Additional analyses performed by ERG: additional amendments of economic comparison of ranibizumab versus dexamethasone intravitreal implant in MO secondary to BRVO

During the Appraisal Committee (AC) meeting, it was highlighted that the manufacturer (Novartis) had used pooled transition probabilities calculated from the BRAVO trial in the economic evaluation of ranibizumab versus dexamethasone intravitreal implant in macular oedema (MO) secondary to branch retinal vein occlusion (BRVO). Transition probabilities calculated from pooled 7–12 month data of the ranibizumab and sham arms of BRAVO were originally applied in the economic model (at 7–12 months and 13–24 months) to account for the effect of grid laser photocoagulation (GLP) in the comparison of ranibizumab with GLP in MO secondary to BRVO. The ERG has previously stated that the pooling of transition probabilities in this way would have an inflationary effect on the efficacy of ranibizumab, with the impact on the efficacy of GLP unknown. The manufacturer did not provide a rationale for using pooled transition probabilities in the comparison of ranibizumab with dexamethasone intravitreal implant. At the request of the AC, the ERG conducted further analyses to assess the impact of using unpooled transition probabilities on the incremental cost effectiveness ratio (ICER). These additional analyses were conducted incrementally as follows:

1. The transition probabilities calculated from the ranibizumab arm of BRAVO at 7–12 months were applied to the ranibizumab arm of the model at 7–12 months;
2. The transition probabilities calculated from the sham arm of BRAVO at 7–12 months were applied to the dexamethasone intravitreal implant arm of the model at 7–12 months;
3. The transition probabilities calculated from the ranibizumab arm of BRAVO at 7–12 months were also applied to the ranibizumab arm of the model at 13–24 months;
4. The transition probabilities calculated from the sham arm of BRAVO at 7–12 months were also applied at 13–24 months in the dexamethasone intravitreal implant arm of the model.

Table 1 displays the cumulative effect of these changes on both the manufacturer's base case and the ERG amended model.

Table 1. Results of additional analyses

Analysis	ICER	QALYs		Costs	
		Rani	Dex	Rani	Dex
Manufacturer's base case	£5,486	[redacted]	7.769	[redacted]	£16,448
1	£13,252	[redacted]	7.769	[redacted]	£16,448
2	£36,326	[redacted]	7.837	[redacted]	£15,709
3	Dominated	[redacted]	7.837	[redacted]	£15,709
4	Dominated	[redacted]	8.002	[redacted]	£14,202
ERG amended model	£31,122	[redacted]	6.107	[redacted]	£9,837
1	£47,745	[redacted]	6.107	[redacted]	£9,837
2	£92,811	[redacted]	6.135	[redacted]	£9,705
3	Dominated	[redacted]	6.135	[redacted]	£9,705
4	Dominated	[redacted]	6.198	[redacted]	£9,434

Abbreviations used in table: Dex, dexamethasone intravitreal implant; ERG, Evidence Review Group; ICER, incremental cost effectiveness ratio; QALY, Quality-adjusted life year; Rani, ranibizumab.

The fact that dexamethasone intravitreal implant dominates ranibizumab when the unpooled transition probabilities are applied at months 13–24 as well as at months 7–12 contradicts the outcome of the ERG's indirect comparison, which indicated that ranibizumab is superior in efficacy to dexamethasone intravitreal implant. The ERG notes that the unpooled transition probabilities for the "sham" arm are marginally more favourable than the unpooled transition probabilities for the ranibizumab arm. This is because the "sham" patients at 7–12 months are actually ranibizumab naïve patients who initiate ranibizumab PRN rather than patients receiving sham treatment.

The relative risks (RRs) of dexamethasone intravitreal implant versus sham calculated by the manufacturer are only applied in month 1 of the model. At month 1, patients in the ranibizumab arm receive substantially more benefit from treatment than patients in the dexamethasone intravitreal implant arm. However, the use of unpooled transition probabilities at months 7–12 applies a marginal benefit to the dexamethasone intravitreal implant arm that depreciates the differential benefit of ranibizumab treatment obtained in month 1 and increases the ICER (Table 1). Reapplication of the unpooled transition probabilities at months 13–24 maintains the marginal benefit in the dexamethasone intravitreal implant arm from month 7 and over year 2, making dexamethasone a more effective treatment option compared with ranibizumab. The model extrapolates these benefits to 15 years, and so the overall effect is to inflate the magnitude of differential benefit in favour of dexamethasone over ranibizumab (Table 1, Analyses 3 and 4).

The ERG concludes that, although the manufacturer's original analysis may be biased towards ranibizumab, in terms of the relative benefit obtained in month 1 and the inflated transition probabilities at month 7, the direction of bias associated with using pooled transition probabilities in the dexamethasone intravitreal implant arm rather than pure sham transitions remains unclear.