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Evidence review: Dexamethasone implants (Ozurdex) for macular oedema after retinal vein occlusion: critique of manufacturer's second submission.

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It should be read in conjunction with the first ERG report: Shyangdan D, Cummins E, Lois N, Royle P, Waugh N. Dexamethasone implants in the treatment of macular oedema due to retinal vein occlusion: a single technology appraisal. Aberdeen HTA group 2010.

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Abbreviations

ACD	Appraisal consultation document
AMD	Age-related macular degeneration
BCVA:	Best corrected visual acuity
BRAVO:	B*RA*nch Retinal *V*ein *O*cclusion: Evaluation of Efficacy and Safety
BRVO:	Branch retinal vein occlusion
BSE:	Better-seeing eye
BVOS:	Branch vein occlusion study
CRUISE:	Central Retinal Vein OcclUsIon Study: Evaluation of Efficacy and Safety
CRVO:	Central retinal vein occlusion
CVOS:	Central vein occlusion study
DMO:	Diabetic macular oedema
DRCR:	Diabetic Retinopathy Clinical Research
FEI:	Fellow eye involvement
GENEVA:	Global Evaluation of implaNtable dExamethasone in retinal Vein occlusion with macular edemA
HR:	Hazard ratio
HRVO:	Hemi retinal vein occlusion
ICER:	Incremental cost-effectiveness ratio
I-CRVO:	Ischaemic central retinal vein occlusion
MI:	Myocardial infarction
MTA:	Multiple technology assessment
MTC:	Multiple treatment comparison
NICE:	National Institute for Health and Clinical Excellence
NI-CRVO:	Non ischaemic central retinal vein occlusion
OCT:	Optical coherence tomography
OP:	Out patient
PDT:	Photodynamic therapy
QALY:	Quality adjusted life year
RCO:	Royal College of Ophthalmologists
RCT:	Randomised controlled trial
RVO:	Retinal vein occlusion
STA:	Single technology assessment
SVI:	Severe visual impairment
VEGF:	Vascular endothelial growth factor
WSE:	Worse-seeing eye

1. Summary

The manufacturer, Allergan, has carried out a number of analyses in response to the requests from NICE.

The first is a cost-minimisation analysis in CRVO, with Allergan arguing that using bevacizumab would be more costly than using dexamethasone. The ERG think that some of the costing assumptions are wrong, and that they bias the analysis against bevacizumab. In particular;

- Allergan assume administration predominantly on a day case basis; the ERG assume all on an outpatient administration (but using a cost which reflects both attendance and procedure)
- Allergan assume that bevacizumab costs £105, but it is available for £50
- Allergan assume that there will be 16 administrations for CRVO in the first two years; there is evidence from use in routine care that the average number of bevacizumab injections is 8.
- We think the Allergan modelling under-estimates the frequency, and hence the costs, of cataracts, which will develop in most people on intra-vitreal steroids over time.

The ERG concludes that bevacizumab would be less costly than dexamethasone.

The second analysis provides an indirect comparison of dexamethasone and bevacizumab in BRVO. This suggests that they have similar clinical effectiveness. Allergan rightly note the uncertainties which arise from the sparse evidence base and an indirect comparison (which was requested by NICE). A cost-utility analysis is then carried out which concludes that the QALY gain with dexamethasone is very slightly less than with bevacizumab, but that costs are less, making dexamethasone the better buy. The cost assumptions are largely those criticised above, except that the number of injections is less for BRVO. The Allergan modelling assumes 10 injections of bevacizumab in the first 24 months; data from routine care suggest less than 4. The ERG is therefore sceptical about the cost assumptions.

The third analysis uses data from a ranibizumab trial as a proxy for the effects of bevacizumab. The analysis concludes that dexamethasone is slightly less effective but less costly than ranibizumab, and hence bevacizumab, and that it is therefore cost-effective. The same caveats regarding cost assumption apply. The effects at 180 days are used, which does not reflect dexamethasone at its best, since maximum benefit is seen around 60-90 days.

The manufacturer revised base case modelling does not quite match what NICE requested in the ACD, in that;

- A ratio of 75:25 day case to outpatient administrations is used instead of analyses with 100% for both as requested in the ACD
- Observation extrapolation remains as before, using the last three months of RCT data (ACD para 4.31). Using the six months of the RCT data would increase the ICERs considerably, for example from a base case for CRVO of £16,522 to £25,336
- Severe visual impairment is not modelled as requiring bilateral involvement, but by adjusting the average annual severe visual impairment costs

The ERG carried out a rapid non-systematic review of studies reporting the incidence of cataract in patients treated with intra-vitreal steroids, and gained the impression that all such steroids cause cataracts, with reports of over 50% by 3 years. Given the effectiveness and safety of the anti-VEGF drugs, the place of steroids in macular oedema after RVO may be in doubt. However some patients might prefer having fewer injections and a cataract operation, to a more frequent injection regimen with the anti-VEGFs.

2. Contents of Allergan submission.

The Allergan submission in response to the ACD, and the NICE requests, has the following sections;

1. A 5–page document entitled Response to ACD
2. A 55-page document entitled Additional Analyses, which has the following sections

Executive summary (pages 2-4)

Section 1: comparing Ozurdex with bevacizumab

1.0 Introduction (pages 5-9)

1.1 cost-minimisation in CRVO (10-15)

1.2 indirect cost-effectiveness

1.2.1 mixed treatment comparison in BRVO (16-18)

1.2.2 cost-utility model based on MTC, for BRVO (19-24)

1.2.3 for CRVO, an indirect comparison of bevacizumab and dexamethasone using data on ranibizumab as proxy (25-30)

Section2: effect on cost-effectiveness of changes to the base case

2.1 Outpatient administration (31-32)

2.2 Use of 0 to 6 month data for transition probability modelling (instead of 3-6 month data) (32-36)

2.3 Effect of fellow eye vision on costs of blindness (36-41)

2.4 Revised base case (42 – 43)

Section 3: scenario analyses examining re-treatment rates (44-51)

Section4: BRVO with macular haemorrhage (52-53)

Appendix A: Report on the ScHARR UK Survey of Ophthalmologists

Appendix B: Details regarding Mixed Treatment Comparison

Appendix C: Details of the OZURDEX vs. bevacizumab Cost Minimisation Analysis

Appendix D: Details of the OZURDEX vs. bevacizumab Cost Utility Analysis based on Mixed Treatment Analysis

Appendix E: Details of the OZURDEX vs. bevacizumab Cost Utility Analysis based on a Crude Indirect Comparison

Appendix F: Detailing additional cost utility results

Appendix G: The effect of duration of Macular Oedema on BCVA outcomes

Appendix H: Converting mean BCVA change to utility scores

Appendix I: Interpreting South West Quadrant ICERS

During this assessment a number of electronic models have been submitted by Allergan, each subsequent model providing some correction to the previously submitted model. Within what follows where the original model is mentioned, this refers to the model submitted by Allergan subsequent to the ERG report but prior to the first assessment committee meeting: *Allergan_Ozurdex_FEO_v2_04_revisedcB.xls*. Where the revised model is mention, this refers to the model submitted by Allergan subsequent to the first assessment committee meeting: *Ozurdex RVO vs. Observation economic model V2 11th March 2011.xls*.

The *NICE_STA_Additional_Analyses_OZURDEX_11th March 2011.docx* is referred to as the Allergan ACD clarifications.

3. Comments on Response to ACD

3.1 The day 180 data.

Allergan note that many patients had their 180 day data collected later than 180 days, and after excluding them, the difference from controls was more marked, with the proportions gaining 15 or more letters being 26% with dexamethasone and 17% with sham. However if there are patients assessed later than 180 days, were there also some assessed earlier?

The Allergan submission says that levels of dexamethasone are not at therapeutic levels after day 180. However, since the peak effect is at 60 days, the level of dexamethasone in the eye must be dropping well before 180 days. In the ERG report, we had wondered about earlier re-treatment. Further research into treatment intervals seems justified.

3.2 The ScHARR survey

This had only 8 responses, a 25% return rate. This raises the possibility of selection bias, and problems arising from small numbers. For example, in the response document, Allegan state that "the majority of centres regard bevacizumab as an occasional or exceptional treatment for this condition". The details in the appendix show that five ophthalmologists used it rarely, one occasionally, and two regularly. This could be re-written as "25% of ophthalmologists used bevacizumab regularly, and 12% occasionally".

The 2009 Patterns and Trends Survey by the American Society of Retina Specialists found that 50% of respondents were using off-label bevacizumab as first-line treatment of CRVO and BRVO.[1]

3.3 Data on bevacizumab.

There is reference (page 8) to observational studies providing "minimal information". We listed those studies in an appendix to the ERG report. In total, 1135 patients had been treated with bevacizumab and had provided a total of 992 person years of observation, including two RCTs. Table attached as Appendix 1. The longest studies were 24 months in duration.

A recent study in Medicare beneficiaries reported that 38,718 had received bevacizumab, compared to 19,026 who had received ranibizumab.[2]

This seems to us more than minimal.

The study by Curtis and colleagues[2] has been cited in the Allergan response (page 12), and in an abstract by Moeremans and colleagues[3] (from an economics consultancy and Novartis). The abstract states that Curtis et al[2] found "significantly higher mortality and stroke rates" with bevacizumab compared to ranibizumab. This assertion has been checked by the ERG. Curtis and colleagues[2] carried out a very large retrospective cohort study (146,942 patients aged 65 and over) with age-related macular degeneration, not RVO. Their aim was to examine the cardiovascular outcomes in patients treated with the four options: photodynamic therapy (PDT), pegaptanib, bevacizumab and ranibizumab. Very little PDT and pegaptanib was used after bevacizumab arrived in September 2005. Ranibizumab use started in September 2006.

Curtis et al[2] reported that one of their comparisons showed an increase in overall mortality and stroke risk with bevacizumab compared to ranibizumab, with hazard ratios 0.86 (0.75 to 0.98) and 0.78 (0.64 to 0.96) respectively. However because of the very large cost differences between bevacizumab and ranibizumab ($30 versus $1950), Curtis et al noted that selection bias might be operating, with poorer people (with poorer health) more likely to be treated with bevacizumab. They therefore carried out another analysis using only ophthalmological clinics which used only one drug, to avoid selection bias. This analysis showed no significant difference: overall mortality HR for ranibizumab 1.10 (0.85 to 1.141); MI 0.87 (0.53 to 1.14); stroke 0.87 (0.61 to 1.24). The analysis was based on use of the drugs for age-related macular degeneration, so the patient group is much older than those who have RVO.

Curtis et al[2] noted that there appeared to be slightly higher mortality in those treated with PDT and pegaptanib. Some patients on those were switched to bevacizumab when that became available, and in theory, they might have taken some of the excess risk with them. Curtis and colleagues therefore compared ranibizumab and bevacizumab outcomes in patients treated only with those drugs, and found no significant difference.

The ERG therefore consider that the statement in the abstract by Moeremans and colleagues[3] about "significantly higher mortality and stroke rates" with bevacizumab is not justified. This is the Duke study referred to on page 25 of the Allergan submission.

3.4 The absence of a licence for eye use of bevacizumab.

Allergan remind us that bevacizumab does not have a license for eye use. It is worth noting that a license has never been refused. The lack of a license is because the manufacturers have never applied for one. Had application been made, bevacizumab would surely have been approved.

3.5 Capacity.

On page 14, Allergan draw attention to

"*current capacity issues in Ophthalmology where there are constraints on the availability of trained specialists, access to clean rooms and theatre time...*"

We argue that theatre time is not necessary, but we agree with Allergan on the general issue of the need for increased capacity, now that we have effective drugs which can be used not only for AMD, but also for RVO and diabetic macular oedema. This appraisal is dealing with only RVO, but the ERG is also involved in the appraisal of ranibizumab for diabetic macular oedema, where the anti-VEGF drugs represent a significant advance in care, but which will increase Ophthalmology workload.

Our belief is that in many Ophthalmology departments, there is insufficient capacity to cope with the advent of new drugs for RVO and DMO.

3.6 Gains of 10 or more letters. Statement: 3.14 (page 3 of Responses document)

Allergan make a comment in page 2 of the Response, about the value of a 10-letter improvement being clinically significant. We agree. Paragraph 3.14 of the ACD slightly misrepresents what was said in the ERG report, where we said (page 24) that;

"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 seems a useful outcome."

However the difference at 180 days was quite small – 6.7% (36.5% versus 29.8%; p = 0.037).

4. Cost-minimisation in CRVO

Critique of Allergan costings

4.1 Costs

4.1.1 Administration

In the first submission, Allergan assumed that dexamethasone would be given on a day case basis at a cost of £648, based on the NHS reference cost BZ23Z – vitreous retinal procedure category 1. The same procedure costs £150 on an outpatient basis. (NB this is more than a standard ophthalmology consultant new OP consultation, which costs £105. The ACD mentions outpatient appointments but BZ23Z is about a procedure on a non-admitted patient.) We argued that dexamethasone would be given on an OP basis but the Appraisal Committee disagreed.

Reference costs cover;

a) direct costs – which can be easily identified with a particular activity (e.g. consultants and nurses)
b) indirect costs – which cannot be directly attributed to an activity but can usually be shared among a number of activities (e.g. laundry and lighting)
c) overheads – which relate to the overall running of the organisation (e.g. finance and human resources).

At the NICE appraisal committee meeting on ranibizumab for diabetic macular oedema, there was discussion about the true cost of intravitreal procedures given in Outpatient departments. The two ophthalmologists thought that £150 was probably too low, but had no firm alternative figure.

For the second submission, Allergan included the views of 8 ophthalmologists. None of them reported that they gave dexamethasone on a day case basis to all patients. Three said they always gave it on an OP basis. One gave it on an OP basis 75% of the time, three gave it in OP to 50% of patients, and one to 25% of patients.

This supports the position we took in the ERG report, that dexamethasone would be given on an outpatient basis.

One of the ERG members is a consultant ophthalmologist who routinely gives ranibizumab on an outpatient basis.

If some clinics give dexamethasone on an OP basis all the time, the ERG sees no reason why OP administration should not be the norm. We are aware that in some hospitals, intra-vitreal injections are given in operating theatres, but the procedure could still be classed as BZ23Z. It is the cost, not the location, which matters.

In their second submission, Allergan have used a cost of £524 based on 75% day case and 25% OP administration, with a sensitivity analysis with a cost of £399 using a 50/50 split.

Had this been handled by the MTA process, the ERG (or in that case, the Assessment Group) would have commissioned some bottom-up costing work to more accurately identify the true costs of OP administration, including costs of provision of a clean room. That is not possible in an STA. We recommend that it should be done.

4.1.2 Cost of drugs

Allegan assumed a cost of £105 (plus VAT) for bevacizumab, quoting a cost from Moorfields Hospital, for a single use pre-filled syringe. They noted that there were two providers of eye doses in the UK. They did not mention that the cost from the other supplier was £50 (NICE report from workshop on bevacizumab, July 2010).[4]

NICE asked for a scenario analysis that involved vial-sharing. Allergan argue that vial-sharing is not good practice, and have not included that option in the revised base case analysis. We are aware that vial-sharing does happen in some places, but we think that Allergan is right about it not being good practice. If it was carried out, say in an OP clinic with 8 to 10 patients treated per session, the drug cost per patient might be £24 to £30.

There is a statement from Allergan that the dose of bevacizumab is "not based on evidence". This is not correct. The standard dose of bevacizumab is 1.25mg, as used in most recent studies. Two studies from the Pan American Collaborative Retina Study group (CRSG), one in BRVO[5] and one in CRVO[6] compared the 1.25mg and 2.5mg doses and found no significant differences in results.

4.1.3 Number of injections

The Allergan submission uses data from a large trial of ranibizumab, as proxy for the number of injections of bevacizumab.

Because bevacizumab is a larger molecule, it is possible that it may diffuse out of the eye more slowly, and administration at 6 to 8-week intervals could be considered, whereas ranibizumab is given

at 4-weekly intervals. We note that the submission from the Royal College of Ophthalmologist (dated 1st March 2011) envisaged that the clinical effect of bevacizumab probably lasts 6 to 12 weeks. However a review of some studies by the ERG (Appendix 3) suggested that there was no difference in the frequency of injections between ranibizumab and bevacizumab. Wide variation was noted.

A review by Brown[1] of the implications of the BRAVO[7] (ranibizumab in BRVO) and CRUISE[8] (ranibizumab in CRVO – Brown was lead investigator) concluded that

"*most physicians will probably give their RVO patients several monthly injections as a loading dose and then either treat on an as-needed basis or with a treat-and-extend strategy."*

The treat-and-extend strategy would be for patients with persistent oedema, and Brown[1] notes that in BRVO, physicians may decide to add grid laser photocoagulation. That might reduce the number of anti-VEGF injections required.

The Allergan cost-minimisation analysis for CRVO (appendix C in the Allergan submission has details) assumes that there would be nine injections of ranibizumab or bevacizumab in year 1, followed by 4.8 in year 2, and 2.8 in year 3. The numbers of dexamethasone implantations are assumed to be 1.9 in year 1, 1.26 in year 2, and 0.74 in year 3. So in years 1 to 3, there are 16.7 injections of anti-VEGFs and 3.9 of dexamethasone (as in the main submission, table 109). The number of anti-VEGF injections is likely to be rather less than used in the Allergan modelling.

In the Pan American CRSG CRVO study,[6] patients had repeat injections of bevacizumab if there was persistent or recurrent macular oedema. The mean time to repeat was 4 weeks for the first 4 injections, but then lengthened, to 7 weeks between fourth and fifth injections. Over the first 24 months, there was a mean of 7 injections per patient.

In the CRSG BRVO study,[5] the mean number of injections was 3.6. Appendix 2 gives details of the time profile and mean number of injections.

4.1.4 Three year timescale

The submission assumes 3-year timescale "after which all costs and benefits are equal". However the BVOS (1984)[9] trial showed that the benefits of laser treatment take years to reach full effect. Most improvement happened in the first 15 or so months, but visual acuity was still improving beyond four years. It is also worth noting that the control group was also still showing improvement beyond three years (figure 2 of BVOS study).[9]

4.1.5 Cost of adverse events

Intravitreal steroids cause cataracts. A recent conference presentation reported that after three years of treatment with another steroid, fluocinolone, most patients had cataract. Not all would need cataract surgery. The Allergan response uses a figure of 8.3% when considering the cost of cataracts. This was derived from the 180 day results, and is an under-estimate of the true frequency of cataract over a longer period. The figure is higher at 360 days.

[redacted]

Cataract takes time to develop. In the FAME study[10] (fluocinolone in DMO), around 75% of patients who were phakic (i.e. having a normal lens) at baseline, had undergone cataract surgery by 24 months. Cataract developed mainly between 6 and 18 months.[1] Other studies have reported high levels of cataracts and cataract surgery after 2-3 years of steroid therapy. In the DRCR trial,[11] which used two doses of triamcinolone, 1mg and 4mg, the proportions having cataract surgery by 3 years were 46% and 83 % respectively. Gillies et al[12] reported that 54% had cataract surgery by 2 years. Islam et al[13] reported 81% as having cataract by 2 years, and Ruiz-Moreno et al[14] 55% by 2 years. However other studies have reported lower prevalences – Batioglu[15] 24% at 2 years; Chew[16] 17% at 2 years. Jonas 2005[17] reported 15-20% at one year.

Time has not permitted a review to examine reasons for the variations in the frequencies of cataract occurrence, but even the lowest rates are well above the figure used in the Allergan modelling. It might be reasonable to assume that by three years, half would have cataracts.

[redacted] At the end of the first 180 days, cataracts were seen in 7.4% of the dexamethasone group and 4.5% of the sham group (page 92).

In the modelling (see appendix C, page 18), it is stated that;
"For Ozurdex the cost of cataract extraction was multiplied by the percentage of CRVO patients experiencing cataracts in GENEVA studies (8.3%)".
This is applied on a six monthly basis with the 8.3% being taken to be the incidence of cataracts among patients remaining on dexamethasone. This results in a three year cumulative rate of cataracts

among those remaining on treatment for the three years of 50%, but it should be borne in mind that the manufacturer also assumes that only 37% of CRVO patients will require dexamethasone treatment for the entire three years.

The quality of life disutility of cataracts and surgery should also be taken into account. Intravitreal steroids also cause raised intra-ocular pressure. At month 24 in the FAME study,[10] 16% of low dose steroid and 22% of high dose steroid patients had IOP >30mmHg, compared to only 3% of sham patients. By 36 months, 5% had needed intervention for glaucoma.

4.2 Cost-minimisation analysis: dexamethasone versus bevacizumab in CRVO

Allergan argue that Ozurdex is less costly than bevacizumab. The main driver for this is the lower frequency of injections.

Some key assumptions disadvantage bevacizumab;

- Administration mainly as day cases affects bevacizumab much more than dexamethasone because of the number of injections.
- The number of anti-VEGF injections is too high
- Using the Moorfields cost rather than the Liverpool one doubles the drug cost
- The cost of cataracts with dexamethasone is under-estimated

Despite all these, bevacizumab still comes out as more cost-effective when all injections are given in outpatient clinics. Allergan refer to this as "the extreme assumption where all administrations are assumed to be performed as outpatient visits", an assertion that does not fit with the results of their survey of ophthalmologists. The ERG remains of the belief that OP administration should be the norm.

There is a large amount of data on the safety of bevacizumab from its use in AMD, RVO and DMO. However, Allergan state that the costs of bevacizumab should include a pharmacovigilance scheme, which would presumably log all uses and monitor adverse events, at least for an initial period. The rate of adverse events in routine practice might be higher than in the trials. That could of course apply to dexamethasone as well, so a similar scheme could operate there, at similar cost.

4.2.1 The Allergan modelling

Comparison with bevacizumab: Cost minimisation for CRVO

The dosing schedule for the first year for bevacizumab is taken from the CRUISE trial as reported by Brown et al (2010),[8] this being split into 5.6 doses in the first 6 months and 3.3 doses in the next six months.

Table 1. Dosing rates for dexamethasone and bevacizumab: CRVO

CRVO	0-180	181-360	361-540	541-720	721-900	900-1080
Dexamethasone	1.00	0.86	0.63	0.63	0.37	0.37
Bevacizumab	5.60	3.30	2.43	2.43	1.41	1.41

Dosing reductions after the first year for bevacizumab are assumed to be proportionate to the dosing assumed for dexamethasone, as drawn from expert opinion. For example, the number of doses of bevacizumab required for the 6 months of days 361-540 is calculated as 3.30 * (0.63 / 0.86) = 2.43. The cost per dose for dexamethasone is £870, while the cost per dose for bevacizumab is taken to be £105 as drawn from the Moorfields pharmacy.

Administration costs are based upon 75% being day cases and 25% being outpatient appointments for both dexamethasone and bevacizumab to give an average cost per administration of £524.

The proportion remaining on treatment and requiring follow up visits for both dexamethasone and bevacizumab are assumed to be as per the dexamethasone dosing schedule. These proportions do not affect the number of doses being administered every 6 months which are as per the above table. They do affect the modelled number of follow up visits, cataract rates and other adverse event costs.

Note that the proportion remaining on treatment in the dexamethasone trials is by definition as per the dosing schedule with the second 6 months dosing being 86% of the first six months dosing. For bevacizumab the second 6 months dosing is only 59% of the first six months dosing. If this reflects not just a reduced dosing frequency but a reduced proportion of patients remaining on treatment, the manufacturer cost calculations are too pessimistic for bevacizumab.

The total number of appointments required for those on therapy was assumed to be 3 for dexamethasone and 6 for bevacizumab during the first 6 months, and 2 for dexamethasone and 6 for bevacizumab thereafter. Subtracting the number of drug administrations and adjusting for the proportions remaining on treatment, this gives rise to the rates of follow up appointments.

Table 2. Additional follow up appointments required: CRVO

CRVO	0-180	181-360	361-540	541-720	721-900	900-1080
Dexamethasone	2.00	0.86	0.63	0.63	0.37	0.37
Bevacizumab	0.40	1.84	1.35	1.35	0.78	0.78

These are costed at the outpatient consultancy follow up cost of £73.
Cataract incidence rates for those remaining on treatment are taken to be 8.3% per 6 months for dexamethasone and 1.6% for bevacizumab and costed at £789 as per the ERG report.

Additional adverse event costs for dexamethasone were applied at a 6 monthly cost of around £105 for those remaining on treatment.

ERG replication of the arithmetic underlying these calculations and applying a 3.5% annual (1.73% six monthly) discount rate results in the following:

Table 3. ERG replication of manufacturer cost minimisation analysis for CRVO

	0-180	181-360	361-540	541-720	721-900	900-1080	Total
Dexamethasone							
Drug cost	£870	£733	£530	£521	£296	£291	£3,241
Administration cost	£524	£441	£319	£313	£178	£175	£1,950
Follow up cost	£146	£61	£44	£44	£25	£24	£345
Cataracts	£65	£55	£40	£39	£22	£22	£244
Other AEs	£105	£88	£64	£62	£36	£35	£390
Total	**£1,710**	**£1,379**	**£996**	**£979**	**£558**	**£548**	**£6,170**
Bevacizumab							
Drug cost	£588	£341	£246	£242	£138	£135	£1,690
Administration cost	£2,932	£1,698	£1,227	£1,206	£687	£675	£8,425
Follow up cost	£29	£132	£96	£94	£53	£53	£457
Cataracts	£13	£11	£8	£8	£4	£4	£47
Total	**£3,561**	**£2,181**	**£1,576**	**£1,549**	**£882**	**£867**	**£10,618**

These differ very slightly from those of the manufacturer, but the differences are slight and relate to six monthly rather than annual discounting being applied. The manufacturer estimates a net saving from dexamethasone use of £4,463 over the three years.

The manufacturer also supplies an additional sensitivity analysis that applies the treatment rates for dexamethasone for days 180+ as all being as per day 180. This estimates a net saving from

dexamethasone use of £5,431 over the three years.

4.2.2 Bevacizumab comparison CRVO Cost Minimisation: ERG additional sensitivity analyses

The manufacturer outlines that off license use of bevacizumab may require additional counselling and patient consent prior to the first administration. But due to bevacizumab requiring simpler anaesthesia and injection than dexamethasone, it is possible that the cost per ongoing administration for bevacizumab will be less than that for dexamethasone. Bevacizumab can be given with a gauge 32 needle, whereas Ozurdex has to be given with a much larger gauge 23 needle, which increase the chance of leakage of vitreous humor, requiring more attention after the needle is withdrawn.

Given this, the result of the cost minimisation can be presented for a range of administration costs for dexamethasone and bevacizumab as below. These are based upon varying the ratio of day case to outpatient appointments necessary for administration, and retain the other manufacturer assumptions. As such they only alter the unit cost of an administration procedure as below.

Table 4. Proportions of day case and outpatient administrations and average cost

Day Case: Outpatient ratio	Average Cost
100:0	£648
75:25	£523
50:50	£399
25:75	£274
0:100	£150

These sensitivity analyses can also be presented for the alternative extreme dosing schedule of the NICE ACD of assuming dosing as at day 180 for doses thereafter. The cost of bevacizumab can also be varied from the £105 used within the manufacturer analysis to £50 as available from Liverpool. In the following negative amounts indicate that dexamethasone is estimated to be cost saving compared to bevacizumab, and positive amount that it is estimated to be more costly compared to bevacizumab.

Table 5. Bevacizumab at £105 and dosing as per base case: CRVO

		Dexamethasone				
		£648	£523	£399	£274	£150
Bevacizumab	£648	-£5,989	-£6,452	-£6,916	-£7,380	-£7,844
	£523	-£3,985	**-£4,449**	-£4,913	-£5,376	-£5,840
	£399	-£1,981	-£2,445	-£2,909	-£3,373	-£3,837
	£274	£22	-£442	-£905	-£1,369	-£1,833
	£150	£2,026	£1,562	£1,098	£634	£171

The manufacturer base case is highlighted in bold. With dosing as per the base case and a unit cost for bevacizumab of £105, dexamethasone is estimated to remain cost saving or broadly cost neutral unless bevacizumab can be administered routinely at an outpatient appointment.

Table 6. Bevacizumab at £105 and dosing as at day 180: CRVO

		Dexamethasone				
		£648	£523	£399	£274	£150
Bevacizumab	£648	-£7,749	-£8,380	-£9,012	-£9,643	-£10,274
	£523	-£5,100	-£5,732	-£6,363	-£6,994	-£7,625
	£399	-£2,451	-£3,083	-£3,714	-£4,345	-£4,977
	£274	£197	-£434	-£1,065	-£1,697	-£2,328
	£150	£2,846	£2,215	£1,583	£952	£321

If dosing is assumed to be as at day 180, the costs and savings are larger but it remains the case that dexamethasone is estimated to remain cost saving unless bevacizumab can be administered routinely at an outpatient appointment.

Table 7. Bevacizumab at £50 and dosing as per base case: CRVO

		Dexamethasone				
		£648	£523	£399	£274	£150
Bevacizumab	£648	-£5,104	-£5,567	-£6,031	-£6,495	-£6,959
	£523	-£3,100	-£3,564	-£4,027	-£4,491	-£4,955
	£399	-£1,096	-£1,560	-£2,024	-£2,488	-£2,951
	£274	£907	£444	-£20	-£484	-£948
	£150	£2,911	£2,447	£1,983	£1,520	£1,056

The reduction in the drug cost of bevacizumab has the anticipated effects, but they are not particularly dramatic. If dexamethasone administrations are 50:50 between day case and outpatient appointments at an administration cost of £399 it is broadly cost neutral compared with bevacizumab on a 25:75 ratio and administration cost of £274. As before, if bevacizumab can be administered routinely at an outpatient appointment, dexamethasone is more costly.

Table 8. Bevacizumab at £50 and dosing as at day 180: CRVO

		Dexamethasone				
		£648	£523	£399	£274	£150
Bevacizumab	£648	-£6,579	-£7,210	-£7,841	-£8,473	-£9,104
	£523	-£3,930	-£4,561	-£5,193	-£5,824	-£6,455
	£399	-£1,281	-£1,913	-£2,544	-£3,175	-£3,807
	£274	£1,367	£736	£105	-£527	-£1,158
	£150	£4,016	£3,385	£2,753	£2,122	£1,491

Moving to the other dosing extreme of all being as at day 180, the picture is broadly as before, though the potential cost savings or additional costs have increased correspondingly. The case of dexamethasone administrations being 50:50 between day case and outpatient appointments with bevacizumab on a 25:75 ratio has moved dexamethasone from resulting in a small cost saving to resulting in a small cost increase, but it remains estimated to be broadly cost neutral at this point.

The above costings are based upon manufacturer assumptions coupled with some sensitivity analyses around the cost per dose for bevacizumab. In terms of dosing frequency, the Pan American CRSG CRVO[6] found an average of 7 doses for bevacizumab in the first two years as compared with the manufacturer assumption of almost double this of 13.75 for the base case.

Slightly arbitrarily, the dosing schedule assumed by the manufacturer for bevacizumab in the first two years can be multiplied by 7/13.75 or around half and coupled the assumption of a 75:25 day case to outpatient administration ratio, while retaining all other manufacturer assumptions.

For the first two years this results in a total cost for dexamethasone of £5,064 compared to £5,190 for bevacizumab at £105 per dose and £4,812 for bevacizumab at £50 per dose: a net cost saving of £126 and a net cost increase of £252 respectively. Note that this retains the assumption of monthly follow up over the two years for the bevacizumab patients, despite the reduced dosing frequency. Further reducing the follow up visit frequency by half to only twice monthly from month 7 and onwards for bevacizumab results in a net cost increase from dexamethasone of £345 and £701 for bevacizumab drug costs of £105 and £50.

Were all administered as day cases, retaining the manufacturer assumptions on monthly follow up, the net savings from dexamethasone would be £601 and £223 for bevacizumab drug costs of £105 and £50. Were all administered as outpatients the net costs from dexamethasone would be £1,301 and £1,679 respectively.

Reducing the follow up visit frequency by half to only twice monthly from month 7 and onwards for bevacizumab, were all administered as day cases the net saving from dexamethasone would be £152 for a bevacizumab cost of £105 and a net cost of £225 for a bevacizumab cost of £50. Were all administered as outpatients, the net costs from dexamethasone would be £1,750 and £2,127 respectively.

5. Mixed treatment comparison and cost utility

The outline and results of the MTC are given on pages 16 to 18, and the details in appendix B. The analysis is done for BRVO only, using the results for dexamethasone at both 60 days and 180 days. The 60 day results are better for dexamethasone because the benefits are at their peak then. The effect of bevacizumab also peaks early, but is then more sustained, by repeat treatments as required.

The ERG have checked the MTC by re-running it in Winbugs. (There is a line of data missing from the foot of the section on Winbugs Code and data on page 16 of appendix B. The manufacturer provided the missing data later.) The MTC appears sound, but there will inevitably be substantial imprecision around the indirect estimates of treatment effect. These arise from;

- Lack of any direct evidence with which to combine the indirect evidence
- The indirect evidence comes from nodes that are two steps from each other, which inflates the variance
- The small size of one of the trials in the nework

The key finding from the MTC is that bevacizumab and dexamethasone appear clinically equivalent. The submission then goes on to carry out a cost-minimisation analysis, using the assumption of equal efficacy (statement page 10 of Allergan submission).

Allergan state, correctly, that the evidence on bevacizumab from RCTs is sparse, and that the results of the MTC should be treated with appropriate caution.

The Allergan network is show in Figure 1 below. The ERG would have liked to have carried out an MTC with a wider network, shown in Figure 2, but were not resourced to so do, because the STA process is based only on critiquing the industry submission, and does not allow for independent analysis. Such an analysis might not have made much difference, because it would only have affected the comparison of bevacizumab and laser, possibly narrowing the confidence intervals around that.

A trial comparing bevacizumab with sham injections has been carried out by the Tehran group, but so far only the results at three months have been published. [18]

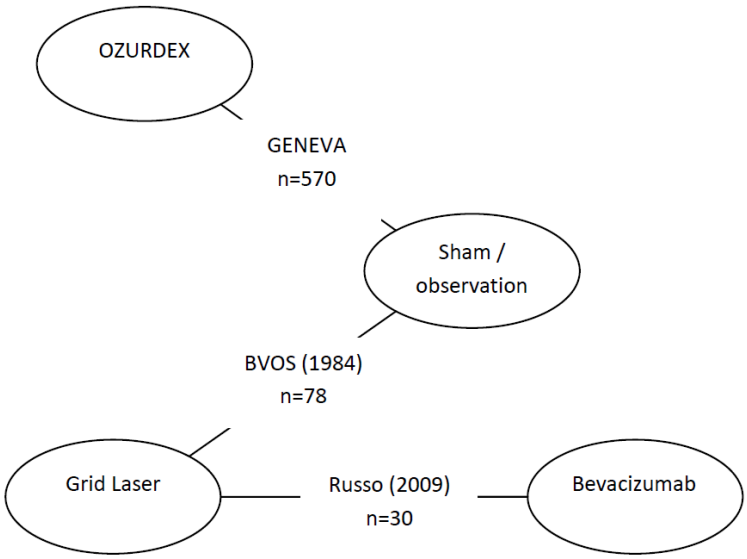

Figure 1. The network of evidence

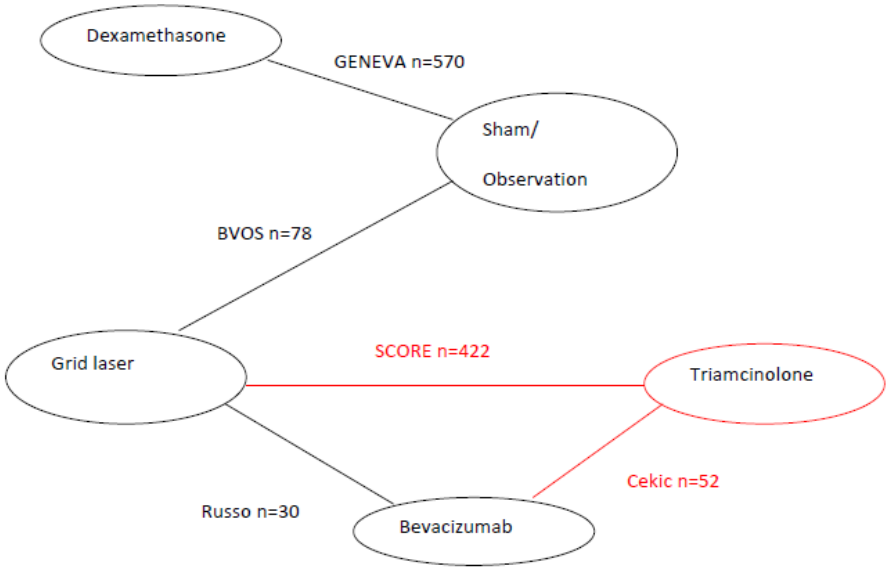

Figure 2. Network diagram

One assumption made (page 20 of submission) is that people having RVO have the same life expectancy as the general population. Patients enter the model age 68. Ho et al[19] from Taiwan reported that patients in the 60-69 age group who had had a RVO, had a 2.3-fold risk (95% CI 1.0 to 5.2) of having a stroke. Similar findings were reported from the USA by Werther et al,[20] with a 2-fold risk of stroke leading to hospital admission in those with a previous RVO. However Werther and colleagues[20] noted that the myocardial infarction rate was not increased.

Cugati et al[21] combined two population based cohorts from Australia and reported that RVO in people ages 43 to 69 was associated with a 2.5-fold risk of cardiovascular mortality (95% CI 1.2 to 5.2).

Hence the assumption that mortality is not increased amongst people with RVO may be incorrect.

6. Cost-utility analysis: dexamethasone versus bevacizumab in BRVO.

In the Pan American CRSG study of BRVO,[5] patients were reviewed monthly, and had OCT at longer intervals. Patients were re-injected if there was persistent or recurrent oedema. The average number of injections over 24 months was 3.6 (range 1 to 8). Most injections were required in the first four months, and none required an injection after 13 months of follow-up.

The Allergan cost analysis for BRVO, comparing dexamethasone and bevacizumab, assumes that there will be 9.7 injections in the first 24 months.

6.1 Allergan modelling

Comparison with bevacizumab for BRVO: MTC with bevacizumab

In terms of drug administration and monitoring costs, this adopts much the same assumptions as for the CRVO cost minimisation analysis. The only differences are in the dosing schedules, with the dosing schedule assumed for dexamethasone for year 2 and beyond being associated with the implied changes to the bevacizumab dosing schedule. This results in the following for the manufacturer base case.

Table 9. Dosing rates for dexamethasone and bevacizumab: BRVO

BRVO	0-180	181-360	361-540	541-720	721-900	900-1080
Dexamethasone	1.00	0.79	0.19	0.19	0.08	0.00
Bevacizumab	5.70	2.70	0.63	0.63	0.27	0.00

Table 10. Additional follow-up visits required: BRVO

BRVO	0-180	181-360	361-540	541-720	721-900	900-1080
Dexamethasone	2.00	0.79	0.19	0.19	0.08	0.00
Bevacizumab	0.30	2.03	0.48	0.48	0.21	0.00

This rolls through to a manufacturer estimated net cost saving from dexamethasone of £2,829 [£2,770 ERG replication] and the following detailed costings.

Table 11. ERG replication of manufacturer cost analysis for BRVO

	0-180	181-360	361-540	541-720	721-900	900-1080	Total
Dexamethasone							
Drug cost	£870	£674	£156	£153	£65	£0	£1,917
Administration cost	£524	£405	£94	£92	£39	£0	£1,154
Follow up cost	£146	£57	£13	£13	£5	£0	£234
Cataracts	£65	£51	£12	£12	£5	£0	£144
Other AEs	£105	£81	£19	£18	£8	£0	£231
Total	£1,710	£1,268	£293	£288	£122	£0	£3,680
Bevacizumab							
Drug cost	£599	£279	£64	£63	£27	£0	£1,032
Administration cost	£2,984	£1,389	£321	£315	£134	£0	£5,143
Follow up cost	£22	£146	£34	£33	£14	£0	£248
Cataracts	£13	£10	£2	£2	£1	£0	£28
Total	£3,617	£1,823	£421	£414	£176	£0	£6,450

As for the CRVO costings, the higher drug costs of dexamethasone are compensated for by the reduced dosing frequency and associated administration cost savings.

These cost savings are coupled with the differences reported in the mean number of letters from the manufacturer MTC to provide two cost utility analyses:

- A loss of 1.74 from dexamethasone compared to bevacizumab at 6 months
- A gain of 2.55 from dexamethasone compared to bevacizumab at 60 days

The manufacturer translates these into lifetime QALY losses and gains from dexamethasone use by applying the utility functions within the original model comparing dexamethasone with observation, and assuming a ratio of 90:10 of WSE to BSE. Assuming the loss or gain is maintained over the patient lifetime, this translates into a lifetime loss of 0.030 discounted QALYs from the 1.74 letter loss, and a lifetime gain of 0.044 discounted QALYs from the 2.55 letter gain.

The 0.030 QALY loss from dexamethasone as drawn from the 6 month data can be equally viewed as a 0.030 QALY gain from bevacizumab. The manufacturer estimates a net additional cost from bevacizumab use of £2,829, which translates into a cost effectiveness for bevacizumab versus dexamethasone of around £94,000 per QALY. Within this analysis, bevacizumab is found to be well outside normal cost effectiveness bounds, this also being mirrored in the net monetary benefit estimates within table 4 of the Allergan ACD clarifications which finds dexamethasone to have

positive net monetary benefits at willingness to pay values of £20,000 per QALY and £30,000 per QALY.

An additional analysis applying the day 180 dosing to days 180+ sees the manufacturer estimate a net cost from using bevacizumab of £4,079 which when coupled with the QALY gain from bevacizumab of 0.030 translates into a cost effectiveness ratio of around £136,000 per QALY which again suggests that bevacizumab use is well outside normal cost effectiveness bounds.

The 0.044 QALY gain from dexamethasone as drawn from the 60 day data when coupled with the estimates of cost savings from dexamethasone use suggest that dexamethasone dominates bevacizumab: i.e. provides additional patient benefits at lower cost.

6.2 ERG comments: bevacizumab comparison cost utility: ERG additional sensitivity analyses.

The considerations around the CRVO cost minimisation analysis apply equally to the costings applied within the cost utility analyses comparing dexamethasone with bevacizumab for both BRVO and CRVO. Some additional consideration of the costings for BRVO is warranted, though this will be limited to the three scenarios of:

- a cost per dose for bevacizumab of £105 coupled with the base case dosing assumptions
- a cost per dose for bevacizumab of £50 coupled with dexamethasone dosing for days 180+ being as per day 180
- dosing for bevacizumab being as per the Pan American CRSG study of BRVO[5] with patients reviewed monthly and with an average number of injections over 24 months of 3.6 which for simplicity is assumed to occur within the first six months

Rather than trying to analyse all possible scenarios and permutations, some simple ready-reckoners are presented that outline for a given letter gain and net cost what the implied ICERs are. These are calculated for a patient aged 67 at baseline and a base case of this gain being maintained for 30 years among those remaining alive, with two additional time horizons of 20 years and 10 years. Appendix 7 *presents the parallel ready reckoners for the maximum net cost that is permissible for willingness to pay values of £10,000 per QALY, £20,000 per QALY, £30,000 per QALY and £40,000 per QALY.*

Table 12. Bevacizumab at £105 and dosing as per base case: BRVO

		Dexamethasone				
		£648	£523	£399	£274	£150
Bevacizumab	£648	-£3,719	-£3,994	-£4,268	-£4,542	-£4,817
	£523	-£2,496	**-£2,770**	-£3,045	-£3,319	-£3,594
	£399	-£1,273	-£1,547	-£1,822	-£2,096	-£2,370
	£274	-£50	-£324	-£599	-£873	-£1,147
	£150	£1,173	£899	£625	£350	£76

The £2,770 highlighted in bold should correspond with the manufacturer base case of £2,829. This appears to be a relatively small discrepancy and is probably the result of a misinterpretation of the manufacturer assumptions by the ERG economic reviewer. As for the CRVO costings, the above suggests that given the manufacturer assumptions dexamethasone remains cost saving unless bevacizumab can be routinely administered as an outpatient appointment.

Table 13. Bevacizumab at £50 and dosing as at day 180: CRVO

		Dexamethasone				
		£648	£523	£399	£274	£150
Bevacizumab	£648	-£5,290	-£5,880	-£6,471	-£7,061	-£7,652
	£523	-£2,983	-£3,574	-£4,164	-£4,755	-£5,345
	£399	-£677	-£1,267	-£1,858	-£2,448	-£3,039
	£274	£1,630	£1,039	£449	-£142	-£732
	£150	£3,936	£3,345	£2,755	£2,164	£1,574

Note that the above costings retain the assumption of bevacizumab requiring monthly visits for either administration or follow-up for those remaining on treatment.

The effect of using the figure of £50 instead of £105 is relatively minor compared to the effects of different numbers of injections.

Applying the Pan American[5,6] dosing for bevacizumab of 3.6 and restricting the costing to the first two years results in dexamethasone being estimate to cost £3,605 and bevacizumab £3,008: a net cost increase of £597 from dexamethasone use.

Table 14. Ready reckoner: ICER for a given letter gain and net cost: 30 year time horizon

			Net Cost					
Letter gain	QoL	QALYs	£250	£500	£1,000	£2,000	£4,000	£6,000
[redacted]	[redacted]	0.215	£1,162	£2,325	£4,649	£9,299	£18,598	£27,896
6.10	[redacted]	0.108	£2,325	£4,649	£9,299	£18,598	£37,195	£55,793
2.55	[redacted]	0.045	£5,561	£11,122	£22,244	£44,488	£88,976	£133,464
1.74	[redacted]	0.031	£8,150	£16,300	£32,599	£65,198	£130,396	£195,594

The above is a very simple ready reckoner. For instance, if there were to be a net gain of [redacted] letters from dexamethasone over bevacizumab the anticipated patient gain over 30 years is 0.215[1] QALYs, which if the net treatment cost is £1,000 translates into an ICER of £4649 per QALY.

The parallel ready reckoners for the shorter time horizons of 20 years and 10 years, with survival at these points being around 40% and 73%, are as below.

Table 15. Ready reckoner: ICER for a given letter gain and net cost: 20 year time horizon

			Net Cost					
Letter gain	QoL	QALYs	£250	£500	£1,000	£2,000	£4,000	£6,000
[redacted]	[redacted]	0.200	£1,248	£2,495	£4,990	£9,981	£19,962	£29,942
6.10	[redacted]	0.100	£2,495	£4,990	£9,981	£19,962	£39,923	£59,885
2.55	[redacted]	0.042	£5,969	£11,938	£23,876	£47,751	£95,502	£143,253
1.74	[redacted]	0.029	£8,748	£17,495	£34,990	£69,980	£139,960	£209,940

Table 16. Ready reckoner: ICER for a given letter gain and net cost: 10 year time horizon

			Net Cost					
Letter gain	QoL	QALYs	£250	£500	£1,000	£2,000	£4,000	£6,000
[redacted]	[redacted]	0.136	£1,835	£3,669	£7,339	£14,678	£29,355	£44,033
6.10	[redacted]	0.068	£3,669	£7,339	£14,678	£29,355	£58,710	£88,065
2.55	[redacted]	0.028	£8,778	£17,556	£35,111	£70,222	£140,444	£210,666
1.74	[redacted]	0.019	£12,864	£25,728	£51,456	£102,912	£205,823	£308,735

[1] Totals differ slightly from manufacturer estimates due to marginally different survival curves

7. Comparison with bevacizumab for CRVO: Indirect comparison with proxy ranibizumab

[redacted]

Allergan carry out this analysis only for CRVO, on the grounds (page 25) that the published data from the trial in BRVO, BRAVO,[7] do not give any subgroup analysis of those with haemorrhages or those who have had previous laser treatment. The ERG confirms this.

The manufacturer's submission, appendix F, suggests that the comparison may disadvantage dexamethasone because the baseline central retinal thickness was higher in the CRUISE trial[8] of ranibizumab – 689um – than in the GENEVA trials CRVO patients (648). They note that letter gain is higher in patients with thicker retinas. However the data used comes from a comparison of patients from CRUISE[8] with CRT above or below 450um, which may not be relevant to a comparison of patients with means 689um and 648um.

8. Comparison with observation: the revised model

Required model changes outlined in the ACD

The NICE ACD outlines a number of changes required to the base case for the comparison of dexamethasone with observation:

1. The costs of dexamethasone treatment based on a day case, with outpatient appointment costs as a sensitivity analysis
2. Using all the RCT trial data for extrapolation in the observation arm as there was no evidence to suggest that only the second half of the trial was relevant to the transition probabilities.
3. Only applying the costs of SVI when both eyes fell below 38 letters

With three dosing scenarios:

a. As per the manufacturer base case of the original model
b. Dosing subsequent to day 180 being as per day 180
c. Dosing subsequent to day 180 being varied to be between the two scenarios above

Manufacturer revisions

The manufacturer implements the change to the costs of dexamethasone treatment by altering the balance to 75% being day case and 25% being outpatient, as within the cost minimisation analyses of the previous sections.

The manufacturer declines to use all the RCT trial data for extrapolation in the observation arm. The manufacturer justifies not using all the RCT trial data for extrapolation in the observation arm and only using the last 3 months data from the RCT trial on the basis that this better mirrors the CVOS and the BVOS studies of natural history, as presented in tables 12 and 13 of the Allergan ACD clarifications. This is coupled with the argument that natural resolution in BRVO renders the first 3 months data of the RCT invalid for extrapolation.

The manufacturer proxies only applying the costs of SVI when both eyes fall below 38 letters by reducing these costs to 25% of the cost of SVI in the first year, with a 10% 6 monthly uplift to these costs thereafter.

Rates of Severe Visual Impairment: Bilateral BCVA < 38 letters

The original model assumed that patients in the following two categories

- initially WSE and going to develop FEI in the BSE with this FEI falling into HS5, or

- initially BSE and this eye falls into HS5

would fall into SVI and so had the average annual of SVI of £5,963 applied. This failed to take into account that both eyes have to fall into HS5 for the costs of SVI to apply. In order to adjust for this, in the revised model the manufacturer reduces the average annual cost of SVI in the first year of the model to 25% of this value: £1,491. This is then uplifted by 10% per cycle to allow for general deterioration in patients' BCVA from other causes. Note that section 2.3 of the Allergan ACD clarifications suggests that the 10% increase in the average cost of SVI is an annual uplift. This appears to be incorrect and the revised model applies this uplift every 6 month cycle.

The 25% rate was taken from expert opinion on the percentage of patients whose BSE is affected at baseline whose fellow eye would be below 38 letters. The source of the 10% 6 monthly uplift is unclear. This results in the evolution of the proportions of patients falling into either of the two categories outlined above being modelled as having SVI and the resultant average SVI cost applied as outlined below.

Table 17. Manufacturer adjustments to average cost of SVI to approximate both eyes <38 letters

Year	% SVI	Mean SVI Cost
1	25%	£1,491
2	28%	£1,640
3	33%	£1,938
4	38%	£2,236
5	43%	£2,534
6	48%	£2,833
7	53%	£3,131
8	58%	£3,429
9	63%	£3,727
10	68%	£4,025

The 10% uplift results in a doubling of the rate of SVI by around year 6 within the two patient categories outlined above.

As there were only around 3% of patients having the BSE affected at baseline there would only be limited trial data from which to estimate the proportion of BSE affected patients at baseline whose WSE was less than 38 letters. But this would be hard data and could help triangulate with the 25% estimate drawn from expert opinion.

Revised model manufacturer base case: Administration costs and average costs of SVI

Table 18 of the Allergan ACD clarifications combines the revised administration costs of 75% as day case and 25% as outpatients, with the revised costs of SVI of 25% in the first year with a 10% 6 monthly uplift to provide the manufacturer's revised base case.

Table 18. Manufacturer revised base case – deterministic results

	QALYs	Cost	ICER
CRVO			
Observation	10.89	£7,600	
Dexamethasone	11.18	£12,332	
Net	0.29	£4,732	**£16,522**
BRVO-MH			
Observation	11.11	£5,558	
Dexamethasone	11.28	£8,677	
Net	0.18	£3,119	**£17,741**
BRVO-PL			
Observation	10.83	£7,684	
Dexamethasone	11.12	£9,542	
Net	0.29	£1,857	**£6,361**

The rise in the cost of the ICER when both adjustments are applied may appear low given that individually, they cause it to rise considerably. This is because the dual adjustment only affects the costs, with an additive effect rather than a multiplicative one.

Probabilistic results were not reported by the manufacturer for the manufacturer revised base case.

Revised model manufacturer sensitivity analyses: SVI rates and costs

Table 15 of the Allergan ACD clarifications outlines the impact of applying the above 25% baseline rate and 10% 6-monthly uplift, while table 16 provides a sensitivity analysis of applying a 5% 6-monthly uplift. The 5% uplift results in a doubling of the rate of SVI by around year 11. These analyses are in the context of all administrations being outpatient appointments at a unit cost of £150 in addition to the £870 drug cost for dexamethasone, so do not reflect the revised manufacturer base case of 75% of dexamethasone administrations being day cases and 25% outpatient appointments.

Table 19. Manufacturer adjustment to average cost of SVI

		25% base 10% uplift		25% base 5% uplift	
	QALYs	Cost	ICER	Cost	ICER
CRVO					
Observation	10.89	£7,600		£6,382	
Dexamethasone	11.18	£10,791		£10,372	
Net	0.29	£3,191	**£11,142**	£3,990	**£13,932**
BRVO-MH					
Observation	11.11	£5,558		£4,758	
Dexamethasone	11.28	£7,668		£7,330	
Net	0.18	£2,110	**£12,001**	£2,573	**£14,634**
BRVO-PL					
Observation	10.83	£7,648		£6,293	
Dexamethasone	11.12	£8,533		£7,964	
Net	0.29	£848	**£2,905**	£1,672	**£5,724**

Table 20. Revised model manufacturer scenario analyses: Alternative dosing scenarios

		Base case		Mid point		As per day 180	
	QALYs	Cost	ICER	Cost	ICER	Cost	ICER
CRVO							
Observation	10.89	£7,600		£7,600		£7,648	
Dexamethasone	11.18	£12,332		£14,181		£15,194	
Net	0.29	£4,732	**£16,522**	£6,581	**£20,257**	£7,546	**£22,083**
BRVO-MH							
Observation	11.11	£5,558		£5,558		£5,980	
Dexamethasone	11.28	£8,677		£11,143		£14,278	
Net	0.18	£3,119	**£17,741**	£5,585	**£31,123**	£8,298	**£45,878**
BRVO-PL							
Observation	10.83	£7,648		£7,684		£8,106	
Dexamethasone	11.12	£9,542		£11,504		£14,394	
Net	0.29	£1,857	**£6,361**	£3,819	**£10,876**	£6,288	**£16,548**

Within the above it is unclear why the costs for observation are the same for the base case and mid point estimates but increase for the "As per day 180" estimates.

Additional manufacturer sensitivity analyses

It should be borne in mind that a considerably more extensive set of sensitivity analyses were presented by the manufacturer within the original submission. These have been requested from the manufacturer for three patient subgroups coupled with the three dosing scenarios.

8.1 Observation comparison: ERG cross check of revised manufacturer base case estimates

Observation comparison: ERG cross check of revised manufacturer base case estimates

The deterministic results reported in Table 18 above cross check with the revised model.

The revised model submitted by the manufacturer appears to apply a mean cost of £150 for dexamethasone administrations within the probabilistic aspects of the model. Revising this to be £524[2] to correspond with the deterministic modelling base case, based upon only 1,000 iterations due to time constraints the probabilistic modelling results in the following.

Table 21. Manufacturer revised base case probabilistic results: CRVO

CRVO	Mean QALY	Mean Cost	ICER
Net change	£4,688	0.27	£17,127
	WTP = £20k	WTP = £30k	WTP = £40k
Probability of cost effectiveness	58%	83%	92%

[2] Implemented within the *Data & References* worksheet by setting cells E62 equal to £524

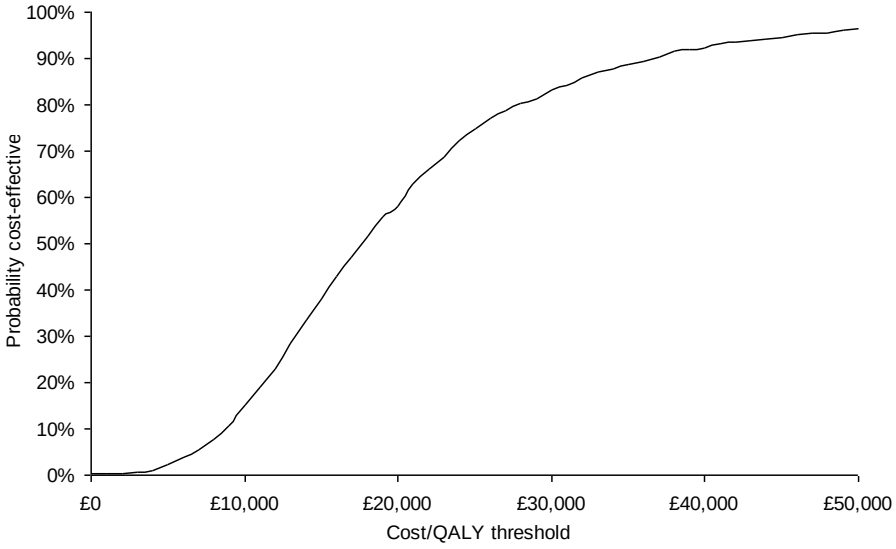

Figure 3. Manufacturer revised base case CEAC: CRVO

Table 22. Manufacturer revised base case probabilistic results: BRVO-MH

BRVO-MH	Mean QALY	Mean Cost	ICER
Net change	0.17	£3,15	£7,489
	WTP = £20k	WTP = £30k	WTP = £40k
Probability of cost effectiveness	56%	84%	95%

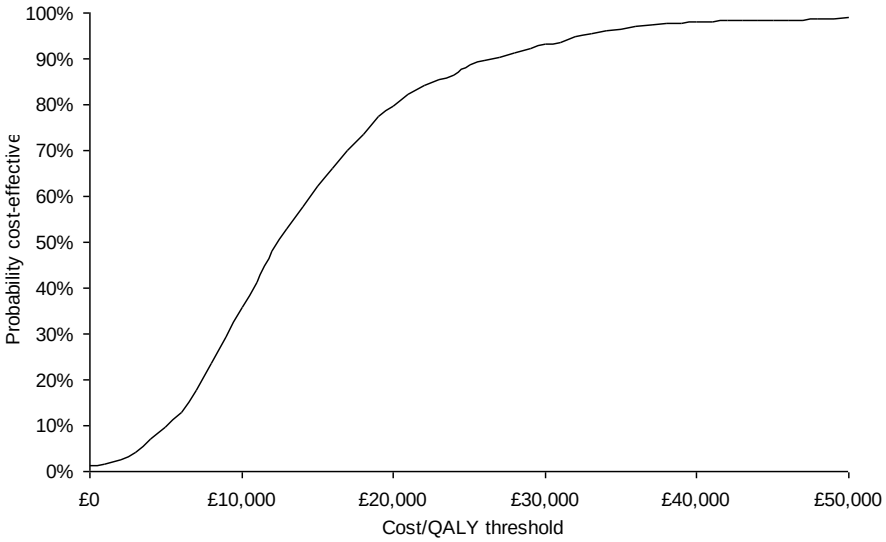

Figure 4. Manufacturer revised base case CEAC: BRVO-MH

Table 23. Manufacturer revised base case probabilistic results: BRVO-PL

BRVO-PL	Mean QALY	Mean Cost	ICER
Net change	0.27	£2,186	£8,148
	WTP = £20k	WTP = £30k	WTP = £40k
Probability of cost effectiveness	88%	96%	98%

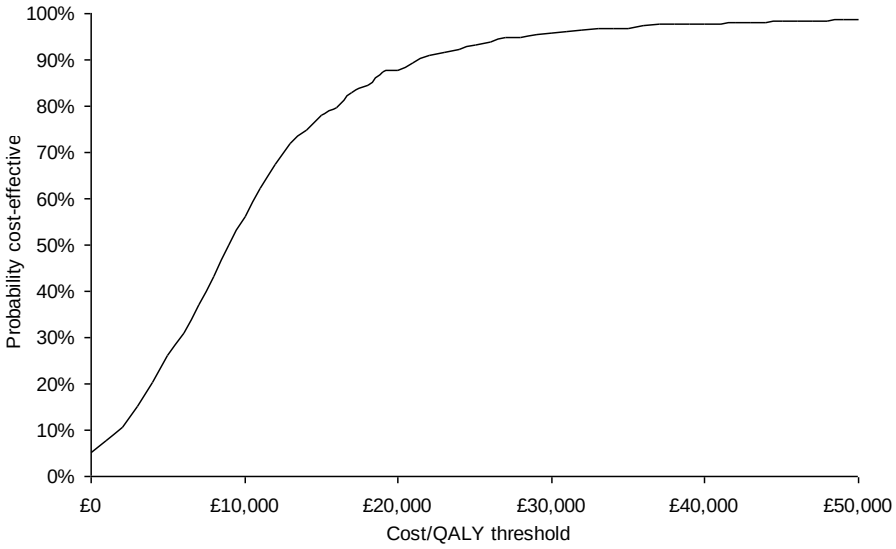

Figure 5. Manufacturer revised base case CEAC: BRVO-PL

8.2 ERG cross check of revised model structure and data inputs

The ERG has not undertaken a formal cross check of the revised model. Cross checking of the revised model is limited to unwinding the changes made to the administration costs and the costs of SVI to verify that the outputs of the revised model correspond with those of the original model, coupled with an examination of the implementation of the revisions to the administration costs and the costs of SVI. Unwinding the changes made to the administration costs and the costs of SVI[3] results in cost effectiveness estimates of £6,221 per QALY for CRVO patients and £8,313 per QALY for BRVO-MH patients. These correspond with the estimates of the original model.

The revised administration costs are reflected in *Summary* worksheet of the revised model and flow through to the other worksheets as in the original model. The revised costs of SVI are transparently applied among those who have their BSE affected from baseline. The description and implementation of the revised costs of SVI among patients have their WSE affected from baseline but go on to

[3] Implemented by setting cell Y7 of the *Summary* worksheet to 0% and cell AW4 of the *CRVO* worksheet to 100%.

develop BSE FEI is less transparent. But within the context of a simplified the model that has no mortality and no discounting, as outlined in Appendix 4.

Justification for not using all RCT data for extrapolation of observation

The CVOS and the BVOS data is presented in table 12 and 13 of the Allergan ACD clarifications. Unfortunately, in comparing this with the results of the modelling the manufacturer does not set the baseline distributions for the modelling to equal those of the CVOS and the BVOS studies. This makes a direct comparison between them difficult. There is also no consideration of anything other than the base case implementation of the revised model.

In order to facilitate this comparison[4], the baseline distributions of the modelling can be revised to better reflect the CVOS and the BVOS baseline distributions. HS0 of the model accords with the best health state reported for the CVOS and the BVOS studies. HS1, HS2 and HS3 of the model approximately accord with the central health state reported for the CVOS and the BVOS studies, so the simple approach is to equally allocate the central health state reported for the CVOS and the BVOS studies equally between these health states in the model. HS4 and HS5 of the model accord with the worst health state reported for the CVOS and the BVOS studies. It is unclear what proportion of patients were in HS5 in the CVOS and the BVOS studies. For the following the simplifying assumption of assuming the percentage as within the GENEVA trials for HS5, with the residual between this and the worst health state proportions reported in the CVOS and the BVOS studies being assumed for HS4. This results in the following baseline distributions for the modelling.

Table 24. Revised baseline distributions for the model to accord with CVOS and BVOS

	Model BCVA	Model CRVO	CVOS	Model BRVO	BVOS
HS0	≥ 20/40	[redacted]	[redacted]	[redacted]	[redacted]
HS1	20/50-20/63	[redacted]	[redacted]	[redacted]	[redacted]
HS2	20/80	[redacted]	[redacted]	[redacted]	[redacted]
HS3	20/100-20/125	[redacted]	[redacted]	[redacted]	[redacted]
HS4	20/160-20/200	[redacted]	[redacted]	[redacted]	[redacted]
HS5	≤ 20/200	[redacted]	[redacted]	[redacted]	[redacted]

When exploring the method of extrapolation and what is reasonable to assume for the base case, it is helpful to examine the following alternatives given the data available as presented by the manufacturer:

1. Re-applying the last 3 months RCT data as per the manufacturer base case
2. Re-applying the 6 months RCT data as per requested in the NICE ACD

[4] The detail of the implementation of the following within the revised model is set out in Appendix 5

It is not possible to explore this further given the data supplied by the manufacturer within the model as the duration of the data being reapplied has to multiply up to the cycle length of 6 months. This results in the following:

Table 25. CRVO modelling of the observation arm versus CVOS data

	Baseline	Year 1	Year 2	Year 3
CVOS				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Base case extrapolation using last 3 months RCT data				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolation using all 6 months RCT data				
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

For the CRVO modelling it appears from the above that reapplying all 6 months data for extrapolation within the observation arm may provide a superior fit to the CVOS data as reported by the manufacturer at 3 years. In particular, the reapplication of the last 3 months data from the RCT appears to over-estimate the proportion of patients falling into the worst health state reported within the CVOS study as summarised by the manufacturer.

Note that the original submission that applied day case costs to dexamethasone administrations, did not adjust the SVI costs for bilateral involvement and retained the structural errors around the implementation of FEI, as outlined within table 38 of the ERG report the manufacturer base case cost effectiveness for CRVO was £6,041 per QALY. Applying the 6 month RCT data for extrapolation within the observation arm worsened this to £15,395 per QALY[5].

Within the revised model structure, applying the changes outlined in Appendix 5 under the CRVO heading but making no other changes, worsens the cost effectiveness estimate for CRVO from the revised manufacturer base case estimate of £16,522 per QALY to £22,129 per QALY.

[5] Note that this sensitivity analysis applied the 6 months RCT data for extrapolation within the observation arm to both CRVO and BRVO patients. The model base case assumes that FEI will be 34% CRVO and 64% BRVO. The ERG economic reviewer is currently uncertain whether the BRVO FEI may be affected by the use of the 6 months RCT data for extrapolation. It appears not, but this remains unclear at present.

Table 26. BRVO modelling of the observation arm versus BVOS data

	Baseline	Year 1	Year 2	Year 3
BVOS				
HS0	[redacted]			[redacted]
HS1	[redacted]			[redacted]
HS2	[redacted]			[redacted]
Base case extrapolation using last 3 months RCT data				
HS0	[redacted]	[redacted]	[redacted]	[redacted]
HS1	[redacted]	[redacted]	[redacted]	[redacted]
HS2	[redacted]	[redacted]	[redacted]	[redacted]
Extrapolation using all 6 months RCT data				
HS0	[redacted]	[redacted]	[redacted]	[redacted]
HS1	[redacted]	[redacted]	[redacted]	[redacted]
HS2	[redacted]	[redacted]	[redacted]	[redacted]

The picture is somewhat different for the BRVO modelling in that the reapplication of all 6 months data from the RCT for extrapolation does appear to be overly optimistic. It seems possible that this is due to the natural resolution in BRVO patients of limited BRVO duration which may tend to be concentrated in the first 3 months of the RCT. As this will not recur, reapplying RCT data that includes those naturally resolving within the first 3 months of the RCT may unfairly bias the analysis. Whether reapplying the last 3 months of the RCT data is the best means of excluding the patients who naturally resolve from the extrapolation for observation within the modelling is a moot point.

Note that applying all 6 months RCT data for extrapolation of observation within the revised model results in the following.

Table 27. Applying all 6 months RCT data for observation extrapolation

	Base Case			6 mth data for Obs. extrapolation		
	QALYs	Cost	ICER	QALYs	Cost	ICER
CRVO						
Observation	10.89	£7,600		10.99	£6,396	
Dexamethasone	11.18	£12,332		11.21	£11,865	
Net	0.29	£4,732	**£16,522**	0.22	£5,469	**£25,336**
BRVO-MH						
Observation	11.11	£5,558		11.27	£4,212	
Dexamethasone	11.28	£8,677		11.37	£8,065	
Net	0.18	£3,119	**£17,741**	0.10	£3,853	**£38,489**
BRVO-PL						
Observation	10.83	£7,684		10.97	£6,450	
Dexamethasone	11.12	£9,542		11.19	£9,061	
Net	0.29	£1,857	**£6,361**	0.22	£2,611	**£11,650**

The manufacturer seeks to justify the choice of 3-6 month data by saying that it provides a better fit with natural history. They cite a reference which reported that BRVO resolves spontaneously in 26%, and go on to say that use of the 0-6 month data would imply that there is a much higher natural recovery rate, of 54%, which is would be "at odds with published estimates of disease resolution in untreated patients". The submission then mentions "the 26% recognised in published literature."

This represents highly selective use of the published literature. The 26% comes from one study. The submission references this as Gutman 1977,[22] but that paper simply repeats the data from an earlier paper, Gutman 1974.[23]

There is a high quality systematic review of the natural history of BRVO by Rogers and colleagues (2010).[24] The authors did systematic searches and then applied quality criteria to select studies for the review. The Gutman study failed to meet the quality cut-off and was excluded.[24] Twenty four good quality studies were included in the review, all of untreated patients, The authors noted that visual acuity improved in most patients, varying with time, with mean VA improving by 15 letters over 18 months. Between a third and three-quarters of eyes with BRVO improved by at least 10 letters.

Hence the natural history results are much more compatible with the figure of 54% which arises from using the 0 to 6 month data, than with the figure of 26% which fits with the 3 to 6 month data.

This high degree of spontaneous recovery in BRVO makes it more difficult for dexamethasone to be cost-effective than the Allergan modelling suggests.

Natural recovery is much less in CRVO,[25] but does occur. Another high quality systematic review by McIntosh and colleagues (the same group as Rogers et al)[25] reported that baseline VA was generally poor and declined over time. However, this was seen more in ischaemic CRVO, with decrease in VA of 3 letters in non-ischaemic, and 35 in ischaemic. In some studies, VA improved in CRVO, and it should be noted that in the CRVO group in the GENEVA trials, VA improved by 15 letters or more in 12% of patients, and by 10 letters or more in 24% of patients by day 180. The 10-letter improvement was mainly in the first three months, being seen in 12% of patients at day 30, 20% by day 60, 23% by day 90, and 24% at day 180. So the month 3-6 data are after natural recovery has mostly happened, and use of that in the modelling will bias it in favour of dexamethasone.

8.3 ERG additional sensitivity analyses

The 10% 6 monthly uplift in to the 25% baseline rate of SVI among those:

- initially WSE and going to develop FEI in the BSE with this FEI falling into HS5, or
- initially BSE and this eye falling into HS5

is justified by the manufacturer "due to age related deterioration and other sight reducing conditions". But there is no obvious reason for this not to apply more generally to all patients' BCVA, with a 6 monthly percentage worsening between adjacent health states being applicable. Implementing this within the revised model is complicated[6]. Perhaps the simplest is to remove the selective assumption of a worsening in BCVA only among those within the above two patient categories[7] and to implement an unchanging baseline rate and so a fixed reduction to the average cost of SVI among those in the two categories above. These scenario analyses result in the following cost per QALY estimates.

[6] Adjusting the identity matrix affects the transitions for all dexamethasone patients not on treatment immediately but only affects the observation arm from year 3, while adjusting and using the "sham alternative" matrices affects all patients but only from year 3. The former appears to somewhat worsen cost effectiveness ratio while the latter improves them. The decay parameters of cells J34 and J35 of the *Summary* worksheet appear to have no effect within the model.

[7] Implemented by revising cell AW5 of the *CRVO* worksheet to be 0%.

Table 28. Sensitivity to the rate of bilateral SVI assumed: SVI cost alone

	Base Case 25% baseline 10% uplift	10% baseline 0% uplift	25% baseline 0% uplift	40% baseline 0% uplift
CRVO	£16,522	£25,077	£22,831	£20,585
BRVO-MH	£17,741	£25,806	£23,847	£21,889
BRVO-PL	£6,361	£14,936	£12,857	£10,779

Note that the above only adjusts the costs of SVI. The model retains a mortality multiplier of 1.54 for patients in the two categories

- initially WSE and going to develop FEI in the BSE with this FEI falling into HS5, or
- initially BSE and this eye falls into HS5.

Sensitivity analyses that crudely adjust the SVI mortality multiplier for the baseline proportions with bilateral SVI show that this has very little impact upon results.

9. Discussion

It is noted that the manufacturer base case does not correspond with that of the ACD request. The manufacturer base case applies:

- 75:25 day case to outpatient administrations
- observation extrapolation remains as before using the last 3 months RCT data
- severe visual impairment is not modelled as requiring bilateral involvement, but rather adjusts the average annual SVI cost to approximate this.

The base case also retains the original manufacturer dosing assumptions, with the alternative assumptions in the ACD request being presented as scenario analyses

The manufacturer estimates of cost savings over three years from dexamethasone use within the comparisons with bevacizumab arise from high total administration costs within the bevacizumab arm. This is based upon 75% being day case administrations, and there being a much higher requirement for bevacizumab administrations compared to dexamethasone administrations. Mainly outpatient administration or a reduced dosing frequency as might be suggested by the Pan American study[5,6] could reverse these cost savings.

The manufacturer has presented a "base case" that applies a 75:25 day case to outpatient administration ratio. This is not in line with the ACD request which specified 100% day case for the base case, with a sensitivity analysis of 100% outpatient administration. The 75:25 ratio can in some sense be described as a goldilocks ratio: neither too cold for the costings of the bevacizumab comparison nor too hot for the cost utility analyses of the comparison of dexamethasone with observation.

For the comparison with observation, the ACD request was that all 6 months RCT data be used for extrapolation in the comparison arm. The manufacturer presents some data from the BVOS study which appears to suggest that applying the last 3 months RCT data within the observation arm provides a better fit than applying the last 6 months RCT data for the BRVO modelling. Whether this is the best means of accounting for natural resolution among BRVO patients within the modelling is a moot point. The ERG is dubious about using the 3-6 month data.

Were it possible to pre-identify those likely to resolve naturally, treatment and modelling among the remaining patient population would be likely to improve the cost effectiveness of dexamethasone. Moradian and colleagues[18] note that there are two schools of thought about when to treat BRVO, with

some favouring immediate treatment, and others favouring a delay to allow spontaneous improvement. They argue that the results in their trial (bevacizumab versus sham) support the case for delaying treatment.

Natural resolution is much less likely in CRVO. The manufacturer presents some data from the CVOS study. But this appears to suggest that applying the last 3 months RCT data within the observation arm provides a worse fit than applying the last 6 months RCT data for the CRVO modelling.

The manufacturer implements the ACD request for bilateral involvement being required for severe visual impairment to apply by reducing the SVI costs in the first cycle of the model to 25% of the previously applied value. This was apparently based upon expert opinion. There is questionable justification for 10% six monthly uplift in SVI average costs thereafter. It is not clear whether this was also from expert opinion, but it appears to be based upon a selective assumption of age related deterioration tending only to pull a higher proportion of patients into SVI.

There is a curious finding in the figure on page 27 of the Allergan submission. It appears that groups having sham injections do much better than those being simply observed. The likely explanation for this is that the trials tend to exclude patients with ischaemic CRVO, who do worse than those with non-ischaemic (NI) CRVO. The review of the natural history of CRVO by Mcintosh and colleagues[25] reported that patients with NI-CRVO had a decrease of 3 letters by 12 months, whereas those with ischaemic (I)-CRVO had a decrease of 35 letters. (The data quoted in the submission are referenced to Gutman 1977[22]).

In a large population-based study, Hayreh (2011)[26] also noted that outcomes were worse in I-CRVO. By 15 months, in NI-CRVO, 28% of patients had improved and 27% had worsened, whereas in I-CRVO 35% had improved and 45% had worsened.

An indirect comparison using natural history?

There are no head to head trials of bevacizumab versus dexamethasone, and no published trials with a common comparator which can be used in an adjusted indirect comparison in CRVO. One option is therefore to use natural history as a comparator. This would be safer in CRVO where natural recovery is less common. If the baseline characteristics and reported outcomes in the sham arms in the trials were similar to those in some natural history studies, then an indirect comparison could be carried out as shown in Figure 6.

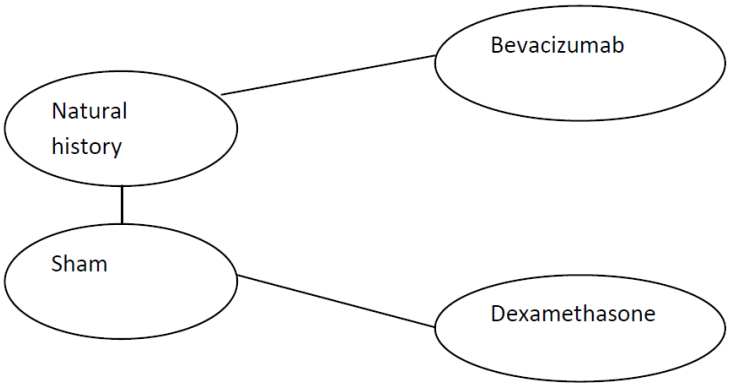

Figure 6. Network diagram

Figure 7 shows that the key outcome of three or more lines gained in the sham arms from 3 RCTs[8,27,28] is indeed similar between the sham arms and natural history (NH), and in marked contrast to bevacizumab. However Figure 8 shows a more mixed pattern. Note that these graphs include only non-ischaemic CRVO, because the trials tend to exclude ischaemic.

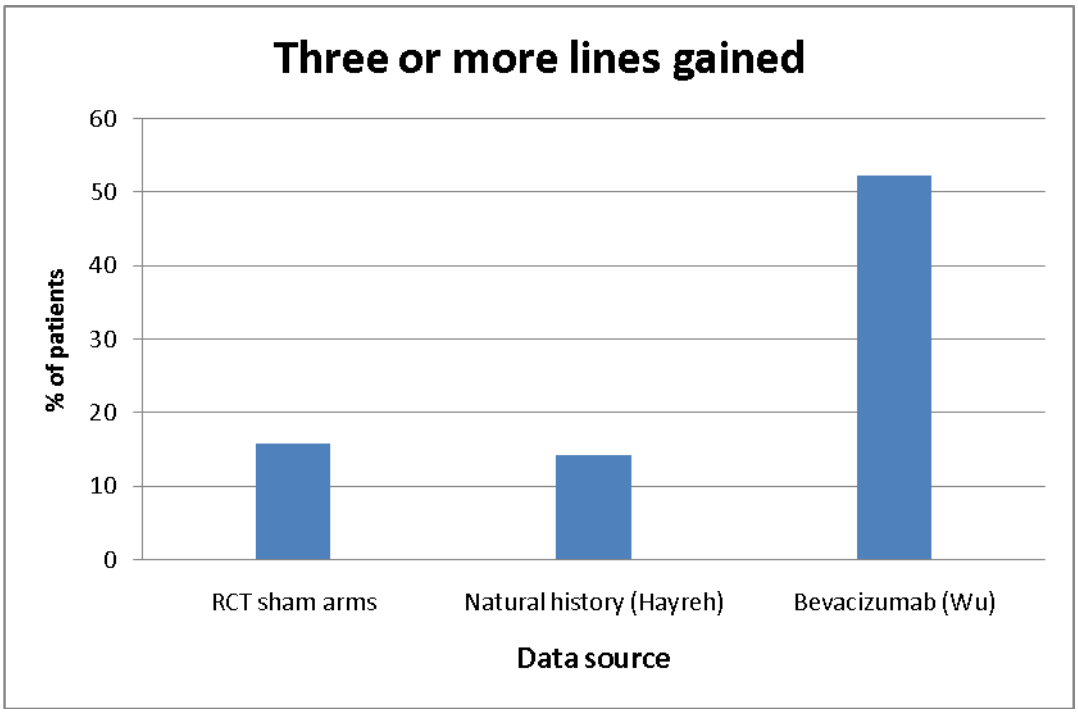

Figure 7. Non-ischemic CRVO: three or more lines gained

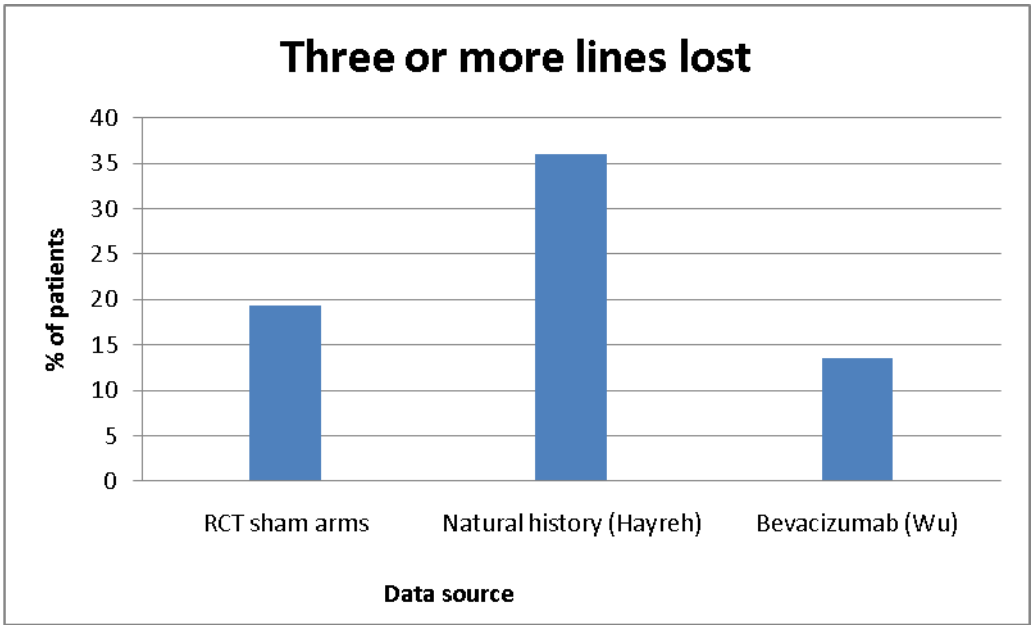

Figure 8. Non-ischaemic CRVO: three or more lines lost

We are not aware of natural history being used in mixed treatment or indirect comparison before, but have not carried out literature searches. The linkage of sham and NH would only be safe if baseline characteristics were similar, and same would apply to the linkage of bevacizumab case series and NH. Table 29 shows baseline characteristics. Propensity scoring might be another option but if that led to loss of numbers, the confidence intervals would widen.

This is an area which requires further research, to determine a set of situations in which an indirect treatment comparison would be safe.

Ideally, there would simply be an RCT of bevacizumab against dexamethasone. However, the frequency of cataract with intra-vitreal steroids is an issue now that the anti-VEGFs have arrived. In macular oedema after RVO (or in diabetic macular oedema), is there now any place for intra-vitreal steroids?

Research needs.

Given the high cataract rates with intravitreal steroids, and the arrival of effective and safe anti-VEGF agents, is there still a place for steroids in RVO? Some patients might prefer having fewer injections and a cataract operation, to the more frequent injections with anti-VEGFs. A trial of steroids versus anti-VEGF treatment, with quality of life and economics assessment, would provide answers.

Table 29. Baseline charactersitics of included studies for natural history indirect comparison of NI-CRVO

Characteristics		**Haller[27]**	**Wroblewski[28]**	**Brown[8]**	**Hayreh[26]**	**Wu[6]**
Age		63.9	59	65.4 (13.1)	61 (16)	60
Gender (%male)		50.8%	59.4%	55.4%	53%	48%
Race	Black	20 (4.7%)		8 (6.2%)	N/R	N/R
	White	318 (74.6%)		113 (86.9%)		
	other	18 (4.2%)		7 (5.4%)		
	Unavailable			3 (2.3%)		
	Asian	44 (10.3%)				
	Japanese	1 (0.2%)				
	Hispanic	25 (5.9%)				
Co-morbidities	DM	63 (15%)		N/R	10%	31.8%
	Arterial hypertension	273 (64%)			240 (43%)	
	IHD	38 (9%)			65 (12%)	
	TIA/CVA				27 (5%)	
Mean VA (letters)		53.3 (10.8)	48.5	49.2 (14.7)	N/R (reported categorically)	
Mean VA (logMar)						1.48
Mean CMT		539 (186)	656	687 (237.6)		635
Eyes type		Only NI-CRVO	Only NI-CRVO	Only NI-CRVO	Only NI-CRVO	Both NI-CRVO (54.5%) and I-CRVO (45.5%)
Macular Oedema present		Yes	Yes	Yes	Yes	Yes
Comment		This data includes CRVO and BRVO together			This data includes MO and non-MO pts together	

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Appendix 1. Patient years of observation in bevacizumab studies

Table 30. Patient year observation for all the bevacizumab studies

No.	Study	No. of patients on bevacizumab (n)	Duration of follow-up (t), **	Patient years of observation (n*t) #
1	Abegg 2008[29]	1.25 mg = 32	[27 to 418 days (median 170 days)] *0.073 to 1.4 year (median 0.46 year)*	15
2	Ach 2010[30]	2.5 mg = 70 (BRVO=32; CRVO= 38)	[20 weeks minimum] *0.42 year*	29
3	Ahmadi 2009[31]	1.25 mg = 42	[Avg. of 356 days] *0.97 year*	41
4	Beutel 2010[32]	1.25 mg = 21	[12 months minimum] *1 year*	21
5	Byun 2010[33]	1.25 mg = 37	[3 months minimum] *0.249 year minimum*	9
6	Cekic 2010[34]	1.25 mg = 14	[6 months] *0.498 year*	7
7	Chen 2010[35]	2.5 mg = 24	[At least 24 weeks] *0.498 year*	12
8	Chung 2008[36]	1.25 mg = 50	[At least 3 months (avg. 7.94 months)] *At least 0.249 year (avg. 0.66 year*	33
9	Figueroa 2010[37]	1.25 mg = 46	[At least 6 months] *0.498 year*	23
10	Fish 2008[38]	1.25 mg = 39	[Avg. 10 months] *0.83 year*	32
11	Funk 2009[39]	1.25 mg = 13	[Up to 15 months (mean 11 months)] *1.25 year (mean 0.91 year)*	12
12	Gregori 2008 CRVO[40]	1.25 mg = 55	[12 months] *1 year*	55
13	Gregori 2009 BRVO[41] or HRVO	1.25 mg = 65	[12 months] *1 year*	65
14	Guthoff 2010 BRVO[42]	1.5 mg = 10	[Mean 13 months] *1.08 year*	11
15	Guthoff 2010 CRVO[43]	1.5 mg = 9	[Mean 10.4 months] *0.86 year*	8
16	Gutierrez 2008[44]	1.25 mg = 12	[24 weeks] *0.498 year*	6
17	Hoeh 2009[45]	2.5 mg = 61	[At least 25 weeks] *0.52 year*	32
18	Hou 2009[46]	1.25 mg = 34	[Up to 1 year] *1 year*	34
19	Hsu 2007[47]	1.25 mg = 29	[Mean 18.1 weeks] *0.38 year*	11
20	Hung 2010[48]	2.5 mg = 25	[Up to 12 months (mean 6.5 months)] *1 year (mean 0.54 year)*	13
21	Jaissle 2009[49]	1.25 mg = 23	*1 year*	23
22	Kim 2009[50]	1.25 mg = 50	[>24 weeks] *0.498 year*	25
23	Kondo 2009[51]	1.25 mg = 50	[12 months]	50

No.	Study	No. of patients on bevacizumab (n)	Duration of follow-up (t), **	Patient years of observation (n*t) #
			1 year	
24	Prager 2009[52]	1 mg = 28	[12 months] *1 year*	28
25	Priglinger 2007[53]	1.25 mg = 46	[6 months] *0.498 year*	23
26	Rensch 2009 BRVO[54]	1.5 mg = 21	[6 months] *0.498 year*	10
27	Rensch 2009 CRVO[55]	1.5 mg = 25	[6 months] *0.498 year*	12
28	Russo 2009[56]	1.25 mg = 15	[12 months] *1 year*	15
29	Stahl 2010[57]	1.25 mg = 10	*2 years*	20
30	Tao 2010[58]	1.25 mg = 30	[3 to 12 months (mean 7.8 months)] *0.249 to 1 year (mean 0.65 year)*	19
31	Wu 2009 BRVO[5]	1.25 mg = 38 2.5 mg = 25	[At least 24 months] *2 years*	1.25 mg = 76 2.5 mg = 50
32	Wu 2010 CRVO[6]	1.25 mg = 44 2.5 mg = 42	[At least 24 months] *2 years*	1.25 mg = 88 2.5 mg = 84
	Total	**1135**		**992**

******If duration of follow-up is in months, converted into years by multiplying with 0.083; if in weeks- first converted to months dividing by 4 and then months converted into years as mentioned earlier.

number of patients (n) multiplied with duration of follow-up (t)

Appendix 2. Numbers and timings of bevacizumab injections in CRSG studies

Bevacizumab injections in patients with central retinal vein occlusion (Wu 2010) [6]

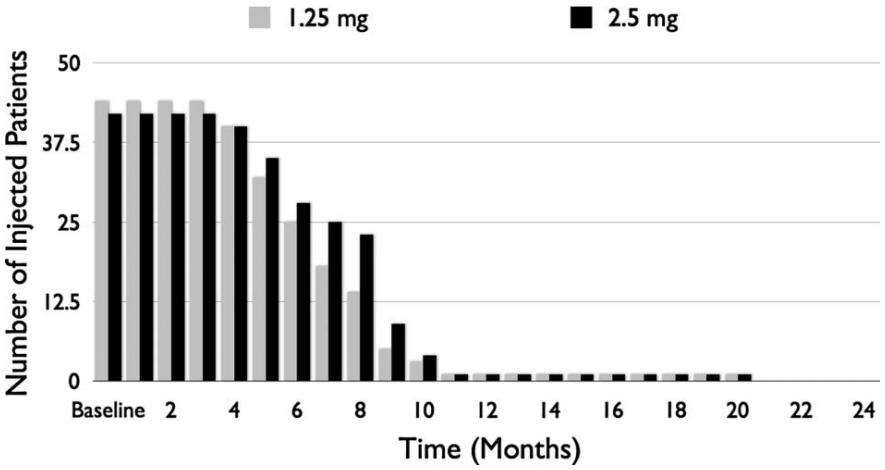


Figure 9. Distribution of the injections as a function of time.

Calculated roughly from the figure above (Figure 9)

Table 31. Number of injected patients during the 24 months period

Time (in months)	No. of injected patients 1.25 mg dose (n=44), N	Average number of injections per patient at each time point, N/n	No. of injected patients 2.5 mg dose (n=42), N	Average number of injections per patient at each time point, N/n
0	44	1	42	1
1	44	1	42	1
2	44	1	42	1
3	44	1	42	1
4	40	0.91	40	0.95
5	31	0.70	35	0.83
6	25	0.57	28	0.67
7	17	0.39	25	0.59
8	13	0.30	22	0.52
9	6	0.14	9	0.21
10	4	0.09	5	0.12
11	2	0.05	2	0.05
12	2	0.05	2	0.05
Injections during first year	316	7.20 (average number of injections per patient in first year)	336	7.99 (average number of injections per patient in first year)
13	2	0.05	2	0.05
14	2	0.05	2	0.05
15	2	0.05	2	0.05
16	2	0.05	2	0.05
17	2	0.05	2	0.05
18	2	0.05	2	0.05

19	2	0.05	2	0.05
20	2	0.05	2	0.05
21	0	0	0	0
22	0	0	0	0
23	0	0	0	0
24	0	0	0	0
Injections during second year	16	0.40	16	0.40
Overall	332	7.60 (average number of injections per patient by end of second year)	352	8.39 (average number of injections per patient by end of second year)

A total of 332 (Table 31-rough estimation from Figure 9) (318 reported in the paper) injections in the 1.25 mg group and 352 (Table 31- rough estimation from Figure 9) (342 reported in the paper) in the 2.5 mg group were recorded during the 24 months period.

In Table 31, it can be clearly seen that most injections occurred in the first year (316 in first year vs. 16 in second year in the 1.25 mg group and 336 vs. 16 in the 2.5 mg group). The average number of injections per patient in the first year was 7.20 (7.2 with range between 4 and 20 in the paper-one patient required 20 injections) in the 1.25 mg group and 7.99 (8.1 with range between 4 and 20 reported in the paper- one patient required 20 injections) in the 2.5 mg group. By the end of second year, average number of injections per patient did not increase considerably (difference of 0.40 for both groups compared to first year).

Mean time to repeat injection in both groups was 4 weeks for the first 4 injections while the difference between the fourth and the fifth injection was 7.0 ± 4.8 weeks for the 1.25 mg group and 7.1 ± 4.8 weeks for the 2.5 mg group (p=0.5646).

Bevacizumab injections in patients with branch retinal vein occlusion (Wu 2009)[5]

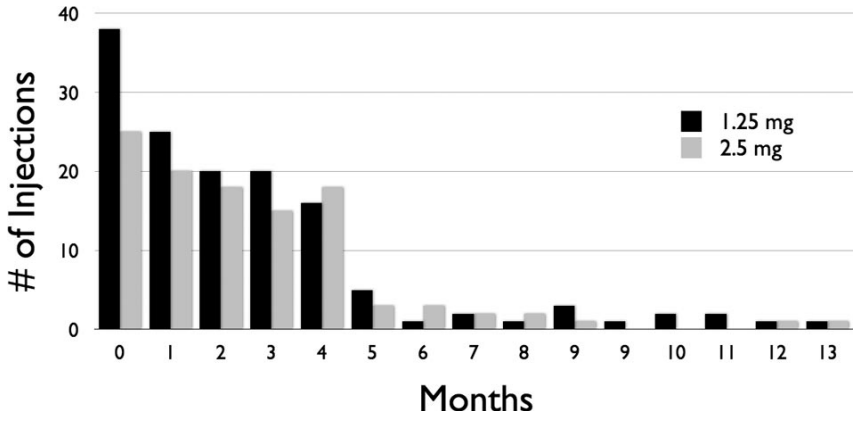


Figure 10. Distribution of the injections as a function of time.

Calculated roughly from the figure above (Figure 10)

Table 32. Number of injected patients during the 24 months period

Time (in months)	No. of injected patients 1.25 mg dose (n=38), N	Average number of injections per patient at each time point, N/n	No. of injected patients 2.5 mg dose (n=25), N	Average number of injections per patient at each time point, N/n
0	38	1	25	1
1	25	0.66	20	0.80
2	20	0.53	18	0.72
3	20	0.53	15	0.60
4	16	0.42	18	0.72
5	5	0.13	3	0.12
6	1	0.03	2	0.08
7	2	0.05	2	0.08
8	1	0.03	2	0.08
9	3	0.08	1	0.04
10	2	0.05	0	0
11	2	0.05	0	0
12	1	0.03	1	0.04
Injections during first year	136	3.59 (average number of injections per patient in first year)	107	4.28 (average number of injections per patient in first year)
13	1	0.03	1	0.04
14	0	0	0	0
15	0	0	0	0
16	0	0	0	0
17	0	0	0	0
18	0	0	0	0
19	0	0	0	0
20	0	0	0	0

21	0	0	0	0
22	0	0	0	0
23	0	0	0	0
24	0	0	0	0
Injections during second year	1	0.03	1	0.04
Overall	137	3.62 (average number of injections per patient by end of second year)	108	4.32 (average number of injections per patient by end of second year)

A total of 137 (Table 32- rough estimation from Figure 10) (138 reported in the paper) injections in the 1.25 mg group and 108 (Table 32- rough estimation from Figure 10) (109 reported in the paper) injections in the 2.5 mg group were recorded during the 24 months period.

From Table 32, it is clearly evident that most injections occur in the first year of the therapy. In the first year, average number of injections per patient was 3.59 (3.6 with a range between 1 and 8 reported in the paper) and 4.28 (4.3 with range between 1 and 7 reported in the paper) in the 1.25 mg and the 2.5 mg group respectively. By the end of second year, average number of injections per patient did not change dramatically (difference of 0.03 for the 1.25 mg group and 0.04 for the 2.5 mg group).

Injections were repeated at the mean time of 12 ± 6.5 weeks in the 1.25 mg group and 10 ± 5.3 weeks in the 2.5 mg group. The interval after each injection seems to increase in both groups. The interval between second and third injections was 13.5 ± 6 weeks whereas 15 ± 7.1weeks between the third and fourth injections in the 1.25 mg group. It was similar for the 2.5 mg group (11 ± 5.5 weeks between second and third; 12.5 ± 5.8 weeks between third and fourth injections).

After 13 months of follow-up, none of the eyes required injections of bevacizumab.

Appendix 3. Number of anti-VEGF injections across different studies

	Study	Dose	Crude rate of injections/month
Ranibizumab	Brown (RCT)[8]	Monthly from 0-6 months, then PRN from 6-12 months (no mean reported)	N/R
	Kinge (RCT)[59]	Monthly from 0-3 months, the PRN from 3-6 months (mean 4.3 injections)	0.72
	Puche (retrospective case series 34pts with BRVO or CRVO) [60]	Mean follow up 7 months, mean number of injection 2.3	0.32
	Rouvas 2010 (prospective interventional case series,28 eyes with BRVO)[61]	9 month follow up with mean of 6 injections	0.66
	Rouvas 2009 (prospective interventional case series12 pts with CRVO)[62]	12 month f/u with mean number of injections 7.4	0.62
	Pieramici 2008 (prospective uncontrolled trial, 10pts with CRVO)[63]	Follow up 9 months, mean number of injections 4.5	0.5
Bevacizumab	Figueroa 2010 (prospective interventional case series)[37]	During a 6-month period, the mean number of injections per patient was 3.7 (BRVO group) and 4.6 (CRVO group).	0.61 (BRVO) 0.76 (CRVO)
	Gregori 2008 (retrospective case series) [40]	Mean number of injection at 12months was 3.2	0.27
	Hoeh 2009 (interventional case series)[45]	Mean follow up was 5 months with mean injections of 4.1 for CRVO and 4.9 for BRVO (retreatment based on OCT result)	0.98 (BRVO) 0.82 (CRVO)
	Priglinger 2007 (prospective interventional case series)[53]	Follow up over 6 months with a mean of 3.0 injections	0.5
	Tao 2010 (comparative retrospective study)[58]	Mean follow up 7.8 months with mean injections of 3.7	0.47
	Wu 2010 (retrospective comparative study)[6]	24 month follow up with mean injections of 7.2	0.3

Appendix 4. Implementation of SVI costs among those with WSE affected at baseline

The following should be read in conjunction with the changes made to the revised model as outlined in *Cross_Check_WSE_FEI_cost_of_SVI.xls*.

The formula for the cumulative cost for patients with WSE in HS5 and with a FEI in their BSE in column DI of C_Oz worksheet, given the simplifying changes made as outlined in the XCheck Changes worksheet, can be simplified to:

=IF($AS40<=CC$22,
    $EM40, [*no FEI as yet cumulattive cost*]
    DI39+ [*previous cumulative total cost for this patient group*]
    $D40* [*adjustment for cycle length being ½ year*]
        IF($AS40<=CC$22+3, [*time from baseline less than or equal time from start of FEI: include treatment costs*]
            OFFSET($AE$27,($AS40-CC$22)*2,0)*(AW39+CC39)/$C$3, [*not reviewed for current purposes*]
            ((AW39+CC39+AW40+CC40)*$L$7+(CC39+CC40)*$I40)/2) [*only the ongoing costs inc SVI*])

Concentrating on [*no treatment costs and only the ongoing costs*] for the element

((AW39+CC39+AW40+CC40)*$L$7+(CC39+CC40)*$I40)/2)

the element $L$7 = 0 so this reduces to:

(CC39+CC40)*$I40)/2

within which the addition and division by 2 is the half cycle correction so can be more simply reviewed as:

CC40*$I40 [*costs of blindness for WSE in HS5 with BSE FEI*]

CC40 is the proportion of patients in this group whose WSE is in HS5, and running down the column to say CC45 and beyond is a steady 16.1% of patients. $I40 is the adjusted cost of bilateral SVI, this being 25% of the total SVI cost in year 1 of the model and growing by 2.5% every 6 months.

In other words the assumption for the 16.1% of WSE patients with their WSE in HS5 is that when BSE FEI occurs among them a minimum of 25% of this BSE FEI will immediately also be in HS5 with this proportion increasing over the model cycles, rising relatively quickly to 50% and beyond for the manufacturer revised base case.

The manufacturer expert opinion is that "in the first year of treatment 25% of patients affected in their BSE at baseline had a WSE BCVA below 20/200" so if the BSE was modelled as falling into HS5 both eyes would then be in HS5. It is not obvious from this that the reverse would apply in that among those whose WSE was affected at baseline and which was modelling as falling into HS5, that among these patients who go on to develop FEI in their BSE that 25% of these BSEs would immediately fall into HS5 if the FEI is in year 1 with this proportion rising as the model progresses [as distinct from the duration of FEI].

Appendix 5. Extrapolation methods within the observation arm

CRVO

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

=CHOOSE(AM$6,MMULT($AE$31:$AJ$36,$AE$31:$AJ$36),$AW$81:$BB$86,$CO$17:$CT$22,$CW$17:$DB$22,$DE$17:$DJ$22,AN$63:AS$68)

Change

MMULT($AE$31:$AJ$36,$AE$31:$AJ$36)

To

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

Where within this the TPMs $D$31:$I$36,$M$31:$R$36,$V$31:$AA$36 and $AE$31:$AJ$36 relate to D0->D30, D30->D60, D60->D90, D90->D180 respectively.

Within the *Transitions* worksheets set the subsequent TPMs for sham of:

AW31:BB36

BF31:BK36

BO31:BT36

BX31:CC36 and

CU63:CZ68

Equal to:

AN31:AS36

BRVO

For the BRVO sham D180->D360 TPM of AN54:AS59 within the cell formulae:

=CHOOSE(AM$11,MMULT($AE$54:$AJ$59,$AE$54:$AJ$59),$AW$96:$BB$101,$CO$17:$CT$22,$CW$17:$DB$22,$DE$17:$DJ$22,AN$70:AS$75)

Change

MMULT($AE$54:$AJ$59,$AE$54:$AJ$59)

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.

Within the *Transitions* worksheets set the subsequent TPMs for sham of:

AW54:BB59

BF54:BK59

BO54:BT59

BX54:CC59 and

CU70:CZ75

Equal to:

AN54:AS59

Reporting of results for comparisons of model outputs with CVOS and BVOS data

Implemented by setting cells D11:E70 of the *Mortality* worksheet to 0, cells J42:J43 of the *Summary* worksheet to 0, cells U20:Z20 of the *CRVO* and the *BRVO* worksheets to the appropriate baseline distribution and reporting baseline, year 1, year 2 and year 3 distributions from cells U20:Z20, U40:Z40, U42:Z42 and U44:Z44 respectively from the *CRVO* and the *BRVO* worksheets.

Appendix 6. Correspondence with manufacturer: late material

Response to ERG Email 24/03/2011.

1. **Please provide the range of sensitivity analyses reported in the *Data and References* worksheet [effectively columns A, E, G, H, L, M] and the *Tornado Diagram* for**
    - **The revised base case runs for CRVO**
    - **The revised base case runs for BRVO-MH**
    - **The revised base case runs for BRVO-PL**

    For the three dosing scenarios of
    - **Dosing as per the base case**
    - **Dosing as per day 180**
    - **Dosing as per the mid point of the two above**

The following assumptions were made in the revised base case (presented in the ACD response documentation previously supplied):

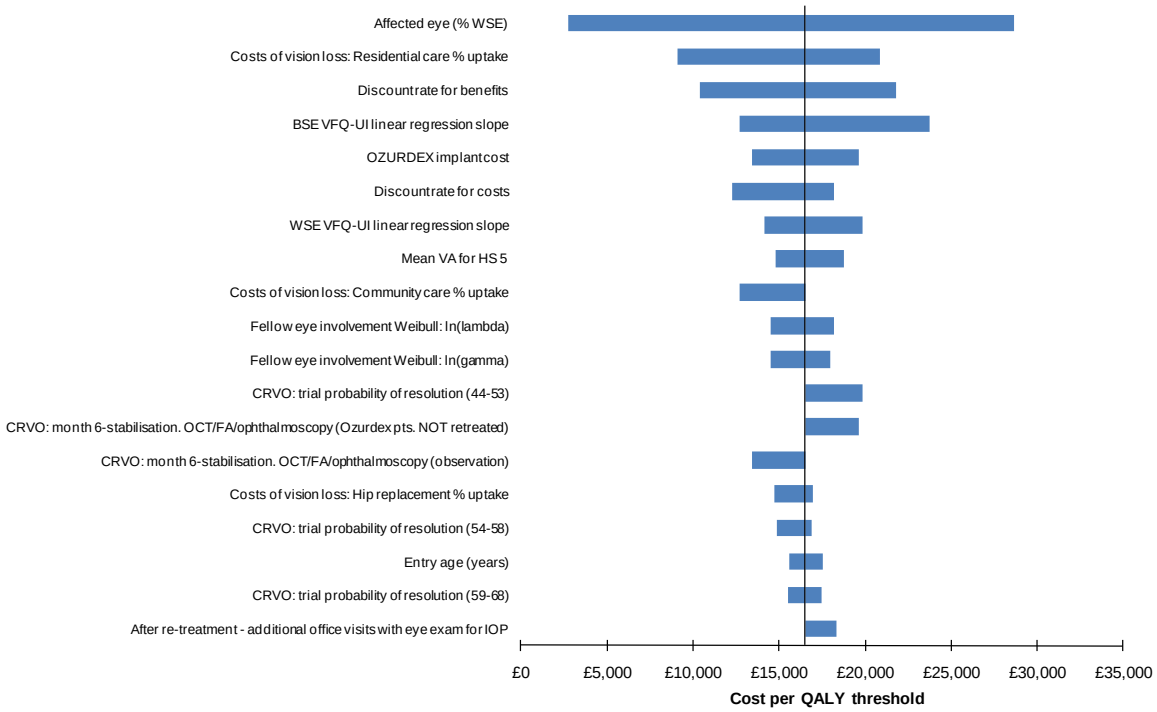
Assumption	Structural component	Revised base-case assumption
Assumption 2.1	Treatment administration procedure	75% of intravitreal injections will be administered as a day case procedure; 25% of intravitreal injections will be administered as an outpatient procedure.
Assumption 2.3	Severe visual impairment	25% of patients in HS05 who are affected in the BSE at baseline have their WSE BCVA below 20/200 (i.e. have severe visual impairment in both eyes); 10% annual increase in this number, up to a maximum of 100% of patients affected in their BSE

The tornado diagram representing the sensitivity analysis for the NICE base case for CRVO is shown in Figure 1. This incorporates assumptions 2.1 and 2.3 given above.

Table 33: *CRVO: NICE revised base case (incorporating assumptions 2.1 and 2.3)*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Observation	£7,600	10.89			
Dexamethasone	£12,332	11.18	£4,732	0.29	£16,522

Figure 11: *CRVO: Tornado diagram for the revised base case (incorporating assumptions 2.1 and 2.3)*

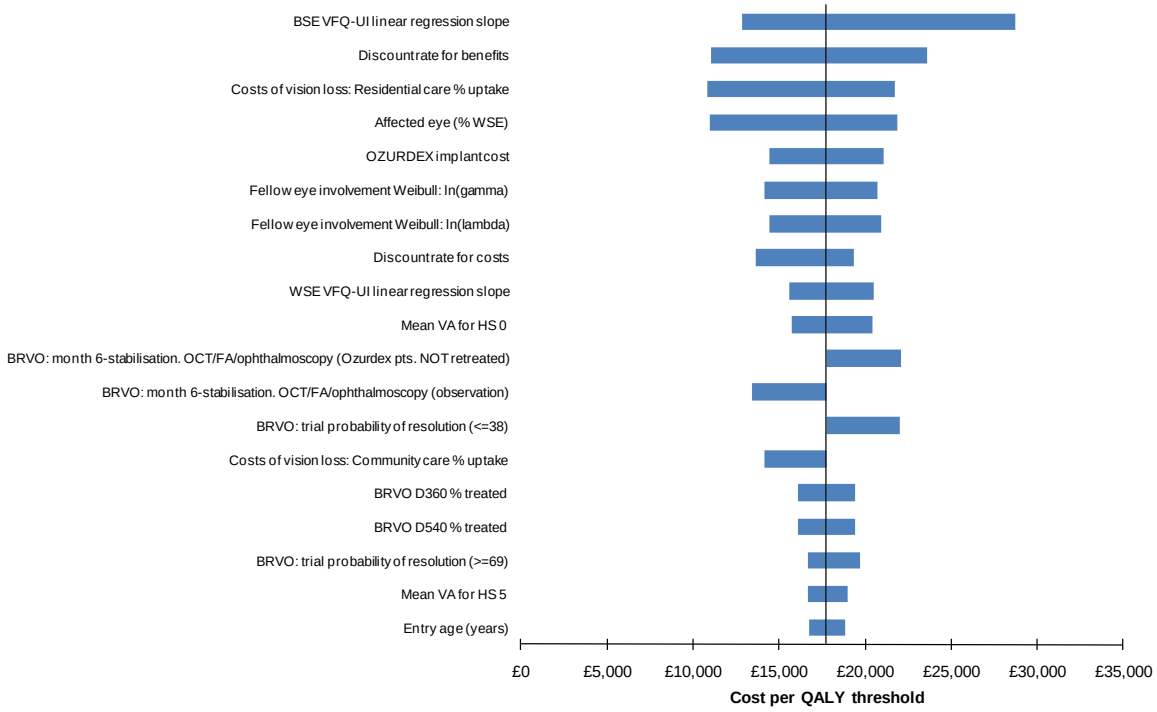


The tornado diagram representing the sensitivity analysis for the NICE base case for BRVO-MH is shown in Figure 2. This incorporates assumptions 2.1 and 2.3 given above.

Table 34: *BRVO-MH: NICE revised base case (incorporating assumptions 2.1 and 2.3)*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Observation	£5,558	11.11			
Dexamethasone	£8,677	11.28	£3,119	0.18	£17,741

Figure 12: *BRVO-MH: Tornado diagram for the revised base case (incorporating assumptions 2.1 and 2.3)*

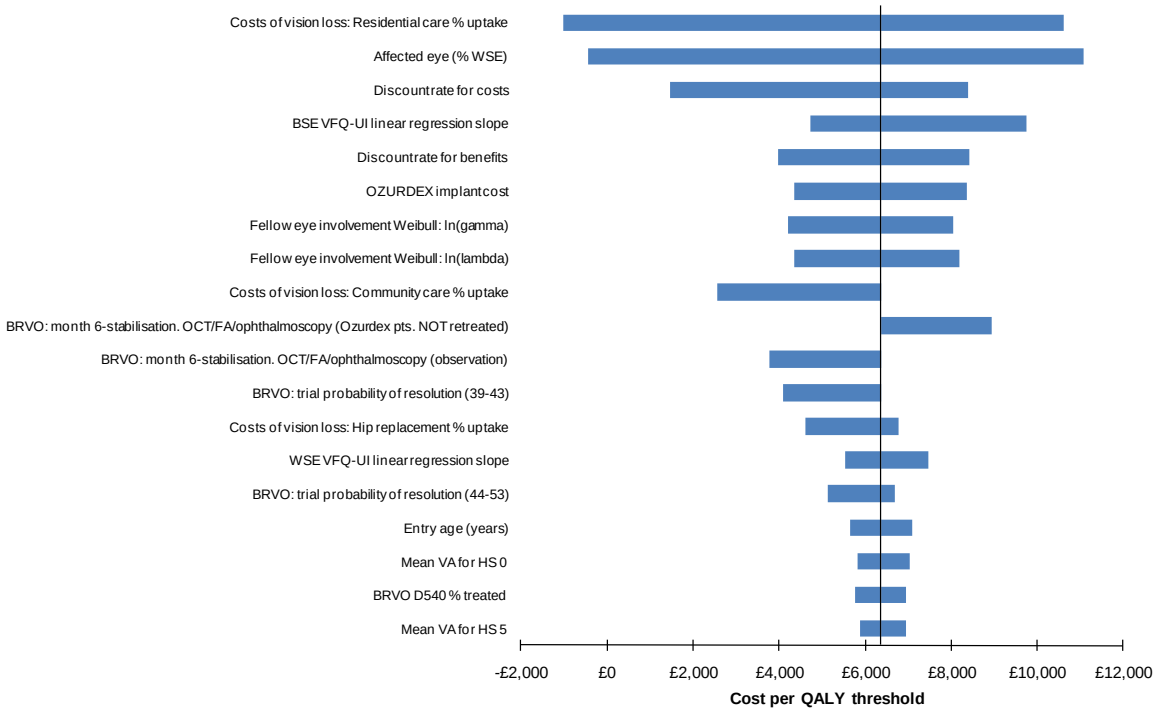


The tornado diagram representing the sensitivity analysis for the NICE base case for BRVO-PL is shown in Figure 3. This incorporates assumptions 2.1 and 2.3 given above.

Table 35: *BRVO-PL: NICE revised base case (incorporating assumptions 2.1 and 2.3)*

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER
Observation	£7,684	10.83			
Dexamethasone	£9,542	11.12	£1,857	0.29	£6,361

Figure 13: *BRVO-PL: Tornado diagram for the revised base case (incorporating assumptions 2.1 and 2.3)*



2. **It is also not obvious why within the clarifications sent in response to the NICE ACD the costs for observation are the same in tables 20 and 21, but differ from these in table 19. An account of this would be appreciated.**

We have investigated the analysis in table 19 and have discovered an error in the analysis and the costs for observation should be the same as in tables 20 and 21. We apologise for this error and have provided an amended version of table 19 below:

Table 19: *Sensitivity analysis investigating the effect on cost effectiveness of treatment with Dexamethasone of varying the retreatment assumptions based on those retreated at day 180 (incorporating assumptions 2.1 and 2.3)*[ab]

Technology	Total costs	Total QALYs	Incremental costs	Incremental QALYs	ICER	Revised Base Case ICER
All RVO						
Observation	£6,207	11.04				
Dexamethasone	£13,217	11.27	£7,010	0.23	£30,234	£17,558
CRVO						
Observation	£7,600	10.89				
Dexamethasone	£14,977	11.24	£7,377	0.34	£21,589	£16,522
BRVO						
Observation	£5,473	11.11				
Dexamethasone	£12,290	11.29	£6,816	0.17	£39,173	£18,472
BRVO- Macular Haemorrhage						
Observation	£5,558	11.11				
Dexamethasone	£12,371	11.29	£6,813	0.18	£37,667	£17,741
BRVO- Prior Laser						
Observation	£7,684	10.83				
Dexamethasone	£12,487	11.21	£4,803	0.38	£12,640	£6,361

[a] *For CRVO patients the proportion re-treated are as at day 180 for the five injections after the first injection*

b For BRVO patients the proportion re-treated are as at day 180 for the four injections after the first injection

3. **The ERG economic reviewer is not entirely familiar with the additional excel workbook supplied by Allergan in response to the NICE ACD. Does the attached workbook broadly reflect the structural assumptions of the Allergan cost minimisation analysis comparison of Dexamethasone with Bevacizumab in CRVO?**

WE have examined the workbooks supplied by the ERG in detail and can confirm that the methods used are analogous to those used in the workbook supplied by Allergan. The only difference in approach is that the ERG has applied the discount rate at 6 monthly intervals whereas Allergan have applied the discount rate annually. This will account for the small difference in outputs between the two workbooks.

Appendix 7. Maximum net cost for a given letter gain and willingness to pay

Table 36. Ready reckoner: maximum net cost for given letter[8] gain 30 year time horizon

Letter gain	QoL	QALYs	WTP 10k	WTP 20k	WTP 30k	WTP 40k
[redacted]	[redacted]	0.215	£2,151	£4,302	£6,452	£8,603
6.10	[redacted]	0.108	£1,075	£2,151	£3,226	£4,302
2.55	[redacted]	0.045	£450	£899	£1,349	£1,798
1.74	[redacted]	0.031	£307	£614	£920	£1,227

The above is a simple ready reckoner. For instance, if there is a net gain of [redacted] letters from dexamethasone over bevacizumab:

- The anticipated patient gain over 30 years is 0.215[9] QALYs.
- If dexamethasone is cost saving, it dominates bevacizumab.
- If not, the maximum lifetime net cost of dexamethasone compared to bevacizumab with it remaining cost effective is:
  - £2,151 at a willingness to pay of £10,000 per QALY
  - £4,302 at a willingness to pay of £20,000 per QALY
  - £6,452 at a willingness to pay of £30,000 per QALY
  - £8,603 at a willingness to pay of £40,000 per QALY

Rather than deal with negative benefits, if dexamethasone results in a loss of letters compared to bevacizumab this is more simply read as bevacizumab resulting in a gain of letters compared to dexamethasone: e.g. a loss of 1.74 letters from dexamethasone is a gain of 1.74 letters from bevacizumab. This translates into a 30 year 0.031 QALY gain from bevacizumab which we would be willing to pay a net lifetime cost of up to £920 at a threshold of £30,000 per QALY.

The parallel ready reckoners for the shorter time horizons of 20 years and 10 years, with survival at these points being around 40% and 73%, are as below.

Table 37. Ready reckoner: maximum net cost for given letter gain 20 year time horizon

Letter gain	QoL	QALYs	WTP 10k	WTP 20k	WTP 30k	WTP 40k
[redacted]	[redacted]	0.200	£2,004	£4,008	£6,012	£8,015
6.10	[redacted]	0.100	£1,002	£2,004	£3,006	£4,008
2.55	[redacted]	0.042	£419	£838	£1,257	£1,675
1.74	[redacted]	0.029	£286	£572	£857	£1,143

[8] Assumes 90% of patients have the gain in their WSE and 10% have the gain in their BSE
[9] Totals differ slightly from manufacturer estimates due to marginally different survival curves

Table 38. Ready reckoner: maximum net cost for given letter gain 20 year time horizon

Letter gain	QoL	QALYs	WTP 10k	WTP 20k	WTP 30k	WTP 40k
[redacted]	[redacted]	0.136	£1,363	£2,725	£4,088	£5,451
6.10	[redacted]	0.068	£681	£1,363	£2,044	£2,725
2.55	[redacted]	0.028	£285	£570	£854	£1,139
1.74	[redacted]	0.019	£194	£389	£583	£777