Cost-effectiveness of ranibizumab in treatment of diabetic macular oedema (DME) causing visual impairment: evidence from the RESTORE trial

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ABSTRACT

Background/aims To evaluate the cost-effectiveness of ranibizumab as either monotherapy or combined with laser therapy, compared with laser monotherapy, in the treatment of diabetic macular oedema (DME) causing visual impairment from a UK healthcare payer perspective.

Methods A Markov model simulated long-term outcomes and costs of treating DME in one eye (BCVA ≤75 letters) based on data from the RESTORE Phase III trial. Outcomes measured in quality-adjusted life-years (QALYs) were simulated for a 15-year time horizon based on 12-month follow-up from RESTORE and published long-term data. Costs included treatment, disease monitoring, visual impairment and blindness (at 2010 price levels).

Results Ranibizumab monotherapy resulted in a 0.17 QALY gain at an incremental cost of £4191 relative to laser monotherapy, yielding an incremental cost-effectiveness ratio (ICER) of £24 028. Probabilistic sensitivity analysis showed a 64% probability of being cost-effective at a threshold of £30 000 per QALY. Combined ranibizumab and laser therapy resulted in a 0.13 QALY gain at an incremental cost of £4695 relative to laser monotherapy (ICER £38 106; 42% probability of ICER £30 000).

Conclusions Based on RESTORE 1-year follow-up data, ranibizumab monotherapy appears to be cost-effective relative to laser monotherapy, the current standard of care. Cost-effectiveness of combination therapy is less certain. Ongoing studies will further inform on disease progression and the need for additional ranibizumab treatment.

INTRODUCTION

Diabetic macular oedema (DME) is the most frequent cause of vision impairment in people with diabetes and can lead to blindness if left untreated. Even when patients receive optimal treatment with the current standard of care for DME, laser photocoagulation, improvements in vision are relatively uncommon and many patients lose vision despite laser therapy.1,2 This continued vision loss is the result of structural and physiological damage to the retinal capillary bed, and from progressive and permanent damage to the macular pigment epithelium, associated with poor control of blood glucose, blood pressure and lipid levels (the three main systemic risk factors for diabetic retinopathy and DME).3

The UK prevalence of visual impairment due to DME is estimated at approximately 3% of the adult (aged 18 years) diabetic population.4 Visual impairment places a substantial socio-economic burden on patients, their caregivers and healthcare systems at large.5 There is, therefore, a strong public health incentive to choose safe therapies that provide increased health gains through improved vision and patient functioning, while offering an acceptable balance between benefits and costs.

Ranibizumab (Lucentis®, Novartis Pharma AG, Switzerland) is a novel agent that is currently licensed for the treatment of visual impairment due to DME.6 Ranibizumab selectively inhibits active isoforms of human vascular endothelial growth factor A (VEGF-A) from binding to its receptors. VEGF-A stimulates growth of new blood vessels and is a major mediator of increased vascular leakage,7–10 mechanisms thought to be associated with retinal damage and progression of DME and the resulting visual impairment.

The Phase III RESTORE trial enrolled 345 patients with visual impairment due to DME and assessed ranibizumab given either as monotherapy or in combination with laser photocoagulation, compared with laser photocoagulation alone. The results showed that ranibizumab alone or in combination with laser provided significantly greater improvements in best corrected visual acuity (BCVA) at 1 year compared with laser therapy alone, with mean average BCVA changes of +6.1 and +5.9 versus +0.8 letters, respectively.11 In addition, health-related quality of life, as assessed using the National Eye Institute Visual Function Questionnaire (NEI VFQ-25), was improved significantly from baseline for both ranibizumab treatment groups compared with laser therapy alone (p<0.05 for composite score and vision-related subscales). RESTORE is ongoing in a 2-year open-label extension phase.

This report summarises the results of a health economic model that was developed based on RESTORE trial data to evaluate the cost-effectiveness of ranibizumab from a UK payer perspective when used as monotherapy or in combination with laser therapy compared with laser therapy alone. The model was developed separately from current assessments of ranibizumab by the UK Health Technology Assessment bodies, such as the National Institute for Health and Clinical Excellence.

METHODS

A Markov model was constructed to simulate costs and changes in BCVA over a 15-year period in a hypothetical cohort of patients with DME (figure 1),

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Figure 1  Markov model structure. Health states are defined by best corrected visual acuity (BCVA) in the treated eye. Patients enter the model at treatment start where they are assumed to have BCVA as in the RESTORE (>39 letters and ≤75 letters). BCVA is evaluated at 3-monthly intervals. After each cycle, patients may transition to any other health state including death; the probability of moving from health state A to health state B is based on RESTORE data (baseline to month 12) and literature.

based on data from the RESTORE trial (in which 87.5% of patients had type 2 diabetes and average baseline glycated haemoglobin was 7.5%). The average age at entry to the model was 63 years, consistent with patient characteristics in RESTORE. The model also assumed the same baseline BCVA distribution, but excluded patients with BCVA >75 letters, consistent with guidance from the ranibizumab summary of product characteristics that such patients may benefit less from treatment than those with baseline BCVA ≤75 letters.9

The model framework allocated eight linear health states defined by BCVA in the treated eye using a set of 10-letter (two-line) categories (table 1). Movement of patients from one health state to another was determined by transition probabilities that depended on the effectiveness of treatment and natural BCVA changes over time. A 10-letter range was used to categorise health states based on evidence that a 10-letter BCVA score loss associated with a substantial decline in health-related quality of life (eg, loss of functional ability, increasing dependency, role limitations and impaired mental health).15 Each health state was assigned a quality-of-life index and cost. Costs and outcomes were accrued over 3-monthly cycles, applying half-cycle corrections. The time horizon in the base case was 15 years; although a lifetime horizon could be justified given the chronic nature of the condition, we selected a more conservative approach for the base case because of the lack of evidence on long-term prognosis.

The key inputs and assumptions are summarised in table 2. Patients were assumed to receive ranibizumab treatment in year 1 at the frequency observed in RESTORE. In year 2, patients were assumed to need fewer injections, as observed in the Diabetic Retinopathy Clinical Research Network (DRCR.net) protocol I study (which included patients with comparable baseline demographics to RESTORE).1 A proportionately smaller number of monitoring visits was therefore assumed in year 2. After year 2, laser therapy was assumed to be administered as required in all arms, with no further need for ranibizumab; the assumed number of monitoring visits was further reduced accordingly.

The average BCVA achieved in year 1 was assumed to be maintained during year 2, as was observed in the DRCR.net protocol I study.1 After year 2, all arms of the model followed natural disease history based on 4-year health state transition outcomes modelled from the Wisconsin Epidemiologic Study of Diabetic Retinopathy (WESDR) reports.17–19 Transition probabilities were calibrated to adjust for the improvement in diabetes management since the WESDR reports (see Supplementary Methods), and predicted that around 50% of patients would be expected to exhibit a worsening in BCVA of at least 10 letters and 20% of patients would show an improvement of at least 10 letters over a 4-year time horizon (Supplementary table 1).

Treatment discontinuation rates observed in RESTORE were applied to the model in year 1; it was assumed there would be no additional withdrawals from treatment in year 2. Adverse events were assumed to have a negligible impact on the cost-effectiveness of ranibizumab therapy based on the established safety profile of ranibizumab in clinical trials in DME and in wet age-related macular degeneration, an indication for which ranibizumab is also licensed.1 20–22

Mortality was estimated by adjusting general UK population death rates according to the increased RR of death in patients with DME. Mulnier et al estimated an increased mortality (HR 1.93) in a UK type 2 diabetes population relative to patients without diabetes,23 while Hira et al estimated an HR of 1.27 for death in patients with clinically significant macular oedema (CSME) and diabetes relative to diabetic patients without CSME.24 We calculated a 2.45 RR of death in a DME population by multiplying these two ratios.

| Health state defined by BCVA category (letters; treated eye) | RESTORE* | Lloyd et al21 | Brown et al22 |
|--------------------------------------------------------------|----------|--------------|--------------|
| Mean utility (SE)                                            |          |              |              |
| 1: 86–100                                                    | 0.860 (0.034) | 0.830 | 0.839 |
| 2: 76–85                                                     | 0.860 (0.014) | 0.750 | 0.839 |
| 3: 66–75                                                     | 0.813 (0.012) | 0.750 | 0.783 |
| 4: 56–65                                                     | 0.802 (0.014) | 0.715 | 0.783 |
| 5: 46–55                                                     | 0.770 (0.018) | 0.680 | 0.732 |
| 6: 36–45                                                     | 0.760 (0.027) | 0.680 | 0.681 |
| 7: 26–35                                                     | 0.681 (0.053) | 0.530 | 0.630 |
| 8: 0–25                                                      | 0.547 (0.083) | 0.340 | 0.579 |

*Utility scores were calculated based on EQ-5D scores in RESTORE; EQ-5D scores were converted to utilities using social tariffs measured in a UK population.14 Mean utility for each BCVA state was calculated using a regression technique for repeated measurements at baseline, month 3, month 6 and month 12. Data from several measurement points were pooled to cover all possible health state transitions with a sufficient sample size. A possible trend effect in the pooled data was rejected (p<0.05).
†Patients underwent a Snellen visual acuity (VA) assessment and were categorised based on the better-seeing eye. Some adjustments were made to published values in order to convert VA ranges in Lloyd et al (obtained in a population of patients with diabetic retinopathy) to health states as defined in the current model.
‡Utilities were elicited from patients with diabetic retinopathy. Patients underwent a Snellen VA assessment and were categorised based on the better-seeing eye. Some adjustments were made to published values in order to convert VA ranges to health states as defined in the current model.
§Restricted to being greater than or equal to the utility in health state 2.
BCVA, best corrected visual acuity.

Data were adjusted for natural disease progression and treatment effectiveness to convert VA ranges in Lloyd et al and Brown et al to health states as defined in the current model. Lloyd et al and Brown et al calculated utilities based on the best-seeing eye. Some adjustments were made to published values in order to convert VA ranges to health states as defined in the current model. Restricted to being greater than or equal to the utility in health state 2.
BCVA, best corrected visual acuity.
Utility scores were calculated based on patient-reported outcomes data from RESTORE (table 2), in which patients completed the EuroQol (EQ-5D) questionnaire at baseline and months 3, 6 and 12. Individual EQ-5D health scores were converted into utility scores using preferences from a UK population survey.\cite{14} Mean utility scores were calculated for each health state (table 1). As these states were defined by BCVA in the treated eye, of which 67.2% were the worse-seeing eye at baseline, this method established an association between utility and BCVA changes in the treated eye.

Health state costs included the costs of treatment and monitoring (Supplementary tables 3–6), and the costs associated with blindness (Supplementary table 2). Treatment costs included the costs of ranibizumab (Novartis UK, personal communication) and its administration, laser therapy and investigative procedures. Monitoring costs, including consultation and procedure costs, were estimated from the UK National Health Service Reference Costs.\cite{25} Costs of blindness included those incurred by the UK National Health Service for items such as low-vision aids, low-vision rehabilitation, residential or home care, depression and hip fracture/replacement as listed in the costing study by Meads and Hyde.\cite{16} Where older cost estimates were used, these were inflated to 2010 prices using the Hospital and Community Health Services index.\cite{26} The cost of blindness would be incurred only in patients reaching health states with BCVA ≤35 letters (Snellen ≤6/60) in the better-seeing eye. However, as the study assesses treatment response according to the enrolled eye, the proportion of patients reaching this level within the time horizon of the model is therefore uncertain. As such, the base case model modifies the costs of blindness on the basis of treated eyes reaching the BCVA ≤35-letter threshold. As with other model parameters subject to uncertainty, deviations from this assumption were explored in sensitivity analyses (Supplementary table 7).

The main outcome measure was the incremental cost-effectiveness ratio (ICER), expressed as the additional cost per quality-adjusted life-year (QALY) gained by one treatment over another. An annual 3.5% discount rate was applied for future costs and utilities, consistent with the standard UK approach.

Univariate sensitivity analyses assessed the uncertainty around specific data sources by exploring the effects on the ICER of inputs, as shown in table 3. Probabilistic sensitivity analysis assessed the overall uncertainty about the ICER based on variations in individual input parameters; details of the applied distributions and results are provided in Supplementary table 7.

### RESULTS

The model predicted that after 1 year, a greater proportion of patients treated with ranibizumab monotherapy or combination therapy would have BCVA >6/18 letters (Snellen score >6/18) compared with patients treated with laser monotherapy (48% and 47%, respectively, versus 58% in the laser arm) (figure 2). After 15 years, the proportion with severe visual impairment in the treated eye (BCVA <6/60, Snellen <6/60) was predicted to be 12% and 13% in the ranibizumab monotherapy and combination therapy groups, respectively, versus 19% in the laser group.

Ranibizumab monotherapy was associated with an incremental gain of 0.17 QALY and cost of £4 191, corresponding to an ICER of £24 028 per QALY gained relative to laser monotherapy (table 3). Combination therapy provided an incremental gain of 0.13 QALY at a cost of £4 695, leading to an ICER of £36 106 per QALY gained. Univariate sensitivity analyses showed that the model was stable and that ICERs were most sensitive to changes in the number of injections and time horizon (table 3). Using utilities elicited by Lloyd et al\cite{12} and Brown et al\cite{13} in patients with diabetic retinopathy led to greater QALY gains and lower ICERs for ranibizumab monotherapy or combination therapy relative to laser monotherapy. Probabilistic sensitivity analysis confirmed the model’s robustness (Supplementary figure 1). Assuming a willingness-to-pay threshold of £50 000 per QALY gained, this
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Table 3 Cost-effectiveness: base case and sensitivity analyses*

| Assumption/parameter | Base case | Sensitivity analyses | Incremental cost | Incremental QALY | ICER | ICER (% change) |
|-----------------------|-----------|---------------------|-----------------|-----------------|------|----------------|
| Ranibizumab monotherapy versus laser monotherapy | | | | | | |
| Base case | | | £4191 | 0.17 | £24 028 | |
| Discount rate of future costs and benefits | 3.50% | 0%–5% | £3593–£4383 | 0.16 to 0.16 | £17 051–£27 042 | -29% to +13% |
| Time horizon | 15 years | 10–20 years | £4738–£3991 | 0.14 to 0.19 | £33 139 to £21 343 | +38% to -11% |
| Cost of blindness | £6477 | -25% to +25% | £4868–£3515 | 0.17 to 0.17 | £27 907–£20 150 | +16% to -16% |
| Long-term progression of VA | Declining | Constant or increasing | £4487–£4693 | 0.17 to 0.17 | £26 198–£28 413 | +9% to +18% |
| Total number of ranibizumab injections | 10 | -4 injections to +4 injections | £2171–£6774 | 0.17 to 0.17 | £12 446–£38 836 | -48% to +62% |
| Baseline age | 63 years | 58 years | £3767 | 0.20 | £19 259 | -20% |
| Source of utilities | RESTORE | Lloyd et al | £4191 | 0.22 | £19 238 | -20% |
| Combination therapy versus laser monotherapy | | | | | | |
| Base case | | | £4695 | 0.13 | £36 106 | |
| Discounting of future costs and benefits | 3.50% | 0%–5% | £4271–£4828 | 0.16 to 0.12 | £26 957–£40 096 | -25% to +11% |
| Time horizon | 15 years | 10–20 years | £5133–£4507 | 0.10 to 0.13 | £49 294–£34 135 | +37% to -5% |
| Cost of blindness | £6477 | -25% to +25% | £5050–£4340 | 0.13 to 0.13 | £38 833–£33 378 | +8% to -8% |
| Long-term progression of VA | Declining | Constant or increasing | £5091–£5276 | 0.13 to 0.12 | £40 852–£44 071 | +13% to +22% |
| Total number of ranibizumab injections | 9 | -4 injections to +4 injections | £3185–£7260 | 0.13 to 0.13 | £24 340–£55 828 | -33% to +55% |
| Baseline age | 63 years | 58 years | £4393 | 0.15 | £29 952 | -17% |
| Source of utilities | RESTORE | Lloyd et al | £4695 | 0.16 | £28 778 | -20% |
| RESTORE | Brown et al | £4695 | 0.16 | £29 576 | -18% |

*Incremental cost measures the additional cost of ranibizumab monotherapy or combination therapy compared with laser monotherapy in the modelled time horizon (15 years in base case). Incremental QALY measures the corresponding QALY gain when ranibizumab monotherapy or combination therapy is compared with laser monotherapy. The ICER is calculated by dividing the incremental cost by the incremental QALY. The ICER is interpreted as the cost of achieving an additional year of life in perfect health.

**DISCUSSION**

This is the first study to evaluate the cost-effectiveness of an anti-VEGF agent for the treatment of patients with DME causing visual impairment. Our economic model, which was based on data from the RESTORE clinical trial, shows that ranibizumab monotherapy provides superior improvements in visual acuity and is cost-effective relative to the current standard of care, laser photocoagulation. Ranibizumab monotherapy was associated with an ICER of £24 028 per QALY gained relative to laser therapy alone, a value within the willingness-to-pay threshold of £50 000 per QALY gained that has generally been considered cost-effective in the UK. The results of our model may be applicable to a broad spectrum of patients with visual impairment due to DME, as the RESTORE trial showed consistent efficacy of ranibizumab therapy across patient subgroups based on a range of demographic and disease characteristics.

The cost-effectiveness of combined ranibizumab and laser therapy was less favourable than that of ranibizumab monotherapy (ICER £56 106 per QALY gained relative to laser therapy alone). While this in part reflects higher treatment costs, combination therapy also provided a lower predicted QALY gain than ranibizumab monotherapy (0.13 vs 0.17 QALY over the 15-year time horizon in the base case). A possible explanation for these results is the observation in RESTORE that combination therapy provided smaller improvements in BCVA in patients who had received prior laser therapy than those who had not (4.7 vs 6.9 letters gained, respectively). In RESTORE, the proportions of patients who received prior laser therapy were 52% (ranibizumab monotherapy), 47% (combination therapy) and 45% (laser therapy).

Sensitivity analyses showed that the model results were robust to reasonable alterations in inputs and assumptions; ICERs were particularly sensitive to changes in the number of ranibizumab injections and the time horizon of the model. The base case assumed an average of 10 ranibizumab injections over 2 years, based on data from the DRCR.net protocol I study.1 Ranibizumab monotherapy remained cost-effective (ICER below £50 000 per QALY gained) up to a total of 13 injections. Increasing the number of injections beyond 13 resulted in an ICER outside the generally accepted threshold, emphasising that additional injections beyond 2 years of treatment will be an important cost driver. However, the current model is conservative in that it includes incremental costs for additional injections beyond year 2, but assumes no incremental benefit. The possible need for re-treatment beyond 2 years remains speculative; forthcoming data from the 2- and 3-year RESTORE follow-up and the DRCR.net 5-year data will improve our understanding of the likely duration of treatment. Longer time horizons would be expected to lead to improved cost-effectiveness of ranibizumab, because the benefits of improved vision accrue over time whereas treatment costs are incurred immediately once treatment is initiated.

We have identified only one previously reported cost-effectiveness study of interventions for DME. Sharma et al modelled the cost-effectiveness of laser therapy alone for DME,27 comparing early and deferred laser treatment with no treatment based on 3-year outcomes from the Early Treatment Diabetic Retinopathy Study.26 The model included health states defined by BCVA and applied a 40-year time horizon based on a population with a mean age of 47 years. Over this time horizon, laser treatment was predicted to provide a gain of 0.236 QALY and was considered highly cost-effective for DME relative to no treatment. Our results cannot be compared directly with the Sharma et al study because RESTORE did not include a ‘no treatment’ arm; moreover, our model applied a 15-year time horizon.
A

![Modelled distribution by health states after (A) 1 and (B) 15 years. BCVA, best corrected visual acuity.](image)

B

Utilities were estimated from the BCVA of treated eyes in RESTORE, irrespective of whether this was the better-seeing or worse-seeing eye. This approach links utility values directly to the eye receiving the intervention. The RESTORE study protocol required the worse-seeing eye to undergo intervention unless there was a medical contraindication; 32.8% of treated eyes were the better-seeing eye at baseline, and 37.3% were the better-seeing eye at 12 months. Using the better eye as reference is supported by quality of life studies in vision-related conditions, which have shown that the better eye is the major driver of overall quality of life and patient functioning. Indeed, patient-preference studies have shown that the utility gains associated with treating the worse-seeing eye are uncertain, even though good vision in two eyes confers better quality of life than good vision in only one eye. As expected, subdividing the elicited utilities in RESTORE by better-seeing or worse-seeing eye showed that patients being treated in the better-seeing eye reported lower utility at a given level of BCVA than those treated in the worse-seeing eye. Nevertheless, utility measured in patients treated in the worse-seeing eye demonstrated significant sensitivity to variation in the BCVA in the treated eye, comparable with that of patients treated in the better-seeing eye. Unfortunately, the small sample of RESTORE patients in each BCVA health state meant that the resulting utility functions were not sufficiently robust to allow separate cost-effectiveness analysis by better-seeing or worse-seeing eye. It should also be stated that the option of not treating visual impairment in a better-seeing eye is not an ethical stance.

We could not find published utility estimates from specific populations with DME. We performed sensitivity analysis using utilities reported in two studies based on populations with diabetic retinopathy (which includes a wider population than DME). Lloyd et al reported utilities elicited by the general population, while Brown et al reported utilities elicited by patients. This showed that applying the Lloyd et al utilities to the model greatly improved the cost-effectiveness of ranibizumab monotherapy, leading to a larger incremental gain of 0.22 QALY and a lower ICER of £19,238 per QALY gained relative to laser therapy alone. Applying the Brown et al utilities also increased the QALY gain with ranibizumab and led to an ICER of £21,955 per QALY gained for ranibizumab monotherapy versus laser therapy alone. The fact that the RESTORE utilities are less sensitive to BCVA decline may simply reflect the fact that the majority of the reference eyes in RESTORE were worse-seeing, while all reference eyes in the Lloyd et al and Brown et al studies were better-seeing.

Limitations of this analysis should be considered. First, we modelled treatment of unilateral DME based on RESTORE data, but did not estimate the cost-effectiveness of treating bilateral DME. While 82.8% of patients in RESTORE had signs of bilateral DME at baseline, the proportion of patients who would have become eligible for treatment because of vision impairment in their fellow eye was not known. Treatment of both eyes may be relevant in many patients with bilateral DME, but there is a lack of evidence for the additional utility benefit of treating the fellow eye. Uncertainty also exists regarding the cost consequences of treating both eyes, where total cost is not likely to double given the possibility of achieving economies of scale from shared categorical spending, such as administrative and monitoring costs. An additional limitation was that the model assumed the cost of blindness would be incurred in patients who have become eligible for treatment because of vision impairment in their fellow eye. Nevertheless, the results would be relevant in many patients with bilateral DME, but there is a lack of evidence for the additional utility benefit of treating the fellow eye. Uncertainty also exists regarding the cost consequences of treating both eyes, where total cost is not likely to double given the possibility of achieving economies of scale from shared categorical spending, such as administrative and monitoring costs. An additional limitation was that the model assumed the cost of blindness would be incurred in patients...
reaching health states with BCVA ≤35 letters (Snellen ≤6/60) in the treated eye.

There is also uncertainty inherent in working with published results of studies, as was necessary for incorporating the DRCR Network Protocol I results, as opposed to using patient-level data. While analysis using patient level data is clearly preferable, incorporation of findings from studies in addition to RESTORE, such as the highly comparable DRCR study, provide very useful data for answering critical questions relating to clinical practice in a broad spectrum of patients with DME. It should be noted, however, that some subgroups, such as patients with the poorest glycemic control (high glycated haemoglobin), were excluded from these trials.

In conclusion, the results of our economic model show that ranibizumab monotherapy is cost-effective relative to laser therapy alone in the treatment of DME causing visual impairment, while combined ranibizumab and laser therapy may be cost-effective depending on patient characteristics. The cost-effectiveness of ranibizumab monotherapy or combination treatment is expected to be higher in younger patients who have a longer life expectancy. These findings have important practical implications, given the high socio-economic burden of DME and the need for new, cost-effective treatments that reduce long-term progression to blindness. Ongoing studies, such as the RESTORE extension, will provide additional clarification of current uncertainties such as the need for ranibizumab injections after 2 years and the likelihood of recurrent DME.

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### Supplementary Table 1 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 ophthalmology 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 ophthalmology non-consultant-led, non-admitted visit) | £60.92    | NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated) |
| Service                  | Cost   | Source                                                                 |
|-------------------------|--------|----------------------------------------------------------------------|
| 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 2** 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 | Annual number of units of ranibizumab monotherapy/combination therapy/laser monotherapy | Unit cost |
|--------------------------|--------|-------|-------|-------|-------|-------|-------|-----|---------------------------------|-----------|
| **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| 12/12/3| 12/12/3| 12/12/3| 12/12/3|£74.10                           |           |
| **Optometrist**          | 12/12/5| 12/12/5| 12/12/5| 12/12/5| 12/12/3| 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 | [ ] | £742.17 |

Ophthalmologist cost=weighted average of ‘ophthalmologist visit’ and ‘additional ophthalmologist visit’ in Supplementary Table 1.

Optometrist cost=weighted average of ‘Pre-injection VA and BCVA assessment’ and ‘optometrist visit’ in Supplementary Table 1.

BCVA, best corrected visual acuity; GP, general practitioner; VA, visual acuity.
**Supplementary Table 3** 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 | 12/8/3 | 12/8/3 | 12/8/3 | 12/8/3 | £74.10   |
| Optometrist              | 12/8/5 | 12/8/5 | 12/8/5 | 12/8/5 | 12/8/3 | 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 1.

Optometrist cost=weighted average of ‘pre-injection VA and BCVA assessment’ and ‘optometrist visit’ in Supplementary Supplementary Table 1.

BCVA, best corrected visual acuity; GP, general practitioner; VA, visual acuity.
**Supplementary Table 4** 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 |     | £742.17   |
| Laser                    | 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| £741.00  |
| 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 1.

Optometrist cost=weighted average of ‘pre-injection VA and BCVA assessment’ and ‘optometrist visit’ in Supplementary Supplementary Table 1.

BCVA, best corrected visual acuity; GP, general practitioner; VA, visual acuity.
**Supplementary Table 5 Cost of blindness**

| Service                                      | 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%            | 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, diabetic 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 4 years 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 HbA1c, based on observational data. The UKPDS 68 study reported an odds ratio of 1.25 for HbA1c 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 Table 6. 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 6 Calibration with WESDR 4-year data

| RESTORE laser, month 9 to month 12 | Equal rates | WESDR calibrated |
|------------------------------------|-------------|------------------|

### Input, 3-month probability

|          | Improve | No change | Worsen |
|----------|---------|-----------|--------|
| Improve  | 0.036   | 0.936     | 0.027  |
| No change| 0.030   | 0.940     | 0.030  |
| Worsen   | 0.035   | 0.920     | 0.045  |

### Output, 4-year incidence of worsening or improvement

|          | Improve | No change | Worsen |
|----------|---------|-----------|--------|
| Improve  | 0.320   | 0.450     | 0.230  |
| No change| 0.270   | 0.460     | 0.270  |
| Worsen   | 0.250   | 0.400     | 0.350  |

Actual, WESDR

|          | Improve | No change | Worsen |
|----------|---------|-----------|--------|
| Improve  | 0.250   | 0.390     | 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.

References

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Moss SE, Klein R, Klein BE. The incidence of vision loss in a diabetic population. *Ophthalmology* 1988;95:1340–8.
The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–86.

UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–53.

Stratton IM, Adler AI, Neil HA et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. *BMJ* 2000;321:405–12.

Clarke PM, Gray AM, Briggs A et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia* 2004;47:1747–59.
**Supplementary Table 7** 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.
Supplementary Figure 1
Probabilistic sensitivity analysis: scatter plot of ranibizumab monotherapy versus laser monotherapy
**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 ophthalmology 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 ophthalmology non-consultant-led, non-admitted visit) | £60.92 | NHS Reference Costs 2008–09 – NHS Trusts and PCTs combined (unless otherwise stated) |
| Service                        | Cost  | Source                                                                 |
|-------------------------------|-------|----------------------------------------------------------------------|
| 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 |     | £742.17   |
| Laser                    | 0/0/0  | 0/0/0 | 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| 12/12/3| 12/12/3| 12/12/3| £74.10  |
| Optometrist              | 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 | £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 | £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 |     |           |

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 |
|--------------------------|--------|-------|-------|-------|-------|-------|-------|-----|----------|
| **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 | 12/8/3 | 12/8/3 | 12/8/3 | 12/8/3| £74.10   |
| Optometrist              | 12/8/5 | 12/8/5 | 12/8/5 | 12/8/5 | 12/8/3 | 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 | 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 |
|--------------------------|--------|-------|-------|-------|-------|-------|-------|-----|-----------|
| **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 | 3/3/3 | 3/3/3 | 3/3/3 | 0/0/0 | £74.10    |
| **Optometrist**          | 5/5/5  | 5/5/5 | 5/5/5 | 5/5/5 | 3/3/3 | 3/3/3 | 3/3/3 | 0/0/0 | £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 | 0/0/0 | £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 | 0/0/0 | £60.92    |
| **Adjustment for double-counting of monitoring visits** | 0 | 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

| Service                                                                 | 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, diabetic 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 4 years 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 HbA1c, based on observational data. The UKPDS 68 study reported an odds ratio of 1.25 for HbA1c 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 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.

**References**

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Clarke PM, Gray AM, Briggs A et al. A model to estimate the lifetime health outcomes of patients with type 2 diabetes: the United Kingdom Prospective Diabetes Study (UKPDS) Outcomes Model (UKPDS no. 68). *Diabetologia* 2004;47:1747–59.
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) |
| Parameter                                      | Value                  | Distribution | Source                     |
|-----------------------------------------------|------------------------|--------------|----------------------------|
| 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.
| Health state defined by BCVA category (letters; treated eye) | RESTORE* Lloyd et al*[13] | Brown et al*[14] |
|-------------------------------------------------------------|---------------------------|-----------------|
| 1: 86–100                                                   | 0.860* (0.034)            | 0.830           |
| 2: 76–85                                                    | 0.860 (0.014)             | 0.750           |
| 3: 66–75                                                    | 0.813 (0.012)             | 0.750           |
| 4: 56–65                                                    | 0.802 (0.014)             | 0.715           |
| 5: 46–55                                                    | 0.770 (0.018)             | 0.680           |
| 6: 36–45                                                    | 0.760 (0.027)             | 0.680           |
| 7: 26–35                                                    | 0.681 (0.053)             | 0.530           |
| 8: 0–25                                                     | 0.547 (0.083)             | 0.340           |
| Time period | Model input          | Combination therapy                                                                 | Ranibizumab monotherapy                                  | Laser monotherapy                                      | Source                              |
|------------|----------------------|--------------------------------------------------------------------------------------|----------------------------------------------------------|--------------------------------------------------------|-------------------------------------|
| Year 1     | BCVA progression     | RESTORE trial data, adjusted for drop-out rates                                      | RESTORE trial data, adjusted for drop-out rates           | RESTORE trial data, adjusted for drop-out rates         | RESTORE data on file                |
|            | Treatment frequency  | 7 injections + 2 laser sessions, as in RESTORE; drop-outs continue in standard care (i.e. laser therapy) | 7 injections; drop-outs continue in standard care (i.e. laser therapy) | 2 laser sessions; drop-outs continue in standard care (i.e. laser therapy) | RESTORE data on file                |
|            | Monitoring visits    | 12                                                                                   | 12                                                       | 4                                                      | SmPC and expert interview (data on file) RESTORE data on file |
|            | Adverse events       | Negligible                                                                          | Negligible                                              | Negligible                                             | RESTORE data on file                |
| Year 2     | BCVA progression     | Equal rates of improvement and worsening (3% in 3 months)                           | Equal rates of improvement and worsening (3% in 3 months) | Equal rates of improvement and worsening (3% in 3 months) | Supported by DRCR.net and RESTORE data on file |
|            | Treatment frequency  | 2 injections + 1 laser session                                                       | 3 injections (no laser)                                  | 1 laser session                                        | Supported by DRCR.net               |
| frequency | session | Monitoring visits | Year 3 | BCVA progression | Treatment frequency | Monitoring visits | Assumption |
|-----------|---------|------------------|--------|------------------|---------------------|------------------|------------|
|           |         |                  |        | Constant rates of change of BCVA with a majority of patients having a decline in BCVA | No additional ranibizumab; laser therapy as required | 4                |            |
|           |         |                  |        | Constant rates of change of BCVA with a majority of patients having a decline in BCVA | No additional ranibizumab; laser therapy as required | 4                |            |
|           |         |                  |        | Constant rates of change of BCVA with a majority of patients having a decline in BCVA | Laser therapy as required | 4                |            |
|           | Any year | Cost of blindness |        | When BCVA ≤35 letters is reached in better-seeing eye | Adapted from costing approach by Meads et al.[16] (Supplementary Table 5) |                  |            |
|           |         |                  |        | When BCVA ≤35 letters is reached in better-seeing eye |                      |                  |            |
|           |         |                  |        | When BCVA ≤35 letters is reached in better-seeing eye |                      |                  |            |

Calibrated to WESDR data (Supplementary Methods)
Assumption

Adapted from costing approach by Meads et al.[16] (Supplementary Table 5)
### Table 3. Cost-effectiveness – base-case and sensitivity analyses

| Assumption/parameter | Base case | Sensitivity analyses | Incremental cost | Incremental QALY | ICER | ICER (%) change |
|----------------------|-----------|----------------------|-----------------|-----------------|------|------------------|
| **Ranibizumab monotherapy versus laser monotherapy** | | | | | | |
| Base case | – | – | £4,191 | 0.17 | £24,028 | – |
| Discount rate of future costs and benefits | 3.50% | 0–5% | £3,593–4,383 | 0.16 to 0.16 | £17,051–27,042 | –29% to +13% |
| Time horizon | 15 years | 10–20 years | £4,738–£3,991 | 0.14 to 0.19 | £33,139 to £21,343 | +38% to –11% |
| Cost of blindness | £6477 | –25% to +25% | £4,868–3,515 | 0.17 to 0.17 | £27,907–20,150 | +16% to –16% |
| Long-term progression of VA | Declining | Constant or increasing | £4,487–4,693 | 0.17 to 0.17 | £26,198–28,413 | +9% to +18% |
| Total number of ranibizumab injections | 10 | –4 injections to +4 | £2,171–6,774 | 0.17 to 0.17 | £12,446–38,836 | –48% to +62% |
| Baseline age | 63 years | 58 years | £3,767 | 0.20 | £19,259 | –20% |
| Source of utilities | RESTORE Lloyd et al.[13] | £4,191 | 0.22 | £19,238 | –20% |
| | RESTORE Brown et al.[14] | £4,191 | 0.19 | £21,953 | –9% |
| **Combination therapy versus laser monotherapy** | | | | | | |
| Base case | – | – | £4,695 | 0.13 | £36,106 | – |
| Discounting of future costs and benefits | 3.50% | 0–5% | £4,271–4,828 | 0.16 to 0.12 | £26,957–40,096 | –25% to +11% |
| Time horizon | 15 years | 10–20 years | £5,133–4,507 | 0.10 to 0.13 | £49,294–34,135 | +37% to –5% |
| Cost of blindness | £6477 | –25% to +25% | £5,050–4,340 | 0.13 to 0.13 | £38,833–33,378 | +8% to –8% |
| Long-term progression of VA | Declining | Constant or increasing | £5,091–5,276 | 0.13 to 0.12 | £40,852–44,071 | +13% to +22% |
| Total number of ranibizumab injections | 9 | –4 injections to +4 | £3,165–7,260 | 0.13 to 0.13 | £24,340–55,828 | –33% to +55% |
| Baseline age | 63 years | 58 years | £4,393 | 0.15 | £29,952 | –17% |
| Source of utilities | RESTORE Lloyd et al.[13] | £4,695 | 0.16 | £28,778 | –20% |
