Web-only Data

Supplementary Table 3 Unit costs

Name of service (definition*)*	**Unit cost**	**Source**
Ranibizumab injection (0.5 mg vial [x1]))	£742.17	Novartis UK, personal communication
Laser treatment per session (weighted average of day cases and outpatient procedures for vitreous retinal procedures category 1)	£274.19	NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated)
Ophthalmologist visit (weighted first attendance and follow-up attendance)	£84.42	NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated)
Additional ophthalmologist visit	£73.16	
Pre-injection VA and BCVA assessment (first attendance for ophthalomology non-consultant-led, non-admitted visit)	£83.97	NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated)
Optometrist visit (follow-up attendance for ophthalomology non-consultant-led, non-admitted visit)	£60.92	NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated)

GP consultation	£35.00	Unit Costs of Health and Social Care 2009: per surgery consultation lasting 11.7 minutes (including direct care staff costs), with qualification costs
Nurse consultation	£60.92	NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated)
VA and BCVA checks	£55.59	NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated)

BCVA, best corrected visual acuity; GP, general practitioner; NHS, National Health Service, PCT, Primary Care Trust; VA, visual acuity.

Supplementary Table 4 Resource use and unit costs in year 1 by health states and treatment

	BCVA (number of letters)								
	86–100	76–85	66–75	**56–65**	**46–55**	**36–45**	**26–35**	**<25**	**Unit cost**
	Annual number of units of ranibizumab monotherapy/combination therapy/laser monotherapy								
Injections	0/0/0	0/0/0	7/7/0	7/7/0	7/7/0	7/7/0	7/7/0	7/7/0	£742.17
Laser	0/0/0	0/0/0	0/2/2	0/2/2	0/2/2	0/2/2	0/2/2	0/2/2	£274.19
Ophthalmologist	12/12/5	12/12/5	12/12/5	12/12/5	12/12/5	12/12/3	12/12/3	12/12/3	£74.10
Optometrist	12/12/5	12/12/5	12/12/5	12/12/5	12/12/5	12/12/3	12/12/3	12/12/3	£62.84
GP	1/1/1	1/1/1	1/1/1	2/2/2	2/2/2	2.5/2.5/2.5	2.5/2.5/2.5	2.5/2.5/2.5	£35.00
Nurse consultant	1/1/1	1/1/1	1/1/1	2/2/2	2/2/2	2.5/2.5/2.5	2.5/2.5/2.5	2.5/2.5/2.5	£60.92
Adjustment for double-counting of monitoring visits	0/0/0	0/0/0	0/–2/–2	0/–2/–2	0/–2/–2	0/–2/–2	0/–2/–2	0/–2/–2	

Ophthalmologist cost=weighted average of ‘ophthalmologist visit’ and ‘additional ophthalmologist visit’ in Supplementary Supplementary Table .

Optometrist cost=weighted average of ‘Pre-injection VA and BCVA assessment’ and ‘optometrist visit’ in Supplementary Supplementary Table .

BCVA, best corrected visual acuity; GP, general practitioner; VA, visual acuity.

Supplementary Table 5 Resource use and unit costs in year 2 by health states and treatment

	BCVA (number of letters)								
	86–100	**76–85**	**66–75**	**56–65**	**46–55**	**36–45**	**26–35**	**<25**	**Unit cost**
	Annual number of units of ranibizumab monotherapy/combination therapy/laser monotherapy								
Injections	3/2/0	3/2/0	3/2/0	3/2/0	3/2/0	3/2/0	3/2/0	3/2/0	£742.17
Laser	0/1/1	0/1/1	0/1/1	0/1/1	0/1/1	0/1/1	0/1/1	0/1/1	£274.19
Ophthalmologist	12/8/5	12/8/5	12/8/5	12/8/5	12/8/5	12/8/3	12/8/3	12/8/3	£74.10
Optometrist	12/8/5	12/8/5	12/8/5	12/8/5	12/8/5	12/8/3	12/8/3	12/8/3	£62.84
GP	1/1/1	1/1/1	1/1/1	2/2/2	2/2/2	2.5/2.5/2.5	2.5/2.5/2.5	2.5/2.5/2.5	£35.00
Nurse consultant	1/1/1	1/1/1	1/1/1	2/2/2	2/2/2	2.5/2.5/2.5	2.5/2.5/2.5	2.5/2.5/2.5	£60.92
Adjustment for double-counting of monitoring visits	0/–1/–1	0/–1/–1	0/–1/–1	0/–1/–1	0/–1/–1	0/–1/–1	0/–1/–1	0/–1/–1	

Ophthalmologist cost=weighted average of ‘ophthalmologist visit’ and ‘additional ophthalmologist visit in Supplementary Supplementary Table .

Optometrist cost=weighted average of ‘pre-injection VA and BCVA assessment’ and ‘optometrist visit’ in Supplementary Supplementary Table .

BCVA, best corrected visual acuity; GP, general practitioner; VA, visual acuity.

Supplementary Table 2 Resource use and unit costs year 3 by health states and treatment

	BCVA (number of letters)								
	86–100	**76–85**	**66–75**	**56–65**	**46–55**	**36–45**	**26–35**	**<25**	**Unit cost**
	Annual number of units of ranibizumab monotherapy/combination therapy/laser monotherapy								
Injections	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	£742.17
Laser	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	0/0/0	£274.19
Ophthalmologist	5/5/5	5/5/5	5/5/5	5/5/5	5/5/5	3/3/3	3/3/3	3/3/3	£74.10
Optometrist	5/5/5	5/5/5	5/5/5	5/5/5	5/5/5	3/3/3	3/3/3	3/3/3	£62.84
GP	1/1/1	1/1/1	1/1/1	2/2/2	2/2/2	2.5/2.5/2.5	2.5/2.5/2.5	2.5/2.5/2.5	£35.00
Nurse consultant	1/1/1	1/1/1	1/1/1	2/2/2	2/2/2	2.5/2.5/2.5	2.5/2.5/2.5	2.5/2.5/2.5	£60.92
Adjustment for double-counting of monitoring visits	0	0	0	0	0	0	0	0	

Ophthalmologist cost=weighted average of ‘ophthalmologist visit’ and ‘additional ophthalmologist visit’ in Supplementary Supplementary Table .

Optometrist cost=weighted average of ‘pre-injection VA and BCVA assessment’ and ‘optometrist visit’ in Supplementary Supplementary Table .

BCVA, best corrected visual acuity; GP, general practitioner; VA, visual acuity.

Supplementary Table 2 Cost of blindness

	Proportion of blind population requiring service	Annual costs of service	Average cost	Assumption/comments
Low vision aids	33.00%	£194.16	£64.07	Inflated to base year 2008–09
Low vision rehabilitation (occupational health therapist)	11.00%	£221.00	£24.31	Section 7.2: NHS community occupational therapist
Residential care (homecare) – 30% private payers	30.00%	£16,998.80	£5099.64	Section 1.2: Private residential care for older people: fees (A) only
Community care	6.00%	£12,064.00	£723.84	Section 9.5: Local authority home care worker
Depression	39.00%	£558.24	£217.71	Inflated to base year 2008–09
Hip replacement	5.00%	£6952.93	£347.65	Weighted average of major hip procedures category – 12B and 12C TPCTEI
Total			**£6477.22**	

Source: based on Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003;**87**:1201–4. The percentage of the blind population requiring service is based on a population with age-related macular degeneration as a substitute for a DME population. Unit costs were updated using same method and source as Mead or inflated if no updated estimates were available.

DME, daibetic macular oedema; NHS, National Health Service.

Supplementary Methods: Estimation of long-term change in BCVA (year 3 and onwards)

The long-term change in best corrected visual acuity (BCVA) is simulated with a simple model, which assumes there is a constant rate of change in visual acuity (VA). This rate is modelled by three parameters:

- improvement of ≥10 letters within 3 months
- worsening of ≥10 letters within 3 months
- no change exceeding 10 letters within 3 months (residual of the first two parameters).

There are only a few sources in the literature that report the progression of VA in patients with diabetic macular oedema (DME). The long-term assumptions have mainly been developed from the following two sources in combination with model calibration.

- Data from the DRCR.net protocol I study (Elman, 2010), which showed that the improvement achieved after 12 months with combination therapy (ranibizumab plus laser therapy) and with laser monotherapy was maintained after 24 months. This is taken as an indication that the mean VA is stable in year 2.
- Observational data from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) (Moss, 1988), which show that the proportion of diabetic patients with a decrease in VA exceeds the proportion with an improvement 4years after onset. This is taken as an indication that VA tends to decrease.

Parameter values for worsening and improving of VA were calibrated with 4-years incidence of worsening and improving in the WESDR population. The health state ‘BCVA 66–75 letters’ was selected for calibration because it represents the most common health state (39% at baseline); furthermore, this range overlaps with the range that was reported in WESDR (equivalent to 60–70 letters).

The reported 4-year incidence in WESDR may overstate the proportion of patients with a worsened VA because the WESDR population received less intensive systemic diabetes management than is current practice. The 4-year incidence was therefore adjusted to reflect more modern practice. Adjustments were guided by data derived from studies investigating the relationship between level of glycaemic control and the risk of developing microvascular complications such as diabetic retinopathy.

The Diabetes Control and Complications Trial (DCCT) (DCCT Trial Research Group, 1993) concluded that intensive therapy resulted in a 23% risk reduction of DME compared with conventional therapy (mean 6.5 years follow-up). The UK Prospective Diabetes Study 33 (UKPDS 33) reported a 25% risk reduction of microvascular endpoints when comparing intensive and conventional therapy (median 10 years follow-up). The UKPDS 35 study reported a 37% risk reduction per 1% reduction of HbA_{1c}, based on observational data. The UKPDS 68 study reported an odds ratio of 1.25 for HbA_{1c} as a predictor of blindness. From this evidence, we decided to adjust the 4-year incidence of worsened VA in the WESDR population by 25%, from 48% to 36%.

The calibration was performed by simulation of a population with an initial VA in the range 66–75 letters. The simulation predicts the incidence of improvement and worsening after 4 years by applying constant change rates to the population. The WESDR data do not include the effect of DME. For this reason, we chose to calibrate from baseline and to year 4 neglecting the progression in year 1 reported in RESTORE. Due to the DME effect, the laser arm in RESTORE showed worsening in 33% of the patients in year 1.

Inputs and outputs of the calibration process are shown in Supplementary Supplementary Table 1. The first column shows the result of using the rates of change from month 9 to month 12 in the laser group in RESTORE. The second column shows the result of assuming equal rates (0.03 worsening and 0.03 improving). The third column shows the best fit with WESDR. If the rates in the laser arm in RESTORE were used, the model would overestimate the proportion with an improvement (0.32 vs 0.25) and underestimate the proportion with

worsening (0.23 vs 0.36) after 4 years. Adjusting the rates of change to be equal (0.03 worsening and 0.03 improving) improves the fit. However, the fit is even better when the rate of change is adjusted to 0.035 for improving and 0.045 for worsening.

Supplementary Table 1 Calibration with WESDR 4-year data

	RESTORE laser, month 9 to month 12	**Equal rates**	**WESDR calibrated**	
		Input, 3-month probability		
Improve	0.036	0.030	0.035	
No change	0.936	0.940	0.920	
Worsen	0.027	0.030	0.045	
	Output, 4-year incidence of worsening or improvement			Actual, WESDR
Improve	0.320	0.270	0.250	0.250
No change	0.450	0.460	0.400	0.390
Worsen	0.230	0.270	0.350	0.360

In the base-case scenarios, we used the calibrated estimates (0.035 improving and 0.045 worsening every 3 months) to simulate long-term progression of VA. Alternative assumptions are tested in sensitivity analyses.

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Supplementary Table 2 Probabilistic model assumptions

Parameter	Input value	Distribution	Source of uncertainty parameters
Ranibizumab injections year 1, monotherapy	7 (0.2630)	Normal	RESTORE
Laser treatments year 1, monotherapy	2 (0.0992)	Normal	RESTORE
Ranibizumab injections year 1, combination therapy	7(0.2706)	Normal	RESTORE
Ranibizumab injections year 2, monotherapy	3(0.2000)	Normal	DRCR.net protocol I study and assumption
Ranibizumab injections year 2, combination therapy	2(0.2000)	Normal	DRCR.net protocol I study and assumption
Laser treatments year 1, combination therapy	2 (0.1000)	Normal	RESTORE
Laser treatments year 2, combination therapy	1.6 (0.1000)	Normal	DRCR.net protocol I study and assumption
Cost of blindness (annually)	£6472.22 (±20%)	Gamma	
Transition probabilities of change of VA in year 1 (by treatment arms, health state, and cycle)	Counts as observed in trial	Dirichlet	RESTORE (counts by treatment arms, health state, and cycles)
Transition probabilities of withdrawal in year 1 (by treatment arms)	Probabilities as observed in trial	Beta	RESTORE (counts by cycles)

Long-term transition probabilities of change in VA, adjusted WESDR	0.045 worsening, 0.035 improving	Dirichlet	Literature and assumption
RR of death in patients with diabetes	2.45 (0.15)	Normal	Literature, reported RR and SE (or 95% confidence intervals)
Mean utility of health state	See Table 2 in main article	Beta	RESTORE

Input values are given as mean (SE) unless otherwise stated.