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Evidence review: Dexamethasone implants (Ozurdex) for macular oedema after retinal vein occlusion

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Sections highlighted in yellow are 'academic in confidence'.

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TABLE OF CONTENTS

List of Tables and Figures

Tables

Figures

Abbreviations

AE: adverse events

AMD: Age-related macular degeneration

BCVA: Best corrected visual acuity

BRVO: Branch retinal vein occlusion

BRVO-PL: BRVO not responding to prior laser surgery

BSE: Better-seeing eye

BVOSG: Branch vein occlusion study group

CMT: Central macular thickening

CRVO: Central retinal vein occlusion

CVOS: Central vein occlusion study

DEX: Dexamethasone

ETDRS: Early Treatment Diabetic Retinopathy Study

FA: Fluorescein angiography

FDA: Food and Drug Administration

FEI: Fellow eye involvement

GENEVA: Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA

HRQoL: Health related quality of life

HS: Health states

ICER: Incremental cost-effectiveness ratio

IOP: Intraocular pressure

MH: Macular haemorrhage

MO: Macular oedema

MRU: Medical resource utilisation

NEI-VFQ-25: National Eye Institute visual functioning questionnaire 25

NICE: National Institute for Health and Clinical Excellence

NS: Not significant

NVG: Neovascular glaucoma

OCT: Optical coherence tomography

QALY: Quality adjusted life years

RCO: Royal College of Ophthalmologists

RCT: Randomised controlled trial

RVO: Retinal vein occlusion

SCORE: The Standard Care vs. COrticosteroid for REtinal Vein Occlusion

TPM: Transition probability matrices

VA: Visual acuity

VEGF: Vascular endothelial growth factor

VFQ-UI: Visual function questionnaire utility index

VL: Visual loss

WSE: Worse-seeing eye

1. SUMMARY

Introduction

Retinal vein thrombosis can affect the main vein from the retina, the central vein (central retinal vein occlusion or CRVO) or one of its branches (branch retinal vein occlusion or BRVO). CRVO is more serious. In both cases, the back pressure causes fluid to leak out of blood vessels and this leads to fluid accumulating in the retina (oedema) with the most serious effects being due to oedema of the macula, which can lead to a reduction in visual acuity and can cause blindness. BRVO is about twice as common as CRVO.

Visual acuity is measured by reading letters of diminishing size on a standard chart.

There is currently no licensed treatment for CRVO, and the natural history outlook is poor. The natural history of BRVO shows that spontaneous recovery does occur in a significant proportion. However laser photocoagulation therapy is a tried and tested, and cost-effective way of improving outcomes, and is the standard approach.

1.1 Scope of the submission

In a logical sequence, the manufacturer gave details of the nature of the problem and its consequences, presented data from the only clinical trial, and then linked the changes in visual acuity to changes in quality of life, for feeding into the economic model. The manufacturer noted the good results in BRVO with laser therapy, and therefore assumed that dexamethasone would be used only in those in whom laser therapy was inappropriate (due to haemorrhage) or in those in whom it had failed.

1.2 Summary of submitted clinical effectiveness evidence

The industry submission provided details from the large GENEVA trial. The most important data from that trial have been published. The data showed that compared to observation alone, dexamethasone improved outcomes. The primary outcome from the trials, visual acuity based on the mean letter count, did not show a large improvement. The more useful outcomes were the proportion of patients in whom treatment led to a clinically significant improvement in visual acuity (VA), such as a gain of 15 in the number of letters that could be read.

Only around 30% of patients had such good improvements in VA. After dexamethasone, the peak improvement was seen at around 60 days, after which visual acuity declined again. The trial

protocol did not allow for early re-treatment. A non-randomised extension in which all patients could get dexamethasone provided follow-up to 360 days.
In CRVO, at day 60, 29% of patients had an improvement of 15 or more letters in the dexamethasone arm compared to 9% in the observation-only arm. By day 180, 18% had 15 or more letters of improvement in the dexamethasone arm compared to 12% in the control arm (showing that even in CRVO, there can be some spontaneous improvement).

In BRVO, 30% of patients had had gains of 15 or more letters at day 60 on dexamethasone compared to 13% on observations alone. The corresponding figures at day 180 were 23% and 20%.

Hence the effect of dexamethasone peaks around day 60.

The trial and the open-label follow-on only gave two injections of dexamethasone. The number of treatments required in longer-term follow-up is not known. The industry submission based the number on clinical opinion from a few (anonymous) experts.

The adverse effects include raised intra-ocular pressure which can lead to glaucoma, and cataract. Both may require treatment including surgery.

The size of needle required for implantation is quite large compared to the fine needles used for injection of anti-VEGF drugs into the eye, and this could lead to complications if repeated implantations are required.

1.3 Summary of submitted cost effectiveness evidence

The manufacturer developed a cost utility markov model based upon the pooled data from the GENEVA 008 and 009 trials. This compared 700µg dexamethasone with observation among three subgroups of patients at baseline: those with CRVO, those with BRVO and macular haemorrhage, and those with BRVO not responding to prior laser surgery. Due to the definition of these patient subgroups, the manufacturer argued that consideration of laser photocoagulation was not required.

The six health states of the model were defined by ranges of best corrected visual acuity (BCVA) in the affected eye. At baseline the affected eye could be either the worse seeing eye or the better seeing eye. The proportion of patients with their worse seeing eye affected at baseline was drawn from expert opinion, rather than from trial data. Where the worse seeing eye was affected at baseline, fellow eye involvement could lead to the better seeing eye becoming affected over time.

Patient HRQoL was estimated as a function of BCVA, with this being differentiated by whether it was the worse seeing eye or the better seeing eye that was affected. Improvements in the BCVA of the worse seeing eye had only a muted impact upon HRQoL, while the impact of improvements in the BCVA of the better seeing eye upon HRQoL were somewhat larger.

Due to HRQoL being dependent upon which eye was affected, and also due to the impacts of severe visual impairment, the model was sensitive to the proportion of patients having their better seeing eye affected, either at baseline or through fellow eye involvement over time.

Unfortunately, the originally submitted manufacturer model contained serious errors around the modelling of fellow eye involvement. These were partially corrected in a revised manufacturer model submitted on the 23rd November 2010 , but perverse results still applied within this revised model.

The base case unit cost per administration of dexamethasone may have been too high. The manufacturer assumed each administration would require one day case at a unit cost of £648. It seems likely that dexamethasone administrations will take place within an outpatient setting, at a unit cost of £150. Given the direct drug cost of £870, the total cost per administration as a day case was £1,518 as compared to £1,020 as an outpatient.

Base case probabilistic modelling using the originally submitted model resulted in central cost effectiveness estimates of £6,188 per QALY for CRVO patients and £7,495 per QALY for BRVO patients with macular haemorrhage. For patients with BRVO previously unresponsive to laser photocoagulation dexamethasone was estimated to dominate observation.

Base case deterministic modelling using the revised model submitted on the 23rd November 2010 resulted in similar cost effectiveness estimates: £6,041 per QALY for CRVO patients, £7,987 per QALY for BRVO patients with macular haemorrhage, and dominance for dexamethasone over observations for patients with BRVO previously unresponsive to laser photocoagulation.

The input parameters to which results were sensitive included: the direct drug and administration cost; the proportion with their better seeing eye affected at baseline; rates of fellow eye involvement; rates of fellow eye involvement RVO conversion to macular oedema; and, the costs of severe visual impairment.

The reliability of the manufacturer estimates of cost effectiveness is severely impaired by the errors around the modelling of fellow eye involvement. Fellow eye involvement had a major impact upon results as it caused more patients to have their better seeing eye affected, with the resulting impacts upon the HRQoL calculation and the likelihood of developing severe visual impairment with its associated costs and mortality. The revised model submitted on the 23rd November 2010, while correcting for one error within the handling of fellow eye involvement, still had errors around this aspect and behaved perversely as a result.

Uncertainties during the period of extrapolation apply to: the number of dexamethasone administrations; the likelihood of resolution; the likelihood of cataract development and extraction; the likelihood of fellow eye involvement and it turning into macular oedema; and, the reasonableness of applying six month data for the extrapolation of dexamethasone, but three month data for the extrapolation of observation.

Based on conversations with clinical experts, the ERG believes that dexamethasone implantations could be given on an outpatient basis, and that the day case cost used in the industry submission is therefore too high, thereby reducing the cost-effectiveness of dexamethasone treatment.

1.4 Commentary on the robustness of submitted evidence

The main weaknesses in the evidence were;

- Lack of long-term follow-up data, particularly on the optimum number of injections. In the absence of data, the number of re-treatments had to be based on clinical opinion.
- In the trial, re-treatment was not given until 180 days. It would be useful to know if earlier treatment, as soon as visual acuity started to fall again, would be more effective
- The cost-effectiveness of re-treating only those with a good response to the first injection should be examined
- Lack of comparisons with other therapeutic options, and in particular the anti-VEGF drugs, ranibizumab and bevacizumab. Admittedly, there are no head to head trials, but an indirect comparison could have been attempted.

1.5 Key issues

The most important outcome is the proportion of people in which dexamethasone improves vision by a clinically significant amount, such as the roughly 18% of people with CRVO who gain 15 or more letters compared to the 12% in the sham arm over 180 days. Around 27% gain 10 or more letters after 180 days, compared to the 24% in the sham arm. In CRVO, the outlook without treatment is poor.

In BRVO, the natural history outlook is better with a greater proportion in which there is natural recovery, so that the difference is smaller, with dexamethasone increasing the proportion gaining 15 or more letters by about 23%, compared to natural recovery i.e. 20% in the sham arm. The numbers gaining 10 letters or more after 180 days are 41% with dexamethasone, compared to 33% in the sham arm. This applies to those in whom laser treatment is contra-indicated, or has not given an adequate response. In other people with BRVO, laser treatment would be first line treatment.

One key issue is that quality of life is determined mainly by vision in the better seeing eye (and indeed people may sometimes be unaware of visual loss in the worse seeing eye). A short-term strictly cost-effectiveness perspective might suggest that treatment of the worse-seeing eye may not always be cost-effective. The ERG would regard this as a controversial issue, given the possibility of recurrence of RVO in the other eye.

There is still a need for more effective treatments for macular oedema after RVO.

2. BACKGROUND

The macula is an oval area near the centre of the retina. It measures approximately 5.5 mm in diameter. Its central portion is called the fovea, and this is responsible for central, high acuity vision.

Macular oedema occurs when fluid collects on or under the macula, causing it to swell up. This is referred to as macular thickening. Some trials measure central macular thickening (CMT) using optical coherence tomography (OCT), an imaging system that can produce sectional images through the macula, though in the short term the correlation with visual acuity is relatively weak.

Loss of central vision is often noted more readily than loss of peripheral vision because central vision is what we use when we focus on objects, in contrast to peripheral vision (what you see "out of the corner of your eye"). However many people do not notice central loss of vision in one eye, and this can be a reason for late presentation.

Visual acuity is traditionally measured by standing a fixed distance (6 metres or 20 feet) from a well-lit wall-chart which has lines of letters, with each line being smaller than the one above. Vision is expressed related to normal vision. So someone with normal vision can be described as having 6/6 vision, or (more in the USA) as having 20/20 vision. Someone with poorer vision might be 6/9, i.e. be able to read at 6 metres what someone with normal vision could read at 9 metres.

Two main visual acuity charts are used, ETDRS and Snellen. Both start with large letters at the top, diminishing in size as you go down the chart. The trials use ETDRS. This is because in the Snellen chart, the steps between lines do not reflect the same differences throughout the whole chart. This, a change from 6/36 to 6/60 is much greater than the step from 6/6 to 6/9.

Visual acuity is abbreviated to VA. If VA is measured while patients are wearing their spectacles, it is referred to as best corrected VA or BCVA.

VA may be expressed in terms of the number of letters which can be read when using the ETDRS charts, or using a fraction when using Snellen charts. For instance, 34 letters as measured in ETDRS charts are equivalent to 20/200 and 68 to 20/50.

Retinal vein thrombosis can affect the main vein of the retina, the central vein (central retinal vein occlusion or CRVO) or one of its branches (branch retinal vein occlusions or BRVO). CRVO is more serious as it usually leads to poorer vision, more severe complications, and does not usually improve spontaneously. In both CRVO and BRVO, blood accumulates in the blood vessels as a result of the blockage, with the subsequent increased back pressure causing fluid (oedema) and blood

(haemorrhages) to leak out of blood vessels into the retina. The accumulation of fluid at the macula (macular oedema) leads to a reduction in visual acuity.

The leakage of fluid is accompanied by an increase in vascular endothelial growth factor (VEGF) which increases the permeability of the blood vessels (increasing the diffusion of fluid through the wall of the blood vessel) and worsens the situation.

The Central Vein Obstruction Study (CVOS) Group reported (1997)[1] that VA at presentation is a strong predictor of outcome.

The population based Beaver Dam Eye Study measured visual loss in 4068 persons living in Beaver Dam, Wisconsin, aged 43 to 86 years of age. On the basis of vision in the better eye, 8.3% of the population at risk developed impaired vision (20/40 or worse) and 0.8% developed severe visual impairment (20/200 or worse) over a 15-year period, with 12% of impaired vision being due to BRVO and CRVO.[2] The RCO guidelines[3] reported that about 50% of untreated eyes with BRVO retain VA of 6/12 or better while 25% will develop impaired vision (VA <6/60).

Retinal vein obstruction is the second most common cause of vascular visual loss, surpassed only by diabetic retinopathy.

The natural history of CRVO

CRVO is divided into two groups: ischaemic and non-ischaemic (or perfused). The natural history of these two forms is different, with ischaemic being associated with a poorer prognosis.[4] About 20% of initial presentations are ischaemic, but about 30% of non-ischaemic cases may convert to ischaemic over three years.[4] In another study (CVOS group 1997),[1] about 34% of initially perfused eyes converted to ischaemic over three years. The term ischaemic means that blood flow into the retina is reduced. Classification into ischaemic and non-ischaemic is based on fluorescein angiography, a process wherein a dye is injected into the blood stream through a vein, and then its progress through the retinal blood vessels if photographed. In normal eyes, the dye is seen passing through arteries, capillaries and veins in turn. Fluorescein angiography can show filling defects due to blocked vessels, areas of ischaemia, and leakage from damaged blood vessels. CRVO is defined as ischaemic when areas equivalent to at least 10 times the area of the optical disk have no capillary perfusion.

The natural history of CRVO has been the subject of a recent good quality systematic review by McIntosh and colleagues. It was funded by Allergan, the manufacturer of Ozurdex, and two of the authors are employees of Allergan. The lead authors are from the Centre for Eye Research in

Melbourne. They carried out thorough searches, and then applied quality criteria to the retrieved studies, and excluded those which did not reach six or more of nine criteria.

McIntosh and colleagues[4] noted that the outlook after CRVO was poor. In most studies, visual acuity declined. In the minority of studies in which VA was reported to improve, it did not reach better than 20/40. Ischaemic CRVO did worse, with a loss of 35 letters by one year, compared to a loss of only 3 in non-ischaemic. Ischaemic CRVO was followed by the development of abnormal new vessels (neovascularisation) in about a quarter of cases over an 8 to 9 month period. Neovascularisation is rare in non-ischaemic CRVO. In ischaemic CRVO, about 23% developed neovascular glaucoma (NVG) within 15 months, whereas it was rare in nonischaemic CRVO.

Macular oedema often resolved spontaneously over time, but this did not lead to improved VA. When macular oedema disappears slowly over time, it can be associated with the development of macular atrophy, with deterioration in vision. Hence reduction in retinal thickness is not always a good sign.

After CRVO in one eye, 5% of patients developed an RVO in the other eye (known as fellow eye involvement or FEI) in the next year, of which most were BRVO.

In summary, the outlook after CRVO is poor without treatment. Laser treatment does not offer benefit to patients with macular oedema following CRVO, and there has until recently been no effective treatment for this complication.

The natural history of BRVO

Rogers and colleagues (the same group as McIntosh et al) have also produced a good quality systematic review of the natural history of BRVO[5] using similar methods. They included both observational natural history studies, and the untreated control arms from randomised controlled trials (RCTs), giving data on 1608 eyes.

They note that the outlook is much better after BRVO than after CRVO. Untreated, there was some improvement in VA, but most patients did not achieve VA better than 20/40. Of those with macular oedema at baseline, 18% to 41% resolved over the first year.

The authors report that after one BRVO, there is a 10% chance of the other eye being affected (known as “fellow eye involvement” or FEI), but note that this is based mainly on one small study with only 29 patients. They estimate from cross-sectional studies that the risk may be around 5%.

The standard treatment[3] for BRVO is laser photocoagulation. The main evidence base for this comes from the trial by the Branch Vein Occlusion Study Group.[6] Their trial in patients with BRVO and

macular oedema (MO) was carried out from 1977 to 1984, and was a good quality trial. The patients recruited had to have had BRVO at least 3 months before treatment, because spontaneous recovery was recognised. Inclusion criteria included VA of 20/40 or worse, MO on fluorescein angiography, and BRVO from between 3 and 18 months before entry. The trial report has good long-term follow-up, which amongst other things, showed that VA in the untreated control group was still improving at four years (figure 2 of paper).

However the lasered group did much better, as shown in Table 1.

Table 1. Visual acuity at 3 years in BVOSG trial.

	Controls (n=35)	**Lasered group (n=43)**	
% gaining 2 or more lines	37%	65%	P = 0.01
% losing 2 or more lines	17%	12%	NS
VA 20/40 or better	34%	60%	P = 0.02
Mean VA at year 3	20/70	20/40 – 20/50	P < 0.0001

The authors commented that there was "no basis for early treatment" in the first 3 months, but also that results were much better in those treated within the first year, compared to those treated later. Seventy percent of the first year group gained two or more lines compared to 32% of those treated between 12 and 18 months (p=0.002).

An independent cost-effectiveness analysis based on this trial by Brown et al concluded that laser therapy was highly cost-effective with a cost per QALY of $6118 (US dollars, year 2000).[7] Two of their base case assumptions might be challenged. The first is that they assumed that people with BRVO would have the same life expectancy as people without, whereas they probably have less. The second was that patients would retain VA at 3 years for life, whereas in fact further improvement occurred to at least year 4.

Brown and colleagues used utility values for different VAs from a previous patient survey using time trade-off analysis, as shown in Table 2.

Table 2. Utility values for visual acuity states

VA	**Utility**
20/20	0.92
20/45	0.785
20/70	0.74

In summary, the natural history of MO following BRVO is much better than that after CRVO, with a significant proportion having early spontaneous improvement, and laser therapy is effective and cost-

effective. The implication from the BVOSG trial[6] is that patients should be observed for 3 months before laser therapy.

The differences between CRVO and BRVO mean that they should be treated as distinct conditions.

2.1 Manufacturer's description of the underlying health problem

The manufacturer (Section 2.1) gives a concise summary of CRVO and BRVO and their consequences, noting that;

- RVO is the second commonest form of retinal vascular disorder after diabetic retinopathy.
- It is usually seen in middle age and later.
- Most people with untreated CRVO become legally blind in the affected eye.
- Sight loss reduces quality of life.
- There are probably around 14,000 new cases of BRVO and around 9,000 cases of CRVO each year in the UK.

Comments on the manufacturer's description;

- There is an emphasis on early treatment, with the BVOS group paper[6] being cited. However "early" is not defined, though other words used include "immediate" and "promptly". There is reference to the results being poorer if patients are treated more than 12 months after onset. Note that as mentioned above, the BVOS group recommended that patients with BRVO need not be treated in the first three months, but should be observed. The manufacturer's submission could be read as implying that treatment should be started without allowing a 3-month observation period. There is support for this from the laser arm of the SCORE study,[8] where the proportions gaining 15 or more letters were 38% in those treated before or at 3 months, and 15% in those treated after 3 months. Those treated within 3 months gained an average of 7.8 letters whereas those treated after 3 months lost on average 0.6 letters. The confidence intervals for these results just overlap (3.6 to 12.0 and – 5.1 to +3.8). However the grouping of patients meant that those with duration under 3 months were compared with cases with onset between 3 and 12 months, and even some with durations of over 12 months. It would have been more useful to compare those with durations under 3 months with those with durations 3-6 months. At present, there is insufficient data to justify early treatment in BRVO.
- In practice, this issue may not be relevant to one of the two subgroups for which dexamethasone is being recommended, those in whom laser has failed. The assumption is that all patients deemed suitable for laser therapy will receive it. It should be noted that only about 10% of patients in the GENEVA trial had previous laser treatment, and data are lacking on the definition of failure, in terms of how well they responded.

- The other subgroup of BRVO is those with macular haemorrhage, in whom laser treatment is deemed to be inappropriate. However, some of these patients could have laser applied around the edges of the haemorrhage, with more laser being applied as the haemorrhage resolves. The RCO 2004 guidelines, which recommended that laser treatment should not be given in BRVO complicated by haemorrhage, for 3-6 months and until the majority of the haemorrhage had been absorbed, are currently being updated. Meanwhile the 2009 interim guidelines[3] maintain the 2004 recommendation.
- The manufacturer also assumes that 100% of patients with MO after BRVO need to be treated. This may be an over-estimate given that some recover spontaneously, but unless there is a period of observation, it is not possibly to identify those.
- The submission correctly notes that quality of life depends on the better-seeing eye, but goes on to make what we consider to be a reasonable case for treating the poorer-seeing eye. It is worth noting that recurrence of RVO is not uncommon in the other eye.

2.2 Manufacturer's description of current service provision

The manufacturer argues (section 2.6) that for the subgroups considered in the submission (CRVO, BRVO with macular haemorrhage (MH), and BRVO with poor response to laser), the standard treatment should be observation, on the grounds that there are no other licensed pharmacological treatments. However Allergan notes that treatments currently used include triamcinolone, a steroid, and the anti-VEGF agent, bevacizumab. There is no mention in this section of the other anti-VEGF agent, ranibizumab.

No data are provided on the extent of use of those drugs.

2.3 Manufacturer's definition of the decision problem

The submission differs in three ways from the scope from NICE (July 2010).

Firstly, the scope states that the population in this appraisal is people with RVO. The industry submission considers a more restricted population, by including only those with BRVO who have MH, or who have not responded sufficiently to laser treatment (though details of response are not clear). Given that laser treatment in BRVO is effective and cost-effective, this seems a reasonable approach.

Secondly, the scope lists triamcinolone and bevacizumab as comparators. These treatments are unlicensed. NICE will only issue guidance on licensed products, but will consider unlicensed products as comparators. This seems illogical, because if an unlicensed comparator was thought to be better, NICE would not feel able to recommend that it be used.

Thirdly, the scope includes contrast sensitivity as an outcome, but the submission notes that this is not routinely used in the UK. This seems a reasonable argument.

3. EVIDENCE ON CLINICAL EFFECTIVENSS

The consultancy which produced the submission carried out searches in Medline, Embase and the Cochrane Library. This is sufficient. In practice, there is only one relevant trial of this dexamethasone implant, the Geneva trial, and this would have been known in advance. Searches by the ERG did not find any other RCTs of Ozurdex.

3.1 The GENEVA trials

At FDA request, two RCTs were carried out, but since they were identical, they are combined into one in the published paper.[9]

Full details are given in the industry submission, but in brief;

3.1.1 Quality

The trial appeared to be of high quality, according to the Cochrane risk of bias table. See Table 3.

Table 3. Risk of bias table for Haller 2010 study

Criteria	Description	Judgement
Adequate sequence generation	Randomised centrally using an interactive voice response system into a 1:1:1 allocation ratio and stratified by the underlying cause of RVO (BRVO or CRVO).	Yes
Allocation concealment	Centrally using an interactive voice response system; treatment investigator kept all study medication information confidential; patients were masked with regard to study treatment.	Yes
Masking	Patients masked to study treatment; follow-up investigators masked to study treatment that collected key efficacy variables and evaluated; central reading centre used to evaluate OCT scans were masked to study group.	Yes
Incomplete outcome data addressed	Primary and secondary efficacy was done on intent-to-treat population; safety analysis included patients who received study treatment after randomisation; adequate description of withdrawals, loss to follow up given.	Yes
Free of selective reporting	All the prespecified and predefined outcomes were reported.	Yes
Groups comparable at baseline	No difference between groups with regard to any demographic or baseline characteristics.	
Sample size calculation	For each of the 2 phase III trials, a sample size of 495 eyes (165 per group) was estimated to provide an 81% power for detecting an 11% difference between treatment groups in the proportion of eyes that achieved at least a 15-letter improvement in BCVA at day 180. Accounting for an estimated dropout rate of 10%, a total of 550 eyes was planned for each study.	Yes

3.1.2 Population

The trial was carried out in 167 centres in 24 countries, and recruited 1267 patients, an average of 7.6 per centre. Patients had reduced visual acuity (VA) due to clinically detectable macular oedema (MO) (details of what is meant by clinically detectable are not given in the published paper or the clinical trial report) due to central retinal vein occlusion (CRVO) or branch retinal vein occlusion (BRVO).

About 66% of patients had BRVO and 36% CRVO. Prior to the treatment, patients with CRVO had to have MO between 6 weeks and 9 months and 6 weeks to 12 months if BRVO. Baseline best corrected VA (BCVA) had to be between 34 and 68 letters (Snellen equivalent to 20/200 and 20/50 respectively). The mean VA at baseline was 54 letters. Ten percent had had previous laser treatment (as expected, nearly all of these had BRVO).

Patients with glaucoma and ocular hypertension needing more than one medication were excluded, as were those with lens opacities including cataract. (The CTR for Geneva 008 states: "Media opacity in the study eye at qualification/baseline that precluded clinical and photographic evaluation, including but not limited to pre-retinal or vitreous haemorrhage or lens opacity".)

The groups were well matched at baseline.

3.1.3 Intervention

There were three arms – 0.35mg and 0.7mg dexamethasone and a sham injection. In the sham arm, a needleless applicator was used to exert pressure on the conjunctiva, which would mimic an intravitreal injection. After the initial steroid implantation at day 0, no further steroid was given until day 180, when patients in both arms entered an open label study wherein they could have another, or a first, implant.

Additional treatments such as laser photocoagulation were prohibited but could be given if considered necessary by local clinicians. Details of how many received additional treatment were not given in the paper, but were obtained from the manufacturer as part of the clarification process. Only seven patients were treated, five with laser, one with triamcinolone, and two with bevacizumab. (One patient received both laser and bevacizumab). The low number is curious given that most patients did not have a good response. Why were more patients, particularly in the sham arm, not treated with laser? The GENEVA study entry criteria did not restrict BRVO entrants to the subgroups being considered in the industry submission, although over half had MH (515). Only 72 had had previous laser therapy, leaving 243 outwith both subgroups.

3.1.4 Outcomes

The principal outcome in the trial was the time from baseline injection to improvement in VA by 15 letters. BCVA was measured using ETDRS.

Secondary outcomes included more important ones;

- Proportions of eyes achieving 10 to 15 letter improvement
- Proportion worsening in VA
- Mean change from baseline
- Adverse effects such as intra-ocular pressure (IOP)

Subgroup analyses were CRVO and BRVO, and by duration of MO at baseline.

3.1.5 Results

Ninety-four percent of patients completed day 180 of the study. Prior to completion of day 360, [redacted]% in the Ozurdex/Ozurdex group and [redacted]% in the Sham/Ozurdex discontinued from the study.

It appears that the 0.35mg dose will not be used in practice, and so the results for that dose will not be considered further. They were very similar to the bigger dose.

Primary outcome. The paper reports that eyes treated with dexamethasone achieved a 15-letter improvement faster (and more often) than the sham control group. However this is reported for the total population, whereas we need it split by CRVO and BRVO. Those results are given in figures 8 and 9, and tables in tables 20 and 21 of the industry submission, reproduced below (Figure 1 and Figure 2; Table 4 and Table 5).

Figure 1: Time to an improvement in BCVA of ≥ 15 letters from baseline in patients with BRVO (Pooled - 180 days)

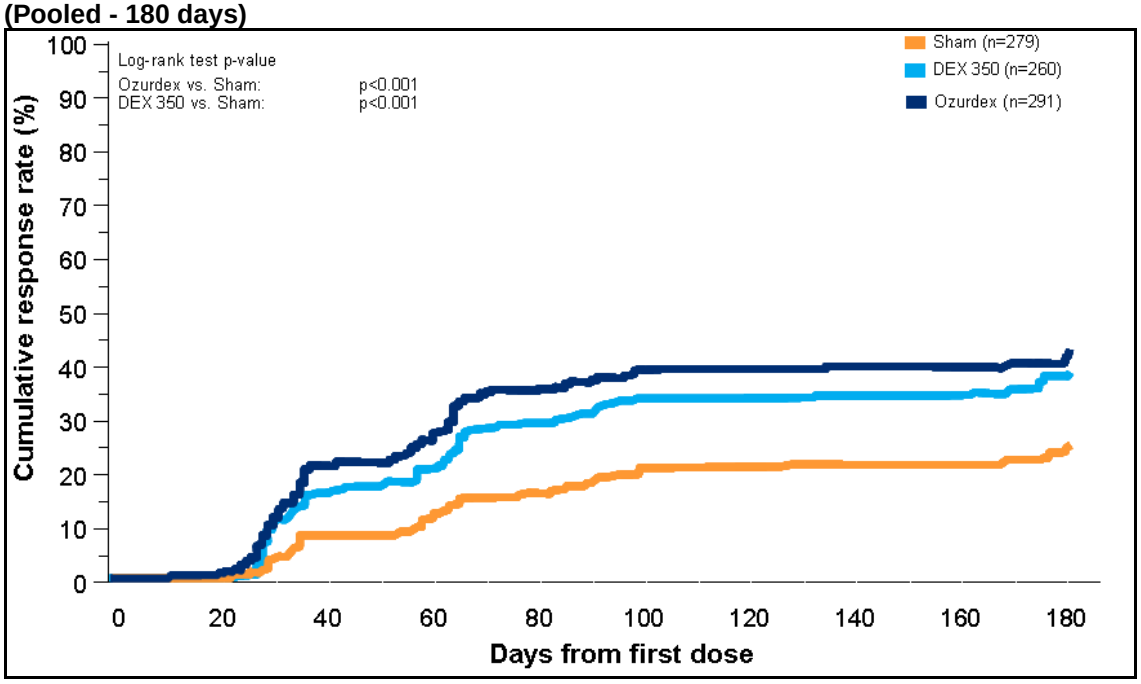
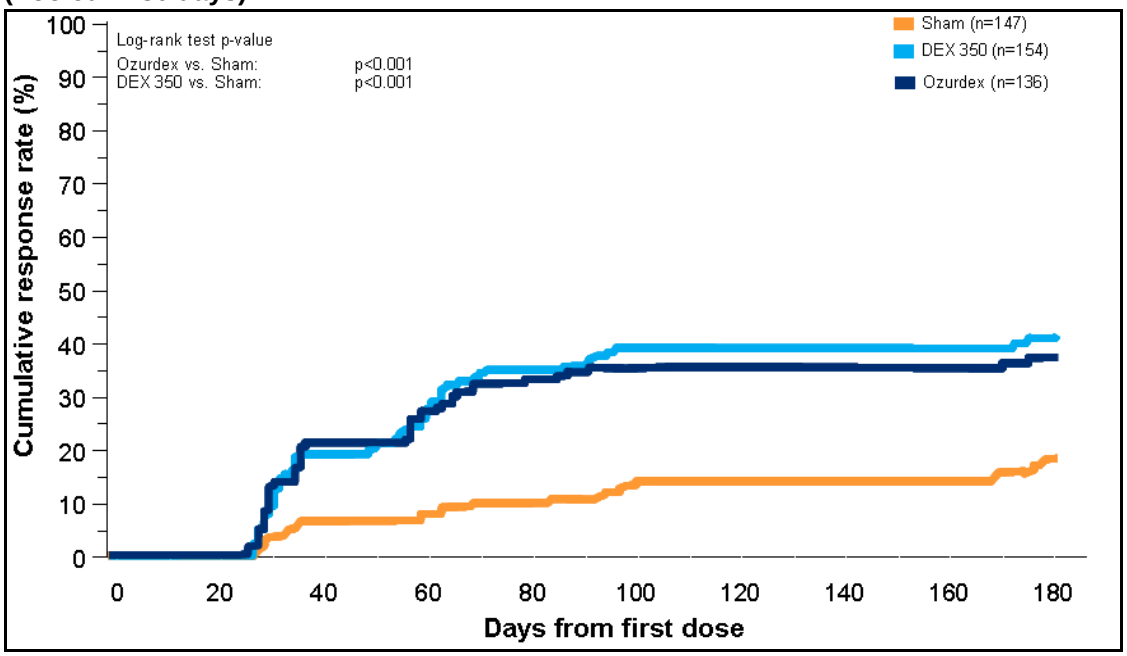


Figure 2: Time to an improvement in BCVA of ≥ 15 letters from baseline in patients with CRVO (Pooled - 180 days)



The tables below are simplified versions of those in the industry submission, which give the pooled results.

Table 4: Proportion of patients with BRVO with an improvement in BCVA of ≥ 15 letters from baseline (~ 180 days)

Visit		
	Ozurdex (n = 291)	**Sham (n = 279)**
Day 30	21.3%†	7.9%
Day 60	29.6%†	12.5%
Day 90	23.7%††	14.7%
Day 180	23.0%	20.4%

† (P < 0.001); ‡ (P = 0.021); § (P = 0.002); ¶ (P = 0.009); †† (P = 0.006)

Table 5: Proportion of patients with CRVO with an improvement in BCVA of ≥ 15 letters from baseline (~ 180 days)

Visit		
	Ozurdex (n = 136)	**Sham (n = 147)**
Day 30	21.3%†	6.8%
Day 60	28.7%†	8.8%
Day 90	17.6%	10.2%
Day 180	18.4%	12.2%

† (P < 0.001); ‡ (P = 0.031)

Other secondary outcomes

As shown above, most patients did not achieve a 15 letter improvement. The mean increase was statistically significantly better in the dexamethasone group, peaking at day 60, declining thereafter, as shown in tables 25 and 26 (See Table 6 and Table 7 below). However the differences of only a few letters do not seem clinically significant.

Table 6: Mean change from baseline BCVA in patients with BRVO (~180 days)

Visit			
	Ozurdex (n = 291)	**Sham (n = 279)**	**difference**
Day 30	8.5†	3.8	4.7
Day 60	10.3†	5.1	5.2
Day 90	8.7†	5.0	3.7
Day 180	7.4¶	4.9	2.5

† (P < 0.001); ‡ (P = 0.001); § (P = 0.018); ¶ (P = 0.008)

Table 7: Mean change from baseline BCVA in patients with CRVO (~180 days)

Visit			
	Ozurdex (n = 136)	**Sham (n = 147)**	**difference**
Day 30	7.2†	0.4	6.8
Day 60	8.7†	-0.5	9.2
Day 90	4.2††	-0.4	4.6
Day 180	0.1	-1.8	1.9

† (P < 0.001); ‡ (P = 0.006); § (P = 0.046); ¶ (P = 0.044); †† (P = 0.005)

The small difference in mean letters comes about because only 40% of patients had a meaningful response, which is why the most useful outcome is probably the proportion who improved by 15 or more letters.

The proportions improving by 10 or more letters also seem a useful outcome. These are not reported in the published paper, but are in tables 31 and 32 of the submission (See Table 8 and Table 9 below).

Table 8: Proportion of patients with BRVO with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days)

Visit		
	Ozurdex (n = 291)	**Sham (n = 279)**
Day 30	42.6%†	20.1%
Day 60	51.9%†	29.4%
Day 90	47.1%†	31.2%
Day 180	41.2%††	33.0%

† (P < 0.001); †† (P = 0.041)

Table 9: Proportion of patients with CRVO with an improvement in BCVA of ≥ 10-letters from baseline (- 180 days)

Visit	**Pooled**	
	Ozurdex (n = 136)	**Sham (n = 147)**
Day 30	45.6%†	12.2%
Day 60	49.3%†	19.7%
Day 90	36.0%‡	23.1%
Day 180	26.5%	23.8%

† (P < 0.001); ‡ (P = 0.017)

Figure 7 of the published paper (Haller 2010)[9] is very useful in showing the results over time. In CRVO, the control group showed no improvement, but instead a slight decline over 180 days. The dexamethasone group showed a prompt improvement, peaking at day 60, followed by a steep decline, so that by day 180, they were back to baseline. The differences in BCVA were 7 letters at day 30, 8 at day 60, 4 at day 90 and at day 180. However the D180 difference was because the control group had deteriorated from baseline.

In BRVO, the picture is different. Both groups improved, so that differences in BCVA from baseline were 5 letters at day 60, 4 at day 90 and 2 at day 180.

In CRVO, one implication may be that patients should be re-treated as soon as their VA starts to decline again, which could be after day 60, on the grounds that some of the subsequent deterioration might be irreversible by day 180. The ERG asked the manufacturer if they had any data on such an approach, but we were informed that there were no data, and that no modelling had been done of earlier re-treatment (Clarification response, November 5th, A30).

Adverse effects.

These can be considered as falling into three groups;

- Adverse effects of any injection into the eye, such as infection
- Adverse effects in the eye specific to dexamethasone
- Systemic effects of intra-ocular steroids

The plasma concentrations of the participants during the initial period of GENEVA studies demonstrated that the majority of plasma dexamethasone concentrations were low and thus a very minimal risk of systemic adverse events. Therefore, the industry submission only considered ocular adverse events in their report

Ocular adverse events:

These will be discussed separately for the initial treatment period (0 to 180 days) and the retreatment period (180 to 360 days).

Initial treatment period (~180 days)

The overall incidence of ocular adverse events was significantly higher in the Ozurdex group (62.9%) than in the sham group (42.8%) ($p<0.001$). The most frequently occurring ocular AEs in the study eye with Ozurdex was an increase in IOP, followed by conjunctival haemorrhage (Table 10).

Other ocular adverse events such as eye pain, ocular hypertension and anterior chamber cells were also significantly more common with Ozurdex than with sham. The incidence of retinal neovascularisation was significantly lower with Ozurdex.

Table 10. Common ocular adverse events (~180 days)

	Ozurdex (n=421)	Sham (n=423)	p value between groups
Increased IOP	106 (25.2%)	5 (1.2%)	p<0.001
Conjunctival haemorrhage	20.2%	14.9%	NS
Anterior chamber cell	5 (1.2%)	0 (0.0%)	p=0.031
Eye pain	31 (7.4%)	16 (3.8%)	p=0.023
Ocular hypertension	17 (4.0%)	3 (0.7%)	p=0.001
Retinal neovascularisation	3 (0.7%)	11 (2.6%)	p=0.032
Retinal detachment	1 (0.2%)	1 (0.2%)	

Changes in IOP in the Ozurdex peaked at day 60 and were not different from sham by day 180. Most eyes with increase in IOP were managed successfully with topical IOP-lowering medication but 3 eyes in the Ozurdex required a procedure to reduce IOP. One eye had its procedure for neovascular glaucoma rather than treatment related increased IOP.

Two patients had retinal detachment in the study eye. Retinal detachment in Ozurdex group was considered to be applicator related.

Nine patients had retinal tears in their study eye at baseline. Three patients reported retinal tears in the study eye during the initial treatment period- 2 (0.5%) with Ozurdex and 1 (0.2%) with sham. All the retinal tears were thought to be related to the applicator. None of the tears were considered serious or progressed to detachments.

No cases of endophthalmitis were reported in the GENEVA studies.

BRVO and CRVO

The overall incidence of ocular adverse events in study eye was significantly higher in patients with BRVO or CRVO treated with Ozurdex (60.4% and 68.4% respectively) than with sham (39.1% and 49.7% respectively). Most common ocular adverse events in patients with BRVO were increased IOP followed by conjunctival hyperaemia and ocular hypertension (Table 11). In patients with CRVO, the most common ocular adverse event was increase in IOP (Table 11).

Table 11. Common ocular adverse events in patients with BRVO and CRVO (~180 days)

BRVO			
	Ozurdex (n=288)	**Sham (n=276)**	**p value between groups**
Increased IOP	66 (22.9%)	3 (1.1%)	p<0.001
Ocular hypertension	16 (5.6%)	1 (0.4%)	p<0.001
Conjunctival hyperaemia	18 (6.3%)	8 (2.9%)	p<0.001
Retinal exudates	3 (1.0%)	12 (4.3%)	p=0.015
Retinal neovascularisation	2 (0.7%)	8 (2.9%)	
Cataract	22 (7.6%)	15 (5.4%)	
CRVO			
	Ozurdex (n=133)	**Sham (n=147)**	**p value between groups**
Increased IOP	40 (30.1%)	2 (1.4%)	p<0.001
Cataract	11 (8.3%)	7 (4.8%)	

Re-treatment period (~360 days)

[redacted]

Table 12. [redacted]

[redacted]			

BRVO and CRVO

[redacted]

Table 13. [redacted]

[redacted]

New onset adverse events following second injection (Re-treated safety population ~360 days):

[redacted]

Nonocular adverse events:

Initial treatment period (~180 days)

Deaths: One patient in the Ozurdex group died but the death was considered not related to the study treatment. No deaths occurred in the sham group.

Serious adverse events: The overall incidence of serious adverse events was similar between the two groups (21/421, 5% in Ozurdex group and 25/423, 5.9% in sham group) but none were considered to be treatment related.

Re-treatment period (~360 days)

[redacted]

Discontinuation due to adverse events

Initial treatment period (0 to 180 days) *(from published paper)*

	Ozurdex (n=421)	**Sham (n=423)**
Total discontinuation	24 (5.70%)	28 (6.62%)
Reasons		
Ocular adverse events	5 (1.19%)	6 (1.42%)
Nonocular adverse events	3 (0.71%)	2 (0.47%)
Lack of efficacy	NR	4 (0.95%)
Lost to follow-up	2 (0.48%)	3 (0.71%)
Personal reasons	7 (1.66%)	4 (0.95%)
Protocol violation	4 (0.95%)	2 (0.47%)
Other	3 (0.71%)	7 (1.65%)

Re-treatment period (180 to 360 days) *(from industry submission)*

	Ozurdex	**Sham**
Total discontinuation	[redacted]	[redacted]
Reasons		
Adverse events	[redacted]	[redacted]
Lack of efficacy	[redacted]	[redacted]
Administrative	[redacted]	[redacted]
Protocol violation	[redacted]	[redacted]
Other	[redacted]	[redacted]

3.2 Re-treatment data

Treatment after 180 days was not part of the randomised trial. Most of those who had been randomised to dexamethasone at baseline had a second implantation (341 of 427), and most of those who had had sham at baseline (327 of 426), were given dexamethasone at 180 days. Those who did not receive an injection at 180 days comprised those who had improved to greater than 84 letters, or whose retinal thickness by OCT was $\leq$ 250 μm.

The re-treatment data can provide information on two aspects;

- Firstly, in those who had dexamethasone at the start, how much benefit is there from a second injection?
- Secondly, in those who had a sham injection at baseline, is there benefit from a late first implantation?

CRVO

Table 14 is drawn from tables 26, 29, 55 and 57 of the industry submission. Percentages and numbers are rounded to whole numbers. Column 2 shows that the initial effect of dexamethasone in terms of proportion gaining 15 or more letters in VA, peaked at around 60 days, but that a second injection

resulted in [redacted] days after the second injection [redacted]

Benefit in terms of mean letters gained (column 3) was [redacted]. This is because many patients [redacted]. The main benefit is in those who [redacted].

Column 4 shows that the proportions which improved by 15 or more letters in the sham group were [redacted], but that a late injection at 180 days [redacted]. As with the initial dexamethasone group, mean numbers of letters gained were [redacted].

Table 14. Benefits of re-treatment and late treatment, CRVO

	Initial dexamethasone, repeated D180		Initial sham, dexamethasone at D180	
Time point	% gaining 15 or more letters	Mean gain in number of letters	% gaining 15 or more letters	Mean gain in number of letters
30 days	21%	7	7%	0
60	29%	9	9%	-1
90	18%	4	10%	0
180	18%	0	12%	-2
[redacted]				

However, we have no data on later injections. Clinical opinion included in the submission envisaged five or six injections being given. There is no evidence base for that, and we wonder about the adverse effects of such numbers of injections with a relatively large needle (relative to the much fine needles use for injections of the anti-VEGF drugs).

BRVO

Table 15 is drawn from tables 25, 28, 55 and 57 of the industry submission.

Table 15. Benefits of re-treatment and late treatment, BRVO

	Initial dexamethasone, repeated D180		Initial sham, dexamethasone at D180	
Time point	% gaining 15 or more letters	Mean gain in number of letters	% gaining 15 or more letters	Mean gain in number of letters
30 days	21%	9	8%	4
60	30%	10	13%	5
90	24%	9	15%	5
180	23%	7	20%	5
[redacted]				

Hence the second injection of dexamethasone provides [redacted] added benefit in terms of percentage gaining 15 or more letters, but the difference is [redacted] – [redacted] versus 23% at 180 days. There is [redacted] benefit in terms of mean letters gained.

For those who had sham injection at baseline, there was a more marked rise in proportion gaining 15 or more letters, but by 360 days [redacted]

3.2 Uncertainties

Comparators

The Allergan submission tries to dismiss the use of off-license comparators, partly on the grounds of the absence of licenses, but also partly on assertions that the evidence base for the comparators is weak. For example;

- Page 9; "the safety and efficacy of triamcinolone and bevacizumab have yet to be established"
- Page 88: "According to the literature search conducted, robust indirect comparison between Ozurdex or bevacizumab were not possible due to a lack of appropriate clinical data"

In fact, there is a lot of evidence for both agents, which we have tabulated in Appendix 1.

There is also evidence for the anti-VEGF drugs, ranibizumab and pegaptanib, which are not mentioned in the scope, but which is likely to be licensed for MO after RVO. Two relevant trials were included in the Cochrane review by Braithwaite and colleagues (2010, issue 10).[10] One trial by Wroblewski and colleagues compared pegaptanib injections to sham injections in non-ischaemic CRVO.[11] The CRUISE trial[12] compared ranibizumab to sham injections. Ranibizumab is licensed for the treatment of RVO in the USA, though not yet in Europe.

The RCO guidelines[3] note that there is evidence on the effectiveness of bevacizumab but comment that;
"*No recommendations on the use of intravitreal bevacizumab can be made at this time. Due to the unlicensed nature of bevacizumab when compounded and distributed to third parties, GMC Guidelines on "Good Medical Practice" as it relates to the use of both off-label and unlicensed medications and the manufacturer's advice should guide physician directed intraocular use."*

Hence there was scope for indirect comparison of Ozurdex with anti-VEGF agents.

In a condition such as CRVO where outcomes are predictably poor, case series such as those using bevacizumab, can provide useful data. They could use the natural history review, or the sham arm of the GENEVA trial for data for comparison.

Number of implants

The data from the trial is limited to one implant, and the open label follow-up adds data on a second. Clinical opinion, based on four people, envisages five or six implants, but there are no data to support this. Repeating the procedure may be of diminishing marginal utility.

Furthermore, we do not as yet have data on the adverse effects which might follow five or six implants using such a large needle.

Selection of responders

The majority of those injected did not have a marked improvement, taking that to be a gain of 15 or more letters, as shown in Table 16 and Table 17.

Table 16. Proportions of patients with CRVO gaining 15 or more letters

	Dexamethasone	Sham	Difference (D – S)
30 days	21%	7%	14%
60 days	29%	9%	20%
90 days	18%	10%	8%
180 days	18%	12%	6%

.

Table 17. Proportions of patients with BRVO gaining 15 or more letters

	Dexamethasone	Sham	Difference (D – S)
30 days	21%	8%	13%
60 days	30%	13%	17%
90 days	24%	15%	9%
180 days	23%	20%	3%

If we regard a gain of 10 or more letters as clinically significant, the proportions achieving that are much higher, implying that most of the gains are in the 10 to 14 range (Table 18).

Table 18. Proportions of patients gaining 10 or more letters

	CRVO		BRVO	
	Dexamethasone	Sham	Dexamethasone	Sham
30 days	46%	12%	43%	20%
60 days	49%	20%	52%	29%
90 days	36%	23%	47%	31%
180 days	27%	24%	41%	33%

One approach which would improve cost-effectiveness, and minimise side-effects in those unlikely to gain from Ozurdex treatment, would be to repeat the treatment only in those who had a good response to the first injection.

4. REVIEW OF ECONOMIC MODELLING

Note that due to errors within the model originally submitted, in response to a request from the ERG the manufacturer submitted a revised model on the 23rd Nov 2010 (only five working days before the ERG report was due in) that partially corrects the errors identified. In the following:

- the *Summary of the case presented by the manufacturer* section presents the base case results and sensitivity analyses as derived from the original manufacturer model, and as such is in line with the written submission;
- the *ERG cross check of the results of the manufacturer model: base cases* section applies the original manufacturer model;
- the *ERG cross check of the structure of the manufacturer model* section presents results from both the original manufacturer model and the revised manufacturer model;
- the *ERG cross check of the structure of the inputs to manufacturer model* section is based upon the original manufacturer model but there is no reason to believe that it does not apply equally to the revised manufacturer model;
- the *ERG additional sensitivity and scenario analyses* uses the revised manufacturer model, on the basis of it at least being a partial correction of the identified errors; and
- the *Comparison with NICE reference case* applies equally to both models.

4.1 Economic literature review

The submission only identified one economic study that was relevant: the Brown et al 2002 study[7] of laser photocoagulation therapy as briefly summarised previously within the ERG clinical effectiveness review above.

4.2 Summary of case presented by the manufacturer

Model structure

The manufacturer developed a cost utility markov model using Excel based around the pooled patent level data from the Geneva 008 and 009 trials. This compared 700µg dexamethasone with observation. Note that the modelling does not consider the possibility of watchful waiting followed by laser among those with BRVO-MH as a comparator, but only models observation.

The model's six health states, excluding death, were defined by patients' BCVA in the treated eye (Table 19):

Table 19. BCVA Model Health States

BCVA Health State	HS0	HS1	HS2	HS3	HS4	HS5
ETDRS letters	≥ 69	59-68	54-58	44-53	39-43	≤ 38
Snellen equivalent						
feet	≥ 20/40	20/50-20/63	20/80	20/100-20/125	20/160-20/200	≤ 20/200
metres	≥ 6/12	6/15-6/20	6/24	6/30-6/38	6/48-6/60	≤ 6/60
Average letters	75	63.5	56	48.5	41	33
Patients at baseline	0.60%	40.20%	19.40%	21.20%	7.90%	10.70%

The reasons for some health states being defined over 10 letters and some over five letters is unclear. This appears to be in part based upon deviation from HS2 within which the average BCVA fell, but it should be noted that only around 20% of patients were in HS2.

Pooled patient level data was extracted from the Geneva 008 and 009 trial to derive the transition probability matrices [TPMs] applied to the dexamethasone arm and to the observation arm for the modelling of patient movements between the above six health states. Days 0 to 180 of the model were split into four cycles: days 0 to 30, days 30 to 60, days 60 to 90 and days 90 to 180. The TPMs up to day 180 were drawn from the 700µg dexamethasone arm and the observation arm of the pooled patient level data, with last observation carried forward for missing data. For days 180 to 360 for the dexamethasone arm the TPM was drawn from the pooled open label data of those who received 700µg at both baseline and day 180. For days 180 to 360 for the observation arm the TPM for days 90 to 180 was applied twice. Thereafter the TPMs for days 180 to 360 were reapplied every six months up to day 1080 to reflect an assumed maximum 6 dexamethasone treatments for CRVO patients, and up to day 900 to reflect an assumed maximum 5 dexamethasone treatments for CRVO patients. NB These assumptions were based on clinical opinion – the trial evidence only extends to 360 days.

Within the dexamethasone arm, all patients were assumed to be treated at baseline. At day 180 the pooled data was applied to yield estimates of [redacted] of CRVO patients and [redacted] of BRVO patients being retreated. Retreatment rates thereafter were drawn from an expert panel convened

in New York by the manufacturer. Those not retreated within each six monthly cycle were assumed to either have resolved and have stable BCVA thereafter, or to have dropped out and so have the observation TPM applied to them. Resolution rates were estimated from the pooled day 180 trial data.

The base case assumed that from year 2.5 for BRVO and from year 3 for CRVO that BCVA was stable and there is no change or worsening in visual acuity thereafter. The modelling also assumed no recurrence of RVO leading to macular oedema within the originally affected eye, or within any fellow eye involvement [FEI] once visual stability was achieved in the fellow eye on a similar basis.

At baseline, the treated eye could be either the worse seeing eye [WSE] or the better seeing eye [BSE]. Those with their WSE affected at baseline who developed macular oedema due to RVO in their BSE crossed over to having their HRQoL defined by their BCVA in their BSE.

HRQoL was modelled as being a function of the BCVA, with this being differentiated by whether it was the WSE affected or the BSE affected. This required two stages:

1. Modelling HRQoL as a function of the VFQ-UI: general population
    a. The six item VFQ-UI subset of the NEI-VFQ-25 was used to define 8 binocular health states.
    b. These eight health states were valued using time trade off by 607 members of the general public of the UK, Canada and the US.
    c. HRQoL was modelled as a function of the six items of the VFQ-UI
2. Modelling the HRQoL implied by the VFQ-UI as a function of BCVA: patient population
    a. The HRQoL implied by patients' day 180 VFQ-UI was imputed
    b. These HRQoL values were regressed on patients' BCVA scores at day 180, differentiated by whether the WSE or the BSE was affected at baseline.

The results of this were that an improvement in the BCVA in the WSE had a relatively small impact upon HRQoL, but an improvement in the BCVA in the BSE had a somewhat larger impact.

Alongside this, severe visual impairment or legal blindness is defined by the BSE falling below 38 letters. Severe visual impairment was associated with a substantial average annual average cost of £8,055 based upon the method within the HTA Monograph[13] examining the cost effectiveness of ranibizumab and pegaptanib for the treatment of AMD. Severe visual impairment was also associated with a mortality hazard ratio of 1.54.

In the light of this, the estimated cost effectiveness of dexamethasone was in large part driven by the proportion of patients having their BSE affected by macular oedema arising from RVO. This in turn was determined by:

- the proportion of patients having their BSE affected at baseline, and
- the proportion of patients who had their WSE affected at baseline but went on to develop fellow eye involvement (FEI) RVO and subsequent macular oedema.

The 10% proportion of patients having their BSE affected at baseline was drawn from expert opinion, as the manufacturer argued that the 3% observed within the trials was unlikely to be representative of that seen in clinical practise.

The likelihood of developing FEI RVO was drawn from the Hayreh paper[14] it also being assumed that all FEI RVO would lead to macular oedema. FEI with its associated costs of treatment and patient benefits was not modelled for those patients whose BSE was affected at baseline, among whom the additional treatment costs with dexamethasone would be as for the initially affected eye but for whom the quality of life impact of the treatment of the fellow WSE would be muted.

Adverse events related to raised intraocular pressure retinal tears and detachments were included within the modelling, though these only affected costs, and not quality of life. Rates were drawn from the pooled trial data, with the resource use required for these estimated from expert opinion and subject to an uplift in costs subsequent to the first two dexamethasone administrations.

The rates of cataracts for the first two dexamethasone administrations were taken from pooled trial data, with this rate being assumed to double with each dexamethasone administration thereafter.

Handling of on treatment, off treatment, resolution and drop outs

An aspect of the modelling that may require greater explanation is the interaction between treatment rates and resolution rates, these both being largely by assumption beyond day 180.

Beyond the first two treatments at day 0 and day 180, within the dexamethasone arm the rate of those being retreated and the rate of those not being retreated were derived from expert opinion.

Table 20. On treatment and off treatment rates assumed

		CRVO			**BRVO**		
		Treated	Not Treated		Treated	Not Treated	
Tr. No.	Day		Prevalence	Incidence		Prevalence	Incidence
1	0	[redacted]	[redacted]		[redacted]	[redacted]	
2	180						
3	360						
4	540						
5	720						
6	900						
7	1080						
* Visual stability is assumed from this point onwards in the modelling							

The effect of these rates was not solely to limit the costs of retreatment. Those not retreated were assumed to not be treated due to either having resolved or having dropped out. The rates of resolution at day 180 were applied to this data, the residual of this being the proportion assumed to have dropped out. This 180 day resolution/drop out data was applied to not only those not treated at day 180, but also to those assumed not to be treated thereafter. The model then assumed that those not treated due to having been assumed to have resolved had a stable BCVA, while those not treated due to having been assumed to have dropped out had the observation arm TPM subsequently applied.

The resolution rates applied within the modelling were based upon the following patient numbers (Table 21):

Table 21. Resolution rates assumed for off treatment for and beyond day 180

CRVO	HS0	HS1	HS2	HS3	HS4	HS5	Total
Resolved Not Treated							
Resolution Rate							

BRVO	HS0	HS1	HS2	HS3	HS4	HS5	Total
Resolved Not Treated							
Resolution Rate							

For HS2 in CRVO the resolution rate of [redacted] was drawn from an average of the resolution rates across the other health states. This appears slightly peculiar given that the data in the above suggests [redacted] in HS2 in CRVO.

One of the main points from the above is that estimates of resolution rates at day 180 in some instances relied upon small numerators and small denominators. One additional patient here or there could affect the estimated resolution rates at day 180 quite significantly.

For simplicity of illustration, assume that the incidence of those not treated is equal across the six health states. Coupling the newly incident not treated rates with the resolution rates results in the following estimates of patients resolving (Table 22):

Table 22. Not treated and off treatment resolution rates combined

CRVO: Patients assumed to resolve								
Tr. No.	Day	HS0	HS1	HS2	HS3	HS4	HS5	Total
2	180	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
3	360							
4	540							
5	720	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
6	900							

BRVO: Patients assumed to resolve								
Tr. No.	Day	HS0	HS1	HS2	HS3	HS4	HS5	Total
2	180	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
3	360							[redacted]
4	540							
5	720	[redacted]	[redacted]	[redacted]	[redacted]			[redacted]
6	900							
empty cells = 0.00%								

As can be seen from the above, much of the modelled resolution within the dexamethasone arm occurs subsequent to day 180. This is largely by assumption rather than being based upon hard data, and is driven by the retreatment rates drawn from expert opinion coupled with the proportions estimated to have resolved at day 180 being reapplied to subsequent cycles.

Note that the manufacturer modelling does undertake sensitivity analyses around the resolution rates, and implements these as beta distributions within the probabilistic modelling. The manufacturer also performs a scenario analysis where all patients assumed not to be treated with dexamethasone have the observation TPM applied.

Base case deterministic results

The modelling resulted in deterministic base case estimates of (Table 23):

Table 23. Deterministic modelling base case results

	All Patients	CRVO	BRVO-MH	BRVO-PL
dexamethasone				
Cost	£12,245	£14,962	£10,943	£12,966
QALY	11.69	11.62	11.73	11.56
observation				
Cost	£10,578	£13,126	£9,434	£14,184
QALY	11.47	11.32	11.54	11.24
net				
Cost	£1,667	£1,836	£1,510	-£1,218
QALY	0.23	0.31	0.19	0.31
ICER	**£7,368**	**£6,008**	**£7,953**	**dominant**

The cohort flows relating to this modelling were presented within the submission, but not in a format that is particularly easy to interpret. These have been recalculated by the ERG and are presented in Appendix 3 for the three patient subgroups up to the point at which visual acuity is assumed to have stabilised. Note that this cohort flow only applies to the BCVA within the initially affected eye. Thereafter there would be only small changes in the distribution between the six health states among those remaining alive within the cohort, this arising from the 1.54 mortality multiplier associated with the severe visual impairment of HS5.

Base case probabilistic results

The modelling resulted in probabilistic base case estimates of (Table 24):

Table 24. Probabilistic modelling base case results

Patients	ICER	@ £20k	@ £30k
All Patients	£7,208	81%	93%
CRVO	£6,188	81%	93%
BRVO MH	£7,495	78%	92%
BRVO PL	dominant	94%	97%

Where @ £20k is the estimate of the likelihood of dexamethasone being cost effective at a willingness to pay of £20,000 per QALY, and @ £30k is the estimate of the likelihood of dexamethasone being cost effective at a willingness to pay of £30,000 per QALY

Sensitivity and scenario analyses within the submission

All sensitivity analyses and scenario analyses used the deterministic model, with the ranges applied and reasons for choosing the ranges applied being outlined in appendix 21: Table 153 of

the submission. Within this results were most sensitive to; the costs of severe visual impairment; the balance assumed between WSE and BSE at baseline; the discount rates, the parameters around the weibull extrapolation of FEI; the regression slope for the BSE utility equation; the dexamethasone implant cost; and, the administration cost per implant.

For the two principal subgroups of CRVO and BRVO-MH, the ranges applied and resulting ICERs were (Table 25):

Table 25. Manufacturer sensitivity analyses

				CRVO		BRVO-MH	
	Basecase ICERs			£6,008/QALY		£7,953/QALY	
Variable	Base	Range		Lower	Upper	Lower	Upper
% WSE	90%	68%	100%	dominant	£21,111	£2,441	£11,195
Vision loss Residential cost	£23,972	£6,864	£47,996	dominant	£19,480	dominant	£20,367
Vision loss Residential %	30%	15%	56%	dominant	£15,472	dominant	£16,650
FEI Weibull: ln(lambda)	[redacted]	[redacted]	[redacted]	£2972	£8,731	£3,132	£12,664
FEI Weibull: ln(gamma)	[redacted]	[redacted]	[redacted]	£2,576	£8,623	£2,376	£12,613
BSE HRQoL slope	[redacted]	[redacted]	[redacted]	£4,599	£9,028	£5,604	£13,694
Discount rate for benefits	3.5%	0.0%	6.0%	£3,742	£8,116	£4,750	£10,755
Discount rate for costs	3.5%	0.0%	6.0%	dominant	£9,928	dominant	£12,070
Dexamethasone cost	£870	£653	£1,088	£3,149	£9,038	£4,847	£11,059
Intravitreal injection cost	£648	£391	£824	£2,620	£8,483	£4,289	£10,473
Blindness mortality HR*	1.54		1.00	..	£4,015	..	£6,677
RVO to MO conversion*	100%		84%	..	£7,438	,,	£10,419
CRVO % resolution in HS0 in HS1 in HS2 in HS3 in HS4 in HS5	[redacted]	[redacted]	[redacted]	..	£10,498	..	£10,535
* described as structural parameter in Table 115							

Figure 29 outlines the results pooled across all RVO, while figures 30 and 32 graph the above figures as a tornado diagram. Figure 28 of the submission also provides more detail on the sensitivity of results to the balance assumed between WSE and BSE at baseline.

Note that including a mortality hazard for severe vision loss may in some cases worsen the estimate of the base case cost effectiveness for dexamethasone. This appears to be due to there being more patients experiencing severe visual loss within the observation arm. Remaining alive with severe visual loss is quite costly given an estimated HRQoL of [redacted] and an annual cost of

around £8,000. It seems that if the cost effectiveness of dexamethasone is below the implied cost effectiveness of patients with severe visual loss remaining alive but with an annual cost of £8,000, modelling these patients as not having an excess mortality hazard improves the overall cost effectiveness of dexamethasone compared to the observation arm. But in situations where the cost effectiveness of dexamethasone is more marginal and towards £20,000 per QALY or £30,000 per QALY, it seems likely that the inclusion of the mortality hazard for severe visual loss will tend to improve the cost effectiveness of dexamethasone. For instance, the base case cost effectiveness among CRVO patients 100% WSE at baseline is estimated as £22,248 per QALY with no excess mortality from severe visual loss, but £21,043 per QALY with a mortality hazard of 1.54 from severe visual loss.

Additional scenario analyses assumptions are outlined in Table 115 of the submission. The main scenario analyses of interest around structural assumptions are (Table 26):

1. Visual acuity is stable from day 360 with no further dexamethasone treatments
2. Those not treated are assumed to all have the observation TPM applied up to year 2.5 for BRVO and year 3 for CRVO
3. The proportions retreated are as at day 180 for the five injections subsequent to the first injection in CRVO and the four injections subsequent to the first injection in BRVO
4. Visual decline of 1.5% of patients in each health state worsening by one health state every six months for long term extrapolation rather than visual stability

Table 26. Manufacturer scenario analyses

	All Patients	CRVO	BRVO-MH	BRVO-PL
Basecase	£7,368	£6,008	£7,953	dominant
1. Visual stability at day 360	£10,764	£4,252	£14,283	£1,028
2. Obs. TPM if not treated	£24,924	£19,644	£29,045	£1,059
3. % treated as at day 180	£19,100	£11,469	£25,871	£1,392
4. Visual acuity decline	£7,685	£6,433	£8,108	dominant

Scenario 1 illustrates that extrapolation and further treatments beyond those observed within the trials, together with the assumptions that feed into these extrapolations, actually worsens the cost effectiveness estimate for CRVO patients. But it greatly improves the estimated cost effectiveness among BRVO-MH patients and given their preponderance in the baseline patient distribution and in any additional FEI, this improves the cost effectiveness estimate across all patients.

Scenario 2 illustrates the importance of the assumed resolution rates among those assumed to not be treated after day 180. Similarly, scenario 3 illustrates the importance of the assumptions around the proportions being treated and not being treated after day 180. As outlined above in the section on the handling of those off treatment, these two scenarios are to a degree two sides of the same coin.

Scenario 4 illustrates that moderate visual decline as a long term extrapolation rather than visual stability does not particularly affect results.

4.3 ERG cross check of results of manufacturer model: base cases

Deterministic modelling results

The values presented within the submission cross check with ERG model runs using the originally submitted model with WSE:BSE of 90%:10% and a Weibull extrapolation for FEI.

Probabilistic modelling results

The results reported for the probabilistic modelling for all patients within the submission correspond with those derived by the ERG using the original manufacturer model.

For the all RVO modelling this resulted in a central estimate of cost effectiveness of £7,576 per QALY as compared to £7,208 per QALY of figure 33 of the submission. The likelihood of cost effectiveness at willingness to pay values of £20,000 per QALY and £30,000 per QALY also cross checked with those of the submission. The central estimates are also similar to the £7,368 per QALY base case estimate from the deterministic modelling.

4.4 ERG cross check of the structure of the manufacturer model

Base case deterministic results and errors within the model

Probably the simplest way of understanding the main model drivers is to examine the base case deterministic results, and to vary:

- the assumed proportion of patients having their BSE affected at baseline to the 3% observed within the trials; and ,
- whether there is FEI.

Note that these are additional sensitivity analyses and as such do not fall directly within the case presented by the manufacturer. These sensitivity analyses underline the importance of involving the BSE for the cost effectiveness results, either by assuming it will be involved at baseline or by modelling its involvement over time through FEI.

The weibull estimate of FEI is that around 6.5% of patients will have FEI within the first year, but with this rapidly declining thereafter. Excluding FEI has been implemented within the model by either assuming a constant annual rate of 0%, or more simply by setting the rate of conversion from RVO to macular oedema to 0%[1]. (Table 27)

Table 27. Original manufacturer model sensitivity to WSE:BSE and fellow eye involvement

	WSE: BSE 90%:10%			WSE: BSE 97%:03%		
Weibull FEI*	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
dexamethasone						
Cost	£14,962	£10,943	£12,966	£14,143	£10,526	£12,004
QALY	11.62	11.73	11.56	11.79	11.87	11.72
observation						
Cost	£13,126	£9,434	£14,184	£10,104	£8,720	£12,188
QALY	11.32	11.54	11.24	11.53	11.69	11.43
net						
Cost	£1,836	£1,510	-£1,218	£4,039	£1,806	-£184
QALY	0.31	0.19	0.31	0.26	0.18	0.28
ICER	**£6,008**	**£7,953**	**-£3,887**	**£15,688**	**£10,157**	**-£650**
	* Approximately 6.5% incidence in the 1st year but declining rapidly thereafter					
No FEI	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
dexamethasone						
Cost	£11,765	£7,431	£8,334	£10,697	£6,740	£7,011
QALY	11.50	11.62	11.49	11.6547	11.75	11.64
Observation						
Cost	£7,739	£3,900	£6,024	£4,298	£2,756	£3,393
QALY	11.27	11.51	11.29	11.476	11.67	11.49
net						
Cost	£4,026	£3,531	£2,310	£6,399	£3,984	£3,618
QALY	0.23	0.10	0.19	0.18	0.08	0.15
ICER	**£17,279**	**£34,277**	**£11,905**	**£35,708**	**£47,301**	**£23,348**

[1] Within the submitted model by setting D8, F8 and D9 of the *Summary* worksheet to zero, or by setting D10 of the *Summary* worksheet to zero.

Note that for the above for the CRVO modelling, the BRVO type was specified as all patients. The BRVO type specified for the CRVO modelling affects results slightly through the balance between types of RVO in the modelling of FEI.

The ICERs show the importance within the manufacturer modelling of involving the BSE, either at baseline or subsequently through FEI.

But the above also highlights a serious error within the modelling of FEI. The sensitivity analysis of moving from the weibull extrapolation of FEI to having no FEI worsens patient outcomes: e.g. within the 90%:10% modelling removing FEI for CRVO patients receiving dexamethasone reduces the aggregate QALYs from 11.62 QALYs to 11.50 QALYs. If there is no FEI this can only improve patient outcomes. Removing the FEI should increase the aggregate QALYs in each treatment arm. Results for the main patient groups of CRVO patients and BRVO-MH patients are perverse. Results for BRVO-PL patients are more varied.

The above concerns were highlighted to the manufacturer by the ERG within the clarification questions. As outlined within Appendix 2. *Errors in the submitted model*

As outlined in the ERG clarification question B17 the submitted model performed counter-intuitively:

	100% RVO to ME conversion			**50% RVO to ME conversion**		
	All RVO	CRVO	BRVO	All RVO	CRVO	BRVO
Discounted		All	All		All	All
Ozurdex						
Cost	£12,245	£14,962	£10,815	£10,567	£13,363	£9,095
QALY	11.6916	11.6246	11.7269	11.6350	11.5638	11.6725
No treatment						
Cost	£10,578	£13,126	£9,236	£7,873	£10,432	£6,526
QALY	11.465	11.319	11.5424	11.449	11.295	11.5307
Ozurdex-no treatment						
Cost	£1,667	£1,836	£1,578	£2,694	£2,931	£2,569
QALY	0.23	0.31	0.18	0.19	0.27	0.14
ICER	**£7,368**	**£6,008**	**£8,554**	**£14,502**	**£10,884**	**£18,119**

B17 The average total QALYs fall if the proportion of RVO resulting in ME is reduced from 100% to 50%, and falls further if the proportion is reduced to 0%. Similar effects appear to be the

case if the method of modelling fellow eye involvement is changed to a simple rate calculation: a lower rate of fellow eye involvement worsens the aggregate patient QALYs. This seems counterintuitive and may suggest a logical flaw in the model structure, which if the case, could have a major impact given the importance of fellow eye involvement to the cost effectiveness argument. Please clarify if this is the case, and any changes necessary to correct the model structure.

The manufacturer clarified that these errors arose from the incorrect treatment of survival, both in the treatment of survival at fellow eye involvement incidence and in the treatment of survival subsequent to this incidence. A method of revising the model to correct the treatment of survival at fellow eye involvement incidence was put forward by the manufacturer as outlined below. There was apparently no ready means of addressing the errors around the treatment of survival subsequent to incidence and the manufacturer presented an account of why this would be expected to have limited impact upon modelling results.

Note that the ERG supplied the manufacturer with a revised cohort flow where all events happened contemporaneously, with these subsequently being conditioned by discount rates and survival. While this cohort flow was not rebuilt or cross checked by the ERG, the cohort flows for the eye affected at baseline corresponded with the manufacturer cohort flow. Revising the model to have all events happening contemporaneously, including fellow eye involvement, would avoid the errors in the manufacturer model and also appears to be a somewhat simpler modelling approach. It would have been a relatively simple matter to rebuild the suggested cohort flow with all events happening contemporaneously, and attach the associated costs and QALYs to these for the deterministic modelling. The only slight difficulty might have been in implementing the mortality multiplier for blindness for baseline to year 3, during which time some patients move out of legal blindness. This should not affect results to any appreciable extent.

Issue 1: Treatment of survival at fellow eye involvement incidence

Corrections necessary to address model error

1. Change CG17:DJ17 to not take account of survival at the time of the FEO

An example of the change in the formula for cell CG17 is:

Submitted model: Summary!$D$10*CG16*
IF($CI$8=0, IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))

Correction: Summary!$D$10*
IF($CI$8=0,IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))

The difference between these formulae is that the multiplicative term CG16 is present in the submitted model and absent in correction. The updated cell for CG17 can be replicated by dragging the bottom right corner across to cell DJ17. Cell DK17 should be left unchanged. Cell CH13 should be changed from 1-DK13 to SUMPRODUCT(CG17:DJ17,CG16:DJ16), so that this proportion is displayed as in the submitted model (i.e., the overall proportion taking account of mortality).

This removes the proportion surviving as a conditioner to the proportion experiencing fellow eye involvement, the change can be implemented as described by the manufacturer.

2. Change CG18:DJ18 and FA18:GD18 to take account of survival at the time of the FEO

An example of the change in the formula for cell CG18 is:

Submitted model*: 1/(1+$D$18)^CG15

Correction: CG16/(1+$D$18)^CG15

*The formula in the submitted model is mathematically equivalent to that shown here (CG18 = 1/(1+$D$18); CG19 = CG18*$CG$18, with CG19 replicated by dragging to DJ18.); i.e. the formula within the submitted model is not as suggested above with this requiring further modification by the ERG.

The difference between these formulae is that the multiplicative term CG16 is absent in the submitted model and present in the correction. The updated cell for CG18 can be replicated by dragging the bottom right corner across to cell DJ18. The formula for FA18:GD18 refers to the discount rate for benefits ($E$18) instead of that for costs ($D$18).

Note that the reference to the discount rate for benefits ($E$18) instead of that for costs ($D$18) was not specified within the model. Rather, the discount rates for benefits for the fellow eye modelling FA18:GD18 were simply equalised to those for discount rates for costs CG18:GD18 for the fellow eye modelling. This appears to be a further error in the revised model which will cause any sensitivity analyses which set the discount rate for benefits to be different from the discount rate for costs to be incorrect.

The manufacturer response suggests that making these changes moves the All RVO cost effectiveness from £7,368 per QALY to £7,403 per QALY.

Issue 2: Treatment of survival subsequent to fellow eye involvement

This error occurs due to patients at baseline having a lower mortality rate than those some years after baseline. The modelling appears to have effectively assumed that where there is fellow eye involvement the mortality that applies is as from baseline, rather than as from the age at which fellow eye involvement occurs.

The manufacturer argues that since

- the incidence of fellow eye involvement as modelled for the base case through a weibull extrapolation occurs mainly relatively early within the simulation
- mortality further reduces the proportion of patients with fellow eye involvement in later years
- discounting further reduces the impact of this

This aspect will be relatively unimportance. These considerations apply. But the model revised to take into account the errors in Issue 1 appears to still give rise to perverse results. As a consequence, it does not seem warranted to suggest that Issue 2 is unimportant unless another error within the modelling is giving rise to the remaining perverse results. Relying on a model that incorrectly models FEI to undertake simulations to suggest the likely importance of the error in the modelling of FEI is also questionable.

It is currently unclear to the ERG, but it is possible that the submitted model rather than modelling patients, the impact of ME on their treated eye, the impact of fellow eye involvement, and patient survival instead might models pairs of eyes where one eye can in effect survive independently of death of its mate.

Updated model

Subsequent to the initial set of ERG questions, at the further request of the ERG the manufacturer submitted an updated model that implements the changes suggested by the manufacturer to resolve Issue 1 outlined above and which does result in a base case estimate across all RVO of £7,403 per QALY. The manufacturer also submitted the updated estimates for cost effectiveness in All RVO patients, All CRVO patients and All BRVO patients, with sensitivity analyses around the percentage of FEI that is assumed to convert to MO.

When assessing the results from the updated model it is helpful to bear in mind the previous manufacturer clarification around the calculation of HRQoL and QALYs:

B10 (Page 160-161, section 6.4.9.) In terms of how the patient utility for a given health state is calculated, please clarify:

i. If only the WSE is affected and the patient is in HS2, is the utility value [redacted]?

ii. [redacted]

[redacted]If only the BSE is affected and the patient is in HS2, is the utility value [redacted]?

iii. [redacted]If the WSE is affected initially and is currently in HS2, with fellow eye involvement in the BSE with the BSE currently being in HS2 is the utility value [redacted]?

[redacted]

The implication of this is that when modelling a cohort that is 100% WSE at baseline, as the percentage of FEI converting from RVO to macular oedema is increased from 0% to 100% the percentage of patients having their BSE also affected with macular oedema in the first year will rise from 0% to around 6.5% based upon the Weibull modelling of FEI. As a consequence, the proportion of patients in the first year having their HRQoL determined by the BSE utility function as described under point iii above will similarly increase from 0% to around 6.5%. This would be anticipated to reduce their HRQoL given the differences between the two functions estimated HRQoL for given health states as outlined in table 106. By year 6 around [redacted]% of patients initially only with their WSE affected will have developed MO in their best seeing eye, with their HRQoL crossing over from being determined by the WSE utility function to the BSE utility function.

The summary of the updated reference case using the Allergan_Ozdurex_NICE_STA_V05.xls model submitted to NICE on the 23 Nov 2010 at the request of the ERG as outlined overleaf does not conform to this expectation. Examining the CRVO 100%WSE column, as the % FEI

converting from RVO to macular oedema increase from 0% to 100% nothing happens to the aggregate QALYs within the dexamethasone arm. In the pooled results the aggregate QALYs actually move in the wrong direction very slightly.

, the manufacturer responded by outlining some changes to the model that would partially correct the errors within the modelling submitted. This was augmented with some suggestions as to why the errors were likely to be relatively unimportant. As gone into in slightly greater detail within Appendix 2. *Errors in the submitted model*

As outlined in the ERG clarification question B17 the submitted model performed counter-intuitively:

	100% RVO to ME conversion			**50% RVO to ME conversion**		
	All RVO	CRVO	BRVO	All RVO	CRVO	BRVO
Discounted		All	All		All	All
Ozurdex						
Cost	£12,245	£14,962	£10,815	£10,567	£13,363	£9,095
QALY	11.6916	11.6246	11.7269	11.6350	11.5638	11.6725
No treatment						
Cost	£10,578	£13,126	£9,236	£7,873	£10,432	£6,526
QALY	11.465	11.319	11.5424	11.449	11.295	11.5307
Ozurdex-no treatment						
Cost	£1,667	£1,836	£1,578	£2,694	£2,931	£2,569
QALY	0.23	0.31	0.18	0.19	0.27	0.14
ICER	**£7,368**	**£6,008**	**£8,554**	**£14,502**	**£10,884**	**£18,119**

B17 The average total QALYs fall if the proportion of RVO resulting in ME is reduced from 100% to 50%, and falls further if the proportion is reduced to 0%. Similar effects appear to be the case if the method of modelling fellow eye involvement is changed to a simple rate calculation: a lower rate of fellow eye involvement worsens the aggregate patient QALYs. This seems counterintuitive and may suggest a logical flaw in the model structure, which if the case, could have a major impact given the importance of fellow eye involvement to the cost effectiveness argument. Please clarify if this is the case, and any changes necessary to correct the model structure.

The manufacturer clarified that these errors arose from the incorrect treatment of survival, both in the treatment of survival at fellow eye involvement incidence and in the treatment of survival

subsequent to this incidence. A method of revising the model to correct the treatment of survival at fellow eye involvement incidence was put forward by the manufacturer as outlined below. There was apparently no ready means of addressing the errors around the treatment of survival subsequent to incidence and the manufacturer presented an account of why this would be expected to have limited impact upon modelling results.

Note that the ERG supplied the manufacturer with a revised cohort flow where all events happened contemporaneously, with these subsequently being conditioned by discount rates and survival. While this cohort flow was not rebuilt or cross checked by the ERG, the cohort flows for the eye affected at baseline corresponded with the manufacturer cohort flow. Revising the model to have all events happening contemporaneously, including fellow eye involvement, would avoid the errors in the manufacturer model and also appears to be a somewhat simpler modelling approach. It would have been a relatively simple matter to rebuild the suggested cohort flow with all events happening contemporaneously, and attach the associated costs and QALYs to these for the deterministic modelling. The only slight difficulty might have been in implementing the mortality multiplier for blindness for baseline to year 3, during which time some patients move out of legal blindness. This should not affect results to any appreciable extent.

Issue 1: Treatment of survival at fellow eye involvement incidence

Corrections necessary to address model error

1. Change CG17:DJ17 to not take account of survival at the time of the FEO

An example of the change in the formula for cell CG17 is:

Submitted model:
```
Summary!$D$10*CG16*
IF($CI$8=0, IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))
```

Correction:
```
Summary!$D$10*
IF($CI$8=0,IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))
```

The difference between these formulae is that the multiplicative term CG16 is present in the submitted model and absent in correction. The updated cell for CG17 can be replicated by dragging the bottom right corner across to cell DJ17. Cell DK17 should be left unchanged. Cell CH13 should be changed from 1-DK13 to SUMPRODUCT(CG17:DJ17,CG16:DJ16), so that this proportion is displayed as in the submitted model (i.e., the overall proportion taking account of mortality).

This removes the proportion surviving as a conditioner to the proportion experiencing fellow eye involvement, the change can be implemented as described by the manufacturer.

2. Change CG18:DJ18 and FA18:GD18 to take account of survival at the time of the FEO

An example of the change in the formula for cell CG18 is:

Submitted model*: 1/(1+$D$18)^CG15

Correction: CG16/(1+$D$18)^CG15

*The formula in the submitted model is mathematically equivalent to that shown here (CG18 = 1/(1+$D$18); CG19 = CG18*$CG$18, with CG19 replicated by dragging to DJ18.); i.e. the formula within the submitted model is not as suggested above with this requiring further modification by the ERG.

The difference between these formulae is that the multiplicative term CG16 is absent in the submitted model and present in the correction. The updated cell for CG18 can be replicated by dragging the bottom right corner across to cell DJ18. The formula for FA18:GD18 refers to the discount rate for benefits ($E$18) instead of that for costs ($D$18).

Note that the reference to the discount rate for benefits ($E$18) instead of that for costs ($D$18) was not specified within the model. Rather, the discount rates for benefits for the fellow eye

modelling FA18:GD18 were simply equalised to those for discount rates for costs CG18:GD18 for the fellow eye modelling. This appears to be a further error in the revised model which will cause any sensitivity analyses which set the discount rate for benefits to be different from the discount rate for costs to be incorrect.

The manufacturer response suggests that making these changes moves the All RVO cost effectiveness from £7,368 per QALY to £7,403 per QALY.

Issue 2: Treatment of survival subsequent to fellow eye involvement

This error occurs due to patients at baseline having a lower mortality rate than those some years after baseline. The modelling appears to have effectively assumed that where there is fellow eye involvement the mortality that applies is as from baseline, rather than as from the age at which fellow eye involvement occurs.

The manufacturer argues that since

- the incidence of fellow eye involvement as modelled for the base case through a weibull extrapolation occurs mainly relatively early within the simulation
- mortality further reduces the proportion of patients with fellow eye involvement in later years
- discounting further reduces the impact of this

This aspect will be relatively unimportance. These considerations apply. But the model revised to take into account the errors in Issue 1 appears to still give rise to perverse results. As a consequence, it does not seem warranted to suggest that Issue 2 is unimportant unless another error within the modelling is giving rise to the remaining perverse results. Relying on a model that incorrectly models FEI to undertake simulations to suggest the likely importance of the error in the modelling of FEI is also questionable.

It is currently unclear to the ERG, but it is possible that the submitted model rather than modelling patients, the impact of ME on their treated eye, the impact of fellow eye involvement,

and patient survival instead might models pairs of eyes where one eye can in effect survive independently of death of its mate.

Updated model

Subsequent to the initial set of ERG questions, at the further request of the ERG the manufacturer submitted an updated model that implements the changes suggested by the manufacturer to resolve Issue 1 outlined above and which does result in a base case estimate across all RVO of £7,403 per QALY. The manufacturer also submitted the updated estimates for cost effectiveness in All RVO patients, All CRVO patients and All BRVO patients, with sensitivity analyses around the percentage of FEI that is assumed to convert to MO.

When assessing the results from the updated model it is helpful to bear in mind the previous manufacturer clarification around the calculation of HRQoL and QALYs:

B10 (Page 160-161, section 6.4.9.) In terms of how the patient utility for a given health state is calculated, please clarify:

iv. If only the WSE is affected and the patient is in HS2, is the utility value [redacted]?

v. [redacted] If only the BSE is affected and the patient is in HS2, is the utility value [redacted]?

vi. [redacted] If the WSE is affected initially and is currently in HS2, with fellow eye involvement in the BSE with the BSE currently being in HS2 is the utility value [redacted]?

[redacted]

The implication of this is that when modelling a cohort that is 100% WSE at baseline, as the percentage of FEI converting from RVO to macular oedema is increased from 0% to 100% the percentage of patients having their BSE also affected with macular oedema in the first year will rise from 0% to around 6.5% based upon the Weibull modelling of FEI. As a consequence, the proportion of patients in the first year having their HRQoL determined by the BSE utility function as described under point iii above will similarly increase from 0% to around 6.5%. This would be anticipated to reduce their HRQoL given the differences between the two functions estimated HRQoL for given health states as outlined in table 106. By year 6 around [redacted]% of patients initially only with their WSE affected will have developed MO in their best seeing eye, with their HRQoL crossing over from being determined by the WSE utility function to the BSE utility function.

The summary of the updated reference case using the Allergan_Ozdurex_NICE_STA_V05.xls model submitted to NICE on the 23 Nov 2010 at the request of the ERG as outlined overleaf does not conform to this expectation. Examining the CRVO 100%WSE column, as the % FEI converting from RVO to macular oedema increase from 0% to 100% nothing happens to the aggregate QALYs within the dexamethasone arm. In the pooled results the aggregate QALYs actually move in the wrong direction very slightly.

the latter were not particularly convincing when viewed in the light of the suggested corrections to the model still resulting in perverse results. Also, the manufacturer arguments around the likely importance of the errors in the modelling of FEI relied upon simulations using the model, which as already outlined models FEI incorrectly.

At the request of the ERG, on 23 Nov 2010 the manufacturer subsequently submitted a revised model that corrected some of the errors in the originally submitted model. The resulted in the following where the CRVO and the BRVO are based upon averaging the 90% WSE and 10% BSE. (Table 28)

Table 28. Revised manufacturer model sensitivity to WSE:BSE and fellow eye involvement

Weibull FEI	CRVO-All	100% WSE	100%BSE	BRVO-All	100% WSE	100%BSE
dexamethasone						
Cost	£14,961	£13,791	£25,496	£10,815	£10,266	£15,753
QALY	11.50	11.72	9.55	11.61	11.79	9.92
observation						
Cost	£13,126	£8,809	£51,978	£9,236	£8,288	£17,769
QALY	11.20	11.49	8.63	11.42	11.63	9.59
net						
Cost	£1,836	£4,982	-£26,482	£1,578	£1,978	-£2,016
QALY	0.30	0.23	0.92	0.18	0.17	0.33
ICER	**6,041**	**21,211**	**dominant**	**8,590**	**11,815**	**dominant**
No FEI	CRVO-All	100% WSE	100%BSE	BRVO-All	100% WSE	100%BSE
dexamethasone						
Cost	£11,765	£10,239	£25,496	£7,375	£6,444	£15,753
QALY	11.50	11.72	9.55	11.62	11.81	9.92
Observation						
Cost	£7,739	£2,823	£51,978	£3,816	£2,266	£17,769
QALY	11.27	11.56	8.63	11.52	11.73	9.59
net						
Cost	£4,026	£7,416	-£26,482	£3,559	£4,178	-£2,016
QALY	0.23	0.16	0.92	0.10	0.07	0.33
ICER	**£17,279**	**£47,493**	**dominant**	**£35,944**	**£57,043**	**dominant**

Within the above, the first point to note is that the correction only affects the results where FEI is modelled. The results for no FEI within CRVO are consistent between the two models. The no FEI results for BRVO-All differ from BRVO-MH previously reported due to the different patient group being modelled by the manufacturer.

The second point to note is that there remains what appears to be a significant error within the modelling of FEI. Without FEI in the CRVO 100% WSE dexamethasone arm the model estimates 11.72 QALYs. With FEI in the CRVO 100% WSE dexamethasone arm the model estimates essentially the same 11.72 QALYs. This is despite FEI implying that in the first year 6.5% of WSE patients will have their BSE affected through FEI, and by year 6 around [redacted]% of WSE patients will have their BSE involved through FEI. Once their BSE is affected through FEI, these patients will have their utility determined by the BSE utility function as outlined in table 108 of the submission. This should move the total QALYs some way towards that of the 100% BSE modelling, but there is no effect. A serious error remains in the modelling of FEI in the revised model submitted on the 23 Nov 2010.

Given the apparent importance of involving the best seeing eye either immediately at baseline or later through FEI, the perverse results of both the initially submitted manufacturer model and the revised partially corrected manufacturer model are a major concern.

Utility impact from cataracts

The manufacturer argued that the utility impact from the development of cataracts and their removal was taken into account in the modelling since the visual impairment from cataracts would be reflected in the distribution of health states and the utility functions derived.

The development of cataracts due to dexamethasone administrations at day 0 and at day 180 would be reflected in the distributions across the BCVA health states as observed within the trials at days 180 and 360. Some patients may have had their cataracts removed at these time points, and as such the distribution across the BCVA health states might underestimate the HRQoL impact of cataracts arising from dexamethasone administrations.

The utility data was pooled across both arms of the trials to yield HRQoL as a function of BCVA, this being dependent only upon whether the WSE was affected or the BSE was affected. As such, the utility functions apply any HRQoL detriment arising from cataracts indiscriminately across both the dexamethasone arm and the observation arm.

This needs to be read in conjunction with the assumption that as the number of dexamethasone administrations increases the rate of cataracts also increases. The base case assumed that with every additional dexamethasone administration after day 180 the rate of cataracts would double. This assumed doubling in the rates of cataracts per administration within the dexamethasone arm will not have been reflected in the transition probabilities within the trials, and will also not be accounted for within the utility functions applied.

As far as the ERG can ascertain, varying the rate of cataracts for dexamethasone administrations subsequent to the first two administrations only affects costs. It does not affect QALYs. The model does have the facility to apply a disutility associated with cataract removal surgery. This could also be used to proxy for the additional disutility of having cataracts develop over a period of time, but this does not appear to have been undertaken within the modelling.

Implementation of probabilistic modelling

The probabilistic modelling assigns a range of distributions to most but not all of the variables within the model as outlined in Table 153 of the submission. It is not immediately obvious that all these variables should be assigned a probabilistic distribution. Some might be seen as more structural in nature.

The definition of the health states within the modelling appears to be treated probabilistically. The average BCVA for the health states HS0 to HS5 is derived from the pooled data from within the GENEVA trials. The central estimates are associated with a standard error, with these being modelled as following a normal distribution. These BCVA values for each health state are then coupled with the utility parameters outlined in the text prior to table 106 of the submission to calculate the HRQoL for each health state. The slope parameters for the utility equations are also treated probabilistically, with these also being modelled as following a normal distribution.

Table 29. Mean and S.E.s of subset of probabilistic model inputs

							HRQoL Slope	
	HS0	HS1	HS2	HS3	HS4	HS5	WSE	BSE
Mean BCVA	75.00	63.50	56.00	48.50	41.00	33.00	[redacted]	[redacted]
S.E.	3.06	2.30	1.02	2.30	1.02	2.55	[redacted]	[redacted]

Within the above, the standard errors associated with the health states central estimate of BCVA have in the manufacturer model been drawn from the ranges given in Table 98. In effect, the modelling appears to have assumed that these ranges formed the 95% confidence interval for the central estimates. This accounts for the central estimates for BCVA for HS1 and HS3 having the same standard error, and the central estimates for BCVA for HS2 and HS4 having the same standard error.

Slightly arbitrarily, since Table 98 of the submission does not specify a continuous range of BCVA values for the health states for the following the one letter gap between health states within Table 98 has allocated to extend the upper range for each health state to yield a continuous distribution.

Table 30. ERG arbitrary definition of continuous BCVA health states

	HS0	HS1	HS2	HS3	HS4	HS5
Maximum		69	59	54	44	39
Minimum	69	59	54	44	39	

The alternative approach of allocating the indeterminate letter to extend the minimum would not be anticipated to particularly affect the following.

ERG simulations of 5,000 iterations of the central BCVA for the individual health states and the HRQoL slope parameters based on the above and treating all as independent resulted in:

- Over 10% of simulations resulting in at least one of the health states having the simulated BCVA falling outside the logical minimum to maximum range of the health state.
- While small, around 0.6% of simulations estimating the mean BCVA in a better health state to be lower than that of the adjacent "worse" health state.
- Around 1.3% of simulations result in a negative slope parameter for one or both of the utility functions, this probably being mainly confined to the slope of the BSE utility function.
- Around 1.9% of simulations estimating for the BSE utility function that the HRQoL in a better health state was lower than that of the adjacent "worse" health state.

As far as the ERG can ascertain, the only logical restriction placed upon these parameters is that the HRQoL cannot exceed 1.

4.5 ERG cross check of the inputs to the manufacturer model

Correspondence between written submission and electronic model

Apart from a few minor errors, there is broad agreement between the written submission and the parameter values within the submitted electronic model.

Table 31. Cross check of inputs in written submission and electronic model

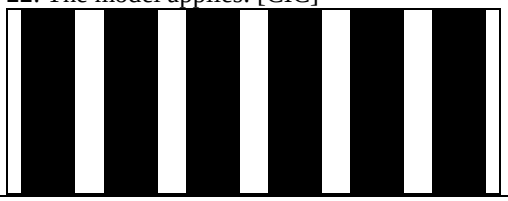
<table>
<tr><th>Table</th><th>Worksheet</th><th>XCheck</th><th>Comment</th></tr>
<tr><td>99</td><td>Summary</td><td>Partial</td><td>The baseline distributions for BRVO correctly reference the appropriate patient numbers depending upon the subgroup selected.
These are weighted by the overall proportions of CRVO and BRVO patients within the Geneva 008 and 009 trials: 34% CRVO and 66% BRVO.
Note that these CRVO: BRVO percentages are treated probabilistically within the PSA.
Note also that within the electronic model this distribution is applied to both CRVO patients and BRVO patients.</td></tr>
<tr><td>103</td><td>Fellow Eye</td><td>Yes</td><td></td></tr>
<tr><td>104</td><td>..</td><td>..</td><td>Not within electronic model</td></tr>
<tr><td>105</td><td>Summary
Transitions
Retreatment

Summary</td><td>Yes</td><td>The assumed split between WSE and BSE at baseline, the assumed time to stabilisation of BCVA, and the assumed retreatment rates, cross check

Note that the model also assumes that 100% of RVO in the fellow eye converts to macular oedema for the base case.</td></tr>
<tr><td>Text</td><td>Summary</td><td>..</td><td>Not tabulated, but the 1.54 mortality multiplier within the text cross checks with the electronic model</td></tr>
<tr><td>Text</td><td>Summary</td><td>..</td><td>Not tabulated, but the parameter values for the BSE and WSE HRQoL calculations of the text cross check</td></tr>
<tr><td>106</td><td>Summary</td><td>Yes</td><td>The values derived from the HRQoL equations of the text for the electronic model cross check with those implied by the HRQoL equations, on the basis of average letter scores of 75.0, 63.5, 56.0, 48.5, 41.0 and 33.0 for HS0, HS1, HS2, HS3, HS4 and HS5 respectively.

Minor 0.001 discrepancies in some values, with the model being correct.</td></tr>
<tr><td>107</td><td>MRU_Cost</td><td>Yes</td><td></td></tr>
<tr><td>108</td><td>MRU_Cost</td><td>Partial</td><td>Table 108 incorrectly multiplies £73 by 3 and by 2 to arrive at £292 and £219 respectively for the ophthalmology consultations. The correct amounts are £219 and £146, which are both correct within the economic model.

Note that it is assumed that OCT, FA and ophthalmoscopy can occur during a single BZ22Z outpatient episode. Where FA is not required, OCT and/or ophthalmoscopy can occur during a single BZ23Z episode. e.g. CRVO 0-6 months requires 1 BZ22Z and 2 BZ23Z.</td></tr>
<tr><td>109</td><td>..</td><td>..</td><td>The cost per patient is derived within the model, rather than an input to it</td></tr>
<tr><td>110</td><td>VL_Cost</td><td>Yes</td><td>Note that the average £8,055 cost is for the base case assumed to apply to all patients ≤38 letters in the BSE</td></tr>
<tr><td>111</td><td>AE_Cost</td><td>Yes</td><td></td></tr>
<tr><td>112</td><td>AE_Cost</td><td>Yes</td><td></td></tr>
<tr><td>113</td><td>AE_Cost</td><td>Partial</td><td>Exceptions
<table>
<tr><th>Variable</th><th>T113</th><th>Model</th></tr>
<tr><td>6th treatment phakic patients</td><td>74.81%</td><td>0.24%</td></tr>
<tr><td>6th treatment cost/patient</td><td>£114.35</td><td>£0.37</td></tr>
</table></td></tr>
</table>

Text	*AE_Cost*	..	Not tabulated, but the values cited for retinal tear and retinal detachment within the text of the submission cross check with the electronic model
114	*Data & References*	Yes	
App. 21	*Parameter_Table*	Yes	
App. 22	*Transitions*	Partial	There is a minor discrepancy with Observation BRVOD0-D30 where [redacted] in appendix 22 reads [redacted] in the model. The dexamethasone BRVO prior laser D180-> TPM is incorrectly copied from the previous TPM within appendix 22. The model applies: [CIC] 

Correspondence between electronic model and sources cited

Severe vision loss hazard for mortality

The model applies a hazard ratio for mortality for severe visual impairment of 1.54 where severe visual impairment was defined as being blind in both eyes, as drawn from the study of the US National Health Interview Study by Christ et al study. [15]

Note that Christ et al[15] also reported a mortality multiplier of 1.23 for those having some visual impairment. It is not obvious how this could have been applied to the health states of the model as the descriptor was not based upon measured BCVAs, but it would appear to definitely apply to where the initially affected eye falls into blindness. Not having attempted to apply this additional hazard ratio within the modelling may as a consequence have been a conservative assumption on the part of the manufacturer.

Note that within the model there are no follow-up costs after treatment with dexamethasone stops. This would not bias results if there was not additional mortality hazard from severe visual impairment, but given an additional mortality hazard this might tend to give rise to a slight bias.

Severe vision loss cost

The submission cites Colquitt JL, et al. 2008. This HTA monograph calculated the annual costs of BCVA falling below 6/60 in the BSE for an assessment of ranibizumab and pegaptanib for wet AMD as outlined below, where 2005 are the costs as calculated by Colquitt et al[13] and 2009 uprates these for inflation using the PSSRU HSCS index.

Table 32. Cost of severe vision loss Colquitt et al

	% patients	Unit Cost	2005	2009
Blindness registation	95%	£115	£109	£127
Low-vision aids	33%	£150	£50	£57
Low-vision rehabilitation	11%	£259	£28	£33
Community care	6%	£6,552	£393	£456
Residential care	30%	£13,577	£4,073	£4,725
Depression	39%	£431	£168	£195
Hip replacement	5%	£5,379	£269	£312
		Year 1	£5,091	£5,905
		Year 2+	£4,903	£5,688

Uprating the values of Colquitt et al[13] for inflation results in an annual cost of blindness that is somewhat less than the £8,055 annual cost derived by the manufacturer. The main source of this difference is the average inflated cost of residential care: £4,725 in the above as compared with £7,192 within table 110 of the submission. Examining Colquitt et al in slightly more detail, the 2005 monthly cost of residential care of £373 implies an annual cost of £19,396. The figure of £13,577 is derived by Colquitt et al applying a multiplier of 70% due to an estimated 30% of patients privately funding their private residential care.

Rate of cataract extraction

Within relatively short trials investigators may tend not to subject patients to surgery unless this is strictly necessary. The pooled data apparently indicates that by the end of the extension phase around 14% of patients had developed subcapsular cataracts, most of which would at some point require surgery. Within the model, the cumulative rate of cataracts extractions including the day 360 figure was around 3%.

Rate of fellow eye involvement

In CRVO, the systematic review by McIntosh and colleagues [4] reported CRVO in fellow eye of 1.4% within 3 years, and around 5% of FE BRVO.

In BRVO, the systematic review by Rogers and colleagues [5] reported a 10% FEI involvement with BRVO but this was based on only one small study with 29 eyes. They reported cross-sectional data suggesting a 5% FIE.

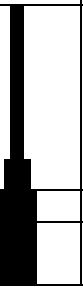
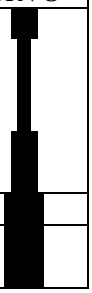
Rate of RVO to MO in fellow eye

It was assumed that all FEI RVO would develop into macular oedema, and implicitly that this macular oedema would not be eligible for laser surgery. This was justified by the manufacturer on the basis of the patients within the Hayreh study having presented at clinic.[14] But this reference was used for the estimation of FEI RVO, and as such the patients may mainly have initially presented due to problems with their initially affected eye, not the fellow eye. Hayreh and colleagues[14] performed a detailed bilateral ocular examination at initial presentation and also at follow up visits, with quarterly follow up during the 1st year, six monthly follow up for the next two years and annual follow up thereafter. In the light of this, it is reasonable to have assumed that the initial presentation would be due to being symptomatic. It is less obvious that the development of FEI RVO as measured by Hayreh and colleagues would necessarily have been symptomatic or involving macular oedema.[14]

Resolution rates

The resolution rates were drawn from the pooled clinical trial data. As outlined in responses to ERG clarification questions, combining tables 7, 7a and 15 the overall resolution rates at day 180 applied within the modelling of [redacted] for CRVO and [redacted] for BRVO were derived as below:

Table 33. Patient numbers underlying calculation of resolution rates

	CRVO	BRVO
ME resolved at day 180 Discontinued prior to day 180 with ME resolved Safety Other Total resolved at day 180 Total not treated at day 180		
Resolution rate at day 180		
Excluding safety Excluding safety and other		

Some patients at day 180 with OCT<250µm were not treated due to safety or other concerns. The model classified these as being resolved. It is possible that some of these patients would have OCT<250µm due to macular oedema having led to atrophy of the retina. This may lead to visual stability in a sense, but whether these patients should be included within the calculation of resolution rates is a moot point.

Cataract extraction unit cost

The ERG has not been able to replicate the costs of cataract extraction, this being £965 made up of £73 for a follow up non-admitted consultant led outpatient appointment coupled with £892 for the cataract extraction. The electronic model cites:

> *National Schedule of Reference Costs 2008-09 for NHS Trusts: Non-Surgical Ophthalmology with length of stay 2 days or more & Non-Surgical Ophthalmology with length of stay 1 day or less. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)*

The written submission in a footnote to table 113 gives:

> *Procedure cost based on NHS reference cost, weighted by activity across elective inpatient, non-elective inpatient, and day cases, using HRG codes BZ24A Non-surgical ophthalmology with length of stay 2 days or more and age ≥ 19, and BZ24C Non-surgical ophthalmology with length of stay 1 day or less and age ≥ 19.*

It seems possible that the £892 per cataract extraction is due to an accidental cut and paste of the annual follow up costs in the absence of treatment, which were also costed at £892.

Pharmacological treatment for increased IOP

The unit costs within Table 111 cross check with BNF 60.

Retinal detachment surgery

The electronic model cites:

> *National Schedule of Reference Costs 2008-09 for NHS Trusts: Vitreous Retinal Procedures Category 1. Weighted by activity across non-elective inpatient (long stay), elective inpatient, non-elective inpatient (short stay)*

to arrive at an average cost of £689 per procedure. Averaging these across NSRC04 2008-09 would seem to result in a unit cost of £1,173. However, including the day cases within this weighted average does result in an average unit cost of £689. Note also that since day cases make up the vast majority of procedures within this latter average, this unit cost is little different from the average day case cost of £648.

Surgical procedures for increased IOP

Table 112 lists the unit costs per procedure based upon glaucoma categories 1, 2 and 3 together with the £689 derived from *Vitreous Retinal Procedures Category 1* as outlined above. As previously, referencing within the electronic model omits day cases, but including these as per the written submission results in average costs for glaucoma procedures from NSR04 2008-09 of £557 for category 1 which is broadly in line with the £571 of table 112 and the *AE_Cost* worksheet of the electronic model. The other unit costs cross check, though the addition of excess bed use to these figures very marginally increases them.

Possible revisions to base case parameters

Unit cost of dexamethasone administration

A key consideration within the modelling is the setting required for the administration of each dexamethasone implant. The default used by the manufacturer is BZ23Z as a day case from NHS reference costs NSRC04 2008-09. While the coding is correct it is questionable whether the procedure would require a day case and it seems more likely that an outpatient visit would be sufficient. The ERG has checked the opinion of clinicians with experience which suggests that outpatient administration would be usual. The respective volume and average costs of these are:

Table 34. Reference cost BZ23Z Outpatient and Daycase

		Out Patient		Day Case	
Code	Description	No.	Cost	No.	Cost
BZ23Z	Vitreous Retinal Procedures - category 1	171,937	£150	57,263	£648

Given the direct drug cost for each dexamethasone implant of £870, the total outpatient cost and day case cost per implant are £1,020 and £1,518 respectively. The outpatient costing reduces the cost per implant by a third. This has a major impact upon the cost effectiveness estimates, as outlined at the end of this chapter.

Unit cost of cataract extraction

It is questionable to have used BZ24A and BZ24C, averaged across a range of admission types. NHS reference costs NSRC04 2008-09 have the following codings specific to cataract surgery:

Table 35. Reference costs for cataract surgery

		Day Case		Elective IP	
Code	Description	No.	Cost	No.	Cost
BZ01Z	Enhanced Cataract Surgery	4,941	£950	682	£1,714
BZ02Z	Phacoemulsification Cataract Extraction & Lens Implant	289,762	£789	6,902	£1,596
BZ03Z	Non-Phacoemulsification Cataract Surgery	7,060	£763	598	£1,866
BZ04Z	Lens Capsulotomy	13,835	£377	76	£1,261

ERG expert opinion suggests that the most appropriate procedure given the circumstances under consideration would be BZ02Z: Phacoemulsification Cataract Extraction & Lens Implant, with this being carried out as a day case. Fortunately, this gives a cost of £789 which is not far out of line with the £892 applied by the manufacturer within the modelling.

Including elective inpatient treatments would yield a marginally higher average cost of £808. Further including non elective short stay, non elective long stay and/or excess bad days has minimal impact upon this average.

Annual cost of blindness

PSSRU suggests a weekly cost for private residential care of £467, equivalent to an annual £24,284 which is similar to the value in table 110. Applying the 70% multiplier results in an average of £16,999 which when substituted into the above together with updated community care costs and hip replacement costs, other values being increased in line with inflation results in:

Table 36. Revised costs of severe vision loss

	% patients	Unit Cost	Average
Blindness registration	95%	£133	£127
Low-vision aids	33%	£174	£57
Low-vision rehabilitation	11%	£300	£33
Community care	6%	£6,708	£402
Residential care	30%	£16,999	£5,100
Depression	39%	£500	£195
Hip replacement	5%	£5,336	£267
		Year 1	£6,181
		Year 2+	£5,964

The ongoing costs of BCVA falling below 6/60 in the best seeing eye of £5,964 are around a quarter less than the £8,055 estimated by the manufacturer and used within the modelling.

4.6 ERG additional sensitivity and scenario analyses

The manufacturer has presented a good range of univariate sensitivity analyses, and the scenario analyses are sufficient to determine the effects of the main structural assumptions that feed into the model. In the light of this and that even the revised model submitted on 23 Nov 2010 contains serious errors around the modelling of fellow eye involvement, the ERG has not undertaken particularly extensive additional sensitivity or scenario analyses.

Additional sensitivity analyses undertaken by the ERG relate to the unit costs applied within the modelling, and the age at entry since the range for this within the manufacturer model was only between 63.9 years and 65.1 years.

1. Unit cost of dexamethasone administration based upon the £150 outpatient cost rather than the £648 day case cost
2. Annual ongoing cost of severe visual impairment of £5,964 as per the method employed by Colquitt et al
3. 1 and 2 combined, together with a unit cost per cataract extraction of £789 day case cost rather than the £892 the source of which is not obvious to the ERG
4. 3 combined with an age at entry of 55 rather than 64.5
5. 3 combined with an age at entry of 75 rather than 64.5

Note that the following sensitivity analyses use the partially corrected manufacturer model submitted on the 23rd November 2010 and not the original model upon which the written submission is based.

Table 37. ERG additional sensitivity analyses

	WSE: BSE 90%:10%			WSE: BSE 97%:03%		
Weibull FEI	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£6,041	£7,987	dominant	£15,800	£10,206	dominant
1. Admin £150	dominant	£846	dominant	£7,683	£2,470	dominant
2. Blindness £5,964	£11,515	£13,067	£1,445	£20,109	£15,285	£4,367
3. 1&2 & Cat. £789	£4,717	£5,910	dominant	£11,966	£7,531	dominant
5. 3 & age 55	dominant	£363	dominant	£6,026	£1,522	dominant
6. 3 & age 75	£15,923	£18,188	£5,447	£25,549	£21,104	£8,868
	WSE: BSE 90%:10%			WSE: BSE 97%:03%		
No FEI	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£17,279	£34,277	£11,905	£35,708	£47,301	£23,348
1. Admin £150	£9,284	£23,553	£6,212	£25,311	£34,186	£16,219
2. Blindness £5,964	£21,095	£35,979	£14,442	£37,196	£47,925	£24,301
3. 1&2 & Cat. £789	£13,072	£25,232	£8,737	£26,764	£34,782	£17,157
5. 3 & age 55	£8,124	£19,379	£5,390	£20,635	£27,586	£13,209
6. 3 & age 75	£24,461	£39,526	£16,565	£41,901	£52,722	£26,888

In terms of the structural assumptions within the modelling, the scenario analyses of the manufacturer provide a good basis for examining the main model drivers, with the following exception. For extrapolation the model reapplies the six month TPM from the open label phase for the dexamethasone arm, but reapplies the final three months TPM from the RCT phase for the observation arm. The reapplication of TPMs of different duration for the extrapolation within the modelling may have affected results. There are three obvious scenario analyses for exploring this:

1. Reapplying the final three months TPMs from the RCT phase for the dexamethasone arm
2. Reapplying the final three months TPMs from the open label phase for the dexamethasone arm

3. Reapplying the six month TPM from the RCT phase for the observation arm
4. Ignoring the open label phase and reapplying the six months TPMs from the RCT phase for both the dexamethasone arm and the observation arm

Given the evolution of visual acuity within the dexamethasone arm as outlined in the likes of Table 29 of the submission, with what appears to be a peak effect on BCVA followed by a worsening over the latter period of the RCTs, options 1 and 2 seem likely to be an unduly pessimistic approach to the extrapolation of results for the dexamethasone arm.

Option 3 of reapplying the 6 month TPM from the RCT to the observation arm appears to be more promising with it not introducing any obvious source of bias, while still aligning the TPM duration used for extrapolation between the dexamethasone arm and the observation arm.

Option 4 would provide the most equal treatment between the arms, but would discard data from the open label phase. It would, however, provide a cross check of the results of applying option 3. It could be argued that a larger placebo effect might apply during the RCT phase than during the open label phase. For BRVO, it could also be argued that there would be a higher rate of natural resolution during the RCT phase than during the open label phase. Both of these arguments might suggest that using the final 3 months of the RCT for extrapolation for the observation arm would be more reasonable.

The ERG has only explored the impact of applying option 3. This has been run for two sets of analyses: option 3 with the base case unit costs as applied by the manufacturer; and, option 3 with the unit costs of sensitivity analysis 3 as outlined above. The method of applying option 3 within the revised manufacturer model is outlined in Appendix 4. *Additional ERG structural analysis: 180 day TPMs for observation*

Within the *Transitions* worksheet:

For the CRVO sham D180->D360 TPM of AN31:AS36 within the cell formulae:

[redacted]

Change

[redacted]

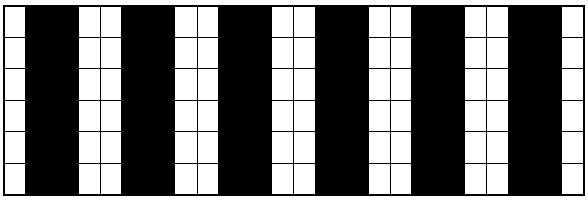
To

MMULT(MMULT(MMULT($D$31:$I$36,$M$31:$R$36),$V$31:$AA$36),$AE$31:$AJ$36)

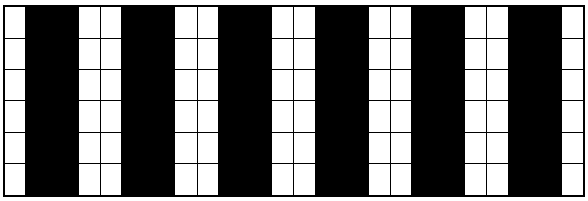
[redacted]

Also set the subsequent TPMs for sham equal to the above: AW31:BB36, BF31:BK36, BO31:BT36, BX31:CC36 and CU63:CZ68.

This changes the TPM from



To



Where the rows sum to 1, the health states working down the rows run from HS0 to HS5 and the columns working from left to right run from HS0 to HS5.

For the BRVO sham D180->D360 TPM of within the cell formulae:

[redacted]

Change

[redacted]

To

MMULT(MMULT(MMULT($D$54:$I$59,$M$54:$R$59),$V$54:$AA$59),$AE$54:$AJ$59)

Where within this the TPMs $D$54:$I$59, $M$54:$R$59, $V$54:$AA$59 and $AE$54:$AJ$59 relate to D0->D30, D30->D60, D60->D90, D90->D180 respectively.

.

For the all CRVO modelling this changed the observation TPM used for extrapolation from:

	HS0	HS1	HS2	HS3	HS4	HS5	Total
HS0							100%
HS1							100%
HS2							100%
HS3							100%
HS4							100%
HS5							100%

To:

	HS0	HS1	HS2	HS3	HS4	HS5	Total
HS0							100%
HS1							100%
HS2							100%
HS3							100%
HS4							100%
HS5							100%

For the all BRVO modelling this changed the observation TPM used for extrapolation from:

	HS0	HS1	HS2	HS3	HS4	HS5	Total
HS0							100%
HS1							100%
HS2							100%
HS3							100%
HS4							100%
HS5							100%

To:

	HS0	HS1	HS2	HS3	HS4	HS5	Total
HS0							100%
HS1							100%
HS2							100%
HS3							100%
HS4							100%
HS5							100%

Note that the above relates to the BRVO All patients group. The model applies slightly different TPMs for the BRVO-MH subgroup, and noticeably different TPMs for the BRVO-PL subgroup.

Revising the model to apply the 6 month RCT TPM data to the observation arm for extrapolation resulted in the following.

Table 38. ERG additional structural sensitivity analyses

	WSE: BSE 90%:10%			WSE: BSE 97%:03%		
Weibull FEI	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£6,041	£7,987	dominant	£15,800	£10,206	dominant
Revised Obs. TPM	£15,395	£28,908	£1,849	£28,422	£29,904	£5,420
Rev. TPM & costs	£11,723	£21,396	£1,366	£21,407	£22,096	£3,991
	WSE: BSE 90%:10%			WSE: BSE 97%:03%		
No FEI	CRVO	BRVO-MH	BRVO-PL	CRVO	BRVO-MH	BRVO-PL
Base case	£17,279	£34,277	£11,905	£35,708	£47,301	£23,348
Revised Obs. TPM	£25,163	£81,587	£19,311	£46,350	£99,018	£31,777
Rev. TPM & costs	£18,981	£60,104	£14,196	£34,728	£72,831	£23,358

These results should be read in conjunction with the explanation around the manufacturer choice of TPMs and TPM duration found within section 6.3.2 of the submission. As can be seen from the above, the choice of the duration of the TPM used within the observation arm for extrapolation is not a minor aspect, and it appears to have a major impact upon the estimated cost effectiveness.

4.7 Comparison with NICE reference case

Table 39. Comparison with NICE reference case

Attribute	**Reference case**	**Does the *de novo* economic evaluation match the reference case**
Comparator(s)	Therapies routinely used in the NHS, including technologies regarded as current best practice	Observation; i.e. no treatment. No consideration of watchful waiting with the possibility of laser photocoagulation for the BRVO-MH subgroup
Perspective costs	NHS and Personal Social Services (PSS)	Yes
Perspective benefits	All health effects on individuals	HRQoL was a function of BCVA in the WSE, unless the BSE was affected at which point HRQoL was a function of BCVA in the BSE. Adverse events were not explicitly modelled as having an effect upon HRQoL.
Form of economic evaluation	Cost-effectiveness analysis	Yes
Time horizon	Sufficient to capture differences in costs and outcomes	40 years or to age 100 which is sufficient give the base case age modelled
Synthesis of evidence on outcomes	Systematic review	N/A: Pooled trial data used No indirect comparisons with other possible agents such as anti-VEGF drugs was done.
Outcome measure	Quality adjusted life years (QALYs)	Yes, though these were only related to the main health states of the model. Adverse events and assumptions around the rates of these, particularly cataract rates, did not affect the QALY calculation
Health states for QALY	Described using a standardised and validated instrument	No. HRQoL values were modelled as a function of the VFQ-UI. The HRQoL values implied by applying this function to day 180 VFQ-UI values within the pooled trial data were regressed on the BCVA day 180 date to derive HRQoL as a function of BCVA. HRQoL as a function of BCVA in

		the affected eye was derived separately for those with their WSE affected and those with their BSE affected.
Benefit valuation	Time-trade off or standard gamble	Time trade off to estimate HRQoL associated with eight health states associated with the VFQ-UI
Source of preference data for valuation of changes in HRQL	Representative sample of the public	607 members of the UK, US and Canadian public undertook the TTO
Discount rate	An annual rate of 3.5% on both costs and health effects	Yes
Equity	An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit	N/A
Sensitivity analysis	Probabilistic sensitivity analysis (PSA)	The base case results are presented for deterministic modelling and for probabilistic modelling. These indicated that the model was not particularly non-linear with the base case estimates of the deterministic modelling being reasonably closely aligned with the central estimates of the probabilistic modelling. Additional sensitivity analyses and scenario analyses were based upon the deterministic model.

5: DISCUSSION

5.1 Summary of clinical effectiveness issues

The clinical effectiveness of dexamathasone is not in doubt. The main uncertainties are;

- Should re-treatment start earlier than in the GENEVA trials, as soon as visual acuity starts to decline?
- We do not know how often patients should be re-treated. The suggestions of five or six repeats in the industry submission is based on opinion in the absence meantime of evidence.
- The effects of such numbers of injections with a relatively large needle are not known
- How does dexamethasone compare with the anti-VEGF agents such as ranibizumab or bevacizumab?

5.2 Summary of cost effectiveness issues

Most of the ICERs in the base case and sensitivity analyses were within the ranges usually considered acceptable, and some were lower than often seen. Errors in the model around the effect of FEI created uncertainties.

We do not have data on the cost-effectiveness of dexamethasone relative to bevacizumab or ranibizumab.

The cost-effectiveness might be improved if only those who responded well (e.g. a gain of 10 or more letters) were re-treated.

The ERG is of the opinion that treatment visits would be classed as outpatient attendances, not as day cases, which reduces the cost significantly.

5.3 Implications for research

The main needs are for;

- Longer follow-up to assess long-term effects including adverse effects, and number of treatments required
- Head to head trials against the anti-VEGF agents

5.4 Conclusions

The most important outcome is the proportion of people in which dexamethasone improves vision by a clinically significant amount, such as the roughly 18% of people with CRVO who gain 15 or more letters compared to the 12% in the sham arm over 180 days. Around 27% gain 10 or more letters after 180 days, compared to the 24% in the sham arm. In CRVO, the outlook without treatment is poor.

In BRVO, the natural history outlook is better with a greater proportion in which there is natural recovery, so that the difference is smaller, with dexamethasone increasing the proportion gaining 15 or more letters by about 23%, compared to natural recovery i.e. 20% in the sham arm. The numbers gaining 10 letters or more after 180 days are 41% with dexamethasone, compared to 33% in the sham arm. This applies to those in whom laser treatment is contra-indicated, or has not given an adequate response. In other people with BRVO, laser treatment would be first line treatment.

One key issue is that quality of life is determined mainly by vision in the better seeing eye (and indeed people may sometimes be unaware of visual loss in the worse seeing eye). A short-term strictly cost-effectiveness perspective might suggest that treatment of the worse-seeing eye may not always be cost-effective. The ERG would regard this as a controversial issue, given the possibility of recurrence of RVO in the other eye.

There is still a need for more effective treatments for macular oedema after RVO.

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APPENDICES

Appendix 1 Evidence base for comparators

Table 40. Comparison of different comparators (Randomised controlled trials)

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Ranibizumab for CRVO								
Brown 2010 (CRUISE study)[12]	Phase III, multicentre, randomised, injection-controlled study	To assess the efficacy and safety of intraocular injections of 0.3mg or 0.5 mg ranibizumab in patients with ME after CRVO	6 months with an additional 6 months follow up	392 patients; rani 0.3mg (n=132); rani 0.5mg (n=130); sham injection	Mean BCVA letters gained with 0.3mg: 12.7, with 0.5mg: 14.9 and with sham: 0.8	At 6months mean change in CFT with 0.3mg: -433.7; with 0.5mg: -452.3; with sham: -167.7	-0.3mg rani vs. sham: p<0.0001; -0.5mg rani vs. sham: p<0.0001	2 serious eye AEs: 1 vitreous haemorrhage (sham grp); 1 iris neovascularisation (0.5mg grp). 2 patients (0.3mg rani grp) and 2 patients (0.5mg rani grp) had cataract. 1 pt each in the 3 grps had MI; 1 pt in the 0.5mg grp had transient ischaemia and angina; 1 pt in the 0.3mg grp had retinal artery occlusion; 1 pt in sham grp had hypertension.
Kinge 2010 (ROCC study)[16]	Prospective, multicenter, randomised, double-masked, placebo-controlled trial	To evaluate the short-term effect of IV ranibizumab injection in patient with ME secondary to CRVO	6 months	32 patients enrolled, 29 completed (16 male, 13 female); rani (n=15); sham (n=14)	Overall mean change in BCVA score was a gain of 12 SD20 EDTRS letters in the ranibizumab grp (p=0.040) and a loss of 1 SD17 ETDRS letters in the sham grp (p=0.765).	Overall change in CMT was -304 SD194 µm in the ranibizumab grp (p<0.001) and -151 SD205 µm in the sham grp (p=0.017)	-BCVA: Rani vs. sham: p=0.067 -CMT: Rani vs. sham: p=0.05	-Ranibizumab grp: 1 pt experienced retinal artery thrombosis shortly after the first injection; 2 pts experienced a small haemorrhage in the vitreous cavity attributable to vitreous traction, which resolved without further complications; No reports of endophthalmitis, other infections, retinal detachment or iatrogenic

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
								cataract formation. <u>-Sham grp:</u> One pt had retinal tear. Another pt developed neovascular disease.
Ranibizumab for BRVO								
Campochiaro 2010[17]	Prospective, randomised, sham injection-controlled, double-masked, multicentre phase III trial	To assess efficacy and safety of intraocular injections of 0.3 mg 0.5mg ranibizumab in pts with ME following BRVO	6 months with an additional 6 months follow up	397 patients; rani 0.3mg (n=134); rani 0.5mg (n=131); sham (n=132)	Mean letters gained with 0.3mg: 16.6 letters; 0.5 mg: 18.3 letters; sham: 7.3 letters; in all treatment grps, the mean improvement in BCVA was greater for patients who were diagnosed with BRVO <3 months before study	Reduction in CFT was rapid and significant with both doses of ranibizumab compared with sham	-BCVA: 0.3 mg vs. sham: p<0.0001; 0.5 mg vs. sham: p<0.0001 -CFT: both doses of rani at all time points vs. sham: p<0.0001	-Retinal detachment and retinal tear occurred in the same patient in 0.3 mg grp and led to study discontinuation; -AEs of cataract -4 pts (sham grp), 1 (0.3mg grp) and 4 (0.5 mg grp); haemorrhagic stroke in 1 pt (sham grp); nonocular haemorrhage (1 intra-abdominal haematoma, 1 rectal haemorrhage) in 2 pt (0.3mg grp); hypertension in 2 pts (0.3 mg grp); 1 fatal cerebral haemorrhage, 1 nonfatal MI, 1 unstable angina, 1 haemorrhage after colonoscopy, 1 intestinal perforation in a pt with intestinal obstruction from haemorrhages -all occurred in the 0.5 mg grp.
Bevacizumab and triamcinolone acetonide for BRVO								

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Cekic 2010[18]	Prospective, randomised, interventional comparative study	To compare the efficacy of IVTA, IVB, and a combination of IVTA + IVB for ME secondary to BRVO	6 months Within 3 months of first injection, 8/17 pts in IVTA, 7/14 in IVB and 9/21 in IVTA+IVB received macular grid laser photocoagulation	52 eyes of 52 patients (29 male, 23 female) with ME and BRVO. IVTA (n=17); IVB (n=14); IVTA + IVB (n=21)	At 6 months, only IVB showed significant improvement in VA(p=0.01)	At 6 months: all grps showed significant reduction (IVTA: p=0.02; IVB: 0.02; IVTA+IVB: p=0.04)		-None developed uveitis, endophthalmitis, or a thromboembolic events; -At 6 months, cataract progression in 5/14 (36%) phakic eyes in IVTA grp, in 1/12 (8%) phakic eyes in IVB grp and in 2/20 (10%) phakic eyes in IVTA+IVB grp; -Macular epiretinal membrane formation in 4 patients (24%) in IVTA group; -Average IOP change from baseline at 1 month was significantly higher in IVTA group while in 2 other groups, it was not different.
Bevacizumab vs. laser therapy for BRVO								
Russo 2009[19]	prospective, randomized study	To evaluate the outcome of cystoid ME treated with IVB inj and macular grid laser photocoagulation (GLP), in patients with perfused BRVO	12 months	30 eyes of 30 pts; GLP [15 pts (11 male; 4 female); IVB [15 pts (12 male; 3 female)]	The group receiving IVB had better BCVA than those receiving GLP at all time points.	The group receiving IVB had lower CMT values than those receiving GLP at all time points.		-No cases of uveitis, endophthalmitis, ocular toxicity, or any obvious systemic adverse events; -No significant changes in IOP, or lens status; minor local adverse events related to the treatment procedure occurred in 9 pts during the first post inj week (conjunctival hyperaemia and subconjunctival haemorrhage)

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Triamcinolone acetonide and laser for RVO								
CRVO 1995[20]	Multicentre, randomised controlled clinical trial	To evaluate the efficacy of macular grid photocoagulation in preserving or improving central VA in eyes with ME due to CRVO and BCVA of 20/50 or poorer	3 years	Grid laser : 77 pts; Control (observation): 78 pts	Mean changes in VA score from baseline to the 36 month visit was a loss of 4 letters in treated eyes and a 3 letters loss in untreated eyes.	Treatment significantly reduced the amount of ME	No significant difference between treated and untreated pts at any f/u visits in either of VA or in change in VA.	Not reported
Parodi 2008[21]	Prospective, pilot randomised clinical trial	To compare the effectiveness of subthreshold grid laser treatment (SGLT) alone or in combination with IVTA injection (SGLT-IVTJ) for the treatment of ME secondary to BRVO	12 months	24 eyes of 24 patients; SGLT (13 eyes); SGLT-IVTJ (11 eyes)	Final VA in the SGLT-IVTJ group and SGLT group were 0.35 and 0.65 respectively, with a statistically significant improvement in favour of the SGLT-IVTJ group. At the 12-month examination, BCVA in the SGLT group showed a stabilisation with respect to the baseline value.	-10 (91%) in the SGLT-IVTJ grp and 8 pts (62%) in the SGLT grp gained at least 10 letters; 1 pt in the SGLT-IVTJ grp and 3 pts (23%) in the SGLT grp maintained the initial VA; 2 pts (15%) lost four lines in the SGLT grp. -At the 6-month f/u, both grps showed a statistically significant reduction in MFT that appeared stable up to the twelfth month.		-IOP increased in 6 pts (54%) of the SGLT-IVTJ group; -No other adverse events, such as cataract, endophthalmitis, vitreous haemorrhages and retinal detachment.
Triamcinolone acetonide vs. Observation for CRVO								
Chew 2009 (SCORE study research group)[22]	Multicentre, randomised, clinical trial	To compare the efficacy and safety of 1 mg and 4 mg doses of preservative-free triamcinolone with observation of eyes with vision loss associated with ME secondary to	12 months for VA and 36 months to monitor adverse events. IVTA given every 4	271 patients;	Fivefold increase in the rates of VA gain with 1 mg or 4 mg IVTA at 1 year f/u; Approx. 7 % in the 1 mg IVTA, 27% in the 4 mg IVTA, and 26% in the	Median reduction in retinal thickness was similar across the grps		-20% in 1 mg, 35% in 4 mg required IOP lowering medications; -26% in 1 mg, 33% in 4 mg had lens progression; -3 eyes in 1 mg, 21 eyes

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
		perfused CRVO	months.		observation grp (grp received standard care of grid photocoagulation for BRVO and standard care of observation for CRVO) gained 3 lines or more vision at 1 year.			in 4 mg required cataract surgeries by 24 months (p=0.001); -None had endophthalmitis or retinal detachment.
SCORE study(Ip 2009)[23]	multicenter, prospective, randomized clinical trial	To compare the efficacy and safety of 1-mg and 4-mg doses of preservative-free IVTA with observation for eyes with vision loss associated with ME secondary to perfused CRVO	12 months	271 participants	% of participants with a gain in VA letter score of ≥ 15 was 6.8%, 26.5%, and 25.6% for the observation, 1-mg, and 4-mg groups, respectively.	- Both triamcinolone grps had a similar change from baseline to month 12 in mean VA letter score (an approx 1-2–letter loss) compared with a mean loss of 12 in the observation grp -At the month 4 visit, the median decrease was greater in the 4-mg triamcinolone group (196 μm decrease) than the 1-mg (77 μm decrease) and the observation groups (125 μm decrease; p<0.001		No cases of infectious or non-infectious endophthalmitis or retinal detachment in any of the 3 study groups; rates of elevated IOP and cataract were similar for the observation and 1-mg groups, but higher in the 4-mg group; ; vitreous floaters and conjunctival haemorrhage reported in a similar proportion of participants in both triamcinolone grps through 12 months (vitreous floaters, 24% for the 1-mg grp and 33% for the 4-mg grp; conjunctival haemorrhage, 29% for the 1-mg grp and 28% for the 4-mg grp); systemic adverse events were similar among the SCORE-CRVO trial grps.
Triamcinolone acetonide vs. Standard care (laser therapy) for BRVO								

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
SCORE study (Scott 2009)[8]	multicenter, prospective, randomized clinical trial	To compare the efficacy and safety of 1-mg and 4-mg doses of preservative-free IVTA with standard laser therapy) for eyes with vision loss associated with ME secondary to BRVO	12 months	411 participants	% of participants with a gain in VA letter score of 15 or more from baseline to month 12, was similar in all 3 grps: 28.9%, 25.6%, and 27.2% in the standard care, and 1-mg and 4-mg triamcinolone groups, respectively.	-After 12 months, mean change from baseline in VA letter score is greater in the standard care group compared with the 2 triamcinolone groups ($p<0.05$). -At the month 12 visit, the median decrease from baseline in OCT-measured center point thickness was similar among the 3 treatment grps		-Rates of adverse events (particularly elevated IOP and cataract) were highest in the 4-mg group; -No reports of infectious endophthalmitis in the standard care group or 1-mg IVTA grp whereas 1 case in the 4-mg IVTA 3 days after the third injection; -Vitreous floaters (31% of 1-mg IVTA grp and 26% of 4-mg IVTA grp) and conjunctival haemorrhage (30% of 1-mg IVTA and 33% of 4-mg IVTA) -Systemic adverse events similar among the SCORE-BRVO trial groups. Highest incidence through 12 month, with 10%, 16%, and 15% of participants reporting at least 1 event in the standard care, 1-mg, and 4-mg groups, respectively.
Pegaptanib sodium for CRVO								
Wroblewski 2009[11]	Dose-ranging, double-masked, multicentre, phase 2	To assess the safety and efficacy of pegaptanib sodium for the treatment of ME following CRVO.	30 weeks	pegaptanib 0.3 mg (n=33); pegaptanib 1 mg (n=33); sham (n=32)	patients receiving 0.3 mg and 1 mg pegaptanib gained an avg of 7.1 and 9.9 letters whereas	-% of treated gaining ≥15 letters of VA: <u>0.3 mg:</u> 12/33 (36%) <u>1 mg:</u> 13/33 (39%)	-avg. letter gain: 0.3 mg vs. sham: p=0.09; 1 mg vs. sham: p=0.02	-No serious ocular adverse events were reported. -None developed

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
	randomised trial				in those treated with sham had lost an avg of 3.2 letters	sham: 9/32 (28%) - mean reduction from baseline was greater in both pegaptanib grps than with sham at all time points	-% of pts gaining ≥15 letters: difference not significant -CRT and centre subfield: 0.3 mg vs. sham: p=0.13; 1 mg vs. sham: p=0.06	endophthalmitis, traumatic cataract or retinal detachment. -No evidence of a sustained effect on IOP. -No evidence of increased risk of systemic effect.

CRT: central retinal thickness; CMT: central macular thickness; CFT: central foveal thickness; FT: foveal thickness; grp: group; SD: standard deviation; AE: adverse events; ME: macular edema; IVTA: intravitreal triamcinolone acetonide; IVB: intravitreal bevacizumab; IOP: intraocular pressure; CRVO: central retinal vein occlusion; BRVO: branch retinal vein occlusion; HRVO: hemi retinal vein occlusion; VA: visual acuity; BCVA: Best corrected visual acuity; f/u: follow up; MI: myocardial infarction

Table 41. Comparison of different comparators. Other type of studies [prospective and retrospective studies]

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Bevacizumab for RVO								
Ach 2010[24]	Retrospective study	To evaluate prognostic baseline factors for IVB therapy of ME due to RVO	minimum of 20 weeks f/u	BRVO (n=32); CRVO (n=38)	Not reported	Prognostic baseline factors for IVB of ME due to RVO: CRVO group: 1st injection- 34.3% complete resolution of ME, in 65.7% ME persisted; last visit- 12.6% did not experience any recurrence of ME, 43.7% had recurrence, 43.7% ME persisted since baseline. VA (p=0.940) and gender (p=0.099) not predictive. BRVO group: 1st injection- 52.7% complete resolution, 47.3% ME persisted; last visit- 5.3% no recurrence, 60.1% had recurrence, 34.6% ME persisted since baseline.		No adverse events; none of the patients developed neovascular complications during f/u
Figueroa 2010[25]	Prospective, non-randomised, interventional case-series	To evaluate the efficacy and safety of IVB as the sole treatment of RVO presenting with decreased VA due to ME	at least 6 months f/u	46 patients (25 male, 21 female). CRVO (n=18), BRVO (n=28)	BRVO grp: VA improved throughout the f/u period, mainly in the first 2 months. Median	BRVO grp: Mean CMT decreased significantly after injection (p<0.001) and persisted. CRVO grp: Mean		No significant complications developed in either group after treatment with bevacizumab.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
					improvement was 2 snellen lines. CRVO grp: VA improved progressively, main improvement in the first month. Median improvement was one snellen line.	CMT decreased significantly after injection ($p<0.001$) and persisted.		
Fish 2008[26]	Retrospective chart review from a large referral retinal practice	To compare IVB to other current treatments of BRVO and HRVO with consideration to visual outcome , cost, convenience, and risk of treatment	avg. f/u time of 10 months; some pts also received IVTA in combination with IVB or during f/u; 39 pts received IVB only	56 patients with BRVO and HRVO	56 patients:. Overall, vision improved or remained stable in 72% of the eyes and worsened in 27% of the eyes. Improvement of 3 lines (0.3 logMAR) occurred in 30%, improvement of 2 lines occurred in 46% and of 6 lines in 13%. A decrease of 3 lines occurred in 18% of eyes. IVB grp only (39 pts): Overall, 74% improved or remained the same visually, and 26% worsened.	56 pts: mean change of 97 μm in the foveal thickness ($p=0.00009$) IVB grp only (39 pts): mean reduction of 128 μm in foveal thickness per injection ($p<0.001$)		-No reports of vitreous haemorrhage, endophthalmitis or retinal detached. -Commonly reported was subconjunctival haemorrhage at the injection site which was self-limiting.
Funk 2009[27]	Prospective clinical trial	To investigate the concentrations of growth factors and inflammatory cytokines in eyes with CRVO and BRVO before and during therapy with IVB	15 months	13 eyes of 13 patients; BRVO (n=8); CRVO (n=5)	Not reported	VEGF levels were reduced from a median value of 117 pg/mL to values below the detection limit during the first 2 months ($P=0.062$). The decrease of		No reports of severe systemic adverse events such as thromboembolism were reported.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
						VEGF levels was associated with a decrease in CRT and improvement in VA.		
Gregori 2009 BRVO or HRVO[28]	Retrospective study	To evaluate the safety and efficacy of IVB for the treatment of ME secondary to BRVO or HRVO	12 months	BRVO (n=52) HRVO (n=13)	12 months: significant improvement in VA (p=0.015) by 15 letters (17 eyes)	12 months: significant reduction in CMT (p=0.002) by 205 µm (17 eyes)		-No cases of endophthalmitis, retinal detachment, retinal tears, traumatic cataract, uveitis, vitreous haemorrhage, or systemic side effects. -1 pt had a substantial increase in IOP of >10 mmHg.
Gutierrez 2008[29]	Prospective, non comparative, interventional case series	To evaluate the efficacy and safety of IVB in the treatment of ME secondary to RVO.	24 weeks	12 eyes of 12 patients	Significant improvement at all times compared with baseline. Mean VA improved from 1.32 +/- 0.24 logMAR at baseline to 0.8 +/- 0.15 at 6 months (p=0.0003)	At baseline, mean FT was 615.50 +/- 116.29 µm and at 6 months it declined to 420 +/- 72.53 µm (p=0.001)		No ocular or systemic averse events were reported.
Hoeh 2009[30]	Interventional case series	To evaluate the long-term outcome of an OCT-guided reinjection scheme for bevacizumab treatment of ME due to RVO	at least 25 weeks follow up	61 eyes of 61 patients; BRVO (n=34); CRVO (n=27)	Significant improvement in VA at last visit. CRVO: VA improved by 1.9±3.2 lines, from 0.18 (0.75 logMAR ± 0.38) to 0.27 (0.57 logMAR ± 0,48), (p<0.01) BRVO: VA improved by 1.8 ± 2.6 lines from 0.32 (0.50 logMAR ± 0.29) to 0.48 (0.32	CRVO: Mean CRT decreased from 748 ± 265 µm to 373 ± 224 µm (p<0.001) BRVO: Mean CRT decreased from 602 ± 207 µm to 386 ± 178 µm (p<0.001)		Only reported that *'This treatment scheme allowed us to keep the total number of injections very low, thus minimizing the risk of endophthalmitis'*.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
					logMAR ± 0.21), (p<0.001)			
Hoeh 2010[31]	Retrospective study	To evaluate the association of different OCT with treatment outcomes in BRVO and CRVO patients treated with IVB	23 to 128 weeks	65 eyes of 65 patients; CRVO (n=33); BRVO (n=32)	CRVO: in eyes with subretinal fluid (SRF), VA improved from 0.69 to 0.49; in eyes without SRF VA improved from 0.69 to 0.58. BRVO: significant change in eyes with (p=0.016) or without (p=0.012) SRF	CRVO: CMT decreased from over 700µm to around 400 µm (p=0.001); . BRVO: significantly decreased with (p=0.002) or without (p=0.005) SRF		-No endophthalmitis or retinal detachment occurred. -No complications from neovascularisation.
Hung 2010[32]	Prospective, interventional case series	To evaluate the efficacy and safety of IVB injections in pt with ME secondary to RVO.	up to 12 months (follow up at 1 month, 3 months and last visit) mean follow up time was 6.5 months	25 eyes of 25 patients (12 male, 13 female); 92% of the patients had repeat injections	Mean Snellen VA improved at baseline, one month, 3 months and at last visit. 20% showed improvements of >3 lines in Snellen chart. Baseline mean BCVA logMAR was 1.09 (0.63) and improved to 0.85 (0.61), 0.71 (0.45), 0.67 (0.54) at 1 month, 3months and last visit respectively following the first injection (p<0.01 at each time point)	Mean baseline CRT was 421.60 µm (171.66) and 263.06 µm (87.56) (p<0.01), 333.44 µm (131.50) (p=0.051) and 239.13 µm (59.20) at 1 month, 3 months and last visit respectively. .		-No ocular adverse events occurred during f/u. -No systemic adverse events.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Patel 2008[33]	Prospective, interventional case series	To assess the long-term safety and efficacy of IVTA injection in the management of ME caused by CRVO, HRVO, or BRVO	1 year	13 eyes of 13 patients; CRVO (n=4); HRVO (n=1); BRVO (n=8)	VA improved by ≥2 Snellen lines in 8 (62%) eyes, but this improvement was not maintained despite further inj of IVTA where appropriate, and by the end of f/u, 12 of 13 (92%) eyes were within 1 Snellen line of the presenting VA. One eye with BRVO failed to respond to IVTA inj and lost vision.	Decreased significantly after treatment . However, this improvement was not maintained despite repeat injections in eyes with recurrent ME		-IOP increased in in 8/13 (62%) eyes. 4 eyes achieved a maximum IOP of <30mmHg. The highest IOP recorded was 40mmHg seen. -No cases of endophthalmitis, vitreous haemorrhage, retinal detachment, visually significant cataract, or acute visual loss.
Prager 2009[34]	Prospective clinical trial	To evaluate functional and anatomical changes after IVB inj in eyes with persistent ME secondary to BRVO or CRVO	12 months	29 eyes of 28 patients; BRVO (n=21); CRVO (n=8)	CRVO grp: after 12 months f/u mean BCVA (n=6) increased by seven letters (+1.5 lines), but the change was not statistically significant (p>0.05). BRVO grp: after 12 months f/u mean BCVA (n=18) increased by 18 letters (p<0.001).	CRVO grp: after 12 months f/u mean CRT decreased significantly by 268 µm (p=0.007); BRVO grp: after 12 months f/u mean CRT decreased significantly by 241 µm (p<0.001).		-No severe ocular (endophthalmitis, retinal detachment, traumatic cataract, uveitis) or systemic (thromboembolic event, systemic hypertension, kidney failure) adverse events reported. -No progression of avascular areas according to fluorescein angiography was observed. -No patient developed neovascularisation of the optic disc, of the iris or elsewhere in the retina.
Bevacizumab for BRVO								

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Abegg 2008[35]	Retrospective study	To evaluate the effect of IVB treatment in patients with ME induced by BRVO	f/u between 27 to 418 days (median 170 days)	32 eyes of 32 patients (17 male, 15 female)	within 6 weeks f/u BCVA had significantly improved ($p<0.01$). Mean BCVA before was0.68 ± 0.3 and after 0.5 ± 0.35 logMAR. Long term: repeat injections needed to sustain improvement.	within 6 weeks follow up (mean 30 +/- 11 days): CMT had significantly improved ($p<0.01$)..		No adverse events observed.
Ahmadi 2009 [36]	Retrospective study	To evaluate the effect of IVB treatment on VA and CMT in patients with ME secondary to BRVO	VA testing: pts f/u every 6 to 8 wks; OCT: f/u at 2 months and 6 months	42 eyes of 42 patients	31 pts (74%) showed some degree of improvements; 11 eyes (26%) remained unchanged. VA at the first f/u visit improved from mean 1.15 SD 0.11 logMAR to 0.9 SD 0.12 logMAR and remained at the similar levels in the next 7 visits with a mean of 0.94 SD 0.14 logMAR at the eight visit ($p<0.04$) [avg f/u 356 days]	Mean CRT improved compared with baseline at both 2 months and 6 months f/u.		-No ocular complications such as endophthalmitis, retinal detachment, retinal tears, or uveitis were observed. -No systemic adverse events occurred.
Chung 2008[37]	Retrospective study-of case records.	To evaluate the prognostic factors for visual outcome after IVB injections to treat ME due to BRVO.	at least 3 months follow up		28/50 (56%) gained 5 or more ETDRS letters after IVB injections..	significant improvement in CMT at all time points.		Serious vision threatening complications such as infectious endophthalmitis, vitreous haemorrhage, scleral perforation, and retinal detachment were not reported.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Jaissle 2009[38]	Prospective interventional case series	To investigate the long-term effectiveness of IVB treatment in eyes with perfused ME due to BRVO.	1 year	23 consecutive, previously untreated eyes with perfused ME	VA improvement was highly significant at weeks 6, 12 and 18, from a median VA of 0.50 logMAR at baseline to 0.3 logMAR ($p<0.001$). At 6 months, the median VA further increased to 0.20 LogMAR ($p<0.001$), corresponding with a total improvement of 3.0 VA lines. This gain was maintained at 1 year, with a highly significant improvement of the median VA to 0.20 logMAR ($p<0.001$).	a significant reduction of the CRT, with the median CRT decreasing from 395 µm to 190 µm by week 6 ($p<0.05$)		-No cases of endophthalmitis, retinal detachment or any other severe procedure-related complications were observed in a total of 78 injections. -No obvious IVB related ocular or systemic adverse events were apparent. -Furthermore, no patient developed any neovascular complications and needed peripheral sectorial laser photocoagulation during the f/u.
Kim 2009[39]	Retrospective study	To compare the effects of IVB to those of IVTA inj for the treatment of ME secondary to BRVO		50 eyes of 50 patients; IVB (n=22); IVTA (n=28)	IVB grp: Mean BCVA before inj was logMAR +0.60 SD0.41 and after 12, and 24 weeks, it was +0.24 SD0.26, and +0.50 SD0.29, respectively. The change at 12 weeks was significant from baseline ($p= 0.001$) but not after 24 weeks ($p=0.064$). IVTA grp: Mean BCVA before inj was log MAR +0.67	IVB grp: Mean CMT reduced; the reduction was significant for all follow-up periods when compared to baseline ($p=0.001$). IVTA grp: Mean CMT decreased; ($p=0.001$).	-BCVA did not show a significant difference between the two groups during the f/u period except for 12 weeks ($p=0.000$) - CMT was not significantly different between the two groups throughout the f/u period	-during the follow-up period, there were no significant differences in IOP from baseline within the IVB grp; the differences in IOP from baseline at 4 and 8 weeks were significant in the IVTA grp; -No cataracts occurred; -No general complications or other ocular complications such as iris neovascularisation,

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
					SD0.28, and after 12, and 24 weeks was, +0.55 SD0.32, and +0.64 SD0.31, respectively; the improvement at 24 weeks was NS (p=0.539).			neovascular glaucoma, retinal detachment, vitreal haemorrhage, or endophthalmitis were observed.
Kondo 2009[40]	Prospective study	To evaluate the 12-month f/u results of IVB therapy for ME secondary to BRVO and to identify the pretreatment factors that were associated with an improvement of the final visual outcome.	12 months	50 eyes of 50 patients (16 men, 34 women)	Mean baseline VA was 0.53 logMAR units which significantly improved to 0.26 at 1 month (P<0.0001). After that, the mean logMAR VA did not change significantly and stabilized at 0.26 at 12 months.	Mean baseline CMT was significantly reduced 1 month after the treatment (p<0.0001). Then the CMT increased again to 300 µm at 3 months after which it did not change significantly.		No serious systemic or local bevacizumab-related adverse events were observed during the 12 months of this study in our 50 patients.
Rensch 2009 BRVO[41]	Prospective non-randomized clinical interventional study	To evaluate the effect of early IVB inj in pts with ME due to non-ischaemic BRVO	6 months	21 eyes of 21 patients	VA was significantly higher than at baseline at 0.55 SD0.46 (p =0.001) at 3 months after the inj and to 0.55 SD0.49 (p = 0.002) at 6 months after the first inj.	Mean CRT decreased significantly (p<0.001).		-Not associated with side-effects, such as an increased IOP or cataract progression during the follow-up. -No conversion to the ischaemic type of BRVO.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Wu 2009[42]	Retrospective, open-label, interventional, comparative, multicenter study	To compare the injection burden, CMT, and change in BCVA after injecting 1.25 mg or 2.5 mg bevacizumab as needed in patients with primary ME secondary to BRVO.	at least 24 months of f/u	63 eyes of 63 patients. IVB 1.25 mg (n=38) ; IVB 2.5mg (n=25)	1.25mg: Significant changes continued throughout the 24 month f/u but the 6, 12 and 24 month did not differ statistically from the 3 month f/u. 2.5mg: There was further improvement between 3 months and 6 months f/u and continued up to 24 months. the 12 and 24 months changes did not differ statically from the 6 month f/u	Statistically significant improvements in mean CMT were seen in both grps-up.		-No endophthalmitis, retinal detachment or vitreous haemorrhage. -The most common adverse event was local hyperaemia or subconjunctival haemorrhage at the site of injection. -No systemic adverse events were noted.
Bevacizumab for CRVO								
Beutel 2010[43]	Retrospective case series	To report on the anatomic and VA response after intravitreal bevacizumab in patients with ME due to non-ischaemic CRVO	12 months	21 eyes of 21 patients with ME secondary to non-ischaemic CRVO	9/21 (42.9%) had decreased BCVA; it improved in 52.4%. No relation between duration of CRVO and improvement of VA	significant decrease in CRT after 6 months (p=0.0094) and 12 months (p=0.0017); in 6 patients (28%), ME completely resolved		-No neovascularisation; -4 developed epiretinal gliosis; -another 4 developed a second event of CRVO;
Gregori 2008 CRVO[44]	Retrospective study	To evaluate the long term safety and efficacy of IVB for the treatment of ME secondary to CRVO	12 months	57 eyes of 55 patients	1 month: mean VA letter gain was 14. 3 months: mean VA letter gain was 13. 6 months: mean VA letter gain was 9 letters (30 eyes examined) 12 months: mean VA letter gain was	1 month: significant reduction (p<0.001) by 299 µm (53 eyes) 3 months: significant reduction (p<0.001) by 144 µm (53 eyes) 6 months: significant reduction		-No serious ocular or systemic complications reported. -IOP remained stable throughout the study. One patient with pre-existing neovascular glaucoma remained stable in terms of IOP and anti-glaucoma

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
					9 letters (17 eyes examined)	(p=0.011) by 127 µm (30 eyes) <u>12 months:</u> significant reduction (p<0.001) by 276 µm (17 eyes)		medications. -Two pts developed neovascular glaucoma (both had refused reinjection of bevacizumab)
Hsu 2007[45]	Retrospective consecutive case series	To describe the effects of IVB in eyes with ME resulting from CRVO		30 eyes of 29 patients	VA improved significantly at 1 month (p=0.04) and 2 months (p=0.008) f/u after injection. No significant changes in VA were found after 4 months	Statistically significant reductions in retinal thickening at at 4 weeks after the injection (P 0.006). At 8 weeks, the reduction was not significant (p=0.15)		-No statistically significant IOP rise. -No ocular or systemic adverse reactions at 1 month. 1 pt developed retinal neovascularisation 3 months after a second IVB injection
Pieramici 2008[46]	Ongoing, prospective, open-label, single-center, uncontrolled study	To assess the biological effect, VA changes, and safety of IV ranibizumab in pts with ME associated with perfused CRVO	9 months [3 monthly injection and when necessary)]	10 patients; IV 0.3 mg rani (n=5); or 0.5 mg rani (n=5)	Mean gain in BCVA at 9 months was 1 ±24 letters compared with baseline (p=0.859).	- After 9 months of f/u, 3 of 10 patients had gained 15 letters compared with baseline, and 3 more patients continued to experience stable vision - The mean retinal thickness at 9 months was 119 ± 153µm less than baseline (p=0 .036).		-No patients developed neovascularisation of the iris or angle or experienced a severe ocular or nonocular adverse event that was attributed to ranibizumab. -In 1 pt, severe recurrence of macular oedema occurred.
Priglinger 2007[47]	Prospective, noncomparative, consecutive, interventional case series	To evaluate the effect of IVB injections on VA and foveal retinal thickness in patients with CRVO	6 months	46 patients (15 females and 31 males)	VA improved from a mean of 20/250 at baseline to a mean of 20/80 at the 6-month f/u (p=0.001).	Mean CRT 535 µm at baseline and had declined to 323 µm at the 6-month f/u		-No side effects such as cataract formation and increased IOP occurred. -Complications such as endophthalmitis, retinal tear, and lens trauma occurred.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Rensch 2009 CRVO[48]	Non-randomized clinical interventional study	To evaluate the effect of early IVB inj for the treatment of ME caused by non-ischaemic CRVO	6 months	25 eyes of 25 patients	VA was significantly higher than at baseline, with an improvement to 0.70 ± 0.42 log-MAR (P = 0.007).	Mean CRT decreased significantly from 530 SD152 µm at baseline to 346 SD129 µm at 6 months (P<0.001) after the first inj.		-No cases of clinically significant cataract. -No conversion to the ischaemic type of CRVO.
Stahl 2010[49]	Retrospective study	To analyse the effect of repeated IVB injections in 10 patients with CRVO after 2 years of treatment	followed up after 2 years of initial treatment	10 patients that were treated with IVB 2 years ago	VA gain was only partially sustained over 2 years compared to the first follow up (i.e. 3 wks): 1.6 vs. 2.9 lines gain over baseline.	Pts with low baseline VA achieved higher long-term VA gains compared to pts with higher base-line VA (r=-50). Pts with strong VA gain after the first IVB injection showed better long-term VA gains (r=-0.21).		NR; The paper in the end says that *'Larger studies are needed to rule out potential side-effects of sustained anti-VEGF treatment on chronic CME or macular ischaemia'*.
Wu 2010[50]	Retrospective, open-label, interventional, comparative, multicenter study	To compare the injection burden, CMT, and change in BCVA after injecting 1.25 mg or 2.5 mg bevacizumab as needed in patients with primary ME secondary to CRVO.	at least 24 months of follow-up	86 eyes of 86 patients. IVB 1.25 mg (n=44) ; IVB 2.5mg (n=42)	Statistically significant improvements in mean logMAR BCVA were seen in both grps within 3 months after the initial injection. The improvement continued up to 24 months but the 6, 12 and 24 months changes did not differ statistically from the 3 month f/u in both grps.	Statistically significant improvements in mean CMT were seen in both grps. The improvement continued up to 24 months but the 6, 12 and 24 months changes did not differ statistically from the 3 month f/u in both grps	No difference between the grps	-None of the eyes had collateral veins at the optic disc at baseline and at the end of 2 years 7 eyes (3 in 1.25mg, 4 in 2.5 mg) had developed collateral veins. -No cases of intraocular neovascularisation. -No endophthalmitis, retinal detachment or vitreous haemorrhage. -One case of uveitis.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
								-Most common side effect was local hyperaemia or subconjunctival haemorrhage at the site of injection. -2 cases of MI and 2 CVA in 1.25mg grp. -1 death due to breast cancer and 1 death due to CVA in the 2.5 mg grp.
Bevacizumab vs. triamcinolone acetonide for BRVO								
Byun 2010[51]	Retrospective comparative case series	To compare visual acquities in patients with ME attributable to BRVO treated with IVTA and IVB	12 months	134 eyes of 134 patients; IVTA (n=87) (64.9%); IVB (n= 37) (35.1%)	Mean change in VA (logMAR) IVTA grp: 0.48 (SD0.34), p<0.001 (6months); 0.49 (SD0.42), p=0.0036 (12 months) IVB grp: 0.47 (SD0.37), p=0.002 (6 months); 0.45 (SD0.35), p=0.002 (12 months)	-Significant improvements (p<0.001) in CMT throughout 12 months in both groups. - Recurrence of ME IVTA grp: in 9 (7.6%). IVB grp: in 19 (26%).	Change in VA: p=0.892 Change in CMT: p=0.612	-No complications like pseudo-endophthalmitis, endophthalmitis, CRO, or retinal detachment were observed. -No statistically significant difference in IOP was noted. IOP rose above 25 mm Hg in 3 patients receiving IVTA but well controlled with antiglaucoma drugs. 3 patients (3.4%) underwent cataract surgery after lens opacity was aggravated by using IVTA.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Chen 2010[52]	Consecutive, retrospective, non randomised, clinical interventional study	To evaluate whether a single IVTA or IVB injection could decrease CMT and increase VA among patients with BRVO induced ME.	at least 24 weeks follow up; 36 weeks and 48 weeks.	83 eyes of 83 patients (50 male, 33 female) with ME and BRVO. IVTA (n=25); IVB (n=24); control (n=34)	Mean change in VA (logMAR) IVTA grp: significant improvement at 4 and 8 wks but not at 12 and 24 wks. IVB grp: significant improvement at 4, 8, 12 and 24 wks. Control grp: slight improvement but did not differ significantly compared to baseline	Compared to baseline, CMT decreased significantly in all grps	-Change in VA: significant difference between IVB and control at 8 weeks. No difference between IVTA and IVB and control group at 8 weeks. -Change in CMT: significant difference between IVTA and control at 4 wks (p=0.0004) and 8 wks (p=0.003); sig diff between IVB and control at 4 wks (p=0.0003) and 8 wks (p=0.0007); No sig diff between IVTA and IVB	-No immediate procedure-related complications or any obvious systemic adverse events in either group. -Delayed complications consisted of steroid induced ocular hypertension in 8 patients (8 eyes, 32%) in IVTA grp, in one eye (3%) in control grp. Posterior subcapsular cataract developed or progressed in 5 eyes (28% of phakic eyes) in IVTA grp. None of these complications occurred in IVB grp.
Guthoff 2010 BRVO [53]	Retrospective study (pair-matched)	To assess the effects of IVB or IVTA for the treatment of ME after BRVO	8 weeks follow up after first injection	IVTA (n=10); IVB (n=10) matched according to BCVA and CMT	IVB grp: significant change in BCVA at 8 wks compared to baseline (p=0.032) but not at the last visit (mean of 13 months) (p=0.18). Mean BCVA change at 8 wks was +3.3 lines and +2.8 lines at the last visit. IVTA grp: No	Mean change in CMT IVB grp: decreased significantly. IVTA grp: No significant change		-Raise in IOP of 30 mmHg was seen in 6 IVTA patients; quick progression of cataract in 1 IVTA and 1 IVB patients. -No cases of endophthalmitis or retinal detachment. -No cases of neovascularisation.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
					significant change in BCVA at 8 wks or later. Mean increase in BCVA at 8 wks was +0.3 lines and +0.6 lines later.			
Hou 2009[54]	Retrospective comparative interventional study	To compare IVB with IVTA for the treatment of ME resulting from BRVO.	f/u at 1 day, 3 days, 1 month, 2 months, 3 months, 6 months and 1 year after each injection	IVB (n=34); IVTA (n=34)	Mean change of BCVA (logMAR) IVB grp: 1 year [–0.14±0.16] IVTA grp: 1 year [–0.33±0.27]	In both groups, compared with baseline, the mean CMT was reduced from 4 weeks to 1 year.	-Mean changes of BCVA (LogMAR) between 2 grps were not statistically significant different - Mean CMT between 2 grps differed at 3-month f/u (P <0.01, Figure) but was similar later.	In IVTA grp: In 1 eye, retinal pigment epithelium tear at 8 weeks after initial inj. In both groups, no iris rubeosis developed postoperatively. During follow-up, in IVTA grp, IOP readings >21 mmHg, >30 mmHg, >35 mmHg and >40 mmHg, respectively, were measured in 12 eyes (35.3%), 6 eyes (17.6%), 5 eyes (14.7%) and 4 eyes (11.8%), while in IVB grp, no abnormal elevated IOP and other severe complications were observed.
Bevacizumab vs. triamcinolone acetonide for CRVO								
Guthoff 2010 CRVO[55]	Retrospective study (pair-matched)	To compare the difference in the impact of IVB and IVTA regarding VA and ME after CRVO	8 weeks follow up after first injection	IVTA (n=9); IVB (n=9) matched according to BCVA and CMT	No significant change in BCVA with both treatments. (p=0.19 with IVB and p=0.65 with IVTA)	Mean change in CMT IVB grp: significant change at 8 wks (p= 0.007) but not at the last visit (p=0.12) IVTA grp: no significant change (p=0.18)	No significant difference between the two.	-Rapid progression of cataract in 2 IVTA pts; in 6 IVTA pts increase in IOP of >30 mmHg; in 1 IVTA pt neovascular glaucoma. -No cases of endophthalmitis or retinal detachment.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Tao 2010[56]	Nonrandomised, retrospective, clinical interventional study	To compare the effect of IVB vs. IVTA for the treatment of non-ischaemic CRVO	follow up to 3 to 12 months; mean 7.8 months	72 patients; IVB (n=30); IVTA (n=42)	IVTA grp: VA improvement significant at 2 months (p=0.03) and 3 months (p=0.02). IVB grp: VA improvement significant at 1 month (p=0.03), 6 months (p=0.04) and 1 year (p=0.04).	IVTA grp: macular thickness decreased significantly (p<0.001). IVB grp: statistically significant reduction at 1 and, 2 months and at 1 yr (p=0.02).	-BCVA: The difference was not significant (p>0.40) - The reduction in the macular thickness was more pronounced with IVTA than IVB (p=0.006)	IVTA grp: 2 eyes (5%) developed iris neovascularisation at 6 months; two eyes (5%) developed vitreous haemorrhage at 3 wks and at 7 months. IOP >21, >30, >35 and >44 mmHg in 18 (43%), 6 (14%), 4 (10%), 1 (2%) eyes respectively. IVB grp: 1 eye (3%) developed iris neovascularisation at 3 months; 1 eye (3%) developed vitreous haemorrhage at 6 wks. IOP did not significantly vary at baseline or during f/u.
Bevacizumab for age related macular degenerations								
Wong 2008[57]	Retrospective study	To systematically study potential adverse events associated with the use of intraocular bevacizumab at a single medical centre		203 eyes of 186 patients	Not reported	Potential adverse events		Five eyes developed retinal pigment epithelial (RPE) tears, all with pre-existing RPE detachments. Other adverse events were rare and included retinal ischemia, subretinal haemorrhage, vitreous haemorrhage, ocular irritation or pain, worsened hypertension, and headache. No death or thromboembolic events were observed.
Bevacizumab use								

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Johnson 2010[58]	Retrospective study	To determine the incidence and characteristics of acute intraocular inflammation after IVB inj from a tertiary care retinal practice	review of a consecutive series of patients receiving IVB inj over a period of 22 months	193 eyes of 173 patients	Not reported	Acute intraocular infection		9 cases of acute intraocular infection for an incidence rate of 1.30%.
Wu 2008[59]	Retrospective, multicenter, open label, uncontrolled interventional case series	To report on the systemic and ocular safety of IV injections of 1.25 mg or 2.5 mg of bevacizumab	12 months	1,310 eyes of 1,173 patients	Not reported	-Ocular adverse events -Systemic adverse events		- Ocular adverse events : Subconjunctival haemorrhage in 838; IOP increase in 7; endophthalmitis in 7; tractional retinal detachment in 7; uveitis in 4; retinal detachment in 1 and vitreous haemorrhage in 1. -Systemic adverse events : Of the 1,173 patients, 18 (1.5%) suffered systemic adverse events and included 5 deaths from MI or CVA (0.4%). Included 6 (0.5%) CVA, 5 (0.4%) MIs and 7 (0.6%) a transient elevation in SBP (the most common adverse event). 2 (0.17%) pts developed iliac artery aneurysms 13 and 14 months after IVB injection.
Ranibizumab for RVO								

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
Puche 2010[60]	Retrospective study	To evaluate the efficacy and safety of IV ranibizumab inj. In eyes with ME secondary to CRVO or BRVO.	mean follow up of 7 months (range 2-20 months).	34 patients (17 men, 17 women)	All but one showed an improvement. Mean change in VA was a gain of 13 letters ($p<0.001$). After second injection, BCVA improved further by 7 letters ($p<0.001$) and after the third and fourth injection, by six letters ($p<0.001$)	After first injection showed a significant reduction of 247µm (45%, $p<0.001$). After second injection CRT decreased by 344 µm to 245 µm (28%, $p=0.022$). After third and fourth injection, the decrease in avg was 193 µm.	-The gain in VA was better in BRVO than in CRVO. - The decrease in CMT was similar in both CRVO and BRVO grp.	-No severe local adverse events such as retinal detachment, retinal tears, endophthalmitis or uveitis. -None showed progression to ischaemia or rubeosis iritis. No systemic side-effects.
Ranibizumab for BRVO								
Rouvas 2010 BRVO[61]	Prospective, consecutive, non comparative, interventional case series	To evaluate the effect of individualised repeated IV injection of ranibizumab on VA and CFT for BRVO induced ME	9 months	28 eyes of 28 patients.	Statistically significant improvement in mean VA occurred at 9 months ($p<0.001$). Mean VA was 76.8 ETDRS letters (logMAR=0.49)	statistically significant change in CFT occurred at 1 month ($p=0.02$), 3months ($p<0.001$), 6 months ($p<0.001$) and 9 months ($p<0.001$)		-No IOP increase; no ocular inflammation such as uveitis; -No endophthalmitis, no retinal detachment or tear; -No hypertension or any other systemic adverse events.
Ranibizumab for CRVO								
Rouvas 2009 CRVO[62]	Prospective interventional case series	To evaluate the effect of individualized repeated IV injections of ranibizumab VA and CFT for CRVO induced ME	12 months	12 eyes of 12 consecutive patients (10 men; 2 women)	Mean VA was 50 ETDRS letters (logMAR= 1.0 +/- 0.4), a statistically significant change compared to baseline ($p=0.006$)	Mean retinal thickness improved to 230± 33 µm (highly significant, $p<0.001$).		No IOP rise, ocular inflammation (such as uveitis), endophthalmitis, retinal detachment or tear, hypertension or any other systemic adverse events due to the ranibizumab injection.
Singh 2010[63]	Retrospective cohort study	To investigate systematically the natural history of visual outcome in CRVO	3 months, 6 months, 2 to 5 years [pts seen in the clinics between 1973	Nonischaemic CRVO: 558 eyes of 559 patients [47 eyes of 48 pts later became	<u>Eyes with initial VA of 20/60 or better:</u> 17% showed VA deterioration during 3 months f/u and 20% showed		Overall the rate of improvement in nonischaemic CRVO was significantly higher ($p=0.0004$)	Neovascular glaucoma developed in 36% patients with ischaemic CRVO and in 33% with nonischaemic CRVO.

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
			to 2000] Follow up protocol in the paper states: f/u approx at 3 months for 3 visits, then 6 months interval for 4 visits, then annually	ischaemic]; Ischaemic CRVO: 109 eyes of 108 patients.	deterioration during 2 to 5 years f/u. <u>Eyes with initial VA of 20/70 or worse:</u> In the eyes with non-ischaemic CRVO , there was a significant increase in the proportion of eyes with improvements in VA during f/u-32% showed improvement during 3 months f/u and 47% showed improvement during 2 to 5 years f/u. <u>In eyes with ischaemic CRVO,</u> only a small proportion showed improvement, 10% at 3 months and 23% during 2 to 5 yrs.		with an odds ratio of 2.96 (95% CI 1.55 to 5.66) for VA improvement for nonischaemic CRVO relative to those with ischaemic CRVO.	
Triamcinolone acetonide for RVO								
Roth 2008[64]	Retrospective nonrandomized interventional series	To report theVA response after IVTA inj in patients with ME due to RVO	12 months	172 pts; BRVO (n=92); CRVO (n=63); HRVO (n=17)	All subtypes of RVOs showed significant improvements in mean VA 1 month after injection. This improvement in VA was maintained over the 12-month period for all but the CRVO group.			-74/172 (43.0%) eyes injected had an IOP >21 mm Hg after inj; -Only 28 (16.3%) eyes had an IOP >30 mm Hg; 37/123 (30.1%) phakic eyes examined for at least 6 months demonstrated cataract progression; -One eye developed a

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
								sterile endophthalmitis.
Triamcinolone acetonide for SOH (Secondary ocular hypertension)								
Vasconcelos-Santos 2008[65]	Retrospective review of charts	To analyze the incidence of secondary ocular hypertension (SOH) after IVTA injection and its risk predictors	f/u for at least 3 months	150 eyes of 150 patients	Not reported	Incidence of secondary ocular hypertension (SOH): 32.0% of injected eyes at some point during a mean follow-up of 7.7 months.		No procedure-related complications, such as infectious endophthalmitis, vitreous haemorrhage, or retinal detachment. 3 eyes (2.0%) had aseptic endophthalmitis on the first day after injection: one with spontaneous resolution and two managed with a subconjunctival injection of dexamethasone. 3 eyes (2.0%) had a pseudohypopyon (triamcinolone crystals deposited in the anterior chamber) that cleared in a few days.
Triamcinolone acetonide for CRVO								
Wang 2009[66]	Retrospective study	To investigate the effectiveness of repeated injections of IVTA in the treatment of ME caused by CRVO		17 pseudophakic or aphakic eyes of 17 patients (10 male, 7 female)	Statistically significant improvements of mean BCVA at 1, 2, 3 and 4 months compared to the baseline, After repeat injections, BCVA also improved significantly at each timepoint.	CFTs at each time-point were statistically significantly improved in first injection and repeat injection groups.		-IOP >21 mmHg occurred in 8 eyes of the initial group and 6 eyes of the repeat group. The highest increase in IOP occurred in 2 patients of the initial group (36 and 39 mmHg) and in 3 patients of the repeat group (56, 50 and 47 mmHg) because of neovascular glaucoma. 3 cases in the repeat group required antiglaucoma surgery. -No other significant

First author	Type of study	Aim of study	Duration of study	Participants	Result of BCVA	Other outcomes	Comparison between groups	Adverse events
								adverse events were noted during the study.

CRT: central retinal thickness; CMT: central macular thickness; CFT: central foveal thickness; FT: foveal thickness; grp: group; SD: standard deviation; AE: adverse events; ME: macular edema; IVTA: intravitreal triamcinolone acetonide; IVB: intravitreal bevacizumab; IOP: intraocular pressure; CRVO: central retinal vein occlusion; BRVO: branch retinal vein occlusion; HRVO: hemi retinal vein occlusion; VA: visual acuity; BCVA: Best corrected visual acuity; f/u: follow up; MI: myocardial infarction; CVA: cerebrovascular accident

Appendix 2. Errors in the submitted model

As outlined in the ERG clarification question B17 the submitted model performed counter-intuitively:

	100% RVO to ME conversion			**50% RVO to ME conversion**		
	All RVO	CRVO	BRVO	All RVO	CRVO	BRVO
Discounted		All	All		All	All
Ozurdex						
Cost	£12,245	£14,962	£10,815	£10,567	£13,363	£9,095
QALY	11.6916	11.6246	11.7269	11.6350	11.5638	11.6725
No treatment						
Cost	£10,578	£13,126	£9,236	£7,873	£10,432	£6,526
QALY	11.465	11.319	11.5424	11.449	11.295	11.5307
Ozurdex-no treatment						
Cost	£1,667	£1,836	£1,578	£2,694	£2,931	£2,569
QALY	0.23	0.31	0.18	0.19	0.27	0.14
ICER	**£7,368**	**£6,008**	**£8,554**	**£14,502**	**£10,884**	**£18,119**

B17 The average total QALYs fall if the proportion of RVO resulting in ME is reduced from 100% to 50%, and falls further if the proportion is reduced to 0%. Similar effects appear to be the case if the method of modelling fellow eye involvement is changed to a simple rate calculation: a lower rate of fellow eye involvement worsens the aggregate patient QALYs. This seems counterintuitive and may suggest a logical flaw in the model structure, which if the case, could have a major impact given the importance of fellow eye involvement to the cost effectiveness argument. Please clarify if this is the case, and any changes necessary to correct the model structure.

The manufacturer clarified that these errors arose from the incorrect treatment of survival, both in the treatment of survival at fellow eye involvement incidence and in the treatment of survival subsequent to this incidence. A method of revising the model to correct the treatment of survival at fellow eye involvement incidence was put forward by the manufacturer as outlined below. There was apparently no ready means of addressing the errors around the treatment of survival subsequent to incidence and the manufacturer presented an account of why this would be expected to have limited impact upon modelling results.

Note that the ERG supplied the manufacturer with a revised cohort flow where all events happened contemporaneously, with these subsequently being conditioned by discount rates and survival. While this cohort flow was not rebuilt or cross checked by the ERG, the cohort flows for the eye affected at baseline corresponded with the manufacturer cohort flow. Revising the model to have all events happening contemporaneously, including fellow eye involvement, would avoid the errors in the manufacturer model and also appears to be a somewhat simpler modelling approach. It would have been a relatively simple matter to rebuild the suggested cohort flow with all events happening contemporaneously, and attach the associated costs and QALYs to these for the deterministic modelling. The only slight difficulty might have been in implementing the mortality multiplier for blindness for baseline to year 3, during which time some patients move out of legal blindness. This should not affect results to any appreciable extent.

Issue 1: Treatment of survival at fellow eye involvement incidence

Corrections necessary to address model error

1. Change CG17:DJ17 to not take account of survival at the time of the FEO

An example of the change in the formula for cell CG17 is:

Submitted model:
```
Summary!$D$10*CG16*
IF($CI$8=0, IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))
```

Correction:
```
Summary!$D$10*
IF($CI$8=0,IF($CK$10>=CG15,$CI$10,0),
1-EXP($CM$11*((CG15-1)^$CK$11-CG15^$CK$11)))
```

The difference between these formulae is that the multiplicative term CG16 is present in the submitted model and absent in correction. The updated cell for CG17 can be replicated by dragging the bottom right corner across to cell DJ17. Cell DK17 should be left unchanged. Cell CH13 should be changed from 1-DK13 to SUMPRODUCT(CG17:DJ17,CG16:DJ16), so that this proportion is displayed as in the submitted model (i.e., the overall proportion taking account of mortality).

This removes the proportion surviving as a conditioner to the proportion experiencing fellow eye involvement, the change can be implemented as described by the manufacturer.

2. Change CG18:DJ18 and FA18:GD18 to take account of survival at the time of the FEO

An example of the change in the formula for cell CG18 is:

Submitted model*: 1/(1+$D$18)^CG15

Correction: CG16/(1+$D$18)^CG15

*The formula in the submitted model is mathematically equivalent to that shown here (CG18 = 1/(1+$D$18); CG19 = CG18*$CG$18, with CG19 replicated by dragging to DJ18.); i.e. the formula within the submitted model is not as suggested above with this requiring further modification by the ERG.

The difference between these formulae is that the multiplicative term CG16 is absent in the submitted model and present in the correction. The updated cell for CG18 can be replicated by dragging the bottom right corner across to cell DJ18. The formula for FA18:GD18 refers to the discount rate for benefits ($E$18) instead of that for costs ($D$18).

Note that the reference to the discount rate for benefits ($E$18) instead of that for costs ($D$18) was not specified within the model. Rather, the discount rates for benefits for the fellow eye modelling FA18:GD18 were simply equalised to those for discount rates for costs CG18:GD18 for the fellow eye modelling. This appears to be a further error in the revised model which will cause any sensitivity analyses which set the discount rate for benefits to be different from the discount rate for costs to be incorrect.

The manufacturer response suggests that making these changes moves the All RVO cost effectiveness from £7,368 per QALY to £7,403 per QALY.

Issue 2: Treatment of survival subsequent to fellow eye involvement

This error occurs due to patients at baseline having a lower mortality rate than those some years after baseline. The modelling appears to have effectively assumed that where there is fellow eye involvement the mortality that applies is as from baseline, rather than as from the age at which fellow eye involvement occurs.

The manufacturer argues that since

- the incidence of fellow eye involvement as modelled for the base case through a weibull extrapolation occurs mainly relatively early within the simulation
- mortality further reduces the proportion of patients with fellow eye involvement in later years
- discounting further reduces the impact of this

This aspect will be relatively unimportance. These considerations apply. But the model revised to take into account the errors in Issue 1 appears to still give rise to perverse results. As a consequence, it does not seem warranted to suggest that Issue 2 is unimportant unless another error within the modelling is giving rise to the remaining perverse results. Relying on a model that incorrectly models FEI to undertake simulations to suggest the likely importance of the error in the modelling of FEI is also questionable.

It is currently unclear to the ERG, but it is possible that the submitted model rather than modelling patients, the impact of ME on their treated eye, the impact of fellow eye involvement, and patient survival instead might models pairs of eyes where one eye can in effect survive independently of death of its mate.

Updated model

Subsequent to the initial set of ERG questions, at the further request of the ERG the manufacturer submitted an updated model that implements the changes suggested by the manufacturer to resolve Issue 1 outlined above and which does result in a base case estimate across all RVO of £7,403 per QALY. The manufacturer also submitted the updated estimates for cost effectiveness in All RVO patients, All CRVO patients and All BRVO patients, with sensitivity analyses around the percentage of FEI that is assumed to convert to MO.

When assessing the results from the updated model it is helpful to bear in mind the previous manufacturer clarification around the calculation of HRQoL and QALYs:

B10 (Page 160-161, section 6.4.9.) In terms of how the patient utility for a given health state is calculated, please clarify:

vii. If only the WSE is affected and the patient is in HS2, is the utility value [redacted]?

viii. [redacted] If only the BSE is affected and the patient is in HS2, is the utility value [redacted]?

ix. [redacted] If the WSE is affected initially and is currently in HS2, with fellow eye involvement in the BSE with the BSE currently being in HS2 is the utility value [redacted]?

[redacted]

The implication of this is that when modelling a cohort that is 100% WSE at baseline, as the percentage of FEI converting from RVO to macular oedema is increased from 0% to 100% the percentage of patients having their BSE also affected with macular oedema in the first year will rise from 0% to around 6.5% based upon the Weibull modelling of FEI. As a consequence, the proportion of patients in the first year having their HRQoL determined by the BSE utility function as described under point iii above will similarly increase from 0% to around 6.5%. This would be anticipated to reduce their HRQoL given the differences between the two functions estimated HRQoL for given health states as outlined in table 106. By year 6 around [redacted]% of patients initially only with their WSE affected will have developed MO in their best seeing eye, with their HRQoL crossing over from being determined by the WSE utility function to the BSE utility function.

The summary of the updated reference case using the Allergan_Ozdurex_NICE_STA_V05.xls model submitted to NICE on the 23 Nov 2010 at the request of the ERG as outlined overleaf does not conform to this expectation. Examining the CRVO 100%WSE column, as the % FEI converting from RVO to macular oedema increase from 0% to 100% nothing happens to the aggregate QALYs within the dexamethasone arm. In the pooled results the aggregate QALYs actually move in the wrong direction very slightly.

Manufacturer submitted results 23 Nov 2010: Updated model reference case

0% FEO converting to ME (i.e. no fellow eye occurrence)

Model output **Ozurdex compared with no treatment**

VFQ-UI utility equation used for BSE

	Blend WSE/BSE			CRVO: All			BRVO: All		
	All RVO	CRVO	BRVO	Blend WSE/BSE	100% WSE	100% BSE	Blend WSE/BSE	100% WSE	100% BSE
Discounted		All	All						
Ozurdex									
Cost	£8,889	£11,765	£7,375	£11,765	£10,239	£25,496	£7,375	£6,444	£15,753
QALY	11.5784	11.5031	11.6180	11.50	11.72	9.55	11.62	11.81	9.92
No treatment									
Cost	£5,169	£7,739	£3,816	£7,739	£2,823	£51,978	£3,816	£2,266	£17,769
QALY	11.433	11.270	11.5190	11.27	11.56	8.63	11.52	11.73	9.59
Ozurdex-no treatment									
Cost	£3,720	£4,026	£3,559	£4,026	£7,416	-£26,482	£3,559	£4,178	-£2,016
QALY	0.15	0.23	0.10	0.23	0.16	0.92	0.10	0.07	0.33
ICER	**£25,615**	**£17,279**	**£35,944**	**£17,279**	**£47,493**	**-£28,637**	**£35,944**	**£57,043**	**-£6,093**

50% FEO converting to ME

Model output **Ozurdex compared with no treatment**

VFQ-UI utility equation used for BSE

	Blend WSE/BSE			CRVO: All			BRVO: All		
	All RVO	CRVO	BRVO	Blend WSE/BSE	100% WSE	100% BSE	Blend WSE/BSE	100% WSE	100% BSE
Discounted		All	All						
Ozurdex									
Cost	£10,567	£13,363	£9,095	£13,363	£12,015	£25,496	£9,095	£8,355	£15,753
QALY	11.5748	11.5040	11.6122	11.50	11.72	9.55	11.61	11.80	9.92
No treatment									
Cost	£7,873	£10,432	£6,526	£10,432	£5,816	£51,978	£6,526	£5,277	£17,769
QALY	11.390	11.236	11.4708	11.24	11.53	8.63	11.47	11.68	9.59
Ozurdex-no treatment									
Cost	£2,694	£2,931	£2,569	£2,931	£6,199	-£26,482	£2,569	£3,078	-£2,016
QALY	0.19	0.27	0.14	0.27	0.20	0.92	0.14	0.12	0.33
ICER	**£14,544**	**£10,918**	**£18,169**	**£10,918**	**£31,706**	**-£28,637**	**£18,169**	**£25,583**	**-£6,093**

100% FEO converting to ME

Model output

Ozurdex compared with no treatment

VFQ-UI utility equation used for BSE

	All RVO	CRVO	BRVO	CRVO: All			BRVO: All		
		Blend WSE/BSE		Blend WSE/BSE	100% WSE	100% BSE	Blend WSE/BSE	100% WSE	100% BSE
Discounted		All	All						
Ozurdex									
Cost	£12,245	£14,961	£10,815	£14,961	£13,791	£25,496	£10,815	£10,266	£15,753
QALY	11.5713	11.5048	11.6063	11.50	11.72	9.55	11.61	11.79	9.92
No treatment									
Cost	£10,578	£13,126	£9,236	£13,126	£8,809	£51,978	£9,236	£8,288	£17,769
QALY	11.346	11.201	11.4226	11.20	11.49	8.63	11.42	11.63	9.59
Ozurdex-no treatment									
Cost	£1,667	£1,836	£1,578	£1,836	£4,982	-£26,482	£1,578	£1,978	-£2,016
QALY	0.23	0.30	0.18	0.30	0.23	0.92	0.18	0.17	0.33
ICER	**£7,403**	**£6,041**	**£8,590**	**£6,041**	**£21,211**	**-£28,637**	**£8,590**	**£11,815**	**-£6,093**

Further interrogation of the updated Allergan_Ozdurex_NICE_STA_V05.xls model submitted to NICE on the 23 Nov 2010 is informed by the manufacturer responses to the previous ERG questions.

B19 question subset paraphrased and response interpreted by the ERG

- Is GE40:GE158 the cumulative discounted QALY among WSE patients never having had fellow eye involvement?
    - Yes
- Is GF40:GF158 the cumulative discounted QALY among all WSE patents?
    - Yes
- Again, as a brief face value check subtracting GF40:GF158 from GE40:GE158 initially results in a positive number with this increasing as time progresses moving down the column but this then starts to fall and turn negative, this possibly giving rise to what appear to be the counterintuitive results around varying the proportion of fellow eye involvement as outlined under clarification point E12 above.
    - Please refer to Question B.17 for a description of the identified issues, the corrections required and their impact on the model output.

In the light of the previous two bulleted questions and the positive responses, the third bullet question effectively asked whether the cumulative QALYs among those never having had FEI compared to the average across all patients including those having FEI was in the early years of the modelling estimated to be positive but as the model progressed estimated to turn negative: i.e. fellow eye involvement increased the aggregate QALY compared to no fellow eye involvement.

The suggested corrections do not correct this, as can be seen within the updated model submitted to NICE on the 23 Nov 2010. Setting the proportion of WSE at baseline to 100% for simplicity, the impact of fellow eye involvement within the dexamethasone arm of the CRVO modelling is still to initially cause the cumulative QALYs of column GF to fall below that for no FEI of column GE, but to then increase the cumulative QALYs to be greater than would apply if there were no FEI. This effect is even more marked if the 1.54 mortality hazard for HS5 is set equal to 1.00.

Appendix 3. Base case cohort flows – originally submitted model

To better understand the impact of the reapplication of the TPMs, the cohort flows for the three patient subgroups of CRVO, BRVO-MH and BRVO-PL can be graphed for the dexamethasone arm and the observation arm to the point from which no more dexamethasone administrations are assumed to occur with stability in visual acuity being assumed from this point. The following assumes no deaths in order to better visualise the balance between health states among those surviving. Note that the following is only for the eye affected at baseline.

For instance, within the CRVO worksheet the cohort flow has been calculated by setting all mortality hazards in column F to zero, summing the three contemporaneous patient rows in the dexamethasone arm for the five cycles this applies to, e.g. summing rows 25, 30 and 35, and place holding these values elsewhere, copying and pasting the values and number formats of the CRVO worksheet in an alternative worksheet, deleting rows 25:39, and cutting and pasting the place held values for the dexamethasone arm into the remaining cells relating to ages 64.5 to 66.5.

CRVO cohort flows

[Confidential information removed]

BRVO-MH cohort flows

[Confidential information removed]

BRVO-PL cohort flows

[Confidential information removed]

Cohort flows tabulated

CRVO	Dexamethasone						Observation					
	HS5	HS4	HS3	HS2	HS1	HS0	HS5	HS4	HS3	HS2	HS1	HS0
D0												
D30												
D60												
D90												
D180												
D360												
D540												
D720												
D900												
D1080												
D1260												

BRVO-MH	Dexamethasone						Observation					
	HS5	HS4	HS3	HS2	HS1	HS0	HS5	HS4	HS3	HS2	HS1	HS0
D0												
D30												
D60												
D90												
D180												
D360												
D540												
D720												
D900												
D1080												
D1260												

BRVO-PL	Dexamethasone	Observation
D0		
D30		
D60		
D90		
D180		
D360		
D540		
D720		
D900		
D1080		
D1260		

Appendix 4. Additional ERG structural analysis: 180 day TPMs for observation

Within the *Transitions* worksheet:

For the CRVO sham D180->D360 TPM of AN31:AS36 within the cell formulae:

[redacted]

Change

[redacted]

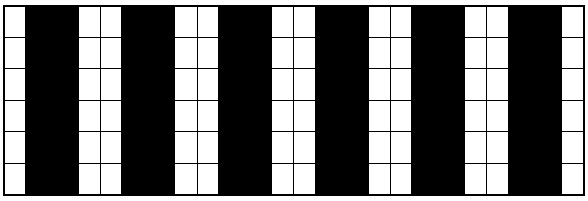
To

MMULT(MMULT(MMULT($D$31:$I$36,$M$31:$R$36),$V$31:$AA$36),$AE$31:$AJ$36)

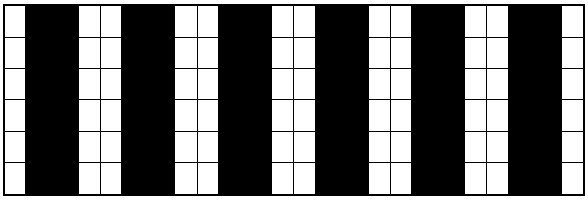
[redacted]

Also set the subsequent TPMs for sham equal to the above: AW31:BB36, BF31:BK36, BO31:BT36, BX31:CC36 and CU63:CZ68.

This changes the TPM from



To



Where the rows sum to 1, the health states working down the rows run from HS0 to HS5 and the columns working from left to right run from HS0 to HS5.

For the BRVO sham D180->D360 TPM of within the cell formulae:

[redacted]

Change

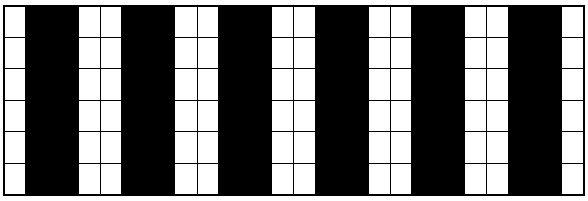
[redacted]

To

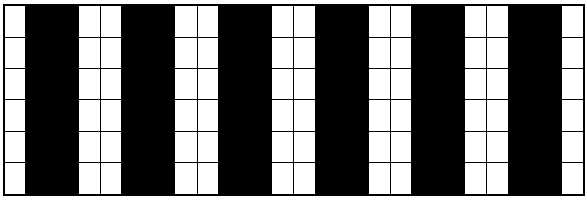
MMULT(MMULT(MMULT($D$54:$I$59,$M$54:$R$59),$V$54:$AA$59),$AE$54:$AJ$59)

Where within this the TPMs $D$54:$I$59, $M$54:$R$59, $V$54:$AA$59 and $AE$54:$AJ$59 relate to D0->D30, D30->D60, D60->D90, D90->D180 respectively.

This changes the TPM from



To



As a cross check of these changes, within the *CRVO* and *BRVO* worksheets to abstract from mortality the values in column F can be set to zero. Within the *CRVO* worksheet this yields the following cohort flow for the observation arm:

	HS0	HS1	HS2	HS3	HS4	HS5
D0						
D30						
D60						
D90						
D180						

Note that the D180 patient distribution corresponds with that of the revised manufacturer model, i.e. with no changes made to it by the ERG, when the mortality risk is set to zero.

Setting the patient distribution at day 180 to be equal to that at baseline results in the following cohort flow between day 180 and day 360.

	HS0	HS1	HS2	HS3	HS4	HS5
D180						
D360						

The above illustrates that the same cohort flow applies between D0 and D180 as between D180 and D360. This suggests that the revision to the model within the CRVO modelling outlined above results in extrapolation for the observation arm that applies the 6 month RCT TPM.

Within the *BRVO* worksheet this yields the following cohort flow for the observation arm:

	HS0	HS1	HS2	HS3	HS4	HS5
D0						
D30						
D60						
D90						
D180						

Setting the patient distribution at day 180 to be equal to that at baseline results in the following cohort flow between day 180 and day 360.

	HS0	HS1	HS2	HS3	HS4	HS5
D180						
D360						

The above illustrates that the same cohort flow applies between D0 and D180 as between D180 and D360. This suggests that the revision to the model within the BRVO modelling outlined above results in extrapolation for the observation arm that applies the 6 month RCT TPM.