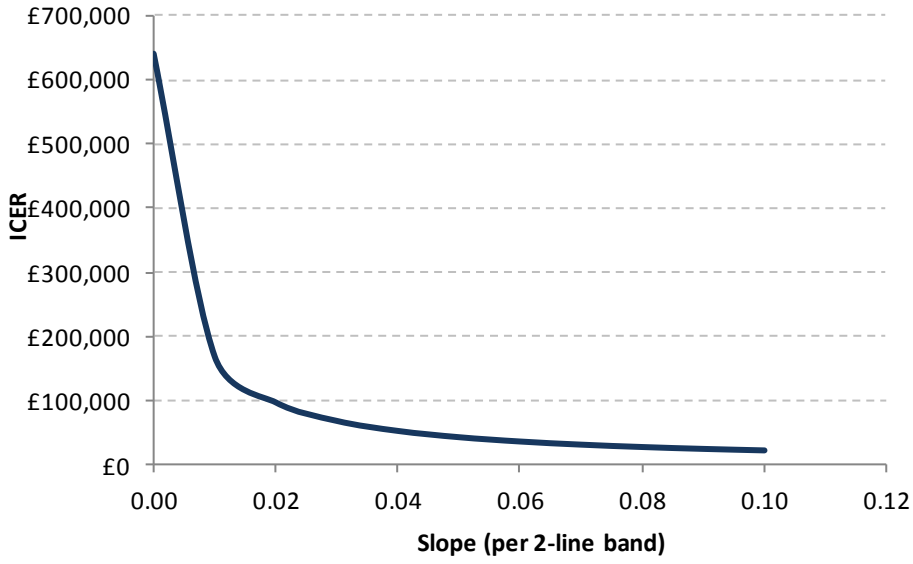


Figure B60 Deterministic sensitivity analysis – BRVO - Slope of utility curve (expected in clinical practice)

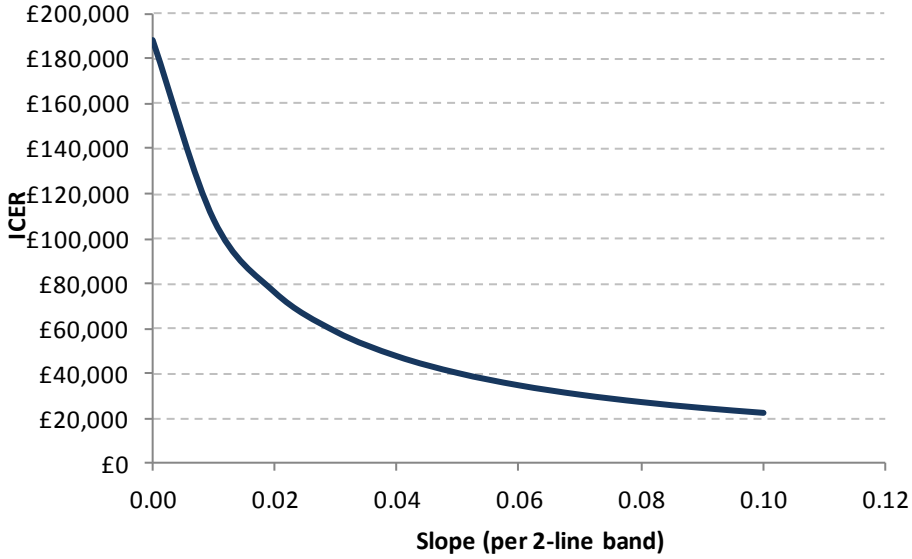


Figure B61 Deterministic sensitivity analysis – CRVO - Slope of utility curve (trial based)

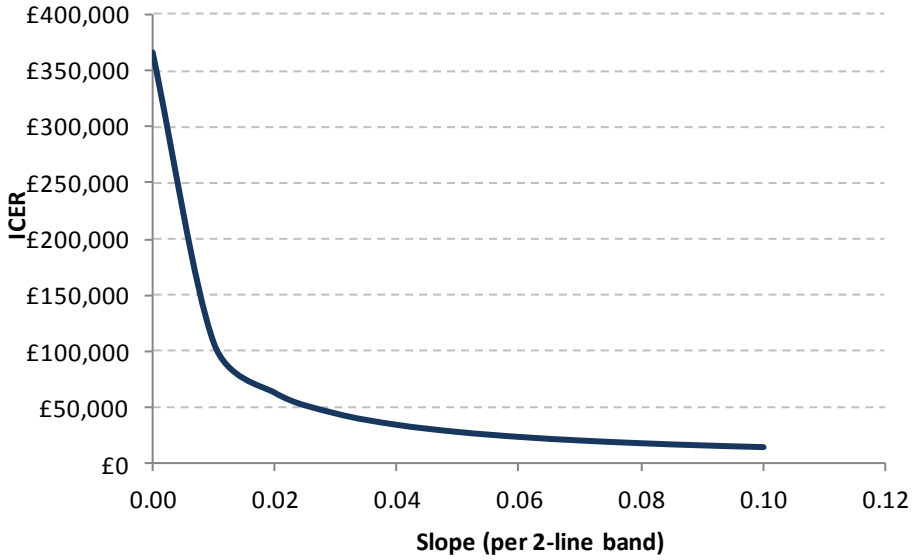
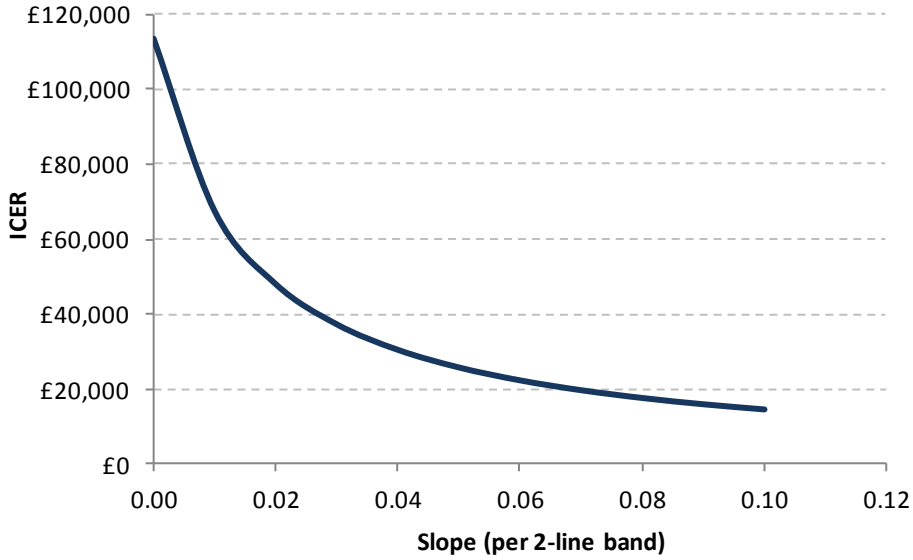


Figure B62 Deterministic sensitivity analysis – CRVO - Slope of utility curve (expected in clinical practice)



6.7.10 What were the main findings of each of the sensitivity analyses?

In general, the 'direction' of the results follows the prior expectations. For example, increasing the effectiveness of ranibizumab treatment (i.e. raising the probability of gaining 2 or more lines and reducing the probability of losing 2 or more lines) results in a lower ICER.

When natural deterioration of vision is increased, or when the overall rate of mortality is increased, ranibizumab becomes less cost-effective. This is because the 'capacity to benefit' (through duration of benefit) is generally reduced and any benefits of treatment tend to be lost sooner.

The model is relatively sensitive to the cost associated with blindness (i.e. when the patient's VA in the BSE falls below 35 letters). Again, this is to be expected, since one of the key benefits of effective treatment is to reduce the burden of patients whose sight becomes significantly affected by the disease.

As expected, the results are sensitive to the frequency of injections and follow up visits. For example, in BRVO, increasing the number of injections in year 2 (from 2.5 to 6) pushes the ICER over the £30,000 per QALY willingness to pay threshold. Of note however, even when administration visit costs are doubled, the ICER remains below the £30,000 per QALY threshold. In CRVO, the ICER remains below £20,000 under all assumptions regarding treatment and follow-up frequency, and cost of visits.

Assumptions regarding excess mortality risk of RVO compared to the general population demonstrate that the results are relatively robust to alternative assumptions.

Finally, it should be noted that the probabilistic analysis allows an overall assessment of the uncertainty within the model. When run, the PSA generates a scatter plot, which is observed to have a downward-sloping pattern. This is to be expected, since there is likely to be an inverse relationship between incremental cost and incremental effectiveness. For example, if the PSA distributions randomly generate a 'favourable' iteration (i.e. where the treatment is much more effective than the comparator), then this is likely to have two effects. Firstly, the patient will gain QALYs, through improved quality of life and, to a much lesser extent, through increased survival. Secondly, the patient will be more likely to avoid costly complications such as blindness and, as such, will see their incremental cost reduced. Similarly, a 'less favourable' iteration will see reduced QALYs and increased long-term costs, thus generating a downward-sloping scatter plot.

For the comparison to dexamethasone implant, the 'direction' of the sensitivity analysis results is again as expected; when the number of ranibizumab injections required in reduced, the ICER is reduced, whereas if the number of dexamethasone injections required is reduced, the ICER is increased. For the deterministic sensitivity analysis on resource use and costs, the ICER of ranibizumab compared to dexamethasone treatment remains below the £30,000 willingness to pay threshold under all assumptions and the majority are below £20,000. The greatest uncertainty in the comparison of ranibizumab to dexamethasone was the relative efficacy of each agent. The sensitivity analysis performed using an effectiveness multiplier demonstrates that increasing or decreasing the effectiveness of either ranibizumab or dexamethasone beyond 1 month can change the ICER considerably. Therefore the results of the comparison to dexamethasone should be interpreted with caution.

6.7.11 What are the key drivers of the cost-effectiveness results?

The time horizon is a driver of cost-effectiveness. As expected, shorter time horizons result in poorer cost-effectiveness because it is not possible to offset the costs of treatment incurred at the start of the model, through cost savings and utility gains from blindness avoided, later in the model. Assuming a lifetime time horizon improves ranibizumab cost effectiveness.

There is uncertainty in the effectiveness data in months 7 and beyond, and varying these values is observed to impact the results. For BRVO, during months 7 to 12 it is assumed that the effectiveness of laser is identical to ranibizumab; Thus reducing ranibizumab effectiveness has a dramatic effect on the ICER. However, even under these conservative assumptions, laser would need to demonstrated more than 15% greater efifcacy than ranibizumab to impact the ICER. Based on the clinical evidence, this is unlikely to be an observed scenario.

Finally, the assumption made in the base case analysis regarding treatment of the BSE is clearly a key driver of cost effectiveness. Under extreme assumptions regarding utility, that is, that there is absolutely no utility gain associated with improved VA in the worse-seeing eye, ranibizumab is not cost effective. However, assuming increasing utility gains are associated with treatment of the WSE improves cost effectiveness towards the threshold of acceptability. The proportion of patients treated in the better-seeing eye is also uncertain, given the limitations of the clinical trial setting and the potential that non-VA based visual impairment may not have been reflected in the categorisation of BSE and WSEs. In the absence of robust data describing the true utility benefit of treating VI due to MO secondary to RVO in the WSE, or the number of BSEs treated in NHS clinical practice, the appropriate approach is to conduct extensive sensitivity analysis as presented.

6.8 Validation

6.8.1 Please describe the methods used to validate and quality assure the model. Provide references to the results produced and cross-reference to evidence identified in the clinical, quality of life and resources sections.

The economic model has been validated by two external reviewers, who undertook extensive analysis to assess the model for internal and external validity. Both review reports are available upon request, along with a commentary to justify any areas where the reviewers' comments were not addressed (for example, due to a lack of data).

Unfortunately, no long-term data beyond treatment exist for patients with BRVO or CRVO and, as such, it is not possible to undertake a long-term validation of the model's outputs. However, survival in the model can be compared against the

(predicted) survival of the general population. In this case, patients in the model were observed to have slightly lower life expectancy. The magnitude of the difference depends upon which treatments and assumptions were selected, but patients in the model tended, on average, to die around one month sooner than patients without RVO.

6.9 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).

6.9.1 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 due to known, biologically plausible, mechanisms, social characteristics or other clearly justified factors? Cross-reference the response to section 5.3.7.

Some key subgroup analyses were undertaken. These subgroups were selected a priori as they are deemed clinically relevant with the potential for differential clinical effectiveness.

6.9.2 Please clearly define the characteristics of patients in the subgroup.

The following sub group analyses were undertaken.

- Baseline BCVA <54 letters
- Baseline BCVA >54 letters
- Time since diagnosis <3 months
- Time since diagnosis 3-<6 months
- Time since diagnosis ≥6 months

6.9.3 Please describe how the statistical analysis was undertaken.

The transition probabilities were re-estimated for each subgroup using data from the BRAVO and CRUISE trials.

6.9.4 What were the results of the subgroup analysis/analyses, if conducted? Please present results in a similar table as in section 6.7.6 (Base-case analysis).

It should be noted that some groups are based on small sample sizes which limits the robustness when the subgroups are further broken down by treatments arms.

Thus the cost-effectiveness results in the subgroups are predominantly driven by the impact of the cost of blindness and by the distribution and number of patients available in the specific subgroup. These results should be interpreted cautiously, but overall, demonstrate consistency with the clinical efficacy results.

Table B91 CEA by subgroups – BRVO

	Incremental cost	Incremental QALY	Cost per QALY	[redacted]
Base case	£6,727	0.273	£24,610	[redacted]
Baseline BCVA<54 letters	£5,757	0.354	£16,286	[redacted]
Baseline BCVA>54 letters	£7,447	0.223	£33,369	[redacted]
Time since diagnosis <3 months	£6,355	0.316	£20,133	[redacted]
Time since diagnosis3-<6 months	£7,450	0.208	£35,777	[redacted]
Time since diagnosis≥6 months	£6,991	0.235	£29,764	[redacted]

Table B92 CEA by subgroups - CRVO

	Incremental cost	Incremental QALY	Cost per QALY	[redacted]
Base case	**£5,600**	**0.490**	**£5,600**	[redacted]
Baseline BCVA<54 letters	£4,661	0.554	£8,421	[redacted]
Baseline BCVA>54 letters	£6,407	0.464	£13,816	[redacted]
Time since diagnosis <3 months	£5,619	0.497	£11,297	[redacted]
Time since diagnosis3-<6 months	£7,733	0.313	£24,704	[redacted]
Time since diagnosis≥6 months	£2,245	0.726	£3,094	[redacted]

6.9.5 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 4.

Although the decision problem identified ischaemic subgroups for consideration in the analysis, these subgroups are not included here because very few patients fulfilled the definition of ischaemia in the two key RCTs for ranibizumab (0 in BRAVO and 2 in CRUISE); most likely because patients with brisk afferent pupillary defect, which equates to severe ischaemia, were excluded from the trials.

In addition, a subgroup of BRVO patients with macular haemorrhage who are unsuitable for laser was not analysed. Exploratory analysis is ongoing in order to identify this group of patients according to an easily operationalisable and consistent definition.

6.10 Interpretation of economic evidence

6.10.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Not applicable. The literature search for cost-effectiveness studies did not identify analyses suitable for comparison with the de novo analysis.

6.10.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology as identified in the decision problem in section 4?

Yes, the model is applicable to all groups of patients who could potentially use the technology.

6.10.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

RVO is a complex disease and there is much debate regarding the factors that should be accounted for within an assessment of the treatment pathway. Combined with uncertainty surrounding many of the quantitative measurements of effectiveness in this area (for example, for quality of life and utility scores associated with VA in the WSE), this is likely to lead to differences of opinion as to what assumptions should be made in the base case analysis. As such, the model described in this analysis has been built to be as flexible in order to assess a variety of different scenarios, based on various inputs and assumptions. This is highlighted by the extensive sensitivity analyses and scenario analyses that have been undertaken. This is far more desirable than a rigid model, which cannot account for alternative methods to assess the impact of different treatments.

A particular weakness is the absence of RVO specific utilities, or robust utility data relating to the WSE. As noted in section 6.4 the Brown utilities are based on patient, rather than public preferences.[1] However, based on evidence of patient versus public valuation of vision loss, it may be that the general public underestimates the true impact of sight loss. Furthermore, utilities based only on BCVA may not capture fully the impact of vision loss. Impaired contrast sensitivity and loss of visual field are also important factors in determining visual function. For patients with monocular vision

loss, these may be especially important as aspects of visual functioning such as depth perception and reading speed may impact on utility but are not captured when utility is mapped solely to VA.

The model used in this analysis is based on clinical data derived from the BRAVO, CRUISE and HORIZON trials, the most appropriate source of evidence to assess the effectiveness of ranibizumab in the treatment of BRVO and CRVO respectively. This allows for a robust comparison of ranibizumab against standard care laser treatment for BRVO and against standard care observation for CRVO.

As with any model based on short-term trial data, there remains some uncertainty over the long-term impact of treatment. In this analysis, it was assumed that the treatment probabilities from months 7 to 12 would remain constant for the second year of the model, but that the rates in the treatment and comparator arm would then converge towards stability and be identical from the third year onwards. In the absence of any observed data, this would seem to be a conservative approach.

One key limitation with the analysis is the lack of reliable data for quality of life in patients with RVO. Whilst several studies exist to demonstrate utility in patients based on the VA in their BSE, there is very little evidence related to the utility of patients based on their WSE's VA. It is worth noting that the absolute value of utility does not drive the model's results. Actually, as demonstrated by the scenario analysis, the incremental QALY gains are largely driven by the slope of the utility curve.

Unfortunately, there remains very little evidence to be able to compare ranibizumab against dexamethasone. Although a systematic review was undertaken, it was concluded that the trial populations were too heterogeneous to allow for a meaningful indirect comparison. As such, it is recommended that the 'crude' cost-effectiveness comparison against dexamethasone is interpreted with a high degree of caution.

Bevacizumab cannot be routinely used in the NHS because it is not routinely funded by commissioning NHS bodies, primarily due to the lack of robust safety and efficacy data. Use of an unlicensed intervention, without regulatory assessment of safety and quality in light of the emerging safety signals, cannot be deemed to represent best practice. Thus, this intervention is not an appropriate comparator in this appraisal based on NICE guidance.[43]

Nonetheless, a comparison with bevacizumab was not possible due to very limited data availability. It is important to note that should data become available in the future

to allow for an economic evaluation of bevacizumab versus ranibizumab key additional costs associated with bevacizumab must be considered. Firstly, as described in Table B37, retrospective and prospective studies have identified potential safety signals associated with bevacizumab treatment. Of particular note, bevacizumab has been consistently associated with a significantly increased risk of stroke compared to ranibizumab. Based on the secondary analysis of the 2010 Curtis et al.[45] paper and a population of 1000 patients, the increased risk of stroke observed with bevacizumab treatment compared with ranibizumab is associated with an increased cost of stroke (5 years direct NHS care) of £88,572 per year (99% CI £16,104 - £144,936), and an additional 7 patient deaths per year (95% CI 12 -1). These increased costs of stroke, in addition to the costs associated with ocular adverse events such as sterile endophthalmitis due to unapproved and inconsistent product quality, must be accounted for in an economic evaluation.

Furthermore, as bevacizumab is not presented in a licensed formulation for administration in the eye and due to the potential systemic and ocular safety signals, a comprehensive pharmacovigilance programme would be required. The costs of implementing and maintaining such a programme would also need to be considered in any economic evaluation of bevacizumab. It is unclear how these costs would be estimated for a programme based in the NHS, rather than being funded by the product sponsor. Clearly, the clinical and administrative expertise to manage a pharmacovigilance programme, in addition to the regular training on adverse event report management, would be significant cost even when calculated on a per injection basis. In addition, given its unlicensed status, an economic evaluation would need to account for the additional clinician time spent with patients to discuss the use of unlicensed bevacizumab over the licensed alternative interventions, to ensure their informed consent can be obtained.

6.10.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

As described above a limitation of the model is the lack of data on HRQL in patients based on their WSE. It should be noted that, ideally, it would be useful to be able to model the patients' BSEs and WSEs simultaneously. In such a case, a patient level simulation would allow the modelling of each eye, and account for the relationship of VA between the two eyes. Although the computational burden of this approach is

likely to be manageable, the level of evidence to populate such a model is, unfortunately, sparse. Such a model would require detailed data on the complex relationship between VA in each eye and, therefore, that approach was not possible in this analysis but could be considered in the future when appropriate data is available.

Section C – Implementation

7 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.

Summary of Budget Impact

- It is estimated that approximately 11,600 people develop visual impairment due to MO secondary to BRVO each year in England and Wales.
- It is estimated that approximately 5,700 people develop visual impairment due to MO secondary to CRVO each year in England and Wales.
- Ranibizumab is predicted to displace the use of observation, laser and dexamethasone implant in BRVO patients and observation and dexamethasone implant in CRVO patients.
- When direct costs of blindness are considered, the net budget impact of ranibizumab in 2015 in England and Wales for MO secondary to BRVO is estimated to be £10,708,766. Over the next 5 years this equates to a total budget impact of £46,440,792 for BRVO.
- When blindness costs are excluded, the net budget impact of ranibizumab for BRVO is estimated at £20,536,732 in 2015 and at £59,255,535 over all 5 years.
- When direct costs of blindness are considered, the net budget impact of ranibizumab in 2015 in England and Wales for MO secondary to CRVO is estimated to be £16,376,492. Over the next 5 years this equates to a total budget impact of £45,265,197 for CRVO.
- When blindness costs are excluded, the net budget impact of ranibizumab for CRVO is estimated at £21,210,086 in 2015 and at £54,683,227over all 5 years.
- Adverse event costs and the societal cost savings due to avoidance of blindness were not considered in the budget impact model.

7.1 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 number of patients eligible for treatment has been calculated separately for BRVO and CRVO, which have different incidence rates, and because treatment options and uptake of interventions vary between the two subgroups. The current number of patients with MO secondary to RVO and the calculation used to derive these values are presented in Table C1. The assumptions used in the calculation are listed below the table.

Table C1 Calculation of yearly patient numbers to be treated[a]

	BRVO	**CRVO**
Total population (45+)[b] of England and Wales (mid-2009 population estimate, ONS)	22,822,900	22,822,900
Annual Incidence of RVO[c]	0.1200%	0.0333%
Of which % with MO within 2 months of diagnosis[d]	85%	75%
Of which % experiencing visual impairment[e]	50%	100%
Yearly number of patients with VI due to MO secondary to RVO initiating treatment (annual incident population)	**11,640**	**5,700**

Abbreviations: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ONS, Office of National statistics; MO, macular oedema; VI, visual impairment

a. A minority of prevalent RVO-MO cases may be eligible for further treatment where (i) laser has failed to treat MO or was not suitable for use, but (ii) MO was not present for more than 1 year. Given that the proportion of patients in these two groups is unknown and is expected to be small, no attempt has been made to establish estimates.

b. The epidemiological data (Klein et al[16]) is based on population aged 43-84 years. Thus incidence is applied to the proportion of patients in England and Wales over 45.

c. Yearly incidence for both BRVO and CRVO is derived from the 15 year incidence reported by Klein et al (BDES)[16]

d. Published data for the proportion of patients with MO secondary to RVO is limited. The estimates used were considered the best available. BRVO: Shroff et al.[120] (OCT based measure of MO). CRVO: CVO Study[22].

e. Not all patients with BRVO experience visual impairment, as many branch occlusions are lateral and are therefore less likely to negatively impact upon vision. The assumption of 50% is conservative (Mitchell et al[7]).

7.2 What assumption(s) were made about current treatment options and uptake of technologies?

Spontaneous Resolution

A proportion of patients are not expected to require the full course of treatment due to spontaneous resolution of their condition. Therefore it was assumed that 41% of BRVO patients (Shroff 2008[28, 120]) and 36% of CRVO (McIntosh 2010[27]) would stop treatment after an average of 6 months. This was modelled by reducing the annual number of people eligible for treatment by 20.5% for BRVO and 18% for CRVO. This gives the total eligible population for treatment for VI due to MO secondary to BRVO each year to be 9,254 and for VI due to MO secondary to CRVO to be 4,674.

Other treatments

Bevacizumab and IVTA (Kenalog) were not considered given their use is experimental and infrequent in the NHS. The impact of this omission was considered to be negligible.

7.3 What assumption(s) were made about market share (when relevant)?

Table C2 and Table C3 below present the predicted five year forecast for the market shares occupied by each treatment option for BRVO and CRVO, respectively, in a situation without ranibizumab.

New drugs expected to be available in subsequent years have not been included in the market share estimates.

Table C2 Current forecast of market share for BRVO without ranibizumab

	No treatment	Dexamethasone implant	Grid laser (standard care)
Year 1	38%	13%	49%
Year 2	36%	15%	49%
Year 3	35%	14%	51%
Year 4	32%	15%	53%
Year 5	29%	19%	52%

Table C3 Current forecast of market share for CRVO without ranibizumab

	Standard care	Dexamethasone implant
Year 1	56%	44%
Year 2	55%	45%
Year 3	49%	51%
Year 4	40%	60%
Year 5	32%	68%

The anticipated uptake of ranibizumab, which is assumed equivalent in BRVO and CRVO, is presented in Table C5. It was assumed that ranibizumab would receive market share from the other treatments in a proportional manner, based on the market share each other treatment option would occupy in a situation without ranibizumab (as presented in Table C3 and Table C4 above). The predicted markets shares following uptake of ranibizumab are displayed in Table C5 for BRVO and Table C6 for CRVO.

Table C4 Anticipated uptake rate for ranibizumab for both BRVO and CRVO

	BRVO	CRVO
Year 1	[redacted]	[redacted]
Year 2	[redacted]	[redacted]
Year 3	[redacted]	[redacted]
Year 4	[redacted]	[redacted]
Year 5	[redacted]	[redacted]

Table C5 New market shares for BRVO treatment after uptake of ranibizumab

BRVO	Ranibizumab	No treatment	Dexamethasone implant	Grid laser (standard care)
Year 1	[redacted]	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]	[redacted]

Table C6 New market shares for CRVO treatment after uptake of ranibizumab

CRVO	Ranibizumab	Standard care	Dexamethasone implant
Year 1	[redacted]	[redacted]	[redacted]
Year 2	[redacted]	[redacted]	[redacted]
Year 3	[redacted]	[redacted]	[redacted]
Year 4	[redacted]	[redacted]	[redacted]
Year 5	[redacted]	[redacted]	[redacted]

Using the estimate of the number of RVO patients with VI due to MO presented in Section 1.1 and the predicted market share, the number of patients estimated to initiate the different treatments each year can be calculated (Table C7 and Table C8).

Table C7 Predicted number of patients initiating treatment each year for BRVO

	2011	2012	2013	2014	2015
Number of BRVO patients with VI due to MO who are eligible to initiate treatment	9,254	9,254	9,254	9,254	9,254
In a situation without ranibizumab					
Number of patients treated with observation only	3,516	3,331	3,239	2,961	2,684
Number of patients treated with Grid laser (standard care)	4,534	4,534	4,719	4,904	4,812
Number of patients treated with Dexamethasone implant	1,203	1,388	1,295	1,388	1,758
In a situation with ranibizumab					
Number of patients treated with observation only	3,376	3,031	2,721	2,280	1,878
Number of patients treated with Grid laser (standard care)	4,353	4,126	3,964	3,776	3,368
Number of patients treated with Dexamethasone implant	1,155	1,263	1,088	1,069	1,231
Number of patients predicted to be treated with ranibizumab	370	833	1,481	2,128	2,776

Table C8 Predicted number of patients initiating treatment each year for CRVO

	2011	2012	2013	2014	2015
Number of CRVO patients with VI due to MO who are eligible to initiate treatment	4,674	4,674	4,674	4,674	4,674
In a situation without ranibizumab					
Number of patients treated with observation only (standard care)	2,617	2,571	2,290	1,870	1,496
Number of patients treated with Dexamethasone implant	2,057	2,103	2,384	2,804	3,178
In a situation with ranibizumab					
Number of patients treated with observation only (standard care)	2,434	2,082	1,718	1,215	748
Number of patients treated with Dexamethasone implant	1,913	1,704	1,788	1,823	1,589
Number of patients predicted to be treated with ranibizumab	327	888	1,169	1,636	2,337

7.4 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 and were therefore also incorporated into the budget impact analysis (please refer to Section 6.5 of the main submission for more detail)

- Cost of administration outpatient visits
- Cost of follow-up hospital visits
- Cost of blindness (the budget impact results are also presented without the cost of blindness due to uncertainty over the indirect comparison of efficacy between treatments)

7.5 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?

Cost break-down by treatment type

Treatment, administration and follow-up visit and blindness costs associated for each treatment were taken from the cost-effectiveness model (please refer to Section 6.5 of the main submission for sources). These costs were based on national reference costs and PbR tariffs. For clarity, the values utilised are displayed below.

These costs represent those associated with a single course of treatment, where the year 1 costs are associated with the 1st year in which the patient develops VI due to MO secondary to RVO and the year 2 costs are associated with their 2nd year of treatment, etc. For example, patients that develop the condition in 2015 will only accrue one year of treatment costs.

Table C9 Costs associated with observation

	Observation in BRVO				Observation in CRVO (standard care)			
Year	Treatment	Admin	Follow Up	Blindness	Treatment	Admin	Follow Up	Blindness
1	£0	£0	£899	£755	£0	£0	£898	£1,513
2	£0	£0	£591	£870	£0	£0	£590	£1,539
3	£0	£0	£291	£857	£0	£0	£579	£1,479
4	£0	£0	£286	£844	£0	£0	£569	£1,453
5	£0	£0	£281	£830	£0	£0	£557	£1,425

Table C10 Costs associated with grid laser

	Grid laser in BRVO (standard care)			
Year	Treatment	Admin	Follow Up	Blindness
1	£0	£165	£375	£755
2	£0	£108	£443	£870
3	£0	£0	£291	£857
4	£0	£0	£286	£844
5	£0	£0	£281	£830

Table C11 Costs associated with dexamethasone implant

	Dexamethasone implant in BRVO				Dexamethasone implant in CRVO			
Year	Treatment	Admin	Follow Up	Blindness	Treatment	Admin	Follow Up	Blindness
1	£1,727	£412	£899	£635	£1,725	£412	£898	£1,362
2	£1,703	£407	£887	£783	£1,698	£406	£884	£1,279
3	£0	£0	£291	£784	£0	£0	£579	£1,188
4	£0	£0	£286	£772	£0	£0	£569	£1,168
5	£0	£0	£281	£759	£0	£0	£557	£1,145

Table C12 Costs associated with ranibizumab

	Ranibizumab in BRVO				Ranibizumab in CRVO			
Year	Treatment	Admin	Follow Up	Blindness	Treatment	Admin	Follow Up	Blindness
1	£5,893	£1,525	£600	£367	£6,624	£1,714	£449	£765
2	£1,816	£470	£517	£558	£2,753	£712	£914	£906
3	£0	£0	£291	£592	£0	£0	£580	£902
4	£0	£0	£286	£583	£0	£0	£569	£887
5	£0	£0	£281	£574	£0	£0	£557	£870

7.6 Were there any estimates of resource savings? If so, what were they?

When the cost of blindness is considered, the introduction of ranibizumab is predicted to accrue cost savings due to its superior efficacy at preventing progression

to blindness compared with the other options. This is reflected in the lower cost of blindness associated with one course of treatment of ranibizumab compared to all other treatment options presented in Table C9 to Table C12 in Section 7.5.

Over the next 5 years, the introduction of ranibizumab is predicted to result in savings of £12,814,743 due to the prevention of blindness in BRVO patients and savings of £9,418,030 due to the prevention of blindness in CRVO patients (refer to Section 7.7).

Savings are also predicted due to the displacement of existing therapies, which have hospital outpatient visits associated with them. These savings help to balance the increased costs associated with ranibizumab treatment and outpatient visits.

7.7 What is the estimated annual budget impact for the NHS in England and Wales?

BRVO

The estimated total annual NHS costs over the next 5 years associated with VI due to MO secondary to BRVO with and without ranibizumab are presented in Table C13 and

Table **C14**, respectively, and in

.

When direct costs of blindness are considered, the net budget impact of ranibizumab in year 1 (2011) in England and Wales for MO secondary to BRVO was estimated to be £2,458,997 and in year 5 (2015) to be £10,708,766 (Table C15). Over the next 5 years this equates to a total budget impact of £46,440,792.

When blindness costs are excluded, the net budget impact of ranibizumab for BRVO increases to £20,536,732 in 2015 and to £59,255,535 over all 5 years (Table C15).

Table C13 Total costs <u>without</u> ranibizumab for BRVO

Year	Drugs	Admin	Follow Up	Blindness	Total with blindness	Total without blindness
1	£2,077,530	£1,242,657	£5,942,651	£6,844,453	£16,107,292	£9,262,839
2	£4,446,050	£2,299,083	£11,098,972	£14,766,239	£32,610,343	£17,844,104
3	£4,601,455	£2,366,664	£13,750,095	£22,599,446	£43,317,660	£20,718,214
4	£4,603,657	£2,417,696	£16,246,399	£30,303,784	£53,571,537	£23,267,753

5	£5,400,505	£2,612,776	£18,894,390	£37,837,969	£64,745,640	£26,907,671
Total	£21,129,197	£10,938,876	£65,932,508	£112,351,891	**£210,352,472**	**£98,000,581**

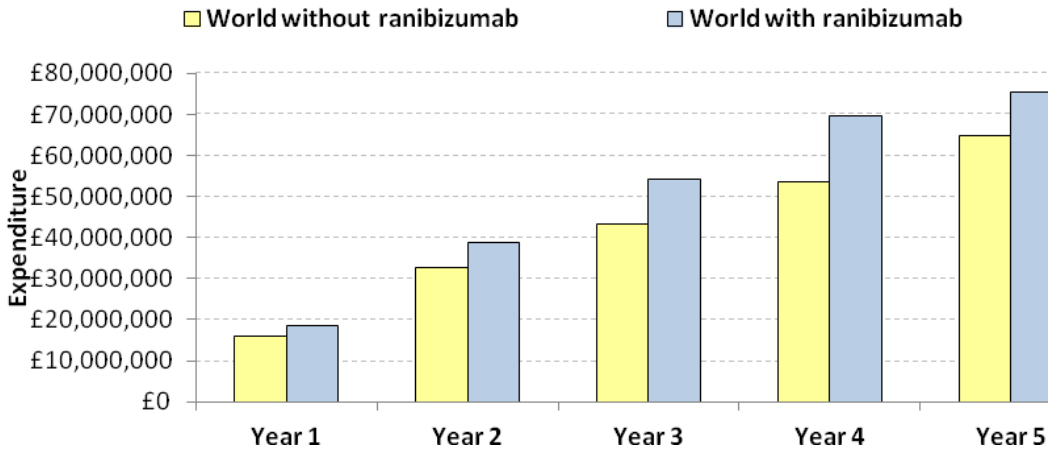
Table C14 Total costs with ranibizumab for BRVO

Year	Drugs	Admin	Follow Up	Blindness	Total with blindness	Total without blindness
1	£4,175,725	£1,757,254	£5,926,846	£6,706,466	£18,566,290	£11,859,824
2	£9,728,546	£3,584,772	£11,048,649	£14,346,560	£38,708,527	£24,361,967
3	£14,268,525	£4,710,405	£13,664,282	£21,706,154	£54,349,367	£32,643,213
4	£18,930,847	£5,874,691	£16,141,172	£28,767,965	£69,714,674	£40,946,709
5	£24,171,176	£7,137,935	£16,135,291	£28,010,004	£75,454,406	£47,444,403
Total	£71,274,819	£23,065,057	£62,916,240	£99,537,148	**£256,793,264**	**£157,256,116**

Table C15 Net budget impact of introducing ranibizumab for BRVO

Year	Drugs	Admin	Follow Up	Blindness	Total with blindness	Total without blindness
1	£2,098,194	£514,597	-£15,806	-£137,988	£2,458,997	£2,596,985
2	£5,282,497	£1,285,689	-£50,323	-£419,679	£6,098,184	£6,517,863
3	£9,667,070	£2,343,741	-£85,813	-£893,292	£11,031,707	£11,924,999
4	£14,327,189	£3,456,995	-£105,228	-£1,535,820	£16,143,137	£17,678,957
5	£18,770,671	£4,525,159	-£2,759,099	-£9,827,965	£10,708,766	£20,536,732
Total	£50,145,622	£12,126,181	-£3,016,268	-£12,814,743	**£46,440,792**	**£59,255,535**

Figure C1 Annual NHS expenditures for BRVO in a world with and without ranibizumab



CRVO

The estimated total annual NHS costs over the next 5 years associated with VI due to MO secondary to CRVO with and without ranibizumab are presented in Table C16 and Table C17**Table C13**, respectively, and in Figure C2.

When direct costs of blindness are considered, the net budget impact of ranibizumab in England and Wales for MO secondary to CRVO in year 1 (2011) was estimated to be £2,050,206 and in year 5 (2015) to be £16,376,492(Table C18). Over the next 5 years this equates to a total budget impact of £45,265,197.

When blindness costs are excluded, the net budget impact of ranibizumab for CRVO increases to £21,210,086 in 2015 and to £54,683,227 over all 5 years (Table C18).

Table C16 Total costs without ranibizumab for CRVO

Year	Drugs	Admin	Follow Up	Blindness	Total with blindness	Total without blindness
1	£3,548,329	£847,316	£4,199,026	£6,761,404	£15,356,076	£8,594,671
2	£7,121,767	£1,700,629	£7,560,750	£13,412,375	£29,795,522	£16,383,147
3	£7,685,012	£1,835,128	£10,282,715	£19,672,137	£39,474,993	£19,802,855
4	£8,887,097	£2,122,177	£13,022,866	£25,727,064	£49,759,205	£24,032,141
5	£10,246,683	£2,446,837	£15,749,491	£31,551,702	£59,994,714	£28,443,011
Total	£37,488,888	£8,952,088	£50,814,849	£97,124,684	**£194,380,509**	**£97,255,825**

Table C17 Total costs with ranibizumab for CRVO

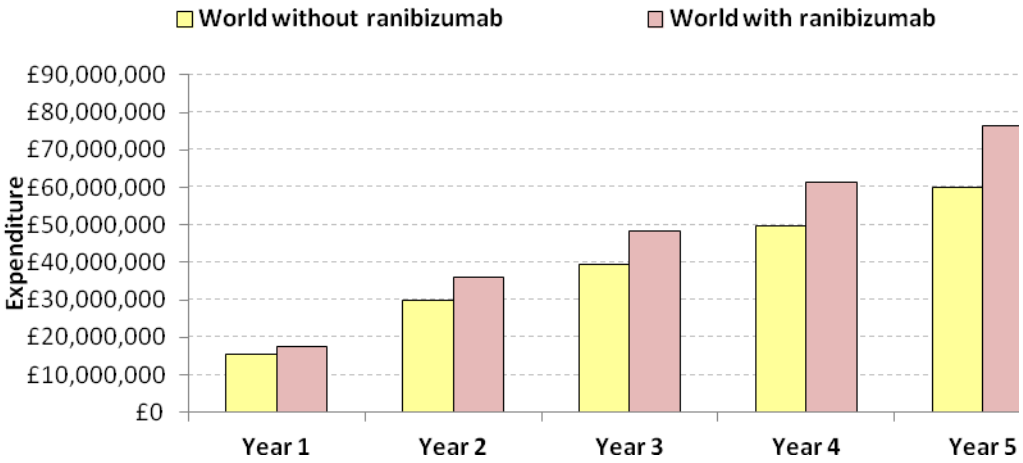
Year	Drugs	Admin	Follow Up	Blindness	Total with blindness	Total without blindness
1	£5,467,042	£1,348,634	£4,052,065	£6,538,541	£17,406,282	£10,867,741
2	£12,970,616	£3,232,325	£7,225,538	£12,639,109	£36,067,588	£23,428,479
3	£16,162,558	£4,062,257	£9,928,121	£18,283,456	£48,436,391	£30,152,935
4	£20,233,834	£5,111,451	£12,491,516	£23,527,439	£61,364,239	£37,836,800
5	£28,185,240	£7,213,136	£14,254,721	£26,718,109	£76,371,206	£49,653,097
Total	£83,019,289	£20,967,803	£47,951,961	£87,706,654	**£239,645,706**	**£151,939,052**

Table C18 Net budget impact of introducing ranibizumab for CRVO

Year	Drugs	Admin	Follow Up	Blindness	Total with blindness	Total without blindness
1	£1,918,713	£501,318	-£146,961	-£222,864	£2,050,206	£2,273,070
2	£5,848,848	£1,531,696	-£335,212	-£773,266	£6,272,066	£7,045,332
3	£8,477,545	£2,227,129	-£354,595	-£1,388,681	£8,961,399	£10,350,080
4	£11,346,737	£2,989,273	-£531,350	-£2,199,626	£11,605,034	£13,804,660
5	£17,938,557	£4,766,299	-£1,494,771	-£4,833,594	£16,376,492	£21,210,086

Total	£45,530,401	£12,015,715	-£2,862,889	-£9,418,030	**£45,265,197**	**£54,683,227**

Figure C2 Annual NHS expenditures for CRVO in a world with and without ranibizumab



7.8 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 due to the uncertainty surrounding the comparison of adverse event rates between the different treatment options, which was difficult due to the low frequency of many of the adverse event types.

From a societal perspective, the potential for resource savings with ranibizumab treatment due to the avoidance of blindness is great; the costs of partial sight and blindness, taken from a societal perspective, would include the costs of lost productivity, tax relief and benefits. These costs would be accrued to patients themselves but also to unpaid carers; family members and friends who provide care to patients with RVO-caused visual impairment. The indirect costs of blindness in UK adults has been estimated as being more than double the direct cost,[121] which suggests that ranibizumab therapy would be associated with greater savings from a societal perspective than from a healthcare provider perspective. The societal costs of blindness were not included in the budget impact model for two reasons: firstly, societal costs are not considered under the NICE reference case and secondly, such costs are difficult to measure accurately.

The use of bevacizumab and other unlicensed ocular interventions for the treatment of MO due to RVO were not included in the budget impact analysis, given their use is not routine. However, even limited use of these interventions could result in costly adverse events, such as stroke and endophthalmitis. The costs of treating adverse events of any intervention were excluded from the budget impact analysis.

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Please use a recognised referencing style, such as Harvard or Vancouver.

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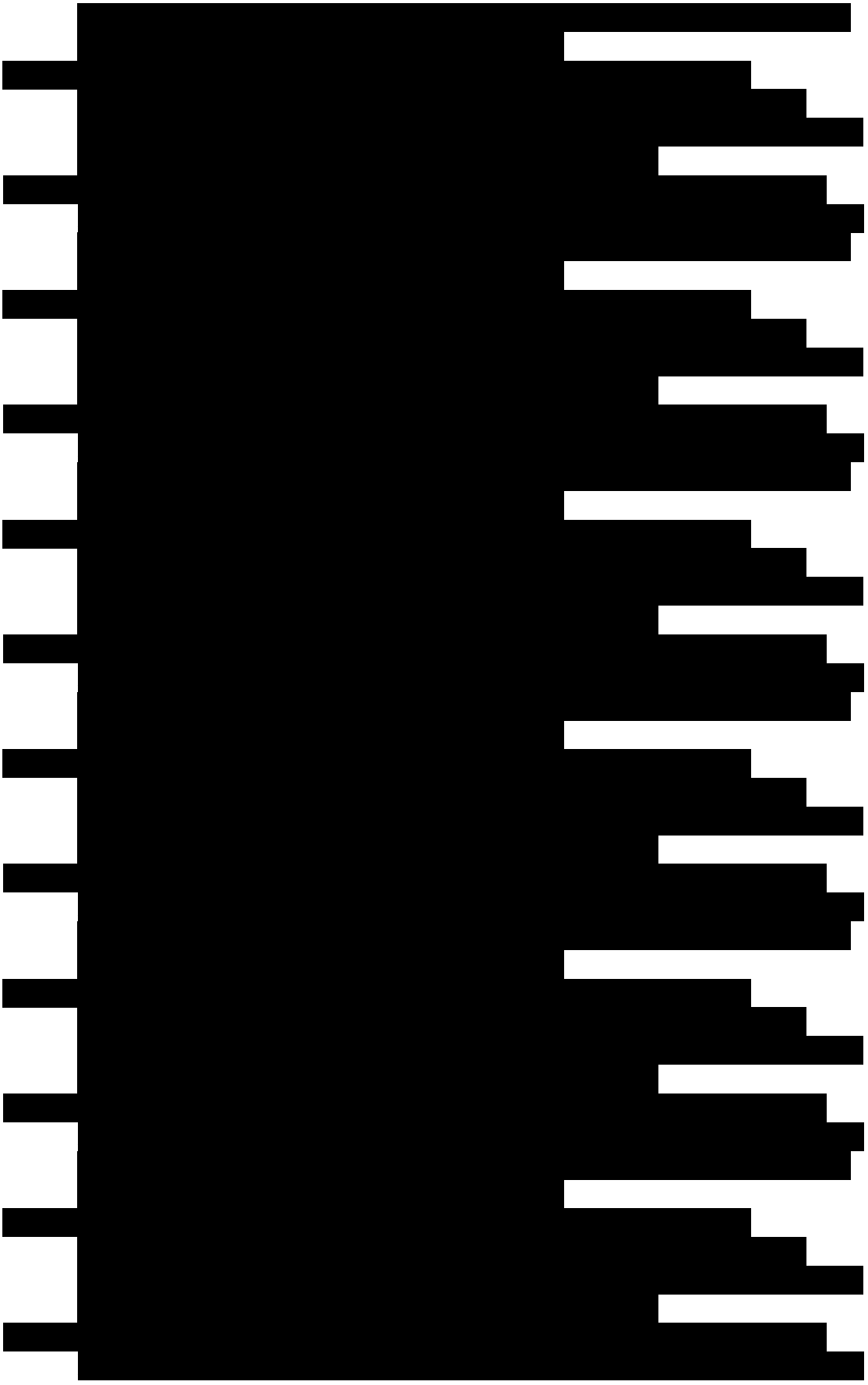

9 Appendices

9.1 Appendix 1

9.1.1 SPC/IFU, scientific discussion or drafts.

9.2 Appendix 2: Search strategy for section 5.1 (Identification of studies)

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- Medline
- Embase
- Medline (R) In-Process
- The Cochrane Library.

The databases searched and the service providers used were as follows:

- MEDLINE (OvidSP)
- MEDLINE In-Process (OvidSP)
- EMBASE (OvidSP)
- Cochrane Database of Systematic Reviews (CDSR) (Cochrane Library/Wiley Interscience)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Cochrane Library/Wiley Interscience)
- Database of Abstracts of Reviews of Effects (DARE) (Cochrane Library/Wiley Interscience)
- Health Technology Assessment Database (HTA) (Cochrane Library/Wiley Interscience)
- Cumulative Index to Nursing and Allied Health Literature (CINAHL) (EBSCO*host*)
- Science Citation Index (SCI) (Web of Science)
- ClinicalTrials.gov (http://ClinicalTrials.gov)
- International Clinical Trials Registry Platform (ICTRP) (http://www.who.int/ictrp/en/)
- Association of Research in Vision and Ophthalmology (ARVO) annual meeting (http://www.arvo.org/)
- European Association for Vision and Eye Research (EVER) Congress (http://www.ever.be)
- Nordic Ophthalmological Societies Congress (Acta Ophthalmologica Supplements)

- Dutch Ophthalmological Society annual meeting (www.oogheelkunde.org/)
- Medical Ophthalmological Society annual meeting (http://www.mosuk.co.uk/)
- Royal College of Ophthalmologists Congress (http://www.rcophth.ac.uk/)
- American Academy of Ophthalmology (AAO) (annual meeting (www.aao.org/)
- World Ophthalmology Congress (WOC) (www.woc2010.org/)
- Retina International World Congress (http://www.retina-international.org/)
- EURETINA Congress (European Society of Retina Specialists) (www.euretina.org/)
- Asia Pacific Academy of Ophthalmology (APAO) Congresses (http://www.apaophth.org/)

9.2.2 The date on which the search was conducted.

All database searches were conducted on 18 November 2010. Searches of conference proceedings websites were undertaken on 22 November 2010. Publications known to the manufacturer to have been published after the searches were run were also included.

9.2.3 The date span of the search.

- MEDLINE (1950-2010/Nov week 1)
- MEDLINE In-Process (16 November 2010)
- EMBASE (1980-2010/week 45)
- Cochrane Database of Systematic Reviews (CDSR) (2010 Issue 11/4)
- Cochrane Central Register of Controlled Trials (CENTRAL)(2010 Issue 11/4)
- Database of Abstracts of Reviews of Effects (DARE) (2010 Issue 11/4)
- Health Technology Assessment Database (HTA) (2010 Issue 11/4)
- Cumulative Index to Nursing and Allied Health Literature (1982-2010/Nov week 2)
- Science Citation Index (SCI) (1899-2010/Nov 13th)
- ClinicalTrials.gov (18th November 2010)
- International Clinical Trials Registry Platform (ICTRP) (18th November 2010)
- Association of Research in Vision and Ophthalmology (ARVO) annual meeting (22nd November 2010)
- European Association for Vision and Eye Research (EVER) Congress (22 November 2010)
- Nordic Ophthalmological Societies Congress (22 November 2010)
- Dutch Ophthalmological Society annual meeting (22 November 2010)
- Medical Ophthalmological Society annual meeting (22 November 2010)
- Royal College of Ophthalmologists Congress (22 November 2010)

- American Academy of Ophthalmology (AAO) (annual meeting (22 November 2010)
- World Ophthalmology Congress (WOC) (22 November 2010)
- Retina International World Congress (22 November 2010)
- EURETINA Congress (European Society of Retina Specialists) (22 November 2010)
- Asia Pacific Academy of Ophthalmology (APAO) Congresses (22 November 2010)

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The search strings were developed to identify both ranibizumab RCTs and comparator RCTs, which could be used for indirect comparison. IVTA was originally included in the searches, but later the protocol was changed to exclude IVTA studies as this agent was no longer considered a relevant comparator for ranibizumab.

MEDLINE and MEDLINE In-Process

1 macular edema/ (3044)
2 exp Edema/ (30716)
3 (macular adj3 (edema or oedema or odema)).ti,ab. (4733)
4 Retinal vein/ (1645)
5 Retinal Vein Occlusion/ (2322)
6 ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (2560)
7 (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1071)
8 (branch vein adj5 occlu$).ti,ab. (222)
9 (central vein adj5 occlu$).ti,ab. (156)
10 or/1-9 (39433)
11 (bevacizumab or avastin or nsc 704865 or nsc704865).ti,ab,rn. (4072)
12 Antibodies, Monoclonal/ (153358)
13 antibodies/tu (1560)
14 vascular endothelial growth factors/ or vascular endothelial growth factor a/ (25799)
15 (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (33304)
16 (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab,rn. (590)
17 Angiogenesis Inhibitors/ (10146)
18 Triamcinolone Acetonide/ (4369)
19 Triamcinolone acetonide.ti,ab,rn. (5023)
20 ivta.ti,ab,rn. (176)
21 exp Dexamethasone/ (40308)
22 ozurdex.ti,ab,rn. (3)
23 exp Light Coagulation/ (9974)

24 (photocoagulation or laser coagulation).ti,ab. (7400)
25 or/11-24 (250837)
26 animals/ not humans/ (3515697)
27 (editorial or letter or news).pt. (1096470)
28 10 and 25 (3069)
29 28 not (26 or 27) (2420)
30 limit 29 to english language (2001)

EMBASE

1 retina macula edema/ (3736)
2 edema/ (48114)
3 (macular adj3 (edema or oedema or odema)).ti,ab. (5650)
4 retina vein/ (1178)
5 retina vein occlusion/ (2513)
6 ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (3221)
7 (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1352)
8 (branch vein adj5 occlu$).ti,ab. (239)
9 (central vein adj5 occlu$).ti,ab. (173)
10 or/1-9 (59202)
11 BEVACIZUMAB/ (14643)
12 (bevacizumab or avastin or nsc 704865 or nsc704865).ti,ab,rn. (10371)
13 monoclonal antibody/ (148644)
14 antibody/dt (1297)
15 vasculotropin/ or vasculotropin A/ (42653)
16 (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (40599)
17 ranibizumab/ (1572)
18 (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab,rn. (1606)
19 angiogenesis inhibitor/ (9547)
20 triamcinolone acetonide/ (9332)
21 triamcinolone acetonide.ti,ab,rn. (5078)
22 ivta.ti,ab,rn. (202)
23 DEXAMETHASONE/ (83660)
24 ozurdex.ti,ab,rn. (3)
25 laser coagulation/ (14482)
26 (photocoagulation or laser coagulation).ti,ab. (8822)
27 or/11-26 (319180)
28 10 and 27 (5758)
29 Animal/ or Animal Experiment/ or Nonhuman/ (5383306)
30 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. (4200760)
31 29 or 30 (5748657)
32 exp Human/ or Human Experiment/ (12090139)
33 31 not (31 and 32) (4534937)
34 (editorial or letter or note).pt. (1493255)
35 28 not (33 or 34) (4750)
36 limit 35 to english language (3906)

Cochrane Library: CDSR, CENTRAL, DARE, and HTA

#1	MeSH descriptor Macular Edema explode all trees	286
#2	MeSH descriptor Edema explode all trees	903
#3	(macular NEAR/3 (edema or oedema or odema)):ti,ab,kw	735
#4	MeSH descriptor Retinal Vein explode all trees	39
#5	MeSH descriptor Retinal Vein Occlusion explode all trees	105
#6	(vein or veins or veinous) NEAR/5 (occlusion* or occluded or obstruction* or obstructed or closed or closure* or stricture* or stenosis or stenosed or block or blocks or blockage* or blocking or embolism* or emboli) NEAR/5 retina*:ti,ab,kw	197
#7	(crvo or cvo or rvo or brvo or bvo or crvome):ti,ab,kw	106
#8	"branch vein" NEAR/5 occlu*:ti,ab,kw	12
#9	"central vein" NEAR/5 occlu*:ti,ab,kw	23
#10	(#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9)	1757
#11	(ranibizumab or lucentis or "rhufab v2" or "347396-82-1"):ti,ab,kw	137
#12	MeSH descriptor Antibodies, Monoclonal explode all trees	3117
#13	MeSH descriptor Antibodies, this term only with qualifier: TU	49
#14	MeSH descriptor Vascular Endothelial Growth Factors, this term only	69
#15	MeSH descriptor Vascular Endothelial Growth Factor A, this term only	341
#16	"vascular endothelial growth" or vegf* or antivegf*:ti,ab,kw	660
#17	(bevacizumab or avastin or "nsc 704865" or nsc704865):ti,ab,kw	342
#18	MeSH descriptor Angiogenesis Inhibitors explode all trees	2117
#19	MeSH descriptor Triamcinolone Acetonide explode all trees	491
#20	(triamcinolone acetonide):ti,ab,kw	859
#21	(ivta):ti,ab,kw	57
#22	MeSH descriptor Dexamethasone explode all trees	1980
#23	(ozurdex):ti,ab,kw	1
#24	MeSH descriptor Light Coagulation explode all trees	508
#25	(photocoagulation or "laser coagulation"):ti,ab,kw	925
#26	(#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25)	9465
#27	(#10 AND #26)	420

CINAHL

S1	(MH "Edema")	2031
S2	TI (macular N3 edema or macular N3 oedema or macular N3 odema) or AB (macular N3 edema or macular N3 oedema or macular N3 odema)	203
S3	(MH "Retinal Vein Occlusion") OR (MH "Retinal Vein")	129
S4	TI (vein* N5 occlusion* N5 retina*) or (vein* N5 occluded N5 retina*) or (vein* N5 obstruction* N5 retina*) or (vein* N5 obstructed N5 retina*) or (vein* N5 closed N5 retina*) or (vein* N5 closure* N5 retina*) or (vein* N5 stricture* N5 retina*) or (vein* N5 stenosis N5 retina*) or (vein* N5 stenosed N5 retina*) or (vein* N5 block* N5 retina*) or (vein* N5 embolism* N5 retina*) or (vein* N5 emboli N5 retina*)	36
S5	AB (vein* N5 occlusion* N5 retina*) or (vein* N5 occluded N5 retina*) or (vein* N5 obstruction* N5 retina*) or (vein* N5 obstructed N5 retina*) or (vein* N5 closed N5 retina*) or (vein* N5 closure* N5 retina*) or (vein* N5 stricture* N5 retina*) or (vein* N5 stenosis N5 retina*) or (vein* N5 stenosed N5 retina*) or (vein* N5 block* N5 retina*) or (vein* N5 embolism* N5 retina*) or (vein* N5 emboli N5 retina*)	31

S6 TI (crvo or cvo or rvo or brvo or bvo or crvome) or AB (crvo or cvo or rvo or brvo or bvo or crvome) 43
S7 TI ("branch vein" N5 occlu*) or AB ("branch vein" N5 occlu*) 2
S8 TI ("central vein" N5 occlu*) or AB ("central vein" N5 occlu*) 0
S9 TI ("central vein" N5 occlu*) or AB ("central vein" N5 occlu*) 73
S10 S1 or S2 or S3 or S4 or S5 or S6 or S7 or S8 or S9
2402
S11 TI (ranibizumab or lucentis or "rhufab v2" or "347396-82-1") or AB (ranibizumab or lucentis or "rhufab v2" or "347396-82-1") 65
S12 (MH "Antibodies, Monoclonal")
5201
S13 (MH "Antibodies/TU") 218
S14 TI ("vascular endothelial growth" or vegf* or antivegf*) or AB ("vascular endothelial
S15 TI (bevacizumab or avastin or "nsc 704865" or nsc704865) or AB (bevacizumab or avastin or "nsc 704865" or nsc704865) 734
growth" or vegf* or antivegf*)
1555
S16 (MH "Angiogenesis Inhibitors")
1052
S17 (MH "Triamcinolone") 333
S18 TI (triamcinolone acetonide) or AB (triamcinolone acetonide) 128
S19 TI (ivta) or AB (ivta) 1
S20 (MH "Dexamethasone")
1296
S21 TI (ozurdex) or AB (ozurdex) 1
S22 TI (photocoagulation or "laser coagulation") or AB (photocoagulation or "laser coagulation") 196
S23 S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22
9159
S24 S10 and S23 136

Science Citation Index

Databases=SCI-EXPANDED Timespan=All Years

#1 5,160 TS=(macular) SAME TS=(edema or oedema or odema)
#2 2,660 TS=(vein or veins or veinous) SAME TS=(occlusion* or occluded or obstruction* or obstructed or closed or closure* or stricture* or stenosis or stenosed or block or blocks or blockage* or blocking or embolism* or emboli) SAME TS=(retina*)
#3 957 TS=(crvo or cvo or rvo or brvo or bvo or crvome)
#4 152 TS=("branch vein") SAME TS=(occlu*)
#5 124 TS=("central vein") SAME TS=(occlu*)
#6 7,491 #1 or #2 or #3 or #4 or #5
#7 809 TS=(ranibizumab or lucentis or "rhufab v2" or "347396-82-1")
#8 >100,000 TS=(monoclonal SAME antibodies)
#9 39,923 TS=("vascular endothelial growth" or vegf* or antivegf*)
#10 5,445 TS=(bevacizumab or avastin or "nsc 704865" or nsc704865)
#11 2,253 TS=(angiogenesis SAME inhibitors)
#12 2,945 TS=("triamcinolone acetonide")
#13 153 TS=(ivta)

#14 38,339 TS=(dexamethasone)
#15 3 TS=(ozurdex)
#16 5,829 TS=(photocoagulation or "laser coagulation" or "light coagulation")
#17 >100,000 #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16
#18 1,939 #6 and #17 AND Language=(English)

ClinicalTrials.gov

(macular edema OR macular oedema OR retinal vein) AND (ranibizumab OR lucentis OR "vascular endothelial growth" OR monoclonal antibodies OR bevacizumab OR avastin OR "angiogenesis inhibitors" OR "triamcinolone acetonide" OR ivta OR dexamethasone OR ozurdex OR "light coagulation" OR photocoagulation OR "laser coagulation")

WHO International Clinical Trials Registry Platform (ICTRP)

The following search lines were searched individually:

macular edema AND ranibizumab
macular edema AND lucentis
retinal vein AND ranibizumab
retinal vein AND lucentis
macular edema AND bevacizumab
macular edema AND avastin
retinal vein AND bevacizumab
retinal vein edema AND avastin

Association of Research in Vision and Ophthalmology (ARVO)

The AVRO annual meeting collection (Jan 2008 through Dec 2010) was searched using the following strategy:

("macular edema" OR "macular oedema" OR "retinal vein") AND (ranibizumab OR lucentis OR bevacizumab OR avastin OR "monoclonal antibodies" OR "vascular endothelial growth" OR "angiogenesis inhibitors" OR "triamcinolone acetonide" OR ivta OR dexamethasone OR ozurdex OR "light coagulation" OR photocoagulation OR "laser coagulation")

European Association for Vision and Eye Research (EVER)

Three congress abstract books were searched online (2008, 2009 and 2010) using the following single search terms:

ranibizumab
lucentis
bevacizumab
avastin
dexamethasone
light coagulation

laser coagulation
photocoagulation
triamcinolone acetonide

Nordic Ophthalmological Societies: Biannual Nordic Congress of Ophthalmology

Abstracts were available via Acta Ophthalmologica supplements. It was not possible to search supplements, so pdf documents were opened and browsed using the search terms below.

- XXXIX Nordic Congress of Ophthalmology. 2010 in Acta Ophthalmologica 2010:88(Suppl 245)

- XXXVIII Nordic Congress of Ophthalmology. 2008 in Acta Ophthalmologica 2008:86(Suppl 241)

ranibizumab
lucentis
bevacizumab
avastin
dexamethasone
light coagulation
laser coagulation
photocoagulation
triamcinolone acetonide

Dutch Ophthalmological Society

Meeting abstracts were not available online.

Medical Ophthalmological Society

Meeting abstracts were not available online.

Royal College of Ophthalmologists

Meeting abstracts were not available online.

American Academy of Ophthalmology (AAO)

We searched the conference programme for 2010, and the scientific posters for 2009 and 2008 using the following single search terms:

ranibizumab
lucentis
bevacizumab
avastin
dexamethasone

light coagulation
laser coagulation
photocoagulation
triamcinolone acetonide

World Ophthalmology Congress (WOC)

Meeting abstracts were not available online.

Retina International World Congress

Meeting abstracts were not available online.

EURETINA Congress (European Society of Retina Specialists)

2008 (Vienna), 2009 (Nice) and 2010 (Paris) EURETINA congresses were available.

We viewed the 'Free papers/Poster Presentations' option available online, and retrieved any potentially relevant abstracts.

APAO Congresses (Asia Pacific Academy of Ophthalmology)

Meeting abstracts were not available online.

9.2.5 Details of any additional searches, such as searches of company databases (include a description of each database).

No additional searches to those described above were performed.

Novartis provided the clinical study reports for BRAVO and CRUISE trials.

9.2.6 The inclusion and exclusion criteria.

For the searches carried out above, the inclusion and exclusion criteria are provided in Chapter 5.2, Table B1.

9.2.7 The data abstraction strategy.

Data from the 3 ranibizumab RCTs were abstracted in accordance with the requirements of Chapter 5.

9.3 Appendix 3: Quality assessment of RCT(s) (section 5.4)

9.3.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table 3: Quality assessment results for RCTs

Trial no. (acronym)	BRAVO[25]	CRUISE[51]
Was randomisation carried out appropriately?	Yes Subjects were randomised centrally using an interactive voice response system (IVRS) to prevent bias in treatment assignment. A dynamic randomisation method was used to obtain an approximately 1:1:1 ratio between the treatment arms, which is designed to achieve overall balance, balance within each category defined by visual acuity score and balance within each study centre between the three treatment arms.	Yes Subjects were randomised centrally using an interactive voice response system (IVRS) to prevent bias in treatment assignment. A dynamic randomisation method was used to obtain an approximately 1:1:1 ratio between the treatment arms, which is designed to achieve overall balance, balance within each category defined by visual acuity score and balance within each study centre between the three treatment arms.
Was the concealment of treatment allocation adequate?	Yes In order to maintain treatment masking, patients assigned to Sham had a needleless hub of a syringe placed against the injection site and the plunger of the syringe was depressed to mimic an injection. Documented procedures were put in place to avoid inadvertent unmasking of study team members, and only the IVRS provider and an external and independent statistical coordinating centre (SCC) responsible for verifying subject randomisation and monthly study drug kit assignments, who are not otherwise involved in the study, will have access to the unmasking codes. Masking was maintained until after completion of the study (after all subjects have either completed the visit at month 12 or discontinued early from the study.	Yes In order to maintain treatment masking, patients assigned to Sham had a needleless hub of a syringe placed against the injection site and the plunger of the syringe was depressed to mimic an injection. Documented procedures were put in place to avoid inadvertent unmasking of study team members, and only the IVRS provider and an external and independent statistical coordinating centre (SCC) responsible for verifying subject randomisation and monthly study drug kit assignments, who are not otherwise involved in the study, will have access to the unmasking codes. Masking was maintained until after completion of the study (after all subjects have either completed the visit at month 12 or discontinued early from the study.
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Yes The three treatment groups were well balanced in terms of baseline demographics. At baseline, the three treatment groups were similar in terms of (study eye): ocular characteristics, fundus photography characteristics, total area of retinal haemorrhage in the centre subfield, mean total area of fluorescein leakage and mean total macular volume. Although the mean central subfield thickness was similar between treatment groups at baseline, the mean central foveal thickness of the study eye was lower in the sham group (488.0 µm) compared with the 0.3 mg and 0.5 mg ranibizumab groups (522.1 µm and 551.7 µm, respectively)	Yes The three treatment groups were well balanced in terms of baseline demographics. At baseline, the three treatment groups were similar in terms of (study eye): ocular characteristics, fundus photography characteristics, total area of retinal haemorrhage in the centre subfield, mean total area of fluorescein leakage, mean central subfield thickness and mean total macular volume.

Trial no. (acronym)	BRAVO[25]	CRUISE[51]
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)?	Yes Subjects, study site personnel (with the exception of site personnel performing or assisting with the injection procedure), the designated evaluating physician (a qualified ophthalmologist), central reading centre personnel, and the Sponsor and its agents (with the exception of drug accountability monitors) were masked to treatment assignment. The investigator performing the injection (and assistant, if needed) were unmasked to treatment assignment (ranibizumab vs. sham injection) but were masked to ranibizumab dose level. The injecting physicians were not involved in any other aspect of the study in any way and did not divulge the treatment assignment to anyone. Evaluating physicians were responsible for evaluating ocular assessments and all other aspects of the study. Visits for study drug injections were scheduled when both physicians were present. Visual acuity examiners were masked to treatment assignment and performed only visual acuity assessments and no other study assessments. Additionally, independent reviews of fundus photography, fluorescein angiography, and OCT were performed at a central reading centre (University of Wisconsin Fundus Photograph Reading Center) to provide an objective, masked assessment of these evaluations.	Yes Subjects, study site personnel (with the exception of site personnel performing or assisting with the injection procedure), the designated evaluating physician (a qualified ophthalmologist), central reading centre personnel, and the Sponsor and its agents (with the exception of drug accountability monitors) were masked to treatment assignment. The investigator performing the injection (and assistant, if needed) were unmasked to treatment assignment (ranibizumab vs. sham injection) but were masked to ranibizumab dose level. The injecting physicians were not involved in any other aspect of the study in any way and did not divulge the treatment assignment to anyone. Evaluating physicians were responsible for evaluating ocular assessments and all other aspects of the study. Visits for study drug injections were scheduled when both physicians were present. Visual acuity examiners were masked to treatment assignment and performed only visual acuity assessments and no other study assessments. Additionally, independent reviews of fundus photography, fluorescein angiography, and OCT were performed at a central reading centre (University of Wisconsin Fundus Photograph Reading Center) to provide an objective, masked assessment of these evaluations.
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No The study had good subject retention, and unexpected imbalances in drop-outs were not reported in the study A total of 376 (94.7%) subjects completed the study through Month 6 • Sham, 123 (93.2%) • 0.3 mg ranibizumab, 128 (95.5%) • 0.5 mg ranibizumab, 125 (95.4%) A total of 356 subjects (89.7%) completed the study through Month 12. • Sham, 114 (86.4%) • 0.3 mg ranibizumab, 119 (88.8%)	No The study had good subject retention, and unexpected imbalances in drop-outs were not reported in the study A total of 363 (92.6%) subjects completed the study through Month 6 • Sham, 115 (88.5%) • 0.3 mg ranibizumab, 129 (97.7%) • 0.5 mg ranibizumab, 119 (91.5%) A total of 349 (89.0%) subjects completed the study through Month 12. • Sham, 109 (83.8%) • 0.3 mg ranibizumab, 126 (95.5%)

Trial no. (acronym)	BRAVO[25]	CRUISE[51]
	• 0.5 mg ranibizumab, 123 (93.9%)	• 0.5 mg ranibizumab, 114 (87.7%)
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No Outcomes were presented in the CSR; only those relevant to the decision problem are presented within this submission	No Outcomes were presented in the CSR; only those relevant to the decision problem are presented within this submission
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using the last observation carried-forward method.	Yes Unless otherwise noted, the intent-to-treat approach was used for efficacy analyses and included all patients as randomised. Missing values for efficacy outcomes were imputed using the last observation carried-forward method.

9.4 Appendix 4: Search strategy for section 5.7 (Indirect and mixed treatment comparisons)

The search strategy for the identification of comparator RCTs to inform the indirect comparison is given in Section 9.2, appendix 2, as this search was performed in parallel to the search for ranibizumab RCT data.

9.5 Appendix 5: Quality assessment of comparator RCT(s) in section 5.7 (Indirect and mixed treatment comparisons)

9.5.1 A suggested format for the quality assessment of RCT(s) is shown below.

Table 4 Quality assessment of RCTs

BVOS (NCT00000162)[23]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Computer-generated random allocation schedule	Yes
Was the concealment of treatment allocation adequate?	Study coordinator assigned the patients to groups from a computer-generated random allocation schedule	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	There were no significant differences between the treatment arms at baseline in terms of demographic and clinical variables and a detailed table is provided.	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)?	Participants were not blinded to treatment allocation. This increases the risk of bias. Investigators measuring visual acuity were blinded to the treatment allocation (and if unblinded this was noted). 78% of examinations were obtained by a masked examiner.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Eleven patients dropped out or died in the control group compared to 6 in the treated group. The reasons for these were not given	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No suggestion of this	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?	All eyes randomised were included in the efficacy analyses	Yes
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CVOS (NCT00000131)[22]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Computer generated random allocation. Separate random treatment assignment lists were generated at the beginning of the study for each clinic and for patients with two levels of CVO. Following assessment of patients, random assignment was then obtained from coordinating centre by telephone.	Yes
Was the concealment of treatment allocation adequate?	No. Probably not feasible.	No
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The table of baseline characteristics presented in the paper shows no significant differences in demographic characteristics and visual acuity.	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)?	VA examiner was blinded to treatment allocation, patients were not blind. In one clinic masking was noted to be operationally difficult and was not enforced. If results from this clinic are deleted from the analysis the authors report that the conclusions are not changed.	No

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	No	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Appears to be free from selective reporting	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	The authors report data for treatment completers.	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Battaglia 1999[65]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Not reported	Not clear
Was the concealment of treatment allocation adequate?	Not reported	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Similar for visual acuity	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)?	Not reported but unlikely to be feasible.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Unclear. Each patient underwent ophthalmic assessment including stereophotograph and fluorescein angiography at entry and after 3, 12 and 24 months.	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	The details are not reported for all follow-up periods.	Yes
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	68 patients out of the 77 randomised were included in the analysis	No
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Laatikainen 1977[66]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Use of pre-prepared sealed envelopes which indicated whether an eye was for treatment by photocoagulation or remained untreated (i.e. control)	No
Was the concealment of treatment allocation adequate?	Treatment allocation was not adequate	No
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The groups had a similar mean age (62 and 61.6) but other details were not provided	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Likely to be impracticable for patients and care providers.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Drop-outs were not stated by treatment group	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Appears to be free from selective reporting	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?	Seems to present results only for treatment completers.	No
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May 1979[67]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomisation method was not reported	Not clear
Was the concealment of treatment allocation adequate?	Concealment of allocation was probably impracticable.	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The average age of patients in the 2 groups was similar. Details of individual patients are provided but no analysis of the similarity between groups is presented.	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not reported, but probably not feasible to blind patients or care providers.	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	2 patients in the treatment group had insufficient follow-up at 6 months, compared to zero in the control group. The reasons for insufficient follow up were not given.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Appears to be free from selective reporting	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?	Not stated but results are presented for individual patients	No
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Haller 2003[68]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomised study - few details reported because this was an abstract	Not clear
Was the concealment of treatment allocation adequate?	Not reported in abstract	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Not reported in abstract	Not clear
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Patients, surgeons and vision examiners were masked as to dose of drug	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not reported in abstract	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not reported in abstract	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not reported in abstract	Not clear
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Haller 2010 (NCT00168298 and NCT00035906)[69]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomization was performed centrally (using an interactive voice response system) and was stratified by the underlying cause of RVO (BRVO or CRVO).	Yes
Was the concealment of treatment allocation adequate?	Central allocation using interactive voice response system. Investigator kept study medication information confidential.	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	The groups were reported to be similar 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 and investigators masked to treatment. The central reading centre staff who evaluated OCT scans were masked to study group.	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	24, 19 and 28 patients discontinued prior to day 180 in the 0.7 mg DEX, 0.35 mg DEX and the sham groups, respectively. Reasons were given for all drop-outs.	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Appears to be free from selective reporting	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 and secondary outcome analysis was intention to treat; Safety outcomes included patients who received study treatment after randomisation	Yes

Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		
Kupperman 2007[70]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Performed centrally and was stratified by underlying cause of MO. Not details given on randomisation method.	Unclear
Was the concealment of treatment allocation adequate?	Performed centrally	Yes
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Demographic and baseline characteristics were comparable among the 3 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 were masked regarding dose. Key efficacy variables were collected and evaluated by personnel who were masked to patient study treatment. Patients in the observation group received no study treatment and no sham procedure.	No
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	In the dexamethasone 350 group 1 patient died and 1 withdrew consent. In the dexamethasone 700 group 4 discontinued (1 for adverse events, 2 deaths and 1 for personal reasons). 14 patients discontinued from the observation group: no deaths and 14 other reasons described.	Yes
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Appears to be free from selective reporting	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?	ITT was used for efficacy analyses and included all patients randomised. Missing values for efficacy outcomes were imputed using last observation carried forward method.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Faghihii 2008[71]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Not reported in abstract or poster	Not clear
Was the concealment of treatment allocation adequate?	Not reported in abstract or poster	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	Poster reports that ocular and demographic patient characteristics were similar	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)?	Participants blinded. Described as double-masked	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	study not yet completed	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not clear	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Study not yet completed; results reported for first patients reaching 18 weeks of treatment (says 63 pts but then 22 in IVB, 29 in IVB/T and 14 in sham = 65)	No
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Moradian 2007[81]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Not reported in abstract or poster	Not clear
Was the concealment of treatment allocation adequate?	Not reported in abstract or poster	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	T he poster reports duration of symptoms and protein C and S abnormality for both groups. The duration of symptoms was longer in the IVB group than in the sham group	No
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)?	sham injection was carried out in the same way as bevacizumab injection but with the plunger of the syringe pressing the conjunctiva. Study was described as double-blind	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	Not reported in abstract or poster	Not clear
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Not reported in abstract or poster	Not clear
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Not reported in abstract or poster	Not clear
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

Russo 2009[73]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Eyes assigned based on retina clinic number (patients with even numbers assigned to IB and odd numbers to GLP); chart numbers not assigned until day of treatment.	No
Was the concealment of treatment allocation adequate?	Seems unlikely to have been achieved	No
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	No statistical difference in duration from onset of BRVO to treatment, in baseline BCVA or CMT. Similar age and sex across groups	Yes
Were the care providers, participants and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?	Not reported	Not clear
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	All patients completed all follow up visits	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	Appears to be free from selective reporting	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?	All patients completed all follow up visits and all patients were reported in the analysis	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

9.6 Appendix 6: Search strategy for section 5.8 (Non-RCT evidence)

The search performed to identify non-RCT evidence for ranibizumab in the indication under consideration in this submission was identical to that outlined in Section 5.1.1 and 9.2 (appendix 2). The search strategy used to identify RCTs did not include search terms that limited the search results to RCTs only. This was to ensure that all studies that reported adverse events were identified. Therefore non-RCTs for ranibizumab in the treatment of visual impairment due to MO secondary to RVO were collected during the review of the search results.

The criteria for identifying non-RCTs were identical to those for identifying RCTs (Section 5.2.1.

Table B2) apart from the study design was not limited to trials that were both randomised and controlled.

9.7 Appendix 7: Quality assessment of non-RCT(s) in section 5.8 (Non-RCT evidence)

9.7.1 Please tabulate the quality assessment of each of the non-RCTs identified.

As there was only one pivotal non-RCT identified (Campochiaro 2008/2010), the complete quality assessment table is presented in the main body of the submission, Section 5.8.1.

9.8 Appendix 8: Search strategy for section 5.9 (Adverse events)

The systematic review described in Sections 5.1and 9.2 (appendix 2) was designed to identify all trials (RCT and non-RCT) that reported safety outcomes of ranibizumab in the treatment of visual impairment due to MO secondary to RVO.

9.9 Appendix 9: Quality assessment of adverse event data in section 5.9 (Adverse events)

Please see Section 9.3, appendix 3

9.10 Appendix 10: Search strategy for cost-effectiveness studies (section 6.1)

The following information should be provided.

9.10.1 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.

A range of databases indexing published research were searched for studies about the costs and cost-effectiveness of interventions in adults with macular edema arising from CRVO or BRVO. The search strategy combined search terms for 'macular edema/retinal vein occlusion' with terms for 'ranibizumab/monoclonal antibodies/vascular endothelial growth factors'. This search has not used a methodological search filter in order to be as sensitive as possible: the search was conducted to inform the review of effects and cost-effectiveness evidence. The search was limited to English language studies, and no date limits were applied. The databases and resources searched are shown in Table 5.

Table 5 Databases and resources searched to identify effects and cost-effectiveness evidence

Resource	Interface/URL
MEDLINE and MEDLINE In-Process	OvidSP
EMBASE	OvidSP
NHS Economic Evaluation Database (NHS EED)	CRD interface
Health Economic Evaluations Database (HEED)	Wiley Interscience
EconLit	OvidSP
RePEC (Research Papers in Economics)	http://repec.org/
ClinicalTrials.gov	http://ClinicalTrials.gov

9.10.2 The date on which the search was conducted.

All searches were conducted on 18th November 2010.

9.10.3 The date span of the search.

The resources were searched over the following time periods or for all records available to be searched at a specific point in time:

- MEDLINE and MEDLINE In-Process (OvidSP) (1950-2010/Nov week 1. 18th November 2010.)
- EMBASE (OvidSP) (1980-2010/week 45. 18th November 2010.)
- NHS Economic Evaluation Database (NHS EED) (Cochrane Library, Wiley interscience). (2010:Issue 4. 18th November 2010.)
- HEED (Wiley interscience) (2010/Oct. 18th November 2010.)
- EconLit (OvidSP) (18th November 2010.)
- RePEC (http://repec.org/) (18th November 2010.)
- ClinicalTrials.gov (http://ClinicalTrials.gov) (18th November 2010.)

9.10.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The complete strategies used are presented below.

MEDLINE and MEDLINE In-Process (OvidSP)

1. macular edema/ (3044)
2. exp Edema/ (30716)
3. (macular adj3 (edema or oedema or odema)).ti,ab. (4733)
4. Retinal vein/ (1645)
5. Retinal Vein Occlusion/ (2322)
6. ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (2560)
7. (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1071)
8. (branch vein adj5 occlu$).ti,ab. (222)
9. (central vein adj5 occlu$).ti,ab. (156)
10. or/1-9 (39433)
11. (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab,rn. (590)
12. Antibodies, Monoclonal/ (153358)
13. antibodies/tu (1560)
14. vascular endothelial growth factors/ or vascular endothelial growth factor a/ (25799)
15. (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (33304)
16. or/11-15 (189079)
17. animals/ not humans/ (3515697)
18. (editorial or letter or news).pt. (1096470)
19. 10 and 16 (812)

20. 19 not (17 or 18) (605)
21. limit 20 to english language (554)

EMBASE (OvidSP)

1 retina macula edema/ (3736)
2 edema/ (48114)
3 (macular adj3 (edema or oedema or odema)).ti,ab. (5650)
4 retina vein/ (1178)
5 retina vein occlusion/ (2513)
6 ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (3221)
7 (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1352)
8 (branch vein adj5 occlu$).ti,ab. (239)
9 (central vein adj5 occlu$).ti,ab. (173)
10 or/1-9 (59202)
11 ranibizumab/ (1572)
12 (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab,rn. (1606)
13 monoclonal antibody/ (148644)
14 antibody/dt (1297)
15 vasculotropin/ or vasculotropin A/ (42653)
16 (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (40599)
17 or/11-16 (200629)
18 10 and 17 (1393)
19 Animal/ or Animal Experiment/ or Nonhuman/ (5383306)
20 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. (4200760)
21 19 or 20 (5748657)
22 exp Human/ or Human Experiment/ (12090139)
23 21 not (21 and 22) (4534937)
24 (editorial or letter or note).pt. (1493255)
25 18 not (23 or 24) (1105)
26 limit 25 to english language (998)

NHS EED (Cochrane Library, Wiley interscience)

#1 MeSH descriptor Macular Edema explode all trees 286
#2 MeSH descriptor Edema explode all trees 903
#3 (macular NEAR/3 (edema or oedema or odema)):ti,ab,kw 735
#4 MeSH descriptor Retinal Vein explode all trees 39
#5 MeSH descriptor Retinal Vein Occlusion explode all trees 105
#6 (vein or veins or veinous) NEAR/5 (occlusion* or occluded or obstruction* or obstructed or closed or closure* or stricture* or stenosis or stenosed or block or blocks or blockage* or blocking or embolism* or emboli) NEAR/5 retina*:ti,ab,kw 197
#7 (crvo or cvo or rvo or brvo or bvo or crvome):ti,ab,kw 106
#8 "branch vein" NEAR/5 occlu*:ti,ab,kw 12
#9 "central vein" NEAR/5 occlu*:ti,ab,kw 23
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) 1757

#11	(ranibizumab or lucentis or "rhufab v2" or "347396-82-1"):ti,ab,kw	137
#12	MeSH descriptor Antibodies, Monoclonal explode all trees	3117
#13	MeSH descriptor Antibodies, this term only with qualifier: TU	49
#14	MeSH descriptor Vascular Endothelial Growth Factors, this term only	69
#15	MeSH descriptor Vascular Endothelial Growth Factor A, this term only	341
#16	"vascular endothelial growth" or vegf* or antivegf*:ti,ab,kw	660
#17	(#11 OR #12 OR #13 OR #14 OR #15 OR #16)	3767
#18	(#10 AND #17)	69

HEED (Wiley interscience)

AX='macular edema' within 3 or 'macular oedema' within 3 or 'macular odema' within 3 (24)
AX='vein occlusion' within 5 or 'veins occlusion' within 5 or 'veinous occlusion' within 5 or 'vein occlusions' within 5 or 'veins occlusions' within 5 or 'veinous occlusions' within 5 (3)
AX='vein occluded' within 5 or 'veins occluded' within 5 or 'veinous occluded' within 5 or 'vein obstruction' within 5 or 'veins obstruction' within 5 or 'veinous obstruction' within 5 (1)
AX=(crvo or cvo or rvo or brvo or bvo or crvome) (0)
AX=(branch vein) or (central vein) (3)
CS=1 or 2 or 3 or 4 or 5 (27)
AX=ranibizumab or lucentis or (rhufab v2) or (347396-82-1) (19)
AX='monoclonal antibodies' within 2 (17)
AX=(vascular endothelial growth) or vegf or antivegf (6)
CS=7 or 8 or 9 (39)
CS=6 and 10 (1)

EconLit (OvidSP)

1 (macular adj3 (edema or oedema or odema)).ti,ab. (0)
2 ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (0)
3 (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1)
4 (branch vein adj5 occlu$).ti,ab. (0)
5 (central vein adj5 occlu$).ti,ab. (0)
6 or/1-5 (1)
7 (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab. (0)
8 (antibodies adj2 monoclonal).ti,ab. (5)
9 (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (0)
10 or/7-9 (5)
11 6 and 10 (0)

RePEC (http://repec.org/)

("macular edema" | "macular oedema" | "retinal vein") + (ranibizumab | lucentis | "vascular endothelial growth" | "monoclonal antibodies")

ClinicalTrials.gov (http://ClinicalTrials.gov)

(macular edema OR macular oedema OR retinal vein) AND (ranibizumab OR lucentis OR "vascular endothelial growth" OR monoclonal antibodies)

Review 2

The complete strategies used for Review 2 (cost-effectiveness of laser, dexamethasone IVT implant, IVTA or bevacizumab in the treatment of visual impairment due to MO secondary to RVO) are presented below.

MEDLINE and MEDLINE In-Process (OvidSP). 1950-2010/Nov week 1.

1. macular edema/ (3044)
2. exp Edema/ (30716)
3. (macular adj3 (edema or oedema or odema)).ti,ab. (4733)
4. Retinal vein/ (1645)
5. Retinal Vein Occlusion/ (2322)
6. ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (2560)
7. (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1071)
8. (branch vein adj5 occlu$).ti,ab. (222)
9. (central vein adj5 occlu$).ti,ab. (156)
10. or/1-9 (39433)
11. (bevacizumab or avastin or nsc 704865 or nsc704865).ti,ab,rn. (4072)
12. Antibodies, Monoclonal/ (153358)
13. antibodies/tu (1560)
14. vascular endothelial growth factors/ or vascular endothelial growth factor a/ (25799)
15. (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (33304)
16. (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab,rn. (590)
17. Angiogenesis Inhibitors/ (10146)
18. Triamcinolone Acetonide/ (4369)
19. Triamcinolone acetonide.ti,ab,rn. (5023)
20. ivta.ti,ab,rn. (176)
21. exp Dexamethasone/ (40308)
22. ozurdex.ti,ab,rn. (3)
23. exp Light Coagulation/ (9974)
24. (photocoagulation or laser coagulation).ti,ab. (7400)
25. or/11-24 (250837)
26. animals/ not humans/ (3515697)
27. (editorial or letter or news).pt. (1096470)
28. 10 and 25 (3069)
29. 28 not (26 or 27) (2420)

30. limit 29 to english language (2001)

EMBASE (OvidSP). 1980-2010/week 45.

1. retina macula edema/ (3736)
2. edema/ (48114)
3. (macular adj3 (edema or oedema or odema)).ti,ab. (5650)
4. retina vein/ (1178)
5. retina vein occlusion/ (2513)
6. ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (3221)
7. (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1352)
8. (branch vein adj5 occlu$).ti,ab. (239)
9. (central vein adj5 occlu$).ti,ab. (173)
10. or/1-9 (59202)
11. BEVACIZUMAB/ (14643)
12. (bevacizumab or avastin or nsc 704865 or nsc704865).ti,ab,rn. (10371)
13. monoclonal antibody/ (148644)
14. antibody/dt (1297)
15. vasculotropin/ or vasculotropin A/ (42653)
16. (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (40599)
17. ranibizumab/ (1572)
18. (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab,rn. (1606)
19. angiogenesis inhibitor/ (9547)
20. triamcinolone acetonide/ (9332)
21. triamcinolone acetonide.ti,ab,rn. (5078)
22. ivta.ti,ab,rn. (202)
23. DEXAMETHASONE/ (83660)
24. ozurdex.ti,ab,rn. (3)
25. laser coagulation/ (14482)
26. (photocoagulation or laser coagulation).ti,ab. (8822)
27. or/11-26 (319180)
28. 10 and 27 (5758)
29. Animal/ or Animal Experiment/ or Nonhuman/ (5383306)
30. (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. (4200760)
31. 29 or 30 (5748657)
32. exp Human/ or Human Experiment/ (12090139)
33. 31 not (31 and 32) (4534937)
34. (editorial or letter or note).pt. (1493255)
35. 28 not (33 or 34) (4750)
36. limit 35 to english language (3906)

NHS EED (Cochrane Library, Wiley interscience). 2010:Issue 4.

#1	MeSH descriptor Macular Edema explode all trees	286
#2	MeSH descriptor Edema explode all trees	903

#3 (macular NEAR/3 (edema or oedema or odema)):ti,ab,kw 735
#4 MeSH descriptor Retinal Vein explode all trees 39
#5 MeSH descriptor Retinal Vein Occlusion explode all trees 105
#6 (vein or veins or veinous) NEAR/5 (occlusion* or occluded or obstruction* or obstructed or closed or closure* or stricture* or stenosis or stenosed or block or blocks or blockage* or blocking or embolism* or emboli) NEAR/5 retina*:ti,ab,kw 197
#7 (crvo or cvo or rvo or brvo or bvo or crvome):ti,ab,kw 106
#8 "branch vein" NEAR/5 occlu*:ti,ab,kw 12
#9 "central vein" NEAR/5 occlu*:ti,ab,kw 23
#10 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9) 1757
#11 (ranibizumab or lucentis or "rhufab v2" or "347396-82-1"):ti,ab,kw 137
#12 MeSH descriptor Antibodies, Monoclonal explode all trees 3117
#13 MeSH descriptor Antibodies, this term only with qualifier: TU 49
#14 MeSH descriptor Vascular Endothelial Growth Factors, this term only 69
#15 MeSH descriptor Vascular Endothelial Growth Factor A, this term only 341
#16 "vascular endothelial growth" or vegf* or antivegf*:ti,ab,kw 660
#17 (bevacizumab or avastin or "nsc 704865" or nsc704865):ti,ab,kw 342
#18 MeSH descriptor Angiogenesis Inhibitors explode all trees 2117
#19 MeSH descriptor Triamcinolone Acetonide explode all trees 491
#20 (triamcinolone acetonide):ti,ab,kw 859
#21 (ivta):ti,ab,kw 57
#22 MeSH descriptor Dexamethasone explode all trees 1980
#23 (ozurdex):ti,ab,kw 1
#24 MeSH descriptor Light Coagulation explode all trees 508
#25 (photocoagulation or "laser coagulation"):ti,ab,kw 925
#26 (#11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25) 9465
#27 (#10 AND #26) 420

HEED (Wiley interscience).

AX='macular edema' within 3 or 'macular oedema' within 3 or 'macular odema' within 3 (24)
AX='vein occlusion' within 5 or 'veins occlusion' within 5 or 'veinous occlusion' within 5 or 'vein occlusions' within 5 or 'veins occlusions' within 5 or 'veinous occlusions' within 5 (3)
AX='vein occluded' within 5 or 'veins occluded' within 5 or 'veinous occluded' within 5 or 'vein obstruction' within 5 or 'veins obstruction' within 5 or 'veinous obstruction' within 5 (1)
AX=(crvo or cvo or rvo or brvo or bvo or crvome) (0)
AX=(branch vein) or (central vein) (3)
CS=1 or 2 or 3 or 4 or 5 (27)
AX=ranibizumab or lucentis or (rhufab v2) or (347396-82-1) (19)
AX='monoclonal antibodies' within 2 (17)
AX=(vascular endothelial growth) or vegf or antivegf (6)
AX=bevacizumab or avastin or (nsc 704865) or nsc704865 (33)
AX='angiogenesis inhibitors' within 2 (1)
AX='triamcinolone acetonide' within 2 (17)
AX=ivta or dexamethasone or ozurdex (75)
AX=(light coagulation) or photocoagulation or (laser coagulation) (33)
CS=7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 (181)
CS=6 and 15 (10)

EconLit (OvidSP).

1 (macular adj3 (edema or oedema or odema)).ti,ab. (0)
2 ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (0)
3 (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1)
4 (branch vein adj5 occlu$).ti,ab. (0)
5 (central vein adj5 occlu$).ti,ab. (0)
6 or/1-5 (1)
7 (ranibizumab or lucentis or rhufab v2 or 347396-82-1).ti,ab. (0)
8 (antibodies adj2 monoclonal).ti,ab. (5)
9 (vascular endothelial growth or vegf$ or antivegf$2).ti,ab. (0)
10 (bevacizumab or avastin or nsc 704865 or nsc704865).ti,ab. (0)
11 (angiogenesis adj2 Inhibitors).ti,ab. (0)
12 Triamcinolone acetonide.ti,ab. (0)
13 (ivta or dexamethasone or ozurdex).ti,ab. (0)
14 (light coagulation or photocoagulation or laser coagulation).ti,ab. (1)
15 or/7-14 (6)
16 6 and 15 (0)

RePEC (http://repec.org/).

("macular edema" | "macular oedema" | "retinal vein") + (bevacizumab | avastin | "monoclonal antibodies" | "vascular endothelial growth" I "angiogenesis inhibitors" | "triamcinolone acetonide" I ivta | dexamethasone | ozurdex | "light coagulation" | photocoagulation | "laser coagulation")

ClinicalTrials.gov (http://ClinicalTrials.gov).

(macular edema OR macular oedema OR retinal vein) AND (bevacizumab OR avastin OR "angiogenesis inhibitors" OR "triamcinolone acetonide" OR ivta OR dexamethasone OR ozurdex OR "light coagulation" OR photocoagulation OR "laser coagulation")

9.10.5 Details of any additional searches (for example, searches of company databases [include a description of each database]).

No additional sources were searched.

9.11 Appendix 11: Quality assessment of cost-effectiveness studies (section 6.1)

As there was only one cost-effectiveness study identified (Brown 2002[92]), the full quality assessment is presented in the main body of the submission, Section 6.1.3.

9.12 Appendix 12: Search strategy for section 6.4 (Measurement and valuation of health effects)

The following information should be provided.

9.12.1 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 specific databases searched and the service providers used were:

- MEDLINE and MEDLINE In-Process (OvidSP);
- EMBASE (OvidSP);
- NHS Economic Evaluation Database (NHS EED) (CRD interface);
- Health Technology Assessment Database (HTA) (CRD interface);
- Health Economic Evaluations Database (HEED) (Wiley Interscience);
- EconLit (OvidSP);
- CEA Registry (https://research.tufts-nemc.org/cear/default.aspx);
- PROQOLID (http://www.proqolid.org/);
- National Institute for Health and Clinical Excellence (NICE) (http://www.nice.org.uk/);
- Scottish Medicines Consortium (SMC) (www.scottishmedicines.org.uk/);
- US Food and Drug Administration (FDA) (www.fda.gov/);
- European Medicines Agency (EMA) (www.emea.europa.eu/).

9.12.2 The date on which the search was conducted.

All searches were conducted on 13th December 2010.

9.12.3 The date span of the search.

The date span of the searches was:

- MEDLINE and MEDLINE In-Process (1950-2010/Nov week 3);
- EMBASE (1980-2010/week 49);
- NHS Economic Evaluation Database (NHS EED) (2010/Dec 8th);
- Health Technology Assessment Database (HTA) (2010/Dec 8th)
- Health Economic Evaluations Database (HEED) (2010/Nov);
- EconLit (1969-2010/Nov);
- CEA Registry (13th December 2010);
- PROQOLID (13th December 2010);
- National Institute for Health and Clinical Excellence (NICE) (13th December 2010);
- Scottish Medicines Consortium (SMC) (13th December 2010);
- US Food and Drug Administration (FDA) (13th December 2010);
- European Medicines Agency (EMA) (13th December 2010).

9.12.4 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 to search each resource are presented below.

MEDLINE and MEDLINE In-Process

1 macular edema/ (3057)
2 (macular adj3 (edema or oedema or odema)).ti,ab. (4753)
3 retinal vein/ (1649)
4 Retinal Vein Occlusion/ (2331)
5 ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (2571)
6 (branch vein adj5 occlu$).ti,ab. (222)
7 (central vein adj5 occlu$).ti,ab. (156)
8 (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1076)
9 or/1-8 (9172)
10 "Quality of Life"/ (87859)
11 ((quality adj3 life) or qol).ti,ab. (100278)
12 value of life/ (5176)
13 Quality-Adjusted Life Years/ (4784)
14 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (3140)
15 disability adjusted life.ti,ab. (715)
16 daly$.ti,ab. (755)
17 (index of wellbeing or quality of wellbeing or qwb).ti,ab. (139)
18 (multiattribute$ health or multi attribute$ health).ti,ab. (46)
19 (utility or utilities).ti,ab. (81955)

20 (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab. (8)
21 classification of illness state$.ti,ab. (1)
22 (euro qual or eruo qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab. (2051)
23 (sf36 or sf 36).ti,ab. (9145)
24 (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. (4244)
25 (sf12 or sf 12).ti,ab. (1283)
26 (short form 12 or shortform 12 or sf twelve or short form twelve).ti,ab. (489)
27 (sf 6d or sf6d or short form 6d or shortform 6d or sf six$ or shortform six$ or short form six$).ti,ab. (216)
28 hrqol.ti,ab. (4130)
29 hrql.ti,ab. (1636)
30 (proms or Patient Reported Outcome Measure$).ti,ab. (218)
31 (Timetradeoff or time tradeoff or time trade off or tto).ti,ab. (846)
32 (sg or standard gamble or hui or vas or visual analog$).ti,ab. (36629)
33 (retinal occlusion adj4 Questionnaire$).ti,ab. (0)
34 best corrected visual acuity score$.ti,ab. (3)
35 Early Treatment Diabetic Retinopathy Study$.ti,ab. (559)
36 ETDR.ti,ab. (0)
37 or/10-36 (254991)
38 9 and 37 (250)
39 animals/ not humans/ (3521849)
40 (editorial or letter or news).pt. (1099476)
41 38 not (39 or 40) (249)

EMBASE

1 retina macula edema/ (3777)
2 (macular adj3 (edema or oedema or odema)).ti,ab. (5694)
3 retina vein/ (1183)
4 retina vein occlusion/ (2523)
5 ((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (3236)
6 (crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (1362)
7 (branch vein adj5 occlu$).ti,ab. (239)
8 (central vein adj5 occlu$).ti,ab. (173)
9 or/1-8 (11368)
10 "quality of life"/ (157472)
11 ((quality adj3 life) or qol).ti,ab. (134257)
12 quality adjusted life year/ (6895)
13 (qaly$ or qald$ or qale$ or qtime$).ti,ab. (4188)
14 disability adjusted life.ti,ab. (846)
15 daly$.ti,ab. (935)
16 (index of wellbeing or quality of wellbeing or qwb).ti,ab. (161)
17 (multiattribute$ health or multi attribute$ health).ti,ab. (55)
18 (utility or utilities).ti,ab. (98590)

19 (multiattribute$ theor$ or multi attribute$ theor$ or multiattribute$ analys$ or multi attribute$ analys$).ti,ab. (12)
20 classification of illness state$.ti,ab. (1)
21 (euro qual or eruo qol or eq-5d or eq5d or eq 5d or euroqual or euroqol).ti,ab. (2828)
22 (sf36 or sf 36).ti,ab. (11495)
23 (short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short form thirtysix or short form thirty six).ti,ab. (4839)
24 (sf12 or sf 12).ti,ab. (1671)
25 (short form 12 or shortform 12 or sf twelve or short form twelve).ti,ab. (557)
26 (sf 6d or sf6d or short form 6d or shortform 6d or sf six$ or shortform six$ or short form six$).ti,ab. (270)
27 hrqol.ti,ab. (5341)
28 hrql.ti,ab. (2051)
29 (proms or Patient Reported Outcome Measure$).ti,ab. (294)
30 (Timetradeoff or time tradeoff or time trade off or tto).ti,ab. (1005)
31 (sg or standard gamble or hui or vas or visual analog$).ti,ab. (45336)
32 (retinal occlusion adj4 Questionnaire$).ti,ab. (0)
33 best corrected visual acuity score$.ti,ab. (3)
34 Early Treatment Diabetic Retinopathy Study$.ti,ab. (577)
35 ETDR.ti,ab. (0)
36 or/10-35 (336569)
37 9 and 36 (337)
38 Animal/ or Animal Experiment/ or Nonhuman/ (5400559)
39 (rat or rats or mouse or mice or murine or rodent or rodents or hamster or hamsters or pig or pigs or porcine or rabbit or rabbits or animal or animals or dogs or dog or cats or cow or bovine or sheep or ovine or monkey or monkeys).ti,ab,sh. (4213171)
40 38 or 39 (5767958)
41 exp Human/ or Human Experiment/ (12132588)
42 40 not (40 and 41) (4547861)
43 (editorial or letter or note).pt. (1500448)
44 37 not (42 or 43) (328)

NHS EED

# 1	MeSH Macular Edema EXPLODE 1	17
# 2	macular AND SAME AND (edema OR oedema OR odema)	13
# 3	MeSH Retinal Vein EXPLODE 1 2	2
# 4	MeSH Retinal Vein Occlusion EXPLODE 1 2 3	8
# 5	(vein OR veins OR veinous) AND SAME AND (occlusion* OR occluded OR obstruction* OR obstructed OR closed OR closure* OR stricture* OR stenosis OR stenosed OR block OR blocks OR blockage* OR blocking OR embolism* OR emboli) AND SAME AND retina*	4
# 6	"branch vein" AND SAME AND occlu*	1
# 7	"central vein" AND SAME AND occlu*	1
# 8	crvo OR cvo OR rvo OR brvo OR bvo OR crvome	3
# 9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	34

HTA

# 1	MeSH Macular Edema EXPLODE 1	17
# 2	macular AND SAME AND (edema OR oedema OR odema)	13
# 3	MeSH Retinal Vein EXPLODE 1 2	2
# 4	MeSH Retinal Vein Occlusion EXPLODE 1 2 3	8
# 5	(vein OR veins OR veinous) AND SAME AND (occlusion* OR occluded OR obstruction* OR obstructed OR closed OR closure* OR stricture* OR stenosis OR stenosed OR block OR blocks OR blockage* OR blocking OR embolism* OR emboli) AND SAME AND retina*	4
# 6	"branch vein" AND SAME AND occlu*	1
# 7	"central vein" AND SAME AND occlu*	1
# 8	crvo OR cvo OR rvo OR brvo OR bvo OR crvome	3
# 9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	34

HEED

AX='macular edema' within 3 or 'macular oedema' within 3 or 'macular odema' within 3
AX='retina vein' within 3 or 'retinal vein' within 3 or 'retina veins' within 3 or 'retinal veins' within 3 or 'retina veinous' within 3 or 'retinal veinous' within 3
AX=(branch vein)
AX=(central vein)
AX=crvo OR cvo OR rvo OR brvo OR bvo OR crvome
CS=1 or 2 or 3 or 4 or 5

EconLit

1	(macular adj3 (edema or oedema or odema)).ti,ab. (0)
2	((vein or veins or veinous) adj5 (occlusion$1 or occluded or obstruction$1 or obstructed or closed or closure$1 or stricture$1 or stenosis or stenosed or block or blocks or blockage$1 or blocking or embolism$1 or emboli) adj5 retina$1).ti,ab. (0)
3	(crvo or cvo or rvo or brvo or bvo or crvome).ti,ab. (0)
4	(branch vein adj5 occlu$).ti,ab. (0)
5	(central vein adj5 occlu$).ti,ab. (0)
6	or/1-5 (0)

CEA Registry

The following search terms were used:

macular edema
macular oedema
retina vein
retinal vein
retina veins
retinal veins
retina veinous
retinal veinous

branch vein
central vein

PROQOLID

The following section was searched; Pathology/Disease; Eye Diseases

NICE website

The following section was searched: NICE Guidance by Topic; Eye

Scottish Medicines Consortium (SMC)

SMC Advice was searched.

Food and Drug Administration (FDA)

Drugs@FDA was searched.

European Medicines Agency (EMA)

European Public Assessment Reports (EPARs) were searched.

9.13 Appendix 13: Resource identification, measurement and valuation (section 6.5)

The systematic review to identify relevant resource use data for the UK was performed alongside the review to identify relevant cost-effectiveness studies and the same methodology and search strategy were used (see Section 6.1.1 and Section 9.10, Appendix 10). Resource use studies were included if they reported on quantities or costs of resources used by RVO patients. Studies from the UK were prioritised, but studies from other countries were included in the absence of studies from the UK.

10 Supplementary Appendices (Added by Novartis)

10.1 Appendix 14: Methodology and Results of the ROCC Study

Methods

Table 6: Methodological summary of ROCC[49]

Trial no. (acronym)	**NCT00567697 (ROCC)[49]**
Location	4 study sites in Norway
Design	A 6-month, prospective, multicentre randomized, double-masked, sham-controlled, monitored study. 32 patients with MO secondary to CRVO in 1 eye, who were previously untreated for this disease, were randomised 1:1 to receive intravitreal injections of ranibizumab 0.5 mg or sham injection each month for the first three months of the study. For the remainder of the 6-month study, treatment was administered at the discretion of the physician if macular oedema with cysts in the central macular area persisted. All patients underwent a broad ophthalmologic examination, including BCVA examination using ETDRS chart at 4 meters, slit-lamp examination including ophthalmoscopy, fundus photography (baseline and months 3 and 6), fluorescein angiography (baseline and months 3 and 6), and OCT measuring the central macular thickness. Blood pressure and pulse rate were also monitored.
Duration of study	6 months
Method of randomisation	Not stated
Method of blinding (care provider, patient and outcome assessor)	The investigation was double-masked, where the investigating physician and nurse were masked toward the injecting physician and vice versa.
Intervention(s) (n =) and comparator(s) (n =)	**Intervention**: Monthly intravitreal ranibizumab 0.5 mg injections for 3 consecutive months (n = 16) **Comparator**: Monthly sham injection for 3 consecutive months (n = 16) Of the 32 patients randomised, only 29 completed the study (ranibizumab 0.5 mg, n = 15; sham injection, n = 14. The efficacy analysis was conducted on the per-protocol patient population): • 1 patient from ranibizumab group developed retinal artery thrombosis and was withdrawn from study shortly after first injection • 2 patients from sham group were withdrawn from the study, 1 for planned surgery because of cholecystitis, 1 following a diagnosis of AMD; a protocol violation
Primary outcomes (including scoring methods and timings of assessments)	• Mean change from baseline in BCVA score up to month 6 • Central macular thickness at month 6
Secondary outcomes (including scoring methods and timings of assessments)	• Number of treatments needed • Safety and tolerability of treatment • The development of neovascularisation

Trial no. (acronym)	NCT00567697 (ROCC)[49]
Duration of follow-up	Patients were followed for only the 6 months of the trial
Abbreviations used in table: AMD, wet age-related macular degeneration; BCVA, best-corrected visual activity letter score; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; MO, macular oedema; OCT, optical coherence tomography	

Participants

Table 7: Eligibility criteria in ROCC[49] NCT00567697

Inclusion criteria	Exclusion criteria
• MO secondary to CRVO in 1 eye • Symptom duration ≤ 6 months • Age ≥ 50 years • BCVA score (using the ETDRS chart) between ≤ 73 and ≥ 6 letters. Macular oedema was confirmed by the presence of intraretinal cysts in the central macular area by OCT using the Stratus OCT (Carl Zeiss Meditec, Dublin, California, USA) at 3 sites and Topcon 3D OCT 1000 (Topcon Corporation, Tokyo, Japan) at 1 site.	• Any concomitant ocular disease that could compromise the assessments in the study eye or induce complications such as active extraocular or intraocular infection or inflammation • Prior treatment of macular disease • History of uncontrolled glaucoma, filtration surgery, or corneal transplantation • Cataract surgery 3 months prior to baseline • Aphakia; • Cataract or diabetic retinopathy in rapid progression • Vitreous haemorrhage, or previous rhegmatogenous retinal detachment. Patients were also excluded if they were or could be pregnant, had received other investigational drugs or current treatment for active systemic infection, or had received medication known to be toxic to the eye, or if there were contraindications for the use of an investigational drug. Patients with a history of hypersensitivity or allergy to fluorescein, or an inability to obtain fundus photographs or fluorescein angiograms of sufficient quality to be analysed, were also excluded.
Abbreviations used in table: BCVA, best-corrected visual acuity; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; MO, macular oedema; OCT, optical coherence tomography	

Table 8: Baseline characteristics of participants in ROCC[49] NCT00567697 (n = 29)

Patient Demographics and Ocular Characteristics	Sham injection (n = 14)	Ranibizumab 0.5 mg (n = 15)
Mean age (range), years	72 (52 - 88)	
Mean duration of CRVO, days	78 (10 - 163)	
Overall mean (SD) BCVA score, ETDRS letters	43 (22) [20/138 Snellen equivalent]	
Mean (SD) BCVA score, ETDRS letters	41 (22) [20/152 Snellen equivalent]	45 (23) [20/126 Snellen equivalent]
Overall mean (SD) macular thickness, µm	625 (159)	
Mean (SD) macular thickness, µm	587 (154)	661 (161)
Number of patients with nonperfusion in an area > 5 disc areas revealed by fluorescein angiography, n	4	1
Abbreviations used in table: BCVA, best-corrected visual acuity; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation.		

Outcomes

The primary outcomes of ROCC[49] were mean change from baseline in BCVA score up to month 6 (BCVA was measured using ETDRS charts at a distance of 4 meters), and central macular thickness at month 6 (measured by optical coherence tomography).

- BCVA is identified as a key outcome in the decision problem and the change in best corrected visual acuity (BCVA) using an Early Treatment of Diabetic Retinopathy Study (ETDRS) eye chart is generally accepted as the gold standard for visual acuity measurements in clinical trials and is used in clinical practice.
- Measurement of foveal thickness by OCT is described as one of the minimum clinical services required for effective management of RVO by the RCO.[8] Its use in decision making regarding treatment in clinical practice is greater, however, than its value as an outcome indicator for patients in clinical trials. This is due to the only modest correlation observed between the centre point thickness as measured by OCT and visual acuity. A wide range of visual acuity may therefore be observed for a given degree of retinal oedema. Thus this outcome is not relevant to the decision problem.

The secondary outcomes of ROCC consisted of the number of treatments needed, the safety and tolerability of treatment and the development of neovascularisation.

- The number of treatments needed was collected as an outcome during the second half of the study when treatment was administered at the discretion of

the physician depending on the persistence of MO. This data was collected to help determine optimal treatment regimen.

- The safety and tolerability of treatment is discussed elsewhere in section 5.9.

Statistical analysis and definition of study groups

Table 9: Summary of statistical analyses in ROCC[49]

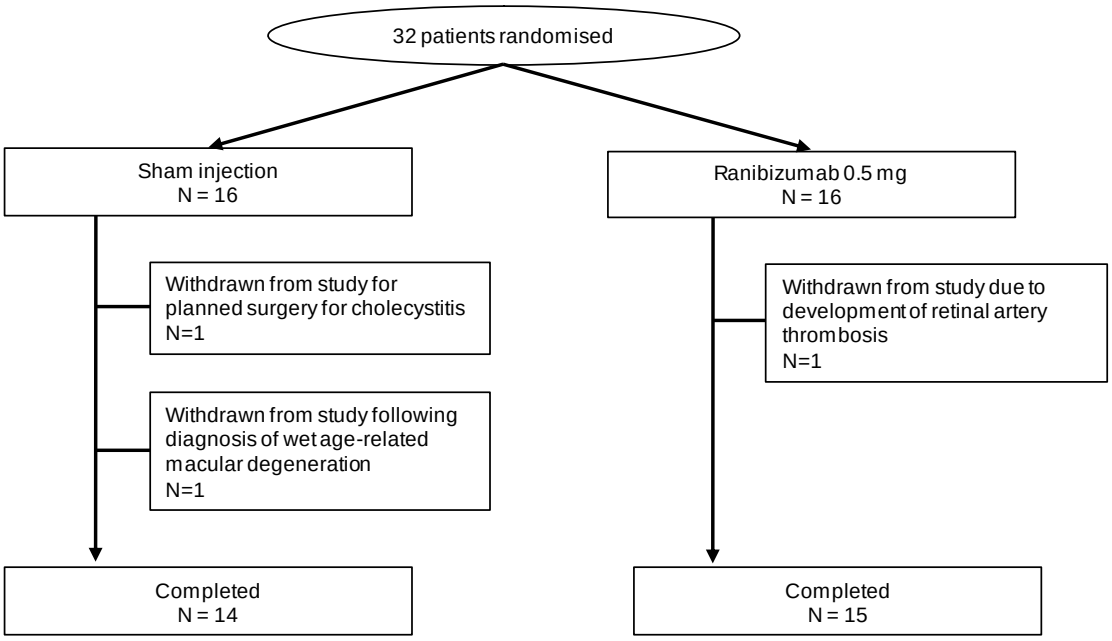
Hypothesis objective	Statistical analysis	Sample size, power calculation	Data management, patient withdrawals
Not specified. The inferred H0 is that mean change in BCVA from baseline up to month 6 is constant across the two groups of sham injection and ranibizumab 0.5 mg	Changes in BCVA from baseline to months 3 and 6 were compared between treatment groups with 2-sample t tests. Within each group, BCVA at months 3 and 6 were compared with baseline using paired t tests. P values less than 0.05 were considered statistically significant	Not specified	The efficacy analysis was done on a per-protocol patient population, which was considered appropriate considering the exploratory nature of this trial. Of the 32 patients randomised in the study, only 29 completed the study and were included in the per-protocol analysis of efficacy (sham injection, n = 14; ranibizumab 0.5 mg, n = 15).

No subgroup analysis was conducted in the ROCC study.[49]

Participant flow

See Figure 1 for a CONSORT flow diagram that illustrates the flow of participants through the ROCC study.[49]

Figure 1: ROCC CONSORT flow diagram of participant flow



Critical appraisal of ROCC

Table 10: Quality assessment results for ROCC[49]

Trial no. (acronym)	Trial 1
Was randomisation carried out appropriately?	Not clear, study reports that patients were randomised 1:1 to one of the two groups, but the method of randomisation was not reported
Was the concealment of treatment allocation adequate?	Not clear, method of allocation concealment was not reported.
Were the groups similar at the outset of the study in terms of prognostic factors?	Not clear, the study does not provide detailed breakdown of the groups' baseline characteristics.
Were the care providers, participants and outcome assessors blind to treatment allocation?	Yes, the patients were blinded to treatments. The investigating physician and nurse were masked toward the injecting physician and nurse and vice versa.
Were there any unexpected imbalances in drop-outs between groups?	There were no unexpected imbalances, but patients did drop-out of the groups: 1 patient in the ranibizumab groups withdrew, and 2 withdrew from the sham injection group.
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	No, the efficacy analysis was undertaken on the per-protocol patient population.

Results of ROCC

In the ranibizumab group, 3 patients had a persistent response throughout the study after the initial 3 injections with a flat macular and improved BCVA score. These patients had a mean symptom duration of 73 days and a mean age of 64 years. All patients in the ranibizumab group responded to treatment with a decrease in central macular thickness (CMT) and an improvement in BCVA.

In the sham group, 4 patients had a decrease in CMT and an improved BCVA score during the study period, which were most pronounced during the first 3 months. These patients had a mean symptom duration of 30 days, a mean age of 61 years at baseline, a mean BCVA score of 69 ETDRS letters and a mean CMT of 226 μm at final visit

At three months, a significant improvement in BCVA scores among those who received ranibizumab every month up to month 3 was observed compared with sham injection. At month 6, a trend toward these results was still present, but the ranibizumab-sham difference was no longer statistically significant.

Table 11: Results of ROCC[49] NCT00567697, (n = 29)

Efficacy Outcome	Sham injection (n =14)	Ranibizumab 0.5 mg (n = 15)	Significance
Mean (SD) change in BCVA at month 1	-8 (14)*	+12 (12)**	* P = 0.055 (NS) month 1 vs. baseline ** P = 0.002 month 1 vs. baseline
Mean (SD) change in BCVA at month 3	-5 (15)†	+16 (14)††	†P = 0.261 (NS) month 3 vs. baseline †† P = 0.001 month 3 vs. baseline P = 0.001, improvement in BCVA at 3 months in ranibizumab vs. sham
Mean (SD) change in BCVA at month 6	-1 (17)‡	+12 (20)‡‡	‡ P = 0.765 (NS) month 6 vs. baseline ‡‡ P = 0.040 month 6 vs. baseline P = 0.067, (NS) change in BCVA at 6 months ranibizumab vs. sham
Proportion of patients who required injections after month 3, n (%)	12 (86%)	12 (80%)	Not reported
Mean (SD) number of injections received during the study, up to 6 months	5.5 (1.1)	4.3 (0.9)	Not reported
Abbreviations used in table: BCVA, best correct visual acuity; NS, non significant; SD, standard deviation;			

10.2 Appendix 15: Summary of anatomical results for BRAVO and CRUISE

Figure 2 BRAVO: Mean study eye excess foveal thickness over time to month 6. ****P*<0.0001 versus sham (prespecified exploratory end point). *P*<0.0001 ranibizumab versus sham at day 7 and months 1–3 (post hoc analyses). Vertical bars are ±1 standard error of the mean.

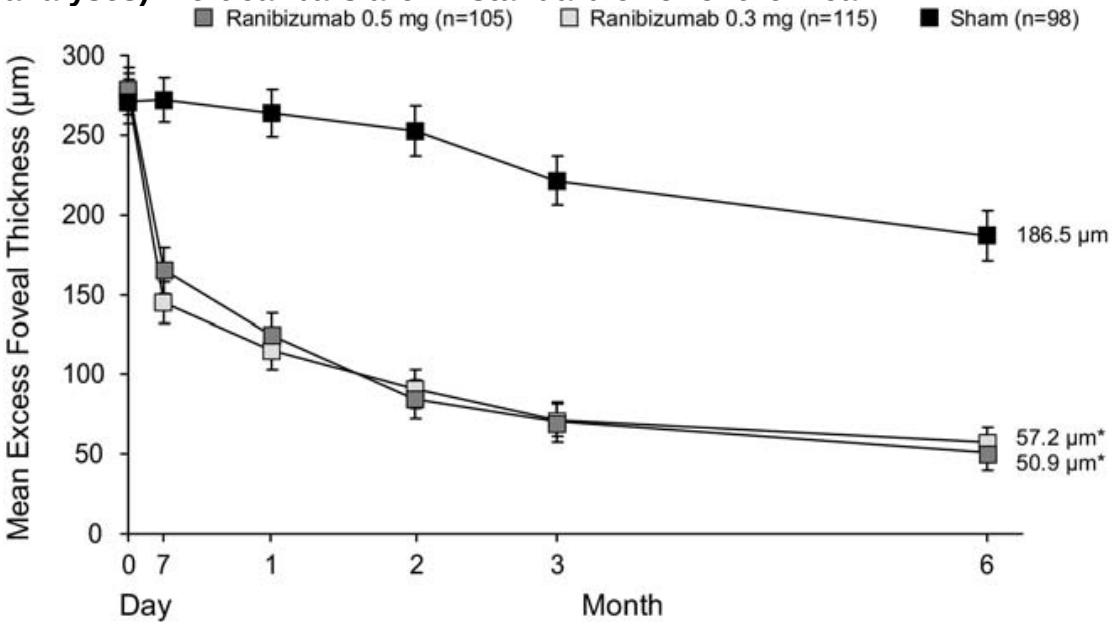
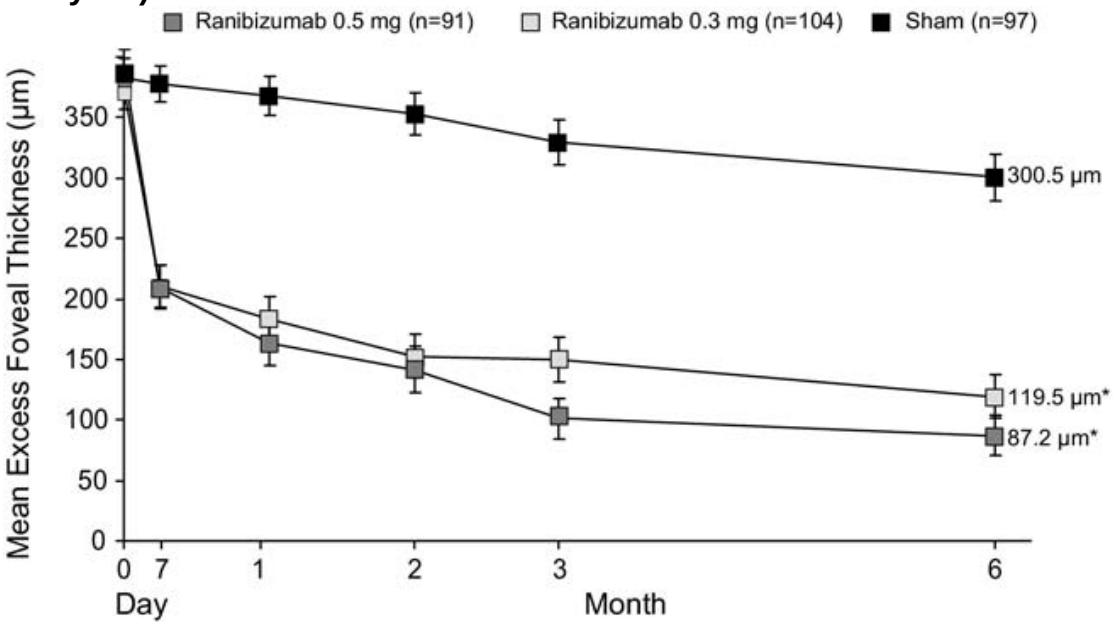


Figure 3 CRUISE: Mean study eye excess foveal thickness over time to month 6. ****P*<0.0001 versus sham (prespecified exploratory end point). *P*<0.0001 ranibizumab vs. sham at day 7 and months 1–3 (post hoc analyses). Vertical bars are ±1 standard error of the mean.



10.3 Appendix 16: Meta-analysis of the CRUISE and ROCC Study Data

10.3.1 Meta-analysis methodology

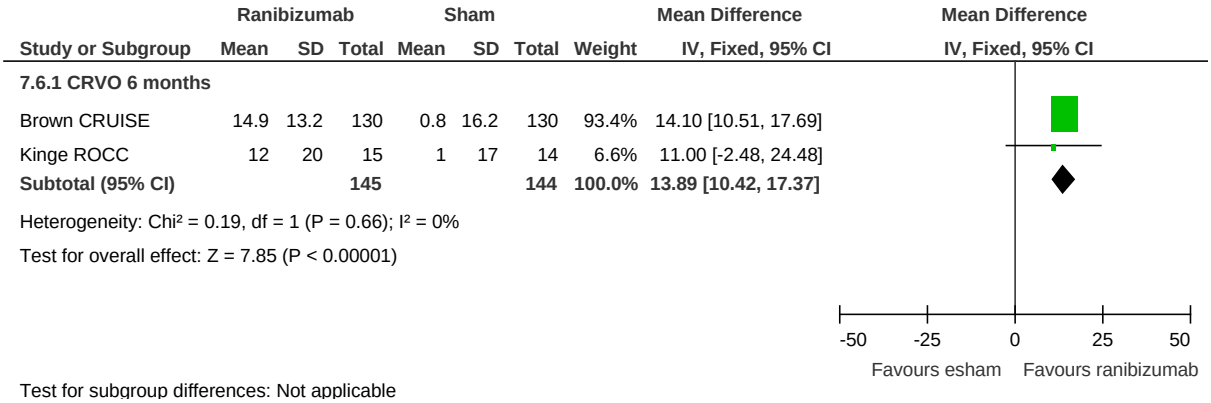
Where meta-analysis was possible (i.e. where there was statistical and clinical homogeneity), data were pooled using both fixed- and random-effects models. Heterogeneity was assessed using the chi-squared and I-squared statistics. For continuous outcomes, results are presented as a weighted mean difference (WMD), with 95% confidence intervals (CIs). The results from meta-analyses are presented as forest plots.

10.3.2 Meta-analysis results

Pooling of data from the CRUISE and ROCC studies was only possible for two outcomes, mean change in EDTRS score at six months (Figure 4) and reduction in foveal thickness at 6 months (Figure 5). Due to the small size of the ROCC study (N=32) compared to CRUISE (N=392), the meta-analysis does not provide any additional value than is provided by the results of the CRUISE study, which are presented in Section 5.5.

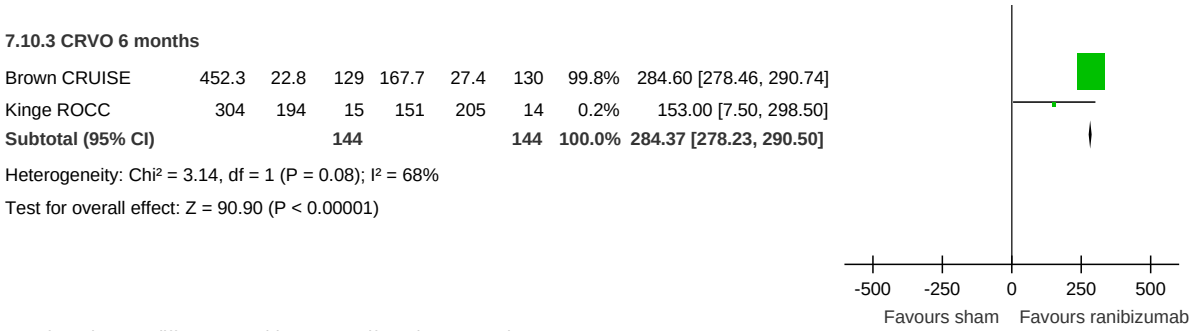
For mean change in EDTRS score at six months, the heterogeneity in results between the studies is low (Chi^2 = 0.19, I^2 =0%). For the reduction in foveal thickness at 6 months, more heterogeneity is seen between the studies (Chi^2 = 3.14, I^2 =68%). This is probably due to the small sample number found in the ROCC study. There were also problems with the reporting and analysis in the ROCC study (see Section 9.3, appendix 3): The randomisation method and allocation concealment were not reported; the study did not provide detailed breakdown of the groups baseline characteristics; the study reported a per protocol not intention to treat analysis.

Figure 4: Forest plot of mean difference between ranibizumab 0.5mg vs. sham treatment in CRVO patients for change in EDTRS score at six months.



Test for subgroup differences: Not applicable

Figure 5: Forest plot of mean difference between ranibizumab 0.5mg vs. sham treatment in CRVO patients in terms of reduction in foveal thickness at 6 months.



Test for subgroup differences: Chi² = 11.39, df = 1 (P = 0.0007), I² = 91.2%

10.4 Appendix 16: List of non-RCTs identified

Table 12 presents the characteristics of the non-RCTs that specifically study ranibizumab treatment for visual impairment due to MO secondary to RVO that were identified by the systematic review presented in Section 9.2, appendix 2. All non-RCTs, apart from Campochiaro 2008/2010[47, 48], were deemed not to provide any results that would be valuable to the decision problem, mainly as they did not report long-term data or did not follow large cohorts of patient. Two studies were excluded for other reasons: Chang 2009[122] reported the use of 1.25 mg ranibizumab, which is not a licensed dose (it is the licensed dose of bevacizumab) and Moustaka 2010[123] did not clearly report the dosing regimen used.

Table 12: List of non-RCTs identified by the systematic review

Trial name	Study Design	Intervention	Population	Objectives	Justification for exclusion
Alfaro 2008[124]	Single-centre, open-label, 12 month study	3 monthly injections of either 1.3 mg or 1.5 mg ranibizumab	Patients with cystoid MO associated with BRVO (N=11)	To evaluate the safety and efficacy of monthly injections	Small sample size and no data beyond 12 months
Basefsky 2009[125]	prospective, open-label study	0.3 mg or 0.5 mg ranibizumab, dosed monthly for 3 months then dosed PRN	Patients with MO associated with perfused CRVO Cohort 1 (N=10) evaluated quarterly, cohort II (N=10) evaluated monthly	To evaluate the biologic effect, visual acuity changes, and safety of intravitreal ranibizumab	Small sample size and no data beyond 12 months
Basefsky 2010[126]	prospective, open-label study	All patients were treated on a monthly PRN basis and patients receiving repeat ranibizumab injections for recurrent macular edema were eligible to receive argon PRP	Patients with MO associated with perfused CRVO (N=20)	To report initial experience with panretinal photocoagulation (PRP) administered as an adjuvant therapy following intravitreal ranibizumab	Small sample size and no data beyond 12 months
Campochiaro 2008/2010[48]	24 month, open label, uncontrolled, randomised dose comparison study	0.3 mg or 0.5 mg ranibizumab, dosed monthly for 3 months then dosed	Adult patients with MO caused by either BRVO or CRVO (N=40)	To determine the long term effects of ranibizumab treatment	**Included:** This study reports on the long term outcomes of ranibizumab therapy, although in a small

Trial name	Study Design	Intervention	Population	Objectives	Justification for exclusion
		PRN			population (N=40)
Chang 2009[122]	24 month, prospective study	1.25 mg ranibizumab dosed monthly for 3 months, then PRN	Patients with decreased VA due to CRVO (N=29)	To report long-term outcomes of a prospective trial of intravitreal ranibizumab	Not licensed dose
Cruz 2010[127]	12 month, prospective study	0.5 mg injection of ranibizumab followed by laser grid photocoagulation 30 days later	Patients with MO secondary to BRVO (N=12 eyes)	To evaluate the efficacy and safety of intraocular injections of Ranibizumab followed by grid photocoagulation	Small sample size and no data beyond 12 months
Eibenberger 2010[128]	12 week, prospective study	0.5 mg ranibizumab at baseline then PRN monthly depending on VA and OCT findings	Patients with clinically significant MO due to BRVO (N=20 consecutive patients)	To evaluate the effect of intravitreal ranibizumab on BCVA and foveal retinal thickness	Small sample size and no data beyond 12 weeks
Frances-Munoz 2009[129]	40 week comparative study (ranibizumab vs. pegaptanib)	Single intravitreal injection of ranibizumab or pegaptanib at baseline, then PRN when macular thickness >300 microns. Doses not reported	Patients with MO secondary to BRVO and macular thickness > 400 microns (N=24)	To evaluate the efficacy of Pegaptanib and Ranibizumab as single initial therapy to improve visual acuity and macular thickness	Small sample size, no data beyond 40 weeks and no dose information given

Trial name	Study Design	Intervention	Population	Objectives	Justification for exclusion
Moustaka 2010[123]	Retrospective study	0.5 mg ranibizumab. Dosing regimen not stated.	Patients with ischaemic and non-ischaemic CRVO (N=25)	To evaluate changes in visual acuity after intravitreal injection of ranibizumab	Dosing regimen unclear
Petrou 2010[130]/ Rouvas 2010[131]	Prospective interventional case series	Repeated ranibizumab injections (when CFT >225 µm). Dose not stated	Patients with MO secondary to BRVO (N=28)	To evaluate the effect of individualized repeated intravitreal injections of ranibizumab on VA and central foveal thickness	Small sample size, no data beyond 12 months, dose unclear
Pieramici 2008[132]	Prospective, open-label, single-centre, uncontrolled study	0.3 mg or 0.5 mg ranibizumab dosed monthly for 3 months, then dosed PRN for 21 months	Patients with MO associated with perfused CRVO (N=10)	of biological effect, visual acuity changes, and safety of intravitreal ranibizumab	Only presents data up to month 9. No follow-up publication identified.
Puche 2010[133]	Retrospective case series	Intravitreal injections of 0.5 mg ranibizumab were administered; retreatment was based on acuity visual changes and optical coherence tomography findings.	Patients with MO secondary to CRVO (N=15) or BRVO (N=19)	To evaluate the efficacy and the safety of intravitreal ranibizumab injection	Small sample size, mean follow-up was 7 months

Trial name	Study Design	Intervention	Population	Objectives	Justification for exclusion
Rouvas 2009[134]	Prospective interventional case series	Repeated (when CFT >220 µm) intravitreal injections of ranibizumab. Dose not stated	Patients with MO caused by CRVO (N=12)	To evaluate the effect of individualized repeated intravitreal injections of ranibizumab on VA and CFT	Small sample size and no data beyond 12 months
Spaide 2009[135]	12 month, prospective, interventional case series	0.5 mg ranibizumab dosed monthly for 3 months, then PRN	Patients with decreased VA due to CRVO (N=20)	To evaluate intravitreal injection of ranibizumab as a potential treatment for decreased VA secondary to CRVO	Small sample size and no data beyond 12 months
Ulltveit-Moe 2010[136]	Retrospective study	Treatment with either ranibizumab or bevacizumab. No doses reported	Patients with CRVO of 3-12 months duration (N=14)	To evaluate the effect of intravitreal ranibizumab and bevacizumab on VA, letter gain, and central macular thickness	Small sample size, no data beyond 6 months
Von Hanno 2010[137]	Two case studies	One patient received ranibizumab, the other bevacizumab	Both patients had MO secondary to CRVO	To assess cases of retinal artery occlusion following intravitreal VEGF inhibitor injections	Very small sample size

Trial name	Study Design	Intervention	Population	Objectives	Justification for exclusion
Wu 2008[138]	One case study	Intravitreal bevacizumab followed by intravitreal ranibizumab	Patients had MO secondary to BRVO	To report affects of intravitreal VEGF in the uninjected eye	Very small sample size

10.5 Appendix 17: Details of Campochiaro 2008/2010[47, 48], the relevant RCT

Methodology

Table 13 Summary of methodology of the relevant non-RCT

Trial no. (acronym)	**Campochiaro 2008/2010[47, 48]**
Location	1 centre, USA
Design	A randomised, dose comparison Phase II study. Patients received monthly injections of ranibizumab for 3 months, Patients were seen at months 4, 5, 6, 9 and 12 months, but were not given routine ranibizumab injections; however, standard care was allowed at the discretion of the treating ophthalmologist. Beyond month 12, patients were seen every 2 months are received an injection of their original dose of ranibizumab if OCT showed evidence of residual MO in the fovea.
Duration of study	The study duration was 24 months. Recruitment of patients started in 2007.
Method of randomisation	The method of randomisation was not stated.
Method of blinding (care provider, patient and outcome assessor)	Both patients and investigators were masked with respect to treatment group. However, the method of blinding was not stated.
Intervention(s) (n =) and comparator(s) (n =)	<u>CRVO</u> Ranibizumab 0.3 mg (n=10) Ranibizumab 0.5 mg (n=10) <u>BRVO</u> Ranibizumab 0.3 mg (n=10) Ranibizumab 0.5 mg (n=10)
Primary outcomes (including scoring methods and timings of assessments)	The percentage of patients at 3 months who achieved an improvement in VA from baseline of ≥15 letters read on an ETDRS VA chart at 4 m.
Secondary outcomes (including scoring methods and timings of assessments)	• Mean and median change in VA (EDTRS letters) at several time points after study entry (day 7, months 1-4, 6, 9, 12, 14, 16, 18 ,20, 22, 24) • Excess foveal thickness measured by OCT at several time points following study entry (day 7, months 1-4, 6, 9, 12, 14, 16, 18 ,20, 22, 24)
Duration of follow-up	24 months

Trial no. (acronym)	Campochiaro 2008/2010[47, 48]
Abbreviations used in table: AEs, adverse events; BCVA, best-corrected visual activity letter score; EFT, excess foveal thickness; ETDRS, Early Treatment Diabetic Retinopathy Study; MO, macular oedema; NEI VFQ-25, National Eye Institute Visual Functioning Questionnaire-25; OCT, optical coherence tomography; RVO, retinal vein occlusion; SAEs, serious adverse events;	

Table 14 Eligibility criteria used in Campochiaro 2008/2010[47, 48]

Trial no. (acronym)	Inclusion criteria	Exclusion criteria
Campochiaro 2008/2010	• Patients >18 years with VA between 20/30 and 20/400 from macular oedema due to CRVO or BRVO • foveal thickness (central subfield) was >250 µm	• VA <20/400 in the fellow eye • A sign of possible permanent vision loss in the study eye such as atrophy or prominent pigmentary change in the macula • Laser photocoagulation or intraocular surgery within the previous 3 months • Intraocular injection of a VEGF antagonist within the previous 3 months • Intraocular steroids within the previous 4 months • Vitreomacular traction or an epiretinal membrane

Baseline Characteristics

The baselines characteristics of the patients enrolled into the Phase II study are presented in Table 15. Gender was not reported. For BRVO, the patients in the 0.3 mg and the 0.5 mg ranibizumab groups were well balanced in terms of baseline characteristics. For CRVO, the patients in the 0.5 mg ranibizumab group were slightly older and had a longer duration of disease. In terms of ocular baselines characteristics for CRVO, however, the 0.5 mg ranibizumab patients had better visual acuity at baseline than the 0.3 mg ranibizumab group.

Table 15 Baselines characteristics of patients enrolled into the Campochiaro 2008/2010 Phase II study[47, 48]

Trial no. (acronym) **Baseline characteristic**	**CRVO**		**BRVO**	
NCT00486018 **Campochiaro 2008/2010** **(n = 40)**	**Ranibizumab 0.3 mg** **(n = 10)**	**Ranibizumab 0.5 mg** **(n = 10)**	**Ranibizumab 0.3 mg** **(n = 10)**	**Ranibizumab 0.5 mg** **(n = 10)**
Patient Demographics				
Age (yrs)				
Mean (SD)	63 (17)	68 (13)	69 (13)	65 (10)
Median	69	70	65	65
Range	34-83	48-83	50-82	50-82
Systemic disease (no. patients)				
Diabetes	3	3	3	3
Hypertension	5	6	9	8
Hyperlipidaemia	4	7	7	3
Elevated homocysteine	1	3	3	6
Ocular disease (no. patients)				
Glaucoma	1	3	0	1
Other	2	5	5	3
Baseline Ocular Characteristics				
Duration of disease (months)				
Mean (SD)	9 (7)	16 (17)	5 (3)	3 (2)
Median	7.4	13	5	3
Range	1-26	0.5-53	0.4-9	0.8-6
Prior treatment (no. patients)				
Bevacizumab	0	0	1	2
Steroids	1	2	2	2
Laser	1	3	4	3
Visual acuity (ETDRS letters read at 4 m)				
Mean (SD)	16 (13)	23 (15)	26 (12)	20 (14)
Median	18	26	29	23

Excess foveal thickness (µm) Mean (SD) Median	346 (88) 340	297 (126) 309	252 (104) 270	288 (101) 294
Abbreviations used in table: BRVO, branch retinal vein occlusion; CRVO, central retinal vein occlusion; ETDRS, Early Treatment Diabetic Retinopathy Study; SD, standard deviation				

Outcomes

Table 16 Primary and secondary outcomes of the Campochiaro 2008/2010 Phase II study[47, 48]

	Outcome(s) and measures	Reliability/validity/ current use in clinical practice	Relevance to decision problem
Primary Outcome	The percentage of patients at 3 months who achieved an improvement in VA from baseline of ≥15 letters read on an ETDRS VA chart at 4 m.	The ETDRS chart is the gold standard measure for visual acuity in clinical practice. An improvement from baseline of 15 or more letters can be considered clinically meaningful.	Medium
Secondary Outcomes	Mean and median change in VA (EDTRS letters) at several time points after study entry (day 7, months 1-4, 6, 9, 12, 14, 16, 18 ,20, 22, 24)	The ETDRS chart is the gold standard measure for visual acuity in clinical practice.	High
	Excess foveal thickness measured by OCT at several time points following study entry (day 7, months 1-4, 6, 9, 12, 14, 16, 18 ,20, 22, 24)	Measurement of fovea thickness by OCT is described as one of the minimum clinical services required for effective management of RVO by the RCO.[8] Its use in decision making regarding treatment is greater, however, than its value as an outcome indicator for patients in clinical trials.	Low
Abbreviations used in table: ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, Optical coherence tomography; RCO, Royal College of Ophthalmology; VA, visual acuity			

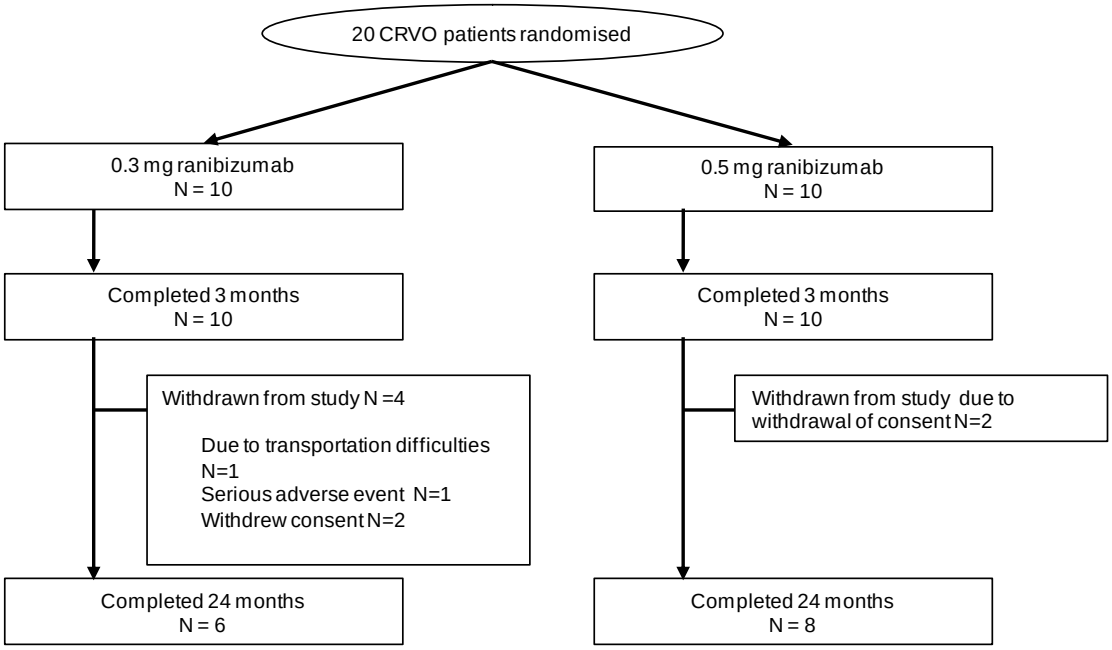
Statistical analysis and definition of study groups

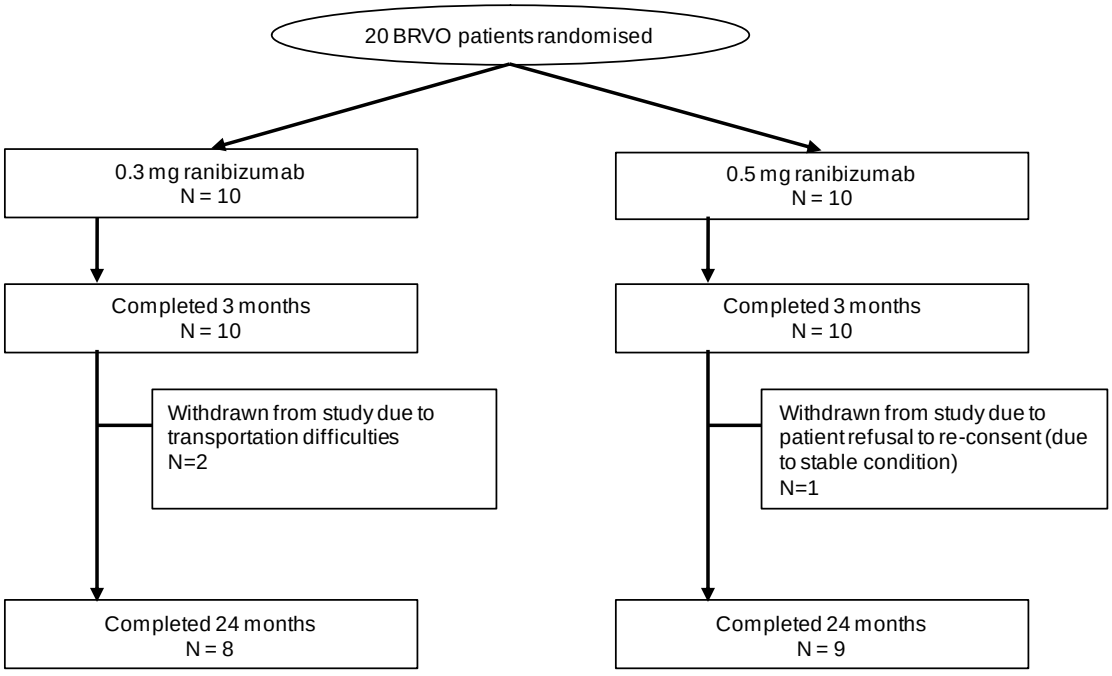
The hypothesis of the study was not explicitly stated, but it is assumed that the hypothesis was that both doses of ranibizumab were equivalent. No statistical test was used to assess whether the primary endpoint, the percentage of patients with a clinically significant improvement in VA from baseline (defined as an improvement of 15 or more ETDRS letter), was different between the two doses of ranibizumab. The Mann-Whitney test was used to determine whether there was a statistically significant difference between groups of different disease duration and of groups with partial or complete destruction of perifoveal capillaries.

No sample size calculation for the study was reported and thus it is unclear whether the study was powered to detect a significant difference between doses.

Data was collected for all patients at the 3 month primary endpoint. Patients who withdrew from the study before month 24 were excluded from the final analysis at 24 months.

Participant flow





Critical appraisal

Table 17 Critical appraisal of Campochiaro 2008/2010

Campochiaro 2008/2010[47, 48]		
Study question	**How is the question addressed in the study?**	**Grade (yes/no/not clear/N/A)**
Was randomisation carried out appropriately?	Randomisation methodology was not stated in the publication	Not clear
Was the concealment of treatment allocation adequate?	The method of treatment allocation concealment was not stated in the publication	Not clear
Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?	BRVO patients were similar at baseline. For CRVO patients, the 0.5 mg ranibizumab group was slightly older and had a longer disease duration, but also a better average visual acuity.	No (for CRVO patients)
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 to the treatment allocation	Yes
Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?	There were no unexpected imbalances in withdrawals between the groups	No
Is there any evidence to suggest that the authors measured more outcomes than they reported?	There is no suggestion that the authors measured more outcomes that they report	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?	All patients were still enrolled in the study at the 3 month primary endpoint. The 24 month analysis presented both an ITT analysis (using last observation carried forward) and an analysis based on completers only.	Yes
Centre for Reviews and Dissemination (2008) Systematic reviews. CRD's guidance for undertaking reviews in health care. York: Centre for Reviews and Dissemination		

10.6 Appendix 18: Critical appraisal of Fekrat et al. 2010 (Resource use study)

Table 18 Critical appraisal of Fekrat et al. 2010

Quality assessment parameter	Comment
Was the research question clearly stated?	Yes
Was the sample representative of the population?	Yes (Elderly people only which was stated in the research question).
Did the authors identify the source of data for costs used to inform the study?	Yes
Did the authors identify the source of data for resource use used to inform the study?	Yes
Did the authors provide details of the subjects from whom costs were obtained?	Yes
Were resources reported separately from their unit costs?	Yes
Were methods for the estimates of quantities of resource use described?	Yes
Were methods for the estimates of the unit costs of direct costs described?	No. No unit costs are reported, only aggregated direct medical costs are reported.
Were the currency and year/month of price data recorded?	Yes
Were details of currency of price adjustments for inflation or currency conversion reported?	Yes
Was the time horizon of costs reported?	Yes
Were costs presented in a disaggregated manner?	No
Did all the relevant cost elements appear to be included?	No
If some costs are omitted, are these the relatively less important costs that do not drive the results?	No
Did the authors make appropriate comparisons of their results with the findings from other studies?	Comparison is made against one other study.
Was the issue of generalisability to other settings addressed?	No
Did the authors present their results selectively?	Unclear
Did authors' conclusions reflect the scope of the analysis?	Yes
Are the authors' conclusions supported by the results of the study?	Yes
Did the authors report any further limitations of their study?	Yes
Final comment of the assessor	Acceptable quality

10.7 Appendix 19: Results of Pieramici 2001[50] (Impact of rescue laser in the BRAVO study)

Table 19 Baseline patient demographics and visual characteristics for patients who did and did not receive rescue laser treatment

	No rescue laser treatment* (n=216)		**Any rescue laser treatment* (n=181)**	
	Sham/ 0.5 mg† n=51	**0.5 mg ranibizumab N=86**	**Sham/ 0.5 mg† n=81**	**0.5 mg ranibizumab N=45**
Baseline characteristics				
Age, years, mean (SD)	64.0 (13.7)	65.9 (11.7)‡	65.9 (12.0)	70.5 (11.6)
Prior treatment for RVO, N (%)	8 (15.7)	14 (16.3)	17 (21.0)	7 (15.5)
Time from diagnosis to Day 0, months, mean (SD)	3.8 (3.7)	4.2 (3.3)	4.7 (3.7)	3.6 (2.8)
Ocular characteristics				
VA, EDTRS letters, mean (SD)	56.5 (11.2)	53.8 (11.3)	53.6 (12.7)	51.4 (14.6)
CFT, µm, mean (SD)	457.2 (220.3)	535.2 (231.6)	507.4 (170.8)	538.2 (20.6.0)

* Any = any rescue laser treatment during the treatment and/or observation periods; No = no rescue laser treatment during the treatment and observation periods

† Patients received sham treatment during the 6 month treatment period, then 0.5 mg ranibizumab PRN during the 6 month observation period

‡P=0.024, None vs. Any within treatment group (ANCOVA stratified by baseline BCVA classification)

Abbreviations: ANCOVA, analysis of covariance; BCVA, best-corrected visual acuity; CFT, central foveal thickness; EDTRS, early treatment of diabetic retinopathy study; PRN, *pro re nata* (as needed); RVO, retinal vein occlusion; SD, standard deviation; VA, visual acuity

Table 20 Month 6 and month 12 efficacy outcomes stratified by rescue laser use

	No rescue laser treatment* (n=216)		Any rescue laser treatment* (n=181)	
	Sham/ 0.5 mg† n=51	**0.5 mg ranibizumab N=86**	**Sham/ 0.5 mg† n=81**	**0.5 mg ranibizumab N=45**
Month 6				
Change in BCVA, mean (SD)	10.4 (12.5)	19.7 (13.5)	5.4 (13.0)	15.6 (12.4)
Patients gaining ≥15 letters, n(%)	21 (41.2)	56 (65.1)	17 (21.0)	24 (53.3)
Month 12				
Change in BCVA, mean (SD)	13.5 (14.2)	20.1 (14.0)‡	11.2 (14.6)	15.0 (15.3)
Patients gaining ≥15 letters, n(%)	25 (49.0)	58 (67.4)	33 (40.7)	21 (46.7)

* Any = any rescue laser treatment during the treatment and/or observation periods; No = no rescue laser treatment during the treatment and observation periods

† Patients received sham treatment during the 6 month treatment period, then 0.5 mg ranibizumab PRN during the 6 month observation period

‡P=0.006 for no laser treatment vs. any laser treatment (ANCOVA stratified by baseline BCVA classification)

Abbreviations: ANCOVA, analysis of covariance; BCVA, best-corrected visual acuity; PRN, *pro re nata* (as needed); SD, standard deviation

10.8 Appendix 20: Non-RCT data for bevacizumab

A full systematic review was performed to identify non-RCT evidence for bevacizumab in the treatment of MO secondary to RVO.

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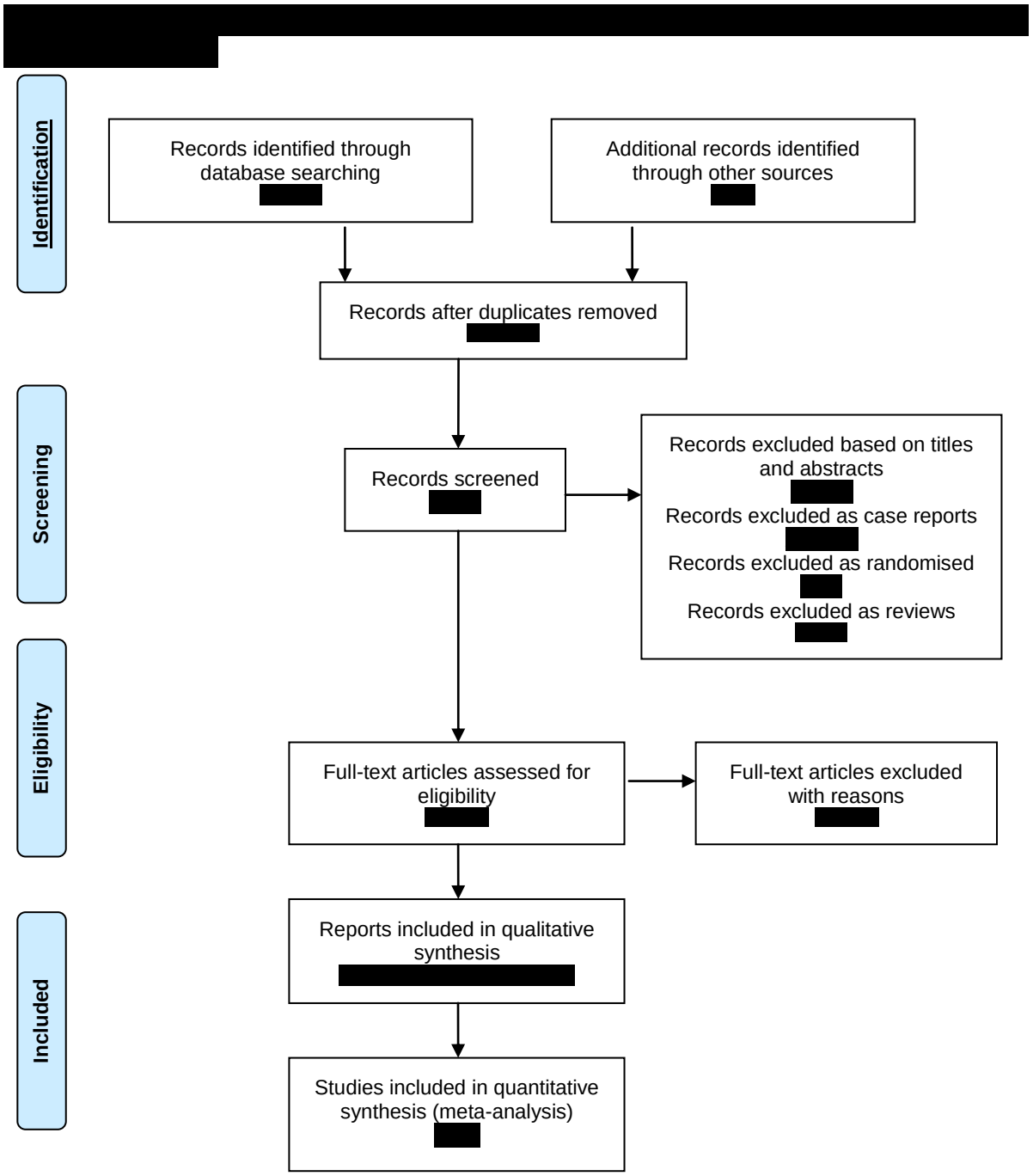
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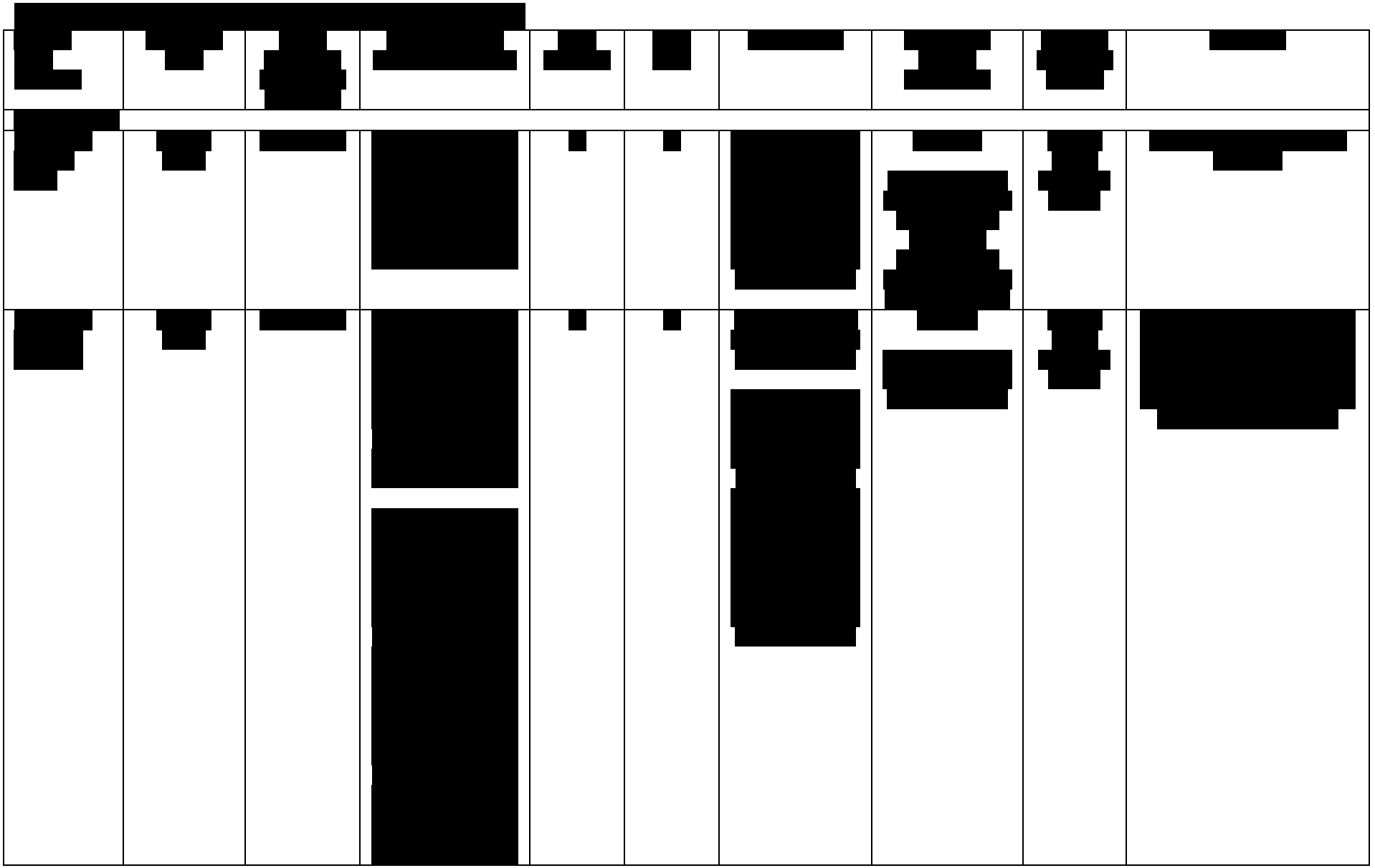
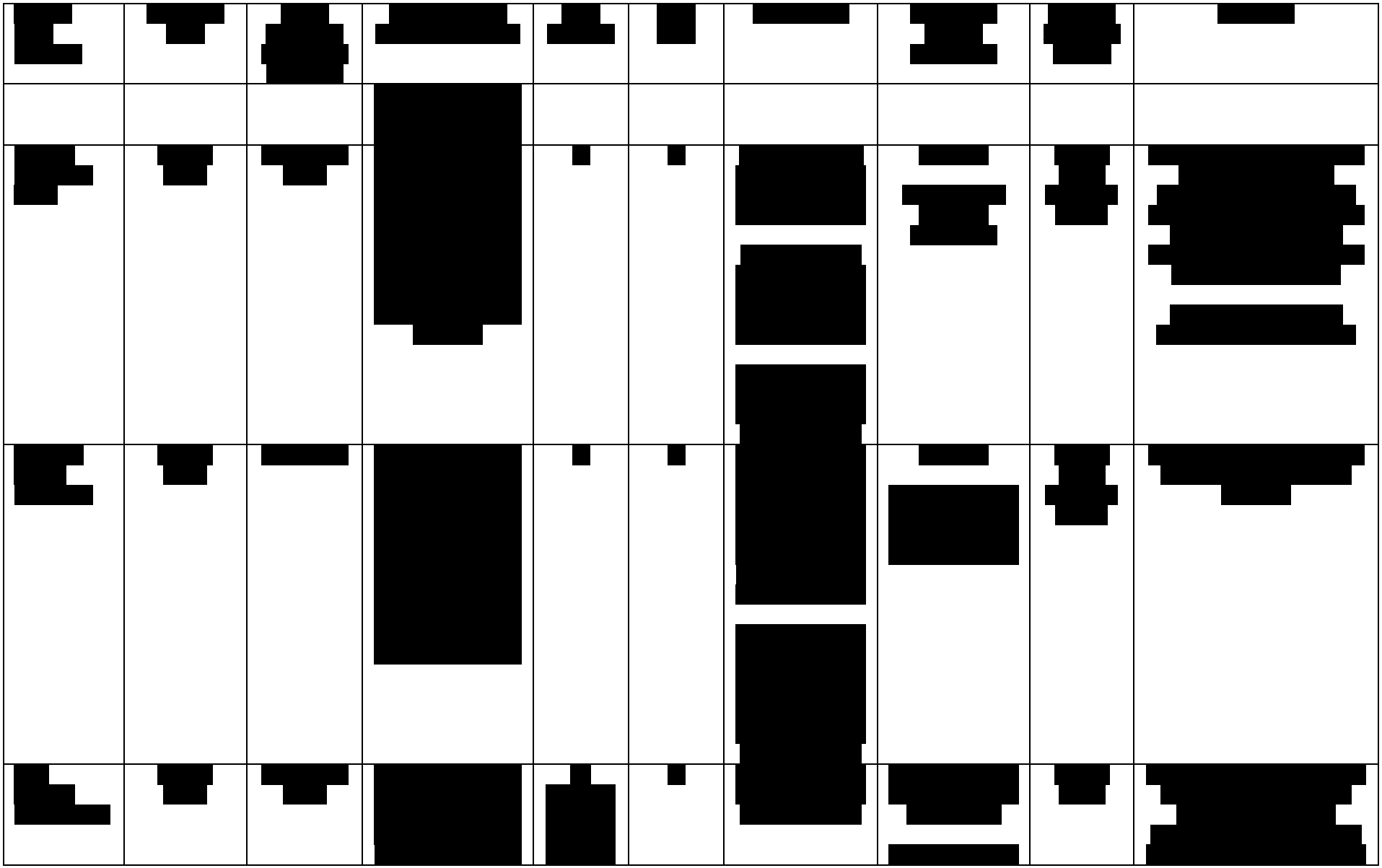
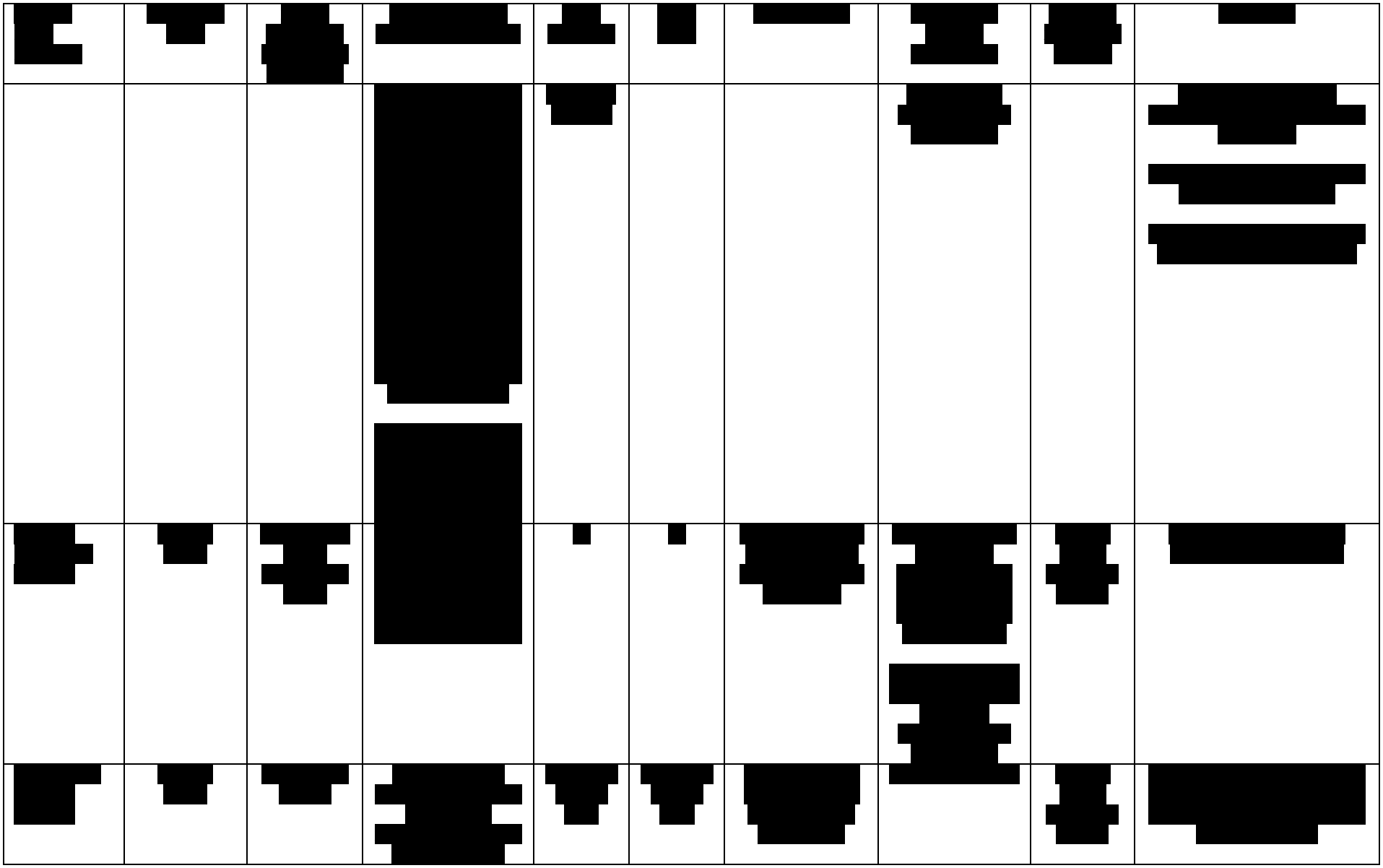
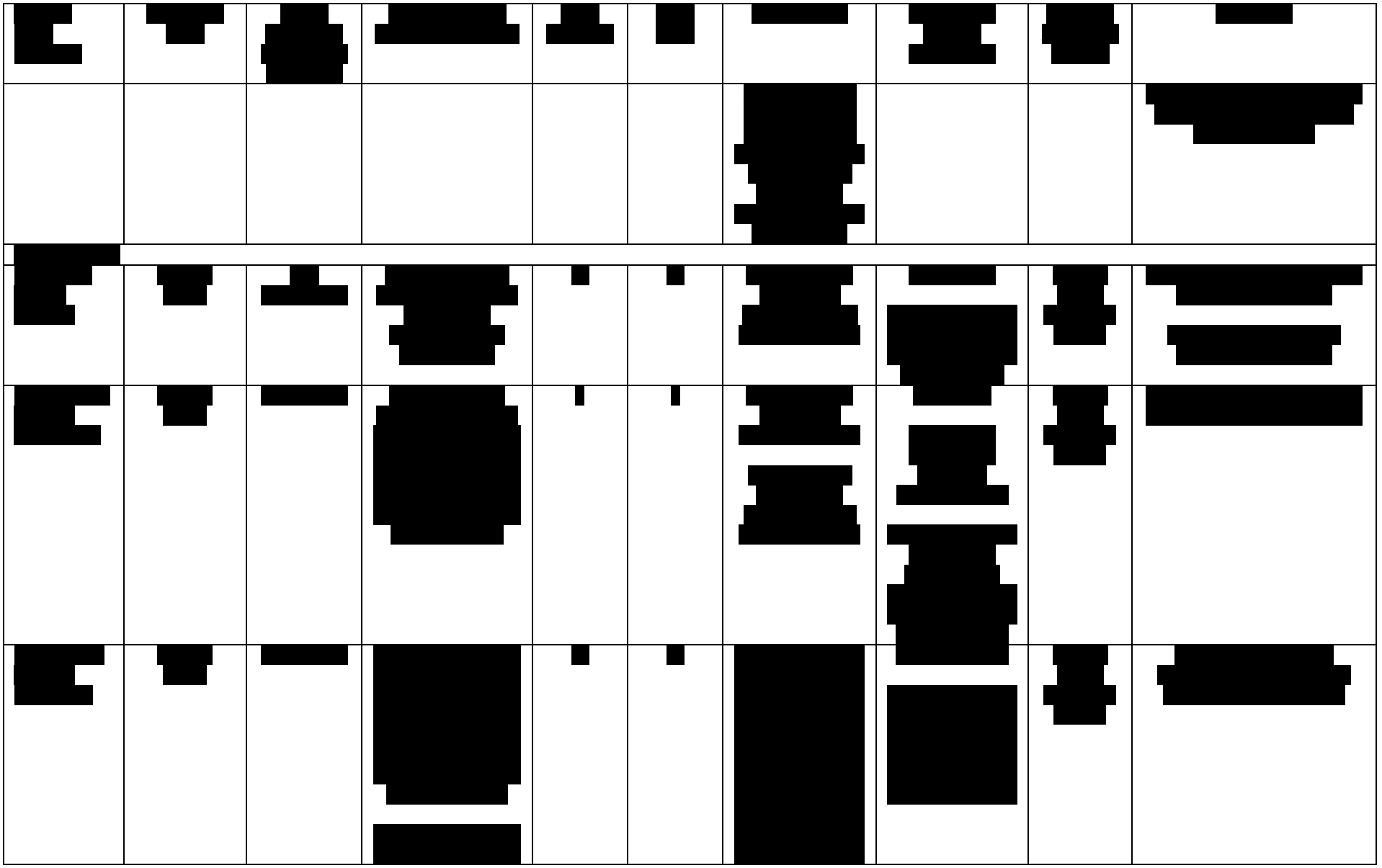
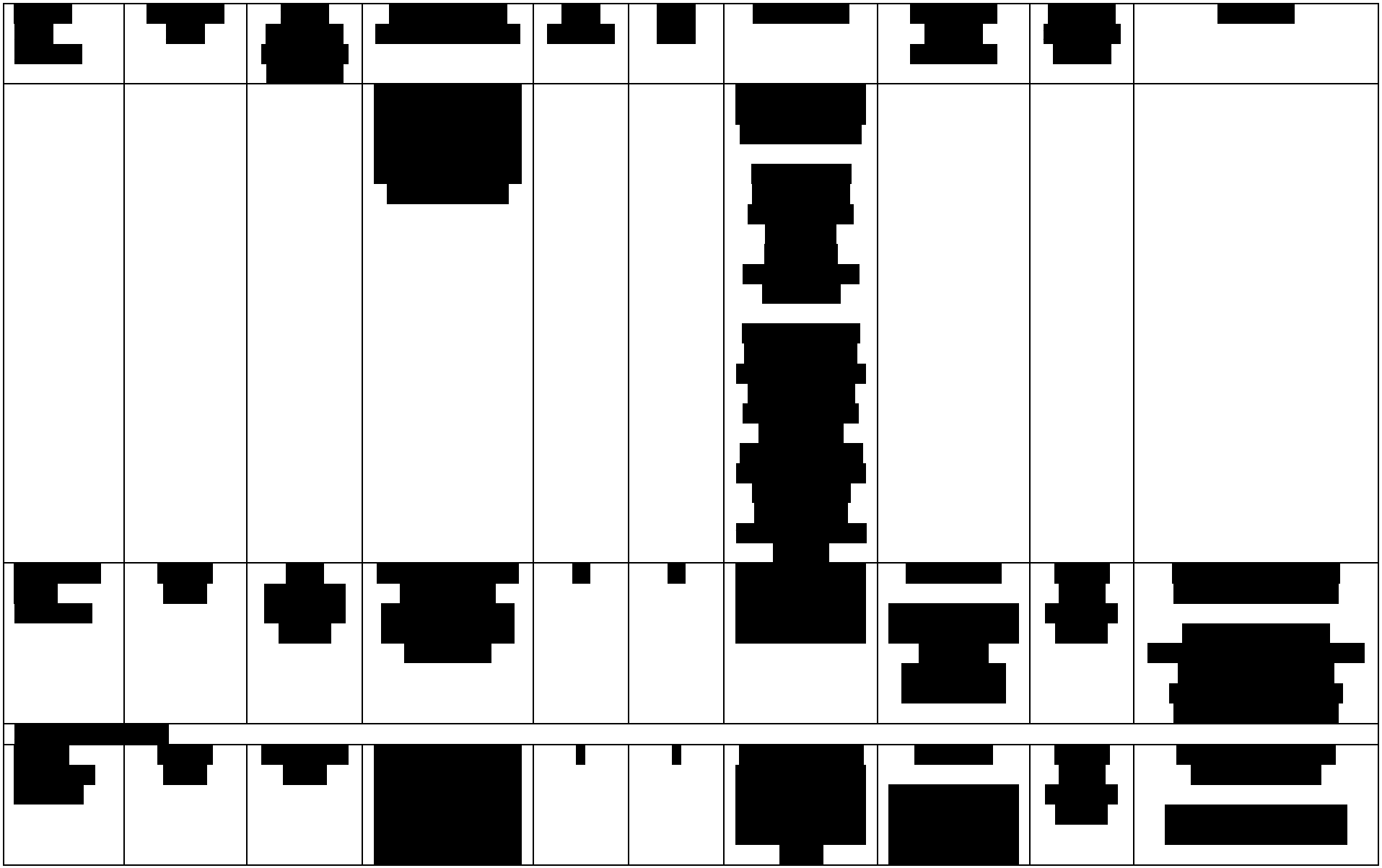
Records identified through database searching
Additional records identified through other sources
Records after duplicates removed
Screening
Records screened
Records excluded based on titles and abstracts
Records excluded as case reports
Records excluded as randomised
Records excluded as reviews
Eligibility
Full-text articles assessed for eligibility
Full-text articles excluded with reasons
Included
Reports included in qualitative synthesis
Studies included in quantitative synthesis (meta-analysis)

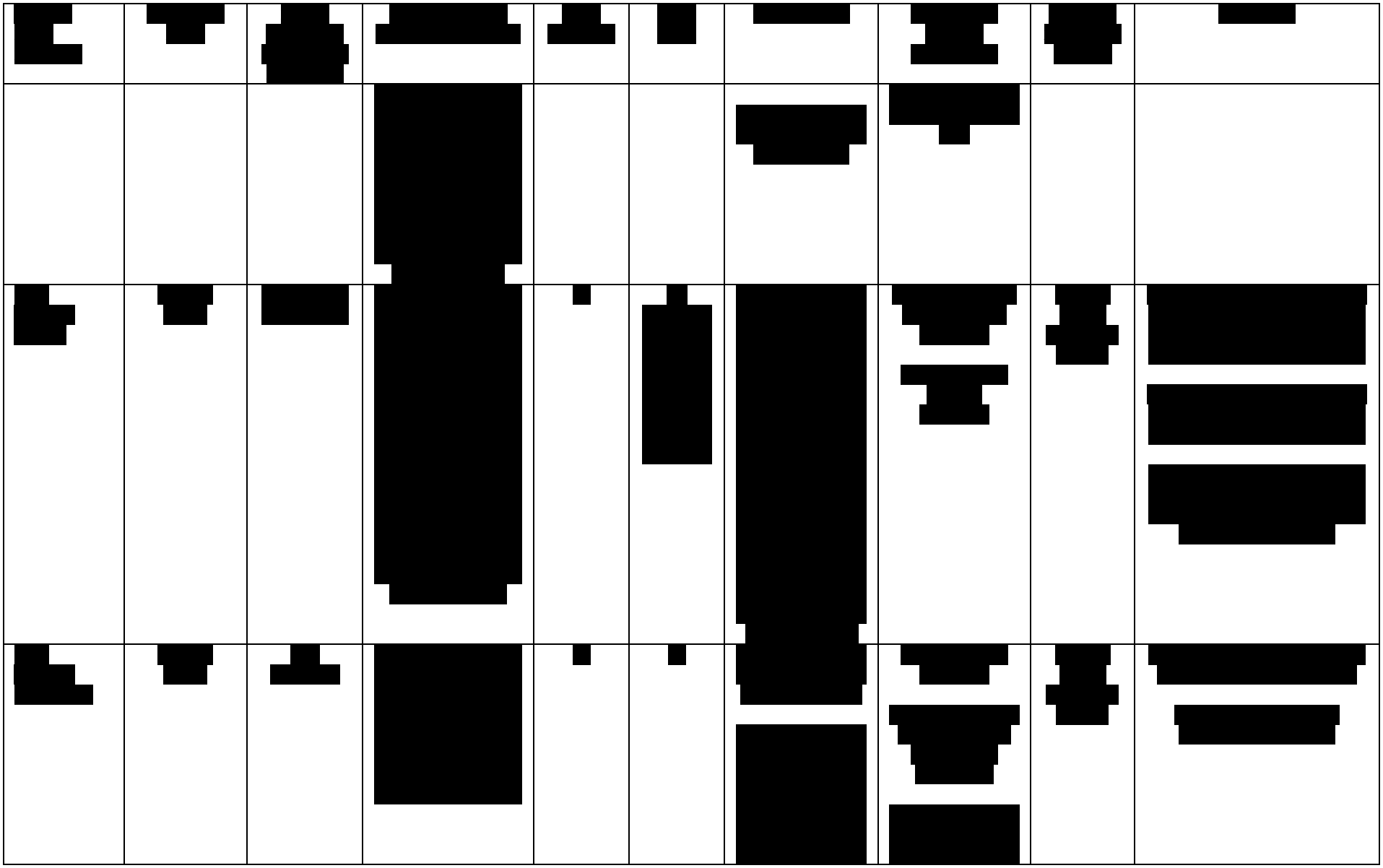


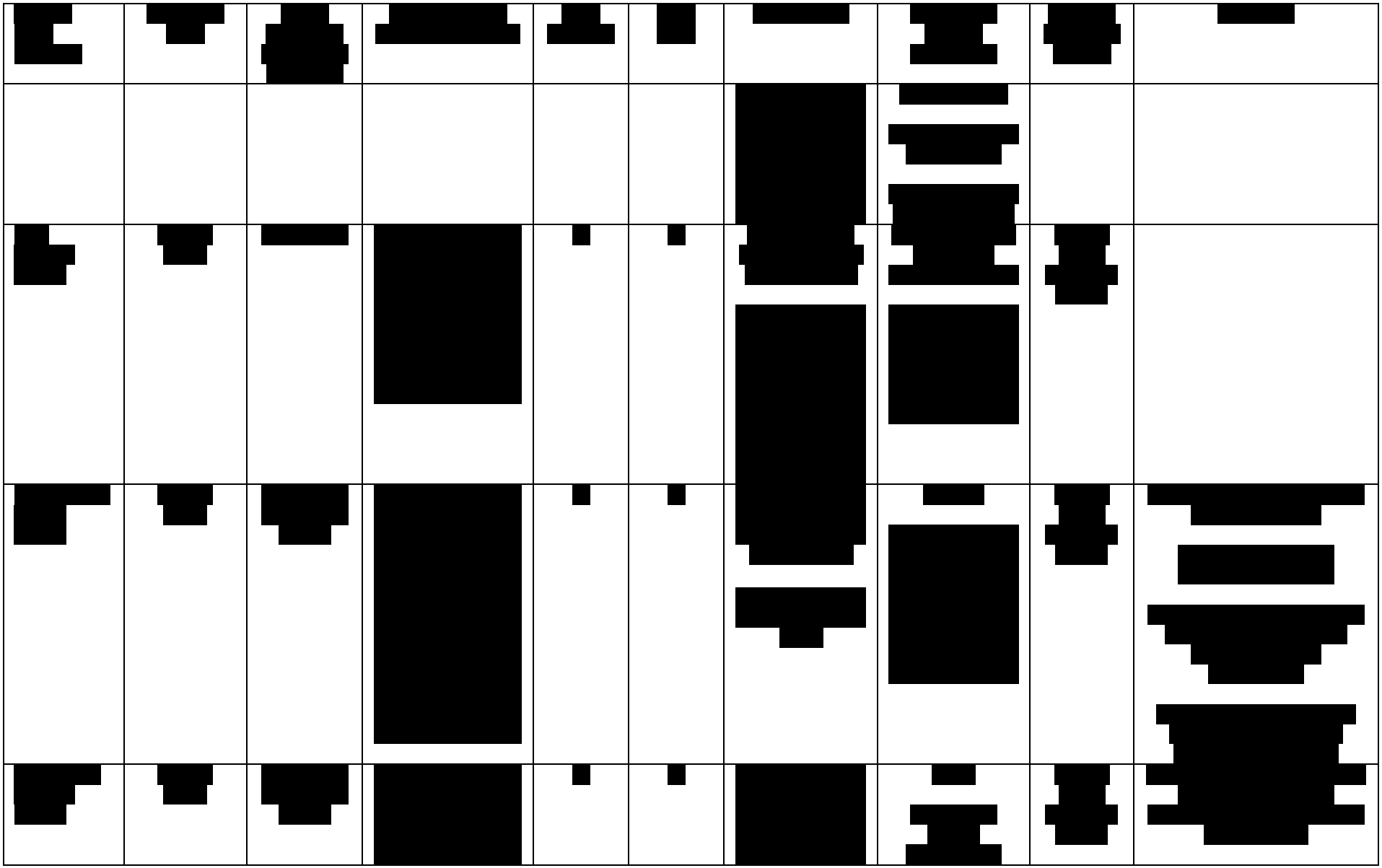


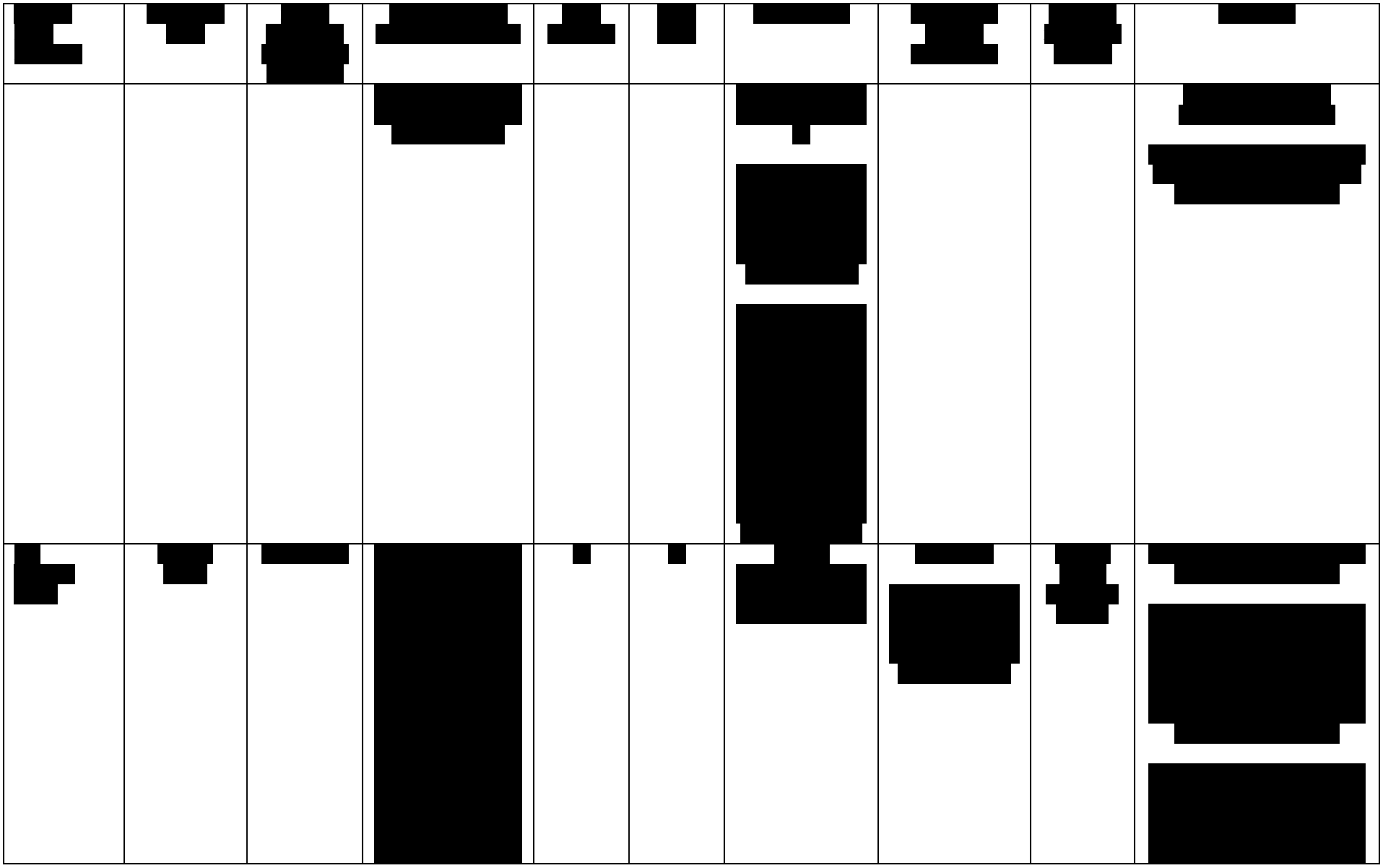


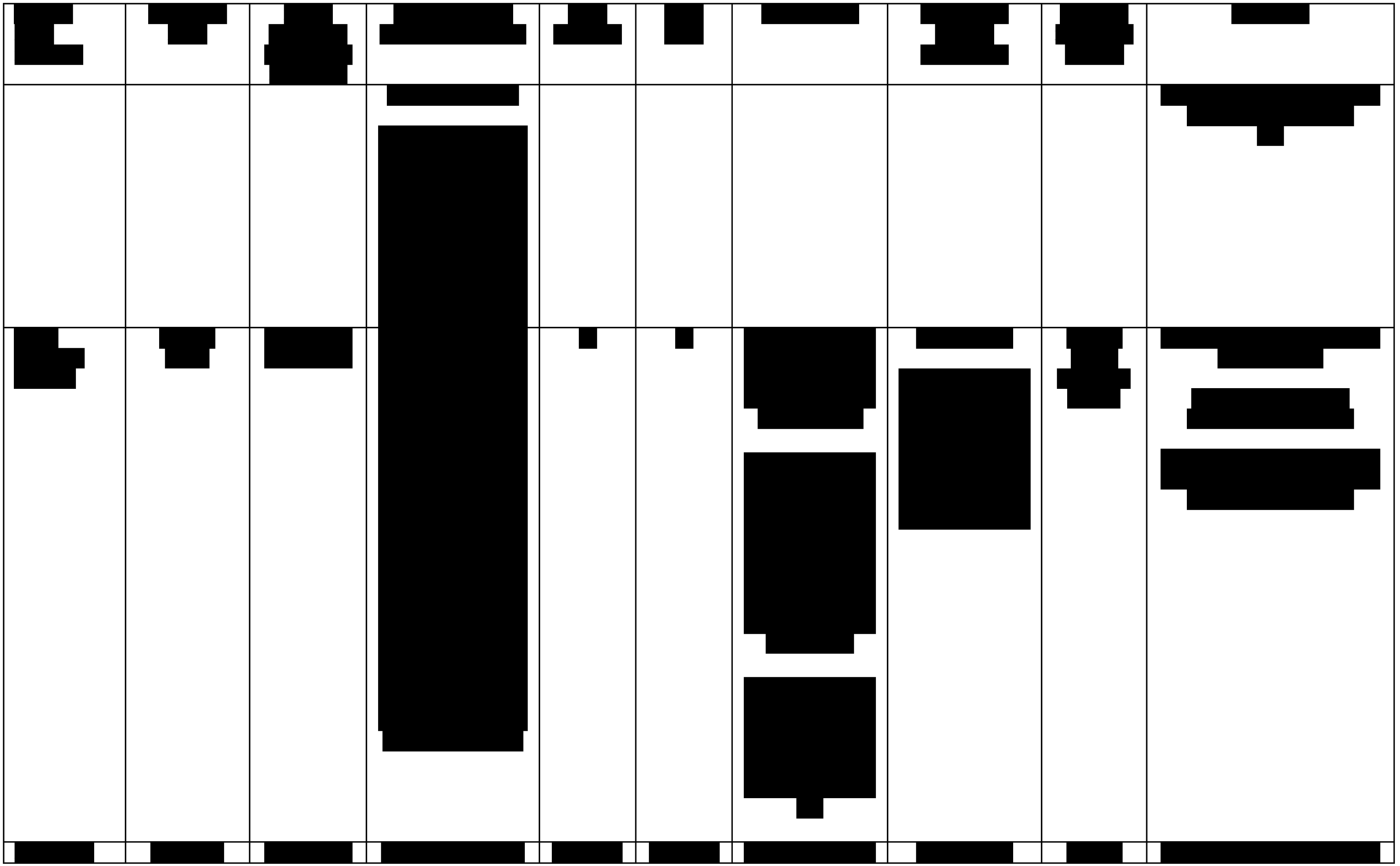


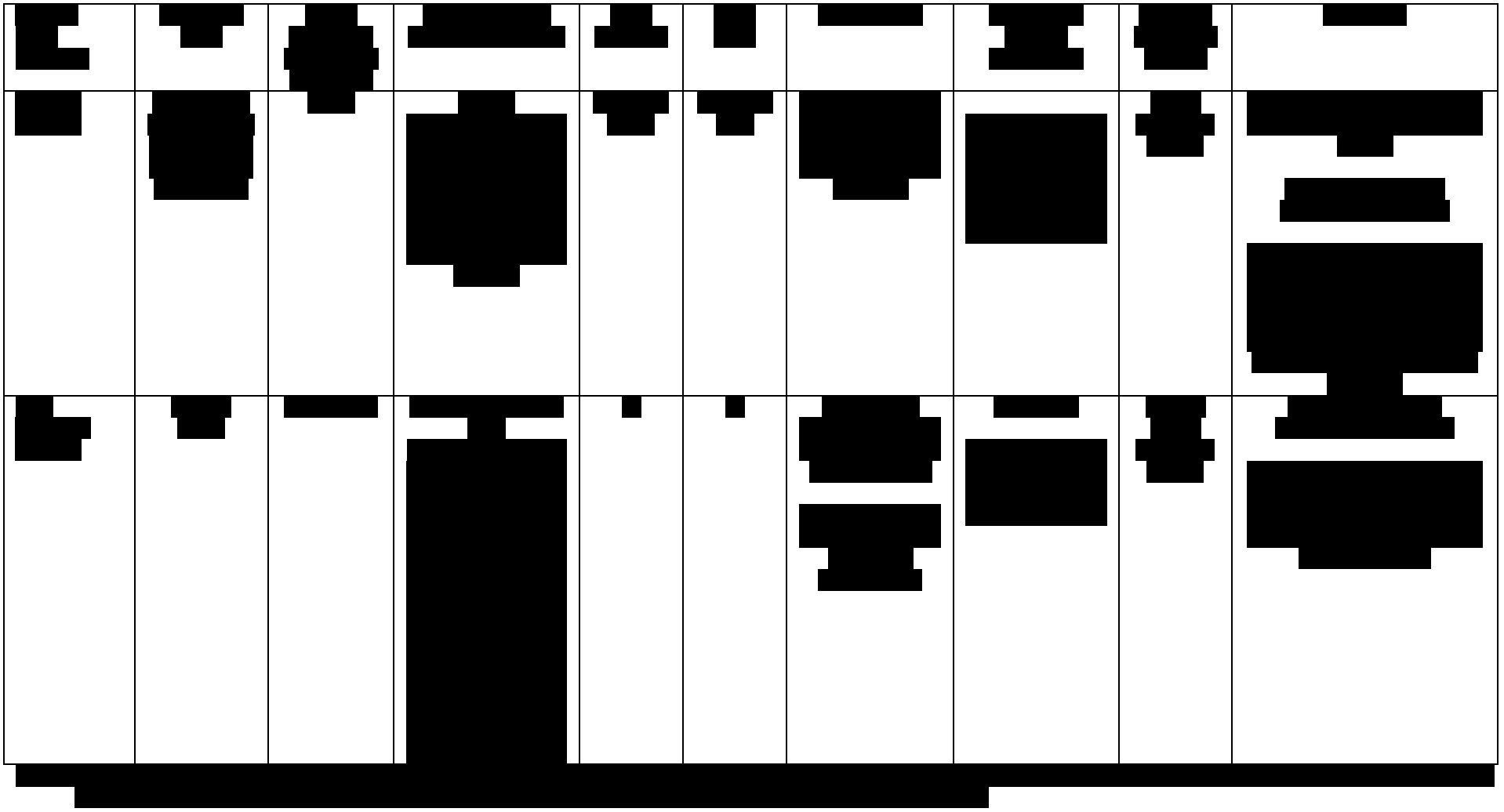












10.9 Appendix 21: Clinical Expert Advice

Discussion Points and Background Material Provided to Experts

Background

Novartis Pharmaceutical UK Ltd (Novartis) is preparing a single technology appraisal (STA) submission to the National Institute of Health and Clinical Excellence (NICE) for ranibizumab (Lucentis®) therapy in patients with visual impairment (VI) due to macular oedema (MO) secondary to retinal vein occlusion (RVO). NICE will appraise the clinical and cost effectiveness of ranibizumab for VI due to MO arising from central and branch vein occlusion (CRVO and BRVO).

The key elements of the appraisal scope, developed by NICE, are reproduced in table 1 below. More information on the appraisal is available on the NICE website at http://guidance.nice.org.uk/TA/Wave23/26.

Table 21: Key elements of the NICE appraisal scope

Intervention	Ranibizumab
Population	Patients with visual impairment due to macular oedema secondary to retinal vein occlusion
Comparators	CRVO: Best supportive care (ischaemic only) Bevacizumab Dexamethasone implant BRVO: Best supportive care (ischaemic only) Bevacizumab Dexamethasone implant Grid pattern photocoagulation
Outcomes	Visual acuity (the affected eye) Visual acuity (the whole person) Adverse events Health-related quality of life
Potential subgroups	The presence or absence of ischaemia Baseline visual acuity Duration of macular oedema (time since diagnosis)

In the submission, the clinical evidence consists primarily of randomised controlled trials (RCTs); two of which have been used to support the cost effectiveness analysis. These RCTs are the BRAVO study and the CRUISE study, including patients with BRVO and CRVO respectively.

The cost effectiveness analysis uses data from these trials to simulate the costs, health outcomes and quality of life experienced by a cohort of patients when treated with the current standard of care or with ranibizumab. Where trial or other data is absent, assumptions have been made about certain clinical inputs.

In order to ensure that the clinical evidence and assumptions are acceptable, we wish to seek the expert opinion of clinicians experienced in the management of patients with VI due to MO secondary to RVO.

Objectives

The objectives of the expert interviews are to:

Assess the feasibility and validity of making comparisons between ranibizumab and other treatments, including dexamethasone implants and unlicensed bevacizumab

Provide validation and/or critique of the key assumptions in the economic evaluation:

1. Treatment and follow-up of patients beyond the initial treatment period
2. The long-term progression of best-corrected visual acuity (BCVA) in patients with MO due to RVO
3. Valuation of the impact of impaired vision on health related quality of life, using data not specific to patients with retinal vein occlusion.
4. Discuss potential subgroups of patients who may derive the most benefit from ranibizumab treatment
5.

Overview of cost-effectiveness analysis in healthcare

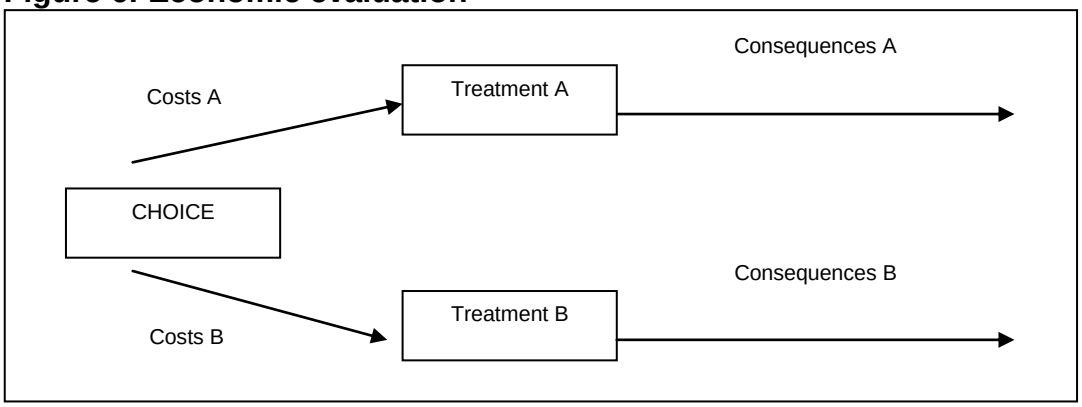
The economic evaluation for discussion is a cost effectiveness analysis. This is the comparative analysis of alternative courses of action in terms of both their costs and consequences.

In short, the basic tasks of a cost-effectiveness analysis are to identify, measure, value and compare the costs and consequences of the alternatives being considered (Figure 6). The difference in costs of the alternatives is compared with the difference in consequences in an incremental analysis.

Consequences or effects of alternative treatments are commonly expressed as Quality Adjusted Life Years (QALYs), which are an expression of the health related quality of life experienced by patients. Thus a *cost per QALY gained* from treating patients with treatment A compared to treatment B can be calculated. This

incremental cost-effectiveness ratio (ICER) is the key output of a cost-effectiveness analysis used to inform decision-making by bodies including NICE and SMC.

Figure 6: Economic evaluation



Economic modelling is a framework for simplifying reality to a level that describes the essential costs and consequences of the alternative treatments.

Economic models are useful for incorporating data from different sources, for estimating data that have not been directly measured and to extrapolate data on costs and health benefits over the longer term. The validity of an economic model rests on whether its assumptions are reasonable, based on the needs and purposes of the decision-maker and whether its implications make sense.

A robust economic model therefore requires that assumptions used to extrapolate treatment effects have clinical validity, be reported transparently and be clearly justified.

Overview of the RVO economic model

The RVO cost effectiveness model compares intravitreal ranibizumab (0.5mg injection) to the current standard of care, using the direct comparisons of the BRAVO and CRUISE trials.

In BRVO, the current standard of care is macular laser photocoagulation in those patients that do not spontaneously resolve by 3 months.

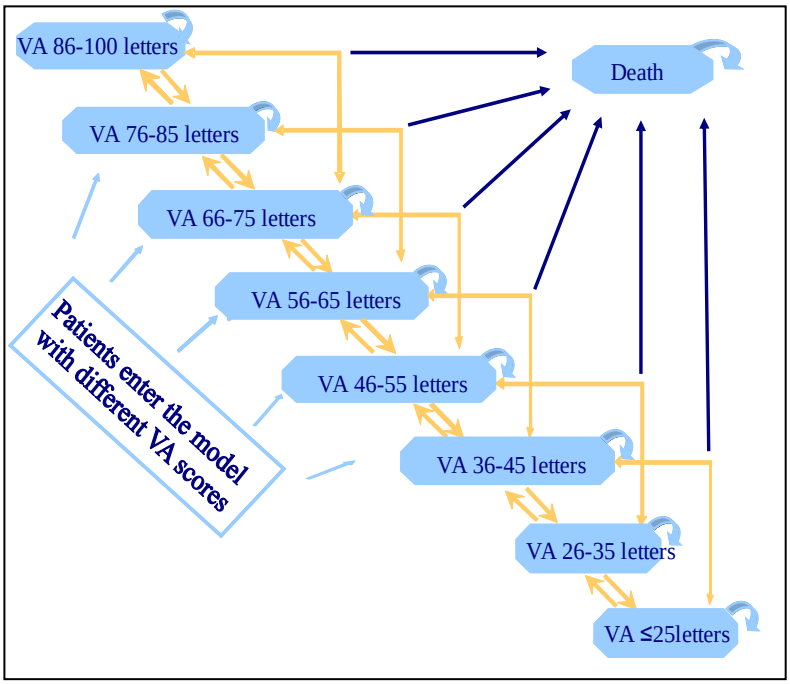
In CRVO, the current standard of care is best supportive care (no active treatment).

The model categorises patients by their level of visual acuity (VA). Figure 7 illustrates the structure of the model with outcome represented by best-corrected ETDRS ≥10-letter-score changes in VA (approximately changes ≥ 2 Snellen line).

A cohort of patients with varying VA enters the model. The progression of VA in the patient cohort is modelled using clinical trial data and data from long term observational studies. Thus the probability of movement between VA health states depends on the treatment received.

The mean age of the cohort of patients at the time of treatment is 63 years and the model follows them for 15 years. Costs and utilities (a measure of health related quality of life) are accrued by the cohort depending upon the length of time spent in each VA health state.

Figure 7: Model structure



Comparators

Data for ranibizumab

The cost-effectiveness model is based primarily on data from the BRAVO and CRUISE studies, which allows a direct comparison of ranibizumab and the current standard of care. This approach also allows the patient-level data to be analysed in the form required to model 1st year treatment outcomes.

In the BRAVO study, rescue laser photocoagulation was permitted once during the treatment period and once during the observation period, beginning at months 3 and 9 respectively, if haemorrhages had cleared sufficiently and specific criteria

suggesting poor response were met (Table 22). Rescue laser was based allowed based on the precedent of BVOS.

Table 22: Patients receiving rescue laser in BRAVO

BRAVO (n=397)	**Sham injection/0.5 mg (n = 132)**	**Ranibizumab 0.3 mg (n = 134)**	**Ranibizumab 0.5 mg (n = 131)**
Rescue laser treatment, n (%)			
Treatment period	72 (54.5)	25 (18.7)	26 (19.8)
Observation period	32 (24.2)	42 (31.3)	31 (23.7)
Rescue laser: Starting from month 3 or 9, patients were eligible for laser treatment if haemorrhages had cleared sufficiently to allow safe application of laser and the following criteria were met: Snellen equivalent BCVA ≤ 20/40 or mean central subfield thickness ≥ 250 µm, and compared with the visit 3 months before the current visit, patient had a gain of < 5 letters in BCVA or a decrease of < 50 µm in mean central subfield thickness. If rescue laser was not given at month 3, the same criteria were applied at month 4, and if rescue laser was not given at month 4, the same criteria were applied at month 5. This same process applied to rescue laser photocoagulation during the observation period for months 9, 10 and 11.			

We are interested in your opinion about whether and how the BRAVO control arm reflects the standard approach to laser treatment.

Data for dexamethasone intravitreal implant

A systematic review of the published literature, including what the manufacturer presented to NICE for their appraisal of dexamethasone, suggests that the patients included in the GENEVA studies are different to the ranibizumab-treated patients in BRAVO and CRUISE. We are concerned that an indirect comparison of ranibizumab and dexamethasone would not compare 'like with like' and the results would be unreliable.

Although the study designs are similar, in that they are all randomised, double-blind, sham-controlled trials, there are a number of significant differences between the patient inclusion criteria for the BRAVO and GENEVA trials:

- BRAVO and CRUISE allowed a longer period of MO prior to entry into the study than the GENEVA studies
- Both the baseline range of BCVA acceptable for inclusion and the eligible value for retinal thickness were different in the BRAVO/CRUISE and GENEVA studies.
- BRAVO and CRUISE excluded patients who had received photocoagulation within the previous 3 months.
- Patients intolerant of steroids were excluded from the GENEVA trial, but not from the BRAVO or CRUISE trials. This is estimated to comprise approximately 5-10% of the general population, but their ocular characteristics with regards to RVO are unknown.

In terms of the characteristics of the patient populations enrolled, again there is substantial variation between the ranibizumab and the dexamethasone IVT implant studies:

- The duration of MO was longer in GENEVA where the majority had <90 days, compared to BRAVO and CRUISE where the mean duration at baseline was 3.5 months.
- The patient demographic data for the BRVO subgroups are not reported separately to the CRVO subgroup for either of the twin studies nor for the pooled GENEVA study.
- The mean central foveal thickness was lower in GENEVA (550 µm) than in BRAVO and CRUISE (approximately 680 µm).

We would like your opinion of the comparability of the results observed in the GENEVA studies, versus the BRAVO and CRUISE studies.

Data for unlicensed bevacizumab

A systematic review of the published literature has identified 3 RCTs comparing bevacizumab to in RVO (Table 23).

Table 23: RCTs investigating bevacizumab

Study	Design	Intervention	Comparator	Population (N)	Duration
Habibabadi 2008	Randomised double blind trial	Bevacizumab 1.25 mg at week 0, 6 and 12	Sham Bevacizumab 1.25 mg +	Patients with visual impairment due to MO secondary to	18 weeks (interim results presented)

			IVTA 2 mg	ischaemic or non-ischaemic CRVO of less than 6 months duration (101)	
Moradian 2007	Randomised placebo controlled double masked trial	Bevacizumab 1.25 mg at 0 and 6 weeks	Sham	Patients with acute BRVO and visual impairment (81)	3 months
Russo 2009	Quasi-randomised, unmasked trial	Bevacizumab 1.25 mg prn if MO unresolved (1, 3, 6 and 12 months)	Laser	Patients with MO due to non-ischaemic BRVO of at least 3 months duration (30)	12 months

We are interested in your opinion of the evidence base for the safety and efficacy of bevacizumab in RVO, and whether there may be adequate data to make a comparison to other treatments.

Key assumptions

Treatment and follow-up of patients after initial treatment

BRVO

- The mean number of ranibizumab injections in Year 1 of the model is **8**. This is based on the average number that patients received in the BRAVO trial (Table 24).
- The mean number of ranibizumab injections in year 2 is **2.5**, based on the HORIZON study.
- Patients are assumed to be monitored monthly in year 1, with a reducing number of monitoring visits over time.
- After 3 years of ranibizumab or laser treatment, patients are assumed to no longer be treated or followed up by an ophthalmologist.

CRVO

- The mean number of ranibizumab injections in Year 1 of the model is **9**. This is based on the average number that patients received in the CRUISE trial (Table 25).

- The mean number of ranibizumab injections in year 2 is **3.8**, based on the HORIZON study.
- Patients are assumed to be monitored monthly in year 1, with a reducing number of monitoring visits over time.
- After 3 years of ranibizumab or laser treatment, patients are assumed to no longer be treated or followed up by an ophthalmologist.
-

We would like your opinion about whether these assumptions are credible, and if a greater or lesser amount of treatment and follow up would be needed.

Table 24: Number of ranibizumab injections (BRAVO)

BRAVO (n=397)	**Sham injection/0.5 mg (n = 132)**	**Ranibizumab 0.3 mg (n = 134)**	**Ranibizumab 0.5 mg (n = 131)**
Received PRN treatment during observation period (month 6 to 12), n (%)	115 (87.1)	106 (79.1)	100 (76.3)
Received ranibizumab injection at month 6, n (%)	104 (78.8)	55 (41.0)	50 (38.2)
Mean number of injections per patient Treatment period Observation period	 5.6 3.6	 5.7 2.8	 5.7 2.7

Table 25: Number of ranibizumab injections (CRUISE)

CRUISE (n = 392)	**Sham injection/0.5 mg (n=130)**	**Ranibizumab 0.3 mg (n=132)**	**Ranibizumab 0.5 mg (n=130)**
Received PRN treatment during observation period (month 6 to 12), n (%)	110 (84.6)	120 (90.9)	111 (85.4)
Received ranibizumab	100 (76.9)	74 (56.1)	64 (49.2)

CRUISE (n = 392)	Sham injection/0.5 mg (n=130)	Ranibizumab 0.3 mg (n=132)	Ranibizumab 0.5 mg (n=130)
injection at month 6, n (%)			
Mean number of injections per patient Treatment period Observation period	5.5 3.7	5.8 3.8	5.6 3.3

Long-term progression of visual acuity

No data is available for the long term outcomes (over 15 years) of patients that have been treated with ranibizumab, and therefore assumptions must be made.

We would like to know what assumptions would be acceptable to you regarding the duration of ranibizumab treatment beyond 3 years, and the progression of visual acuity after treatment has ceased.

Sources of utility data

Utilities are values that reflect an individual's preferences for different health outcomes. In a cost effectiveness analysis, utilities are combined with survival estimates and aggregated across individuals to generate quality-adjusted life years (QALYs).

In BRAVO and CRUISE, patients' health related quality of life was measured using the VFQ-25 but utility values were not directly measured. No published utilities for patients with VI due to RVO (with or without MO) have been identified. In the cost effectiveness analysis, we will therefore have to apply utilities derived from patients with visual impairment due to other diseases.

We would like your views about the impact of visual impairment caused by different diseases on health related quality of life.

Subgroups and treatment rules

NICE is interested in subgroups of patients in whom ranibizumab may have a greater or less effectiveness, and therefore in whom treatment may be more of less cost effective. Similarly, there may be patients for whom starting or continuing treatment is unnecessary; for example because their vision is not severely impaired and/or there is likelihood of spontaneous resolution. Novartis is analysing the efficacy data in the cost effectiveness model to identify potential subgroups of patients:

- by BCVA at baseline
- time since diagnosis
- central retinal thickness at baseline.

We would like your clinical opinion about types of patients that do not respond well to the current standard of care, those in whom you may expect ranibizumab treatment to be most effective and treatment starting/stopping rules that you would find acceptable.

Table 26 Clinical Expert 1

Topic	Key points
BRAVO control arm	Use of terminology ('rescue') misleading as approach closely reflects how laser would be administered in current clinical practice. It would be interesting to see data on the subgroup of ranibizumab-treated patients that also received laser. That is, was there improvement in their vision / reduction in their thickness in the 3 months after laser treatment compared to the 3 months before laser treatment? It is possible that those patients that meet the criteria for laser may not have been responders to laser either. The BVOS study is an older study, where OCT was not used as standard practice (whereas now OCT is standard practice in trials and in clinical care for patients with RVO and MO). There are other difference in that study and current clinical practice, which limit its comparability to the BRAVO study.
Comparison to dexamethasone	The study populations in GENEVA and BRAVO/CRUISE are different. In particular the differing mean durations of MO is a big confounder. Baseline CRT was also different between the populations – these issues all raise doubt as to whether the studies can be compared. For example, increased CRT may be a surrogate marker of outcome. The proportion of patients treated with prior (macular) laser is important – there is potential that a more resistant population has been included if they are pre-treated.

	High IOP is a risk factor for RVO, thus excluding these patients (and steroid responders) in GENEVA implies a different population. Unclear in what way this difference may affect safety/efficacy though. Important to remember that IOP lowering medications, even if medication is stopped, requires longer term monitoring. Additional follow-up to stop IOP lowering meds would be required after stopping Ozurdex. This would require a trial off pressure-lowering eye drops then a review at three months and 1 year before discharge (thus two extra appointments).
Comparison to bevacizumab	There are differences across the RCTs identified – it seems that pooling of the results would not be possible. Study design is an important factor in being able to draw meaningful conclusions. The size of the study is also important – studies with 100 or more patients would be more credible. Larger retrospective studies, such as PACORES, also have limitations due to inherent bias of retrospective analysis. The number of drop outs in the study will also be important with regards to potential for bias. This study is the first port of call for data for 'real life' outcomes of bevacizumab, but it is unclear how one would draw comparisons to other interventions.
Treatment and follow-up of patients after initial treatment	The HORIZON 12 month extension is important to emphasise as it demonstrates for reduced treatment and monitoring after first year of treatment. Given lower number of injections in year 2, mean of 1 injection in year 3 (BRVO) is a realistic estimate. In CRVO a more intensive follow-up and more injections is likely, as borne out by HORIZON. Currently, a minimum follow-up of 2 years is needed for CRVO patients – this might increase to 3 years treatment with ranibizumab injections. BRVO in year 2: 6-8 follow-up visits would be adequate given the reduced number of injections CRVO in year 2: 10 follow up visits BRVO in Year 3: 2 follow up visits CRVO in year 3: 3 follow up visits The same duration of treatment and follow-up would be expected across all interventions. The duration of macular oedema is related to the nature of the disease, not the type of treatment.
Long-term progression of visual acuity	Reasonable to assume that after 3 years treatment gains in vision are maintained in BRVO, but in CRVO there may be more drift in vision, reversion back and more worsening over time.
Subgroups and treatment rules	Patients with diabetes may have more widespread retinal disease, and systemic factors may generate a poorer response to treatment. Could consider whether diabetic patients are a poorer-responding sub-group It would be acceptable to wait and treat after 3 months, in patients who present with mild visual impairment. However, it is expected that ranibizumab would be used first line. Could consider two different starting rules - 1) start early if poor baseline visual acuity e.g. =< 6/36 and 2) delay for 3 or 6 months if VA >6/36. It may be that patients with ischaemia ought to cease treatment, but effect of ranibizumab is not yet known in ischaemic patients.

Table 27 Clinical Expert 2

Topic	Key points
BRAVO control arm	In BRAVO, 20% lasered in first six months – of those, about half were re-lasered (36% total, 19.8% in first year, 23.7% in second 6 months). This is consistent with clinical practice. Also consistent with BVOS, where majority of patients received laser in the first year. Most patients received 1 or 2 laser treatments, with very few in the second year. It would be important to understand how well the laser-treated ranibizumab patients did compared to those not lasered (i.e. was there an incremental effect of laser)? It would also be interesting to know when laser was applied. The need for rescue laser could be applied as a treatment stopping rule - i.e. no further ranibizumab treatment for those patients that meet criteria for laser rescue.
Comparison to dexamethasone	The primary endpoints of the GENEVA and BRAVO/CRUISE studies were different. It is not clear how important is the difference in CMT at baseline between the study populations. More important is the duration of MO at baseline.
Comparison to bevacizumab	The RCT data is limited by short treatment duration and small numbers of patients. A more credible evidence base would include studies of more than 12 months duration and more than 100 patients. The PACORES study is an important source of evidence for bevacizumab treatment in clinical practice. However, the re-treatment criteria are based on CRT only, with no basis on VA; this limits the applicability to UK clinical practice where retreatment would be based primarily on stability in VA.
Treatment and follow-up of patients after initial treatment	Natural history in year 3 in BVOS study: very few laser treatments were administered in year 2. This is consistent with current approach and expectation for future practice. Thus after 2 years of treatment, expect the macular to be dry with or without improvement of vision. That is, vision would be stable even if not improved, and continued treatment is not warranted. On this basis, expectation is that no further ranibizumab injections would be necessary in year 3 for BRVO patients. CVOS study should be explored to identify evidence of natural history of CRVO. However, clinical experience suggests that similarly to BRVO the macular would be dry by year 3 and further vision gains would be unlikely to be achieved through continued treatment. In CRVO, there is potential for continued treatment into year 3 but the expectation, based on evidence currently available, is that the mean number would be low – perhaps as low as 1 further injection in year 3. It is important to consider the development of neovascular glaucoma in CRVO patients. This is a costly and painful complication, particularly in ischaemic patients. In year 2 of treatment, monthly follow-up visits are unlikely to be required given low number of injections and slower progression of VA (compared to other retinal diseases). Would suggest 3-monthly follow-up for BRVO in year 2 and 6-monthly in year 3. Frequency of monitoring in BRVO might be reduced as early as the second six months following treatment initiation. For CRVO, 2-monthly in year 2 and 4 to 6 monthly in year 3. Would be comfortable to discharge BRVO patients if stable (no injections required) after 6 months.

Long-term progression of visual acuity	There might be expected to be a 'floor effect' of VA progression in the untreated arm, particularly for CRVO, because they have worse BCVA there is less potential to lose vision over the longer term. A bigger drop in VA over the longer term might be expected in the patients with better BCVA. A difference in this reduction in VA over time would not be specific to the treatment received, but to the VA level.
Subgroups and treatment rules	In clinical practice, there may be 3 treatment scenarios for BRVO following introduction of ranibizumab: - Commence ranibizumab monotherapy for patients with moderate to severe VI: vision improves - Commence ranibizumab monotherapy, but cease if rescue laser criteria applied to BRAVO are met - Commence laser for patients with mild VI: for those that do not respond well to laser at 6 months, initiate ranibizumab monotherapy (as sham/ranibizumab arm of BRAVO) A treatment rule based on letter change is more acceptable than one based on CRT (although both are important which means if visual acuity continues to improve then continue retreat until vision does not improve anymore, regardless of OCT. When visual acuity is not improving or worsening on consecutive visits then look for response on OCT to guide decision on continuation. If OCT also shows no further resolution or complete resolution in oedema then stop.) For BRVO, the subgroup of patients with macular haemorrhage may be important to identify. Similarly, with respect to potential budget impact, the proportion of ischaemic patients is important to identify.

Table 28 Clinical Expert 3

Topic	Key points
BRAVO control arm	The criteria (CRT and BCVA) and timing of the rescue laser in BRAVO reflect clinical practice. In clinical practice, should anti-VEGFs become more widely available then these would be preferred as monotherapy to laser. One would not expect a ranibizumab + laser combination regimen to be standard clinical practice.
Comparison to dexamethasone	Differences between the dexamethasone and ranibizumab trials are important. CRT and duration of MO inclusion criteria allowed for more chronic patients to be included in the GENEVA studies. Duration of MO is a determinant for outcome. Also important to remember that the control arm of the studies were not the same for BRVO patients, with respect to laser being permitted and widely given in BRAVO. There were also differences in terms of glaucoma in study eye – these patients were excluded from GENEVA whereas patients with controlled glaucoma were permitted in BRAVO/CRUISE.
Comparison to bevacizumab	In particular, the bevacizumab studies are not sufficiently large to answer the safety question. Ideally safety registries would be in place to assess bevacizumab, whereby all patients treated were registered and followed. However, reliance of self-reporting means this may not be sufficiently comprehensive or robust. Particularly when patients with ATEs would not necessarily be known to the ophthalmology clinic, as they would be seen elsewhere and not return for continued injections. Expected to be a higher risk of stroke amongst RVO patients than those with wet AMD. This is based on clinical expectation, given the common risk factors

	(eg, hypertension) in the RVO population. The bevacizumab RCTs are too small and too short in duration to reliably base a decision with regards to efficacy.
Treatment and follow-up of patients after initial treatment	BRVO patients are discharged at 2 years currently – difficult to know if/how this might change with introduction of ranibizumab. Would anticipate 2 years treatment, seeing once more during third year to ensure stability for 6 months then discharge from ophthalmology clinic. In year 2, would expect to see patients 2- or 3-monthly. RVO is less acute than wet AMD, it is acceptable to see patients less frequently as damage from MO is less rapid (in RVO photoreceptors appear to be able to tolerate MO for some time, unlike DMO and wet AMD). Would expect to treat CRVO patients for a longer period than those with BRVO. Would see 1- or 2-monthly in year 2, and 3-monthly in year 3. Difficult to know as currently CRVO patients are often discharged even when MO is present, as there are no treatment options.
Long-term progression of visual acuity	The natural history of RVO-MO is that the macular will dry up over time (2-3 years) with or without treatment. Treatment success determines whether MO is resolved with or without permanent damage to vision. RVO is an acute retinal vascular condition – analogous to a stroke in the eye – one assumes that it resolves and stabilises, rather than continuing as a chronic condition. After 2-3 years, expect that vision is stable (improved or not) but would deteriorate over time (with age).
Subgroups and treatment rules	For BRVO, an acceptable treatment rule would be to wait for 3 months to assess for spontaneous improvement, treat for 3 months (3 injections) and then cease treatment if no improvement. For CRVO, waiting to treat is less acceptable as vision loss is generally more profound. Trial data for both ranibizumab and dexamethasone suggests better outcomes if treatment is initiated early. Thus, waiting to treat patients with BRVO (as is currently the approach with laser) may change in the future. Starting/stopping rules based on BCVA are more acceptable than those based on CRT. For example, patients below 6/10 (legal driving limit) would be more likely to be treated earlier without waiting for spontaneous improvement. BRVO patients with macular haemorrhage have high unmet need as these cannot be treated with laser. A definition of macular haemorrhage would be based on the inability to provide laser treatment; for example those in whom it would not be possible to give more than 20 laser burns. The total area of macular haemorrhage would also be a way in which to define this subgroup.

10.10 Appendix 22: Analysis of Poor Responders

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