Modelling of both eyes: treatment costs and likelihood of severe visual impairment

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Due to time constraints, the ERG derivation of the approximations within what follows has not been rebuilt or cross checked by the ERG.

Background

In the light of the pre AC-meeting teleconference briefing, issues around the modelling of two eyes were identified as being concerns for which it might help the AC to have some ball park estimates of the effects of:

1. Modelling of the BSE being revised to include WSE FEI, with the associated costs of treatment for the WSE FEI

2. Modelling both eyes as having to fall into HS5 for the costs of severe visual impairment to apply:

    a. Assuming perfect correlation between the BCVA in affected eyes, so only requiring:

        i. the WSE FEI falling into HS5 to be included in the modelling of patients whose BSE is initially affected at baseline.

    b. Assuming no correlation between the BCVA in affected eyes, so requiring both:

        i. the WSE FEI falling into HS5 to be included in the modelling of patients whose BSE is initially affected at baseline, and

        ii. an adjustment to be made to the proportion of patients whose WSE is affected at baseline with FEI in the BSE to account for the probability of both eyes falling into HS5

3. Modelling both eyes as having to fall into HS5 for the 1.54 mortality multiplier of severe visual to apply, much as for the concerns around the application of the costs of severe visual impairment of point 2 above.

Summary

The modelling of the BSE including WSE FEI with the associated costs of treatment for the WSE FEI is likely to have only a limited impact upon results. It seems likely that a possible additional error within the manufacturer model of not accounting for monitoring visits serving both the initially affected eye and the fellow eye where FEI occurs relatively soon after presentation will tend to balance out any impact of the modelling of the cost impacts of BSE modelling including WSE FEI. The impact of monitoring visits doubling for the initially affected eye and the fellow eye may be the larger effect. Neither effect appears likely to be a key model driver.

Approximations around the potential impact of modelling both eyes as having to fall into HS5 for the costs of severe visual impairment to apply suggest that this may significantly adversely affect cost effectiveness estimates. With perfect correlation between a patient's affected eyes' BCVA the approximations suggest that the base case cost effectiveness estimates of dexamethasone for CRVO patients may worsen from £6,221 per QALY to £15,956 per QALY, while for BRVO-MH patients it may worsen from £8,313 per QALY to £9,674 per QALY. With zero correlation the approximations suggest that the base case cost effectiveness of dexamethasone for CRVO patients may worsen from £6,221 per QALY to £18,091 per QALY, while for BRVO-MH patients it may worsen from £8,313 per QALY to £21,443 per QALY.

However, comparing the approximations of the base case modelling to the base case modelling of the manufacturer model suggests that the approximations of the base case net cost impact of applying the costs of severe visual impairment are around 20% too high. These errors are likely to apply with equal or greater force to the approximations of the impact of modelling both eyes as having to fall into HS5 for the costs of severe visual impairment to apply. The approximations are only indicative of the possible impacts of model revisions. They are intended as crude rules of thumb to help the AC determine whether there is a need for the manufacturer model to give more explicit consideration of both eyes having to fall into HS5 for the costs of severe visual impairment to be applied.

Unfortunately, the model structure does not lend itself to approximating the effects of modelling both eyes having to fall into HS5 for the mortality multiplier associated with severe visual impairment to apply. But univariate sensitivity analyses suggest that results are not particularly sensitive to this variable.

Consequently, the main concern is around the modelling applying the costs of severe visual impairment without having modelled this as requiring both eyes to fall into HS5.

- If a patient with both eyes affected tends to have a similar BCVA in each eye before treatment and to have a similar BCVA in each eye after treatment the main modelling concern is not having modelled FEI for the WSE for patients whose BSE was initially affected at baseline.
- If a patient with both eyes affected does not tend to have a similar BCVA in each eye before treatment or to have a similar BCVA in each eye after treatment the modelling concerns are wider and are likely to encompass all the modelling of severe visual impairment and its associated costs.

The application of the costs of severe visual impairment is a major model driver.

Revisions to the costs of treatment: BSE with FEI in the WSE

The modelling of patients having their BSE affected and treated at baseline ignores FEI of the WSE. In practice, any FEI with the WSE may also be treated with dexamethasone in the dexamethasone arm. Ignoring the costs of cataracts and adverse events, the approximate average additional cost per patient eye treated with dexamethasone per cycle and the total average additional cost discounted to the incident year is as outlined below.

Table 1: CRVO additional average cost per treated eye

DEXA		Admin		Monitor		Total		% treated	Current		DF	Disc	
£	870	£	150	£	-	£	1,020	100%	£	1,020	100.00%	£	1,020
£	870	£	150	£	446	£	1,466	86%	£	1,256	98.29%	£	1,235
£	870	£	150	£	446	£	1,466	63%	£	923	96.62%	£	892
£	870	£	150	£	446	£	1,466	63%	£	923	94.97%	£	877
£	870	£	150	£	446	£	1,466	36%	£	535	93.35%	£	499
£	870	£	150	£	446	£	1,466	36%	£	535	91.76%	£	491
											Total	£	5,014

Table 2: BRVO additional average cost per treated eye

DEXA		Admin		Monitor		Total		% treated	Current		DF	Disc	
£	870	£	150	£	-	£	1,020	100%	£	1,020	100.00%	£	1,020
£	870	£	150	£	446	£	1,466	79%	£	1,155	98.29%	£	1,136
£	870	£	150	£	446	£	1,466	19%	£	271	96.62%	£	262
£	870	£	150	£	446	£	1,466	19%	£	271	94.97%	£	258
£	870	£	150	£	446	£	1,466	8%	£	117	93.35%	£	109
											Total	£	2,785

For FEI this requires amendment in that monitoring costs will be double counted if the FEI occurs when the original eye is still being treated. If both eyes can be treated with dexamethasone at the same outpatient visit, administration costs will also be double counted. But in line with the SPC for what follows assume that only one eye can be treated at each OP administration visit. This results in the following total average treatment and monitoring cost for dexamethasone discounted to the incident year for FEI:

Table 3: Evolution of FEI treatment costs over model cycles

FEI incidence after initial eye treatment	CRVO	BRVO
+ 6 mth	£3,948	£2,281
+ 12 mth	£4,100	£2,359
+ 18 mth	£4,367	£2,439
+ 24 mth	£4,638	£2,785
+ 30 mth and beyond	£5,014	£2,785

It appears that all models submitted to NICE, including the third revised model submitted by the manufacturer to NICE on the 12th Dec 2010, do not make this correction and so may overestimate the costs of monitoring of the treatment of FEI in the dexamethasone arm. Since FEI mainly occurs in the early cycles of the model, an error such as the double counting of monitoring costs

within the dexamethasone treatment arm may be non-trivial. But in itself it seems unlikely to drive modelling results.

But retaining the manufacturer modelling assumptions, this results in total average additional costs discounted to the FEI incident year of £5,104 for CRVO and £2,785 for BRVO. Given the assumed balance between FEI CRVO:BRVO of 34:66 results in an average of £3,543 per incident FEI.

Applying this average of £3,543 to the survival curve and weibull rates of FEI as in worksheet *C_Oz AW16:BZ17* and discounting at 3.5% results in an average additional FEI cost for patients who had their best seeing eye affected at baseline of approximately ███. This results in a relatively trivial average increase in costs of ███ for the 97:03 WSE:BSE modelling and a minor average increase in costs of ███ for the 90:10 WSE:BSE modelling.

The ERG has not estimated the overall effect of the errors noted above. But it seems possible that the double counting of monitoring costs for FEI may outweigh the omission of the dexamethasone treatment, administration and monitoring costs associated with FEI when the initially affected eye was the BSE.

Revisions to the costs of severe visual impairment

Excluding the costs of severe visual impairment

As a simple indication of the importance of the costs of severe visual impairment within the third model submitted by the manufacturer, they can be excluded. This results in the following changes to the cost effectiveness estimates.

Table 4: Changes to cost effectiveness estimates excluding costs of SVI[1]

	WSE:BSE 90:10				WSE:BSE 97:03			
	CRVO		BRVO-MH		CRVO		BRVO-MH	
	Base case	Sens. anal	Base case	Sens. anal	Base case	Sens. anal	Base case	Sens. anal
Dexa								
Cost	£11,649	£9,231	£8,413	£6,394	£11,009	£9,300	£8,098	£6,476
QALY	11.181	11.181	11.281	11.281	11.307	11.307	11.387	11.387
Obs.								
Cost	£9,868	£3,161	£6,952	£2,637	£7,551	£3,187	£6,364	£2,666
QALY	10.895	10.895	11.105	11.105	11.068	11.068	11.223	11.223
Net								
Cost	£1,782	£6,070	£1,461	£3,757	£3,458	£6,112	£1,734	£3,811
QALY	0.286	0.286	0.176	0.176	0.240	0.240	0.163	0.163
ICER	£6,221	£21,194	£8,313	£21,371	£14,430	£25,504	£10,614	£23,327

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[1] Implemented by setting cell Q29 of the *Summary* worksheet to £0

Approach adopted and caveats

In the following it must be stressed that the estimates of possible revisions to the base case are crude and do not directly revise the manufacturer model. Rather, from the third manufacturer model as submitted to NICE on the 12 December 2010 they take:

- the approximate proportions of patients being estimated as falling into HS5;
- the weibull curve modelling of fellow eye involvement; and
- the survival curve.

These are then relatively crudely combined with the estimate of the annual cost of severe visual impairment of £5,963 to yield estimates of:

- the cost savings from fewer patients falling into HS5 due to dexamethasone use that seem likely to have been modelled by the manufacturer
- possible revisions to these on the basis of 100% correlation between the BCVA of the initially affected eye and any FEI
- possible revisions to these on the basis of 0% correlation between the BCVA of the initially affected eye and any FEI

These estimates are extremely approximate and prone to error. They are not estimates of cost effectiveness as such. Their main function is as indicators of how large the changes to the estimates of cost effectiveness may be under different assumptions. This is in order to help inform any requirement for a more formal modelling of both eyes falling into HS5 for the costs of severe visual impairment to apply.

Note that the manufacturer modelling assumes that the distribution of BCVA at baseline for the initially affected eye and the distribution of BCVA at the incidence of the FEI for the fellow eye are identical. This seems to be a reasonable assumption to make where the initially affected eye is the WSE with any FEI being in what was initially the BSE. It may not be a reasonable assumption to make where the initially affected eye is the BSE with any FEI being in what was initially the WSE. Among patients whose BSE is affected at baseline there may be some whose WSE at baseline is already in or close to HS5. Given this, the indicative costings that follow may be too pessimistic. But this aspect cannot be addressed without revisiting the trial data and constructing a model that properly allows for FEI when calculating the costs of severe visual impairment.

Note also that the following assumes independence between the likelihood of FEI and the health state of the originally affected eye. If patients with an originally affected eye at baseline in a worse health state are more likely to develop FEI than those with an originally affected eye at baseline in a better health state, the following indicative costings may again be too pessimistic

100% correlation between BCVA of originally affected eye and BCVA of any FEI
The modelling assumes that if the WSE is affected at baseline and there is FEI in the BSE with the BSE falling into HS5, the costs of severe visual impairment should be applied. This is correct if there is 100% correlation between the BCVA of the WSE and the BCVA of any FEI in the BSE, as this would imply that the WSE is in HS5 prior to the BSE falling into HS5.

The modelling also assumes that if the BSE is affected at baseline, if the BSE falls into HS5 the costs of severe visual impairment should be applied. This is incorrect. The WSE also needs to fall into HS5 for the costs of severe visual impairment to be applied. Even if there is 100% correlation between the BCVA of the BSE and the BCVA of any FEI in the WSE, only a proportion of patients who had their BSE initially affected with this eye falling into HS5 would have FEI in their WSE which, given the assumption of 100% correlation, would also fall into HS5. By the end of the 30th year of the weibull modelling, only ▆▆▆▆▆▆ of patients are modelled as developing FEI.

100% correlation for the CRVO modelling: CRVO in the fellow eye
Of the CRVO patients alive who have their BSE affected at baseline, from age 67 around ▆▆▆ of dexamethasone patients are modelled as falling into HS5 while ▆▆▆▆▆▆ of observation patients are modelled as falling into HS5. Given the average annual cost of severe visual impairment of £5,963 this suggests that among CRVO patients alive who have their BSE affected at baseline the modelling applies an annual ongoing average cost of ▆▆▆ in the dexamethasone arm as compared to ▆▆▆▆ in the observation arm: an annual net saving of around £2,266 among BSE patients. While approximate, taking into account the survival curve and discounting at 3.5% this suggests a total cost of severe visual impairment in the dexamethasone arm of ▆▆▆▆▆ compared to ▆▆▆▆▆: a net saving of ▆▆▆▆▆ from dexamethasone among BSE patients[2]. For the WSE:BSE 97:03 modelling this results in an approximate cost saving per patient of ▆▆▆▆,

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[2] It appears that the manufacturer base case model anticipates a lower net impact of around ▆▆▆ which illustrates that the base case approximations may be around 20% too high, in line with the later section on the reasonableness of the approximations.

while for the WSE:BSE 90:10 modelling this results in an approximate cost saving per patient of ███████.

If the weibull FEI prevalence rates are applied to the proportions of CRVO patients modelled as having their BSE as falling into HS5, the prevalence of the FEI also falling into HS5 in the early years is around ███ in the dexamethasone arm compared to ██ in the observation arm[3]. As time passes and FEI prevalence increases these rates increase to ████ for the dexamethasone arm and ████████ for the observation arm. Applying the annual cost of severe visual impairment, adjusting for survival and discounting at 3.5% suggests a total cost of severe visual impairment in the dexamethasone arm of ██████ as compared to ██████ in the observation arm: a net saving of ██████ per BSE patient. For the WSE:BSE 97:03 modelling this results in an approximate cost saving per patient of ████, while for the WSE:BSE 90:10 modelling this results in an approximate cost saving per patient of £███.

Netting these out suggests that the cost savings for the WSE:BSE 97:03 modelling are overestimated by £742, and for the WSE:BSE 90:10 modelling are overestimated by £2,475. Applying these changes to the model supplied by the manufacturer on the 12th December results in the following.

Table 5: CRVO cost effectiveness estimates: 100% correlation and CRVO FEI

	Man. estimates		CRVO in FEI	
WSE:BSE	90:10	97:03	90:10	97:03
Cost adjustment			£2,475	£742
Net Cost	£1,782	£3,458	£4,256	£4,201
Net QALY	0.29	0.24	0.29	0.24
ICER	£6,221	£14,430	£14,862	£17,528

100% correlation for the BRVO modelling: BRVO in the fellow eye

Of the BRVO patients alive who have their BSE affected at baseline, from age 67 around ██ of dexamethasone patients are modelled as falling into HS5 while around ███ of observation patients are modelled as falling into HS5[4]. Adopting the same approach as previously, this suggests manufacturer estimates of around an average severe visual impairment cost ████████

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[3] For instance, in the year 4 the rate of HS5 among living patients being treated with dexamethasone who had their BSE affected at baseline is estimated as around ████ The prevalence of FEI is estimated as ██%. Multiplying these together yields an estimate of FEI among living patients being treated with dexamethasone in HS5 who had their BSE affected at baseline of ███ The assumption of 100% correlation results in all of the FEI falling into HS5 and the patient falling into severe visual impairment.

[4] These figures are marginally different for the BRVO-MH subset, around ████████████ respectively, but time constraints have precluded re-running the approximations for these figures.

for those treated with dexamethasone among those whose BSE was affected at baseline and
███████ for those under observation: a net impact of £4,906 per BSE patient, or ███ for the
BSE:WSE 97:03 modelling and ████ for the BSE:WSE 90:10 modelling.

Revising these by rates of FEI results in estimates of ██████ for dexamethasone patients and
███████ for observation patients: a net impact of ████ per BSE patient, or ███ for the BSE:WSE
97:03 modelling and ████ for the BSE:WSE 90:10 modelling. This suggests revising the net costs
by £120 for the BSE:WSE 97:03 modelling and by £401 for the BSE:WSE 90:10 modelling.

Table 6: BRVO cost effectiveness estimates: 100% correlation and BRVO FEI

	Man. estimates		BRVO in FEI	
WSE:BSE	90:10	97:03	90:10	97:03
Net cost adjustment			£401	£120
Net cost	£1,461	£1,734	£1,862	£1,854
Net QALY	0.18	0.16	0.18	0.16
ICER	£8,313	£10,614	£10,593	£11,350

100% correlation: mix of CRVO and BRVO in the fellow eye

The modelling of the base case assumes a mix between CRVO and BRVO for any FEI with 34%
of FEI being CRVO and 66% of FEI being BRVO. Since the adjustment to costs is being made to
approximations of the manufacturer base case estimates which adopt this balance, it is more
correct to apply this balance to the adjustments.

Adopting the same approach as above but applying the balance between CRVO and BRVO for
any FEI results in the same anticipated average costs of severe visual impairment per BSE patient
whether CRVO or BRVO at baseline[5]: ██████ in the dexamethasone arm and ██████ in the
observation arm, and a net saving of ██████ among BSE patients. But as outlined below the cost
adjustments required differ between patients whose originally affected eye was CRVO and
patients whose originally affected eye was BRVO due to the different manufacturer estimates of
net costs for these groups.

Table 7: CRVO cost effectiveness estimates: 100% correlation and balanced FEI

CRVO	Man. estimates		FEI balanced	
WSE:BSE	90:10	97:03	90:10	97:03
Cost adjustment			£2,788	£836
Net Cost	£1,782	£3,458	£4,570	£4,295
Net QALY	0.29	0.24	0.29	0.24
ICER	£6,221	£14,430	£15,956	£17,920

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[5] This is conditioned by the rate of FEI not exceeding the proportion whose originally affected eye is in
HS5, which does not apply given current inputs.

Table 8: BRVO cost effectiveness estimates: 100% correlation and balanced FEI

BRVO	Man. estimates		FEI balanced	
WSE:BSE	90:10	97:03	90:10	97:03
Net cost adjustment			£239	£72
Net cost	£1,461	£1,734	£1,701	£1,806
Net QALY	0.18	0.16	0.18	0.16
ICER	£8,313	£10,614	£9,674	£11,054

0% correlation between BCVA of originally affected eye and BCVA of any FEI

If there is 0% correlation between the BCVA in the originally affected eye and the BCVA in the FEI this will affect the likelihood of falling into severe visual impairment for both those whose WSE was affected at baseline and those whose BSE was affected at baseline.

For those whose WSE is affected at baseline, suppose 20% have their WSE fall into HS5. Suppose the balance between fellow eye involvement is 34% CRVO and 66% BRVO, of whom ▮▮▮▮▮▮ respectively fall into HS5 so resulting in ▮▮ of FEI falling into HS5. Given a FEI prevalence of say 16% this would imply that a little over ▮▮ of these patients would have FEI with the fellow eye in HS5. Assuming independence, the proportion of patients who have both eyes falling into HS5 would be ▮▮▮▮▮▮▮▮▮▮ Similar arithmetic applies when the BSE is affected at baseline.

Again, it should be stressed that the figures that follow are crude and more an indication of how the arithmetic may change rather than formal estimates of cost effectiveness as such. The following assumes a balance of 34:66 for the balance between CRVO:BRVO in the FEI.

Table 9: CRVO cost effectiveness estimates: 0% correlation and balanced FEI

CRVO	Man. estimates		FEI balanced	
WSE:BSE	90:10	97:03	90:10	97:03
Cost adjustment			£3,400	£1,422
Net Cost	£1,782	£3,458	£5,181	£4,880
Net QALY	0.29	0.24	0.29	0.24
ICER	£6,221	£14,430	£18,091	£20,363

Table 10: BRVO cost effectiveness estimates: 0% correlation and balanced FEI

BRVO	Man. estimates		FEI balanced	
WSE:BSE	90:10	97:03	90:10	97:03
Net cost adjustment			£2,308	£2,119
Net cost	£1,461	£1,734	£3,770	£3,853
Net QALY	0.18	0.16	0.18	0.16
ICER	£8,313	£10,614	£21,443	£23,589

The estimates for BRVO-MH are particularly affected as BRVO-MH relates only to the initially affected eye: the fellow eye involvement is balanced 34:66 CRVO:BRVO.

Indicative cross check of approximations

The approximations outlined above indicate that for the WSE:BSE 90:10 modelling the net impact of the costs of severe visual impairment for the base case is ▆▆▆▆▆ for CRVO and ▆▆▆▆▆ for BRVO. The sensitivity analyses that exclude the costs of severe visual impairment show that within the current manufacturer model the net impact of the costs of severe visual impairment for the base case is £4,289 for CRVO and £2,296 for BRVO-MH. The approximations are around 20% too high for the base case modelling. This is a large discrepancy within what are the simpler quantities to approximate. The errors arising from the approximations around the impact of modelling both eyes having to fall into HS5 for the costs of severe visual impairment to apply are likely to be as large, if not larger.

Revisions to the mortality multiplier for severe visual impairment

Unfortunately, the 1.54 mortality multiplier associated with severe visual impairment alters the cohort flow within the model. There are no obvious approximations that can be drawn from the manufacturer model to suggest how the modelling of both eyes being required to fall into HS5 for the 1.54 mortality multiplier associated with severe visual impairment to apply might affect results.

A univariate sensitivity analysis excluding the 1.54 mortality multiplier worsens the cost effectiveness as below.

Table 11: Changes to cost effectiveness estimates from mortality multiplier of SVI = 1.00[6]

| | WSE:BSE 90:10 | | | | WSE:BSE 97:03 | | | |
| | CRVO | | BRVO-MH | | CRVO | | BRVO-MH | |
	Base case	Sens. anal	Base case	Sens. anal	Base case	Sens. anal	Base case	Sens. anal
Dexa								
Cost	£11,649	£11,972	£8,413	£8,694	£11,009	£11,249	£8,098	£8,331
QALY	11.181	11.217	11.281	11.313	11.307	11.335	11.387	11.414
Obs.								
Cost	£9,868	£10,810	£6,952	£7,588	£7,551	£8,201	£6,364	£6,931
QALY	10.895	10.995	11.105	11.174	11.068	11.138	11.223	11.286
Net								
Cost	£1,782	£1,161	£1,461	£1,106	£3,458	£3,048	£1,734	£1,400
QALY	0.286	0.222	0.176	0.138	0.240	0.196	0.163	0.128
ICER	£6,221	£5,226	£8,313	£8,004	£14,430	£15,516	£10,614	£10,958

The source of the 1.54 mortality multiplier for severe visual impairment also notes a morality multiplier of 1.23 for those having some visual impairment, which appears to apply where only

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[6] Implemented by setting cell L40 of the *Summary* worksheet to 1.00

one eye falls into blindness. A univariate sensitivity analysis that applies the 1.23 mortality multiplier worsens the cost effectiveness as below.

Table 12: Changes to cost effectiveness estimates from mortality multiplier of SVI = 1.23[7]

	WSE:BSE 90:10				WSE:BSE 97:03			
	CRVO		BRVO-MH		CRVO		BRVO-MH	
	Base case	Sens. anal	Base case	Sens. anal	Base case	Sens. anal	Base case	Sens. anal
Dexa								
Cost	£11,649	£11,817	£8,413	£8,559	£11,009	£11,134	£8,098	£8,219
QALY	11.181	11.200	11.281	11.298	11.307	11.322	11.387	11.401
Obs.								
Cost	£9,868	£10,358	£6,952	£7,282	£7,551	£7,888	£6,364	£6,658
QALY	10.895	10.947	11.105	11.141	11.068	11.105	11.223	11.256
Net								
Cost	£1,782	£1,459	£1,461	£1,277	£3,458	£3,246	£1,734	£1,561
QALY	0.286	0.253	0.176	0.156	0.240	0.217	0.163	0.145
ICER	£6,221	£5,768	£8,313	£8,175	£14,430	£14,946	£10,614	£10,778

These suggest that the mortality multiplier associated with severe visual impairment is not a major model driver. As a consequence, while it may be more correct to explicitly model both eyes having to fall into HS5 for the multiplier associated with severe visual impairment to apply doing so may have only a limited impact upon results.

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[7] Implemented by setting cell L40 of the *Summary* worksheet to 1.23