Fluocinolone acetonide intravitreal implant for the treatment of chronic diabetic macular oedema

Produced by: Warwick Evidence

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Sections highlighted in yellow are ‘academic in confidence’.
Sections highlighted in aqua are ‘commercial in confidence’.
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Glossary and list of abbreviations

Aphakic – absence of lens in the eye

Capsulotomy – surgical incision of the capsule covering the natural crystalline lens of the eye

Cataract – the lens of the eye becomes opaque, reducing vision

Endophthalmitis – inflammation of inside of the eye, such as aqueous humour, vitreous humour, caused usually by infection

Fluorescein angiography – a test used to examine circulation of retina using a fluorescent dye which is injected into patient’s bloodstream

Glaucoma – increased intra-ocular pressure (increased IOP) leading to visual loss

Myodesopsia – perception of shadows (floaters) in the eye

Phakic – having a normal lens in the eye

Pseudophakic – having an artificial lens in the eye after removal of the natural one, usually for cataract.

Retinal detachment – separation of retina from its supporting tissues

Rubeosis – formation of new blood vessels and connective tissues on the surface of iris

Trabeculectomy – a surgical procedure wherein some parts of the eye (trabecular’s meshwork and its adjacent parts) are removed to create holes in the eye to relieve intraocular pressure of the eye. It is carried out to reduce intra-ocular pressure

Trabeculoplasty – laser is used to create holes in the eye to relieve intraocular pressure. It is carried out to reduce intra-ocular pressure

Uveitis – inflammation of the middle layer of the eye (uvea or uveal tract)

Vitrectomy – a surgical procedure to remove part or whole of vitreous humour from the eye
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AMD</td>
<td>Age-related Macular Degeneration</td>
</tr>
<tr>
<td>BCVA</td>
<td>Best Corrected Visual Acuity</td>
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<tr>
<td>BSE</td>
<td>Better Seeing Eye</td>
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<tr>
<td>CI</td>
<td>Confidence Interval</td>
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<tr>
<td>CMT</td>
<td>Central Macular Thickness</td>
</tr>
<tr>
<td>CRT</td>
<td>Central Retinal Thickness</td>
</tr>
<tr>
<td>CSAS</td>
<td>Commissioning Support Appraisals Service</td>
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<tr>
<td>CSMO</td>
<td>Clinically Significant Macular Oedema</td>
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<tr>
<td>CTR</td>
<td>Clinical Trial Report</td>
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<tr>
<td>CVD</td>
<td>Cardiovascular disease</td>
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<tr>
<td>DM</td>
<td>Diabetes Mellitus</td>
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<td>DME</td>
<td>Diabetic Macular Edema</td>
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<tr>
<td>DMO</td>
<td>Diabetic Macular Oedema</td>
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<tr>
<td>ECCE</td>
<td>Extracapsular Cataract Extraction</td>
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<tr>
<td>ERG</td>
<td>Evidence Review Group</td>
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<tr>
<td>ETDRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
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<tr>
<td>FA</td>
<td>Fluocinolone Acetonide</td>
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<td>FAME</td>
<td>Fluocinolone Acetonide for Macular Edema</td>
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<tr>
<td>FDA</td>
<td>Food and Drug Administration</td>
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<tr>
<td>GPRD</td>
<td>General Practice Research Data</td>
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<tr>
<td>HbA1c</td>
<td>Glycated haemoglobin</td>
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<tr>
<td>HRQoL</td>
<td>Health Related Quality of Life</td>
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<tr>
<td>HCHS</td>
<td>Hospital and Community Health Services</td>
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<td>HTA</td>
<td>Health Technology Assessment</td>
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<tr>
<td>ICER</td>
<td>Incremental Cost Effectiveness Ratio</td>
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<td>IOP</td>
<td>Intra-ocular pressure</td>
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<td>ITT</td>
<td>Intention to Treat</td>
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<tr>
<td>mETDRS</td>
<td>Modified ETDRS</td>
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<tr>
<td>MHRA</td>
<td>Medicines and Healthcare products Regulatory Agency</td>
</tr>
<tr>
<td>OCT</td>
<td>Optical Coherence Tomography</td>
</tr>
<tr>
<td>ONS</td>
<td>Office of National Statistics</td>
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<tr>
<td>OPT</td>
<td>Off Protocol Treatment</td>
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<tr>
<td>PCO</td>
<td>Posterior Capsular Opacification</td>
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<tr>
<td>PCT</td>
<td>Primary Care Trust</td>
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<tr>
<td>PSA</td>
<td>Probabilistic Sensitivity Analysis</td>
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<tr>
<td>QALY</td>
<td>Quality Adjusted Life Year</td>
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<tr>
<td>QOF</td>
<td>Quality and Outcomes Framework</td>
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<tr>
<td>RCO</td>
<td>Royal College of Ophthalmologists</td>
</tr>
<tr>
<td>RR</td>
<td>Relative Risk</td>
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<tr>
<td>SD</td>
<td>Standard Deviation</td>
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<tr>
<td>SMD</td>
<td>Subthreshold Micropulse Diode</td>
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<tr>
<td>SMR</td>
<td>Standardised Mortality Ratio</td>
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<tr>
<td>SOC</td>
<td>Standard of Care</td>
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<tr>
<td>SPC</td>
<td>Summary of Product Characteristics</td>
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<tr>
<td>TPM</td>
<td>Transition Probability Matrices</td>
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<tr>
<td>VA</td>
<td>Visual Acuity</td>
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<tr>
<td>VEGF</td>
<td>Vascular Endothelial Growth Factor</td>
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<tr>
<td>WSE</td>
<td>Worse Seeing Eye</td>
</tr>
<tr>
<td>WTP</td>
<td>Willingness to Pay</td>
</tr>
<tr>
<td>YHPHO</td>
<td>Yorkshire and Humber Public Health Observatory</td>
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1. SUMMARY

1.1 Introduction

Diabetic macular oedema (DMO) is an important cause of visual loss amongst people with diabetes. Standard treatment has been laser photocoagulation, but that is better for preserving vision than restoring it, and better treatments are required. Two classes of drugs injected into the eye have been developed in recent years: steroids such as triamcinolone, dexamethasone and fluocinolone; and the “anti-VEGF” drugs, bevacizumab, ranibizumab and pegaptanib.

Triamcinolone has been widely used but is not licensed for use in the eye. A new long-acting form of dexamethasone has been developed, and has been approved by NICE for use in macular oedema following retinal vein occlusion. It has not yet been licensed for DMO. Fluocinolone has recently been licensed for use in DMO.

Ranibizumab has been licensed for use in DMO, but was not approved by NICE, being considered to be not cost-effective compared to laser photocoagulation, at the current price of ranibizumab. Bevacizumab is much less expensive than ranibizumab, but is not licensed for use in the eye. It has never been submitted for licensing for ophthalmic use. However it is commonly used off-licence for eye conditions including age-related macular degeneration and DMO.

Scope of manufacturer’s submission

The submission from Alimera is based on the findings of the clinical trial of fluocinolone versus sham injection, which showed that fluocinolone was most relatively effective in a subgroup of patients who had chronic DMO, initially defined as being of 3 or more years duration. Alimera anticipate that fluocinolone will be used in patients in this chronic DMO subgroup who have had an insufficient response to other treatments. It could therefore, to some extent, be regarded as a treatment of last resort. This is reflected in the marketing authorisation which states that

“Iluvien is indicated for the treatment of vision impairment associated with chronic diabetic macular oedema considered insufficiently response to available therapy.”

So in PICO terms, the scope is:

- Population: patients with chronic diabetic macular oedema with visual impairment.
- Intervention: fluocinolone insert, trade name Iluvien. This is inserted into the eye, and releases fluocinolone slowly over about 3 years.
- Comparator: other drugs having been tried and failed, and laser therapy not having been very effective, the comparator will be observation and laser if thought useful.
• Outcomes: visual acuity and consequent associated quality of life, and adverse events.

1.2 Summary of the clinical effectiveness evidence submitted by the manufacturer

All the evidence on clinical effectiveness came from two identical FAME trials, which the manufacturer’s submission and the ERG treated as a single trial. The FAME trial recruited people with diabetes who had visual impairment due to DMO. The duration of DMO was at least a year, and patients had nearly all had previous laser and sometimes other treatments, without sufficiently resolving the oedema. The trial had three arms, two with fluocinolone and a control arm. Two doses of fluocinolone were used, in inserts designed to release 2 µg or 5 µg per day over 3 years. The control arm had a sham injection (pressure on the eye but no penetration). Patients in all arms could have other treatments if necessary, including laser therapy. The “sham” control group could be regarded as receiving standard care for this group. There were 209 participants in the lower dose fluocinolone arm and 112 in the sham arm.

The main findings were that;

• The larger dose conferred little extra benefit but caused more adverse effects, so will not be used.
• Relative to standard care, the best results from fluocinolone were seen in patients with duration of DMO of 3 years or more. This was mainly because patients with shorter duration of DMO did quite well in the control arm, showing much less difference from the fluocinolone arm
• Hence the focus is on the use of the lower dose in patients with 3 or more years duration, referred to as chronic DMO.
• Follow-up was for 3 years.
• At 3 years, 34% on fluocinolone had improved vision by 15 letters or more, compared to 13% in the control arm (difference 21%, 95% CI 11.6 – 29.6). The greatest difference was seen at 30 months, when of the fluocinolone group had achieved a gain of 15 or more letters, compared to of the control group.
• At 3 years, of the fluocinolone group and of the sham group had improved vision by 10 letters or more
• The mean best corrected visual acuity (BCVA) improved by 7.6 letters in the fluocinolone group and by 1.8 letters in the control arm (95% CI of difference 2.0 – 10.2 letters).
Adverse effects were common. Cataract, in which the normally clear lens of the eye goes opaque, is a well-known adverse effect of steroids. Of those patients who had a natural lens at baseline, in the fluocinolone group developed cataract in the injected eye by 3 years (compared to 42% in their non-study eyes, and in the sham group), and 85% of fluocinolone eyes had cataracts removed. However cataract is more common in people with diabetes, and 43% had already had cataract removed and an artificial lens implanted before fluocinolone treatment started. Of those who still had a natural lens at baseline, 42% already had some degree of cataract. So in many patients, fluocinolone only accelerated progression of existing cataracts, as opposed to causing new ones.

The other main adverse effect was raised intra-ocular pressure (IOP), which if sufficiently high and not treated, can develop into glaucoma and cause visual damage. 34% of patients had raised IOP in the injected eye (compared to in their non-injected eye). Most could have their pressure controlled with eye-drops, but 5.3% needed laser trabeculoplasty or surgery in the study eye. No patients in the sham group needed glaucoma surgery.

1.3 Summary of ERG’s critique of clinical effectiveness evidence submitted by the manufacturer.

The ERG regarded the Alimera account of the FAME trial as accurate but lacking in detail. Further information had to be obtained from other documents including the clinical trial reports. Alimera provided two useful reports from the integrated FAME trial, one on efficacy and one on safety, and provided answers to most of 50 clarification questions.

In particular, the section on safety was very short – surprisingly so for a drug rejected by the FDA on safety grounds in 2011. The ERG relied mainly on the clinical trial reports for safety data. There were also missing baseline data on patient characteristics. These had been in the published account of the FAME trial and were obtained during the clarification process.

Quality of life data had been collected in the FAME trial but were not presented in the manufacturer’s submission. As far as the ERG is aware, none of the quality of life data from FAME have been published.

The manufacturer included an indirect comparison against laser treatment but because of the methods used, the ERG regarded it as being of limited value.
1.4 Summary of cost effectiveness submitted evidence by the manufacturer

The manufacturer submission provides a base case estimate for the cost effectiveness of fluocinolone versus the sham arm of the fluocinolone trial among patients with chronic DMO and visual impairment of £22,655 per QALY, and versus laser of £16,463 per QALY. The ERG views the comparison with sham as more relevant to the decision problem. The comparison with laser is also hampered by the quality of the indirect comparison undertaken to enable it.

Within the response to the ERG clarification questions the manufacturer provides a revised estimate for the cost effectiveness of fluocinolone versus sham of £19,268 per QALY, and versus laser of £17,171 per QALY. The model underlying the revised estimates suffers from problems with the mortality data applied within it and undocumented changes to the model structure concerning the quality of life uplifts that are applied for bilateral treatment. For these reasons, the ERG views the original submission as the appropriate starting point for the consideration of the cost effectiveness evidence submitted by the manufacturer.

- The manufacturer submission is broadly in line with the NICE reference case with the exceptions of: the quality of life values being drawn from a previously published direct time trade off exercise among patients with visual impairment due to age-related macular degeneration
- The central estimates from a probabilistic analysis and resulting probabilistic ICER not being presented.

Note that the submission does not present the quality of life data collected using the VFQ-25 during the trial, or make any attempt to use this data within the model.

The model adopts a 15 year horizon and a quarterly cycle length. It has 13 health states which are defined by 5 ETDRS letter bands of the BCVA in the treated eye, plus a 14th of death. The model does not distinguish between whether the treated eye is the worse seeing eye (WSE) or the better seeing eye (BSE) in calculating treatment costs, quality of life values or the costs of blindness. In effect, patients are modelled as having only the treated eye with an ad hoc adjustment being made to the model outputs to take into account possible rates of bilateral treatment. In the trial, % had their WSE treated and % their BSE.

The model has a mixed structure. For the first 3 years or 12 cycles the distribution between health states is drawn directly from the pooled FAME trials’ data. For extrapolation beyond the 3 year point
A Markov model structure is adopted with transition probability matrices (TPMs) based upon trial data being applied.

In the fluocinolone arm patients are split into responders and non-responders based upon $\%$ having satisfied the responder rule of having improved by at least 5 letters between baseline and 36 months. Note that at clarification the manufacturer supplied an estimate of $\%$ of fluocinolone patients satisfying a 10 letter responder rule. The responder percentage is further conditioned by the $\%$ drop-out rate during the trial within the fluocinolone arm.

For the 12 year extrapolation period, among the fluocinolone 36 month responders 5% are assumed to improve by a further 5 letters every quarter. Fluocinolone is re-administered every 3 years, though the discontinuation rate of $\%$ is also re-applied every 3 years. Among the fluocinolone non-responders 3% are assumed to worsen by 5 letters every quarter and fluocinolone treatment is stopped. It is also assumed among the sham arm and the laser arm that 3% worsen by 5 letters every quarter.

The above is conditioned by a DMO age specific mortality rate derived from all-cause mortality data conditioned by a 2.45 relative risk of death amongst patients with diabetes and DMO.

The total costs in each arm are estimated on the basis of one eye being treated, as above. These are then qualified by a 35% bilateral treatment rate in the sham arm, this estimate being drawn from the manufacturer submission to the NICE STA of ranibizumab for DMO. Due to around $\%$ of patients in the fluocinolone arm having a raised IOP, the bilateral treatment rate in the fluocinolone arm is reduced to $\%$. A 25% QALY uplift for bilateral treatment is also applied to the aggregate QALYs estimated in each arm, qualified by the $\%$ and $\%$ proportions assumed to receive bilateral treatment in the sham arm and the fluocinolone arm respectively.

Manufacturer sensitivity analyses show results to be sensitive to whether only one fluocinolone administration is required every 3 years, or whether dosing would reflect that of the trial, in which re-treatment with fluocinolone was allowed. The ERG accepts the manufacturer assumption of one fluocinolone administration every three years as the more realistic of the two, though given the trial data there may be grounds for an assumption of the average being every 30 months since after that there is a slight decline in VA. However there is no marked decline, suggesting that some patients may postpone re-treatment beyond 36 months. Further manufacturer sensitivity analyses show results to be also sensitive to the extrapolation assumptions, the drop-out rate applied to fluocinolone responders, and the quality of life values that are applied.
1.5 Summary of the ERG’s critique of cost effectiveness evidence submitted

The ERG has corrected a number of errors within the model implementation in order to align the electronic copy of the model with what appears to be the manufacturer intended model structure. This changes the base case estimate for the cost effectiveness of fluocinolone versus sham from £22,655 per QALY to £26,526 per QALY.

The strengths and weaknesses of the cost effectiveness evidence are summarised in section 1.6 below.

1.6 ERG commentary on the robustness of evidence submitted by the manufacturer

1.6.1 Strengths
The three year data that feeds into the first three years of the economic model is robust. But while this is a strength, it only really reiterates the trial results. As there is no modelling employed during this period the data cannot be manipulated to explore different scenarios: such as the cost effectiveness estimate among those having their best seeing eye treated at baseline.

1.6.2 Weaknesses and areas of uncertainty
The submission presentation of the modelling employed and the underlying assumptions is very poor. The majority of the ERG critique of the submission has had to rely upon teasing out the electronic model structure and the assumptions underlying by reconstructing it, rather than drawing upon the manufacturer submission.

The ERG notes that the majority of the errors in the manufacturer model structure uncovered during this process appear to improve the cost-effectiveness of fluocinolone.

The model mainly simulates the BCVA of the WSE since around % of patients had their WSE at baseline treated. But quality of life and the costs of blindness are driven by the bilateral BCVA. As a consequence it seems likely that the model overestimates the QALY gains and the savings from reduced rates of blindness.

The electronic model inputs in terms of adverse event rates and laser administrations are not obviously aligned with those of the submission or the trial. In many instances the differences are not that large, but this complicates the cross checking and reduces the faith that can be placed in the written submission. The source and derivation of the unit costs applied to adverse events is also not entirely transparent.
Reasonably large cost offsets arise from the fluorescein angiography costs modelled in the sham arm. It seems likely that these have been overstated.

Applying the overall fluocinolone drop-out rate every three years to the fluocinolone responders does not seem valid. Note that a higher drop-out rate improves the cost effectiveness estimate.

The extrapolation estimates drawn from the last year of the trial data may not apply for the 12 years of the extrapolation period. It is also not valid to have entirely ignored the sham arm data when forming the extrapolation estimate to apply to the sham arm.

The method applied by the manufacturer to estimate the quality of life uplift from bilateral treatment is flawed and results in bias against fluocinolone.

1.7 Summary of exploratory and sensitivity analyses undertaken by the ERG

The manufacturer submission provides a base case estimate for the cost effectiveness of fluocinolone versus sham of £22,655 per QALY. As noted above, the ERG has corrected a number of errors within this to provide a revised estimate of £26,526 per QALY. This largely reflects the stated model inputs and the apparently intended manufacturer model structure.

The ERG has further revised the model to reflect:

- the number of laser administrations within the trial
- that it is more appropriate for the costs of fluorescein angiography to be applied per laser administration than assumed to be on an annual basis and only within the sham arm
- the cited 2010-11 NHS reference costs for the adverse event costs
- the proportions improving and worsening for the extrapolation period for fluocinolone responders, fluocinolone non-responders and sham patients, based upon data supplied by the manufacturer at clarification
- the fluocinolone drop-out rate to not include deaths at years 6, 9 and 12 as this is modelled separately
- the probable baseline bilateral treatment rate, based upon data supplied by the manufacturer at clarification
- a cost of blindness conditioned by the bilateral treatment rate, though the ERG recognises that this is an ad hoc adjustment that is open to criticism

This results in a revised cost effectiveness estimate for fluocinolone versus sham of £37,740 per QALY when a 5 letter responder rule is applied, and £35,940 per QALY when a 10 letter responder
rule is applied. These results show some sensitivity to the costs of blindness, the treatment of fluorescein angiography costs and are reasonably sensitive to the extrapolation percentages assumed. They are also sensitive to the mortality risk. The relative risk of mortality used in the modelling, of 2.45 compared to the general non-diabetic population, may be too low.

But the main sensitivity is to the source of quality of life values. Applying the quality of life values used within the manufacturer submission to the NICE STA of ranibizumab for DMO results in cost effectiveness estimates of £145,886 per QALY for the 5 letter responder rule and £145,035 for the 10 letter responder rule. The reason for the size of these changes in the ICERs is not currently apparent to the ERG.

A key issue is whether it is both feasible and desirable to explicitly model patients as having two eyes. The ERG is of the opinion that it is, and that this might address many of the issues around quality of life and the costs of blindness being driven by the bilateral BCVA.

A key assumption within the model implementation is that the distribution between health states among fluocinolone responders at month 36 is the same as the distribution across all patients in the fluocinolone arm at month 36. This cannot be correct and may have quite seriously biased the analysis against fluocinolone. It may also render the sensitivity analyses around the responder rule largely meaningless.

1.8 Conclusion

The fluocinolone insert is clinically effective in diabetic macular oedema, improving vision by 10 or more letters in about 52% the participants, compared to about 30% in the control arm. The most common adverse event was cataract, but this is very common in people with diabetes and DMO without steroid treatment. The most serious adverse event was glaucoma, but this was usually controlled with eye drops.

The cost-effectiveness is uncertain.
2. INTRODUCTION

2.1 Diabetes Mellitus (DM)

There are two main types of diabetes mellitus. The common defining feature is raised blood glucose (hyperglycaemia).\(^1\) Over time, hyperglycaemia can damage small and large blood vessels, resulting in a higher risk of several conditions including ophthalmic problems, the main one being known as retinopathy – pathology of the capillaries, arterioles and venues in the retina, and the effects of subsequent leakage from or occlusion of these small vessels.

Most cases of diabetes are of type 2 diabetes, which is largely a consequence of overweight and obesity. Recent data show that the proportion of people of all ages who are obese or morbidly obese has risen from 15.7% in 1993 to 25.4% in 2009; 63.4% of the population are now overweight or obese, and this trend is predicted to continue.\(^2\) The Association of Public Health Observatories (APHO) Diabetes Prevalence Model estimates that the prevalence of diabetes amongst people aged 16 years and over will rise by 28.3% between 2010 to 2030, and 54.5% of this increase can be attributed to the rise in obesity.\(^3\)

The number of people with diabetes is also related to the increasing age of the population.

Holman and colleagues estimate the prevalence in people over 16 years of age in England to be 3.1 million people (7.4%). It is estimated that about a quarter of these are undiagnosed.\(^3\) However, the number undiagnosed is expected to fall since screening for diabetes will be included in the Government's proposed vascular risk screening programme.\(^4\)

The APHO Diabetes Prevalence Model estimates that in 2010 there were about 219,000 people aged over 16 with diabetes in Wales, a prevalence of 9%, expected to rise to 9.6% (242,000 people) by 2015.\(^5\)

QOF data give rise to estimated prevalences of 5.5% in England and 5.0% in Wales.\(^6\)

Type 1 diabetes is due to insulin insufficiency. Insulin is crucial for regulating blood sugar levels, and lack of it leads to hyperglycaemia. Insulin insufficiency is believed to be an autoimmune process, resulting in destruction of the pancreatic beta-cells which make insulin.\(^1\) Life expectancy among people with type 1 diabetes is approximately 20 years less than the general population.\(^7\)
Type 2 diabetes is much more common than type 1 diabetes. It is characterised initially by resistance to the effects of circulating insulin, followed by inadequate insulin production. Compared to the general population, it is more common among particular ethnic groups (e.g. people of Indian, Pakistani, Bangladeshi or Caribbean origin). The risk of developing the condition rises with increasing body weight, and most people who develop type 2 diabetes are overweight. Life expectancy among people with type 2 diabetes is approximately 10 years less than the general population.

Note however that mortality data observed in recent years reflects the lifetime experiences of diabetes and its care over decades, and may not apply to those developing diabetes more recently.

2.2 The macula

Within the retina, there are two principal types of photoreceptor cell: rods and cones. Rod cells are found throughout the retina (except at the very centre of the macula – the fovea) and at the periphery and contribute to peripheral vision. Cone cells are present throughout the retina but are concentrated at the fovea. They contribute to colour vision and are important for detailed vision. Therefore, the macula is important for detailed vision.

![Figure 1. Retina, macula & fovea](image)
2.3 **Diabetic retinopathy**

Diabetic retinopathy results from retinal changes arising from damage to small blood vessels associated with hyperglycaemia. When the macula is affected, this is termed diabetic maculopathy.°

Macular oedema refers to the accumulation of fluid in the retina at the macular area. It may arise predominantly from leakage from vascular abnormalities, mainly microaneurysms, or from macular ischaemia (areas of capillary non-perfusion) affecting the perifoveal capillaries. The prognosis of the latter is worse since these patients cannot be treated with laser, because that could cause further loss of perifoveal capillaries. The ischaemic areas release vascular endothelial growth factor (VEGF), and it is believed that this increases the permeability of the blood vessels leading to oedema.

The accumulation of fluid in the retina leads to a deterioration in detailed vision.° Vascular endothelial growth factor (VEGF-A in particular) plays a role in the development of DMO.° If oedema persists, photoreceptor cell damage occurs with subsequent loss of vision.

Clinically significant macular oedema (CSMO) was defined in the ETDRS as°

- ‘Thickening of the retina at or within 500um of the centre of the macula;
- Hard exudates at or within 500um of the centre of the macula if associated with thickening of adjacent retina;
- Zone(s) of retinal thickening one disc diameter or larger (1500um), any part of which is within one disc diameter of the centre of the macula.’

Diabetic maculopathy can be classified as focal, diffuse, ischaemic or mixed, depending on the location and cause of the leakage. Focal maculopathy is localised leakage of tissue fluid from tiny swellings (microaneurysms) in the wall of retinal capillaries.

Diffuse maculopathy refers to generalised thickening of the central macula caused by widespread leakage from dilated capillaries. There are areas of diffuse leakage from dilated capillary beds and/or intraretinal microvascular abnormalities, or inefficiency of the outer blood-retinal barrier (retinal pigment epithelium - RPE) to pump out fluid from the retina.

Ischaemic maculopathy occurs when the blood vessels in the macula become constricted and starve the macula of oxygen and nutrition, and is associated with a significant risk to vision.

Mixed maculopathy refers to cases with a combined pathology, particularly of diffuse oedema and ischaemia.
It is possible that the source of the fluid might affect responses to different treatments. Fluorescein angiography is used to distinguish the types of maculopathy previously described.9

DMO can be classified by severity. If it is located within 500 microns from the centre of the macula, or is greater than one disc diameter in size and less than one disc diameter from the centre of the macula, it is termed clinically significant macular oedema (CSMO). Retinal thickening involving the centre of the macula (CSME) is also known as centre-involving macular oedema and is the most severe form of DMO.

It can be classified as;10
- Location – central, peri-central
- The amount of oedema as measured by macular thickness
- The presence or absence of vitre-retinal interface abnormalities
- The presence or absence of hard exudates in the central subfield.

**Epidemiology**

People with diabetes are at risk of visual loss from a number of conditions, some unrelated to diabetes, some not specific to diabetes but increased in diabetes, notably cataract, and some specific to diabetes, including proliferative retinopathy and macular oedema. A study from the Gloucestershire Eye Unit11 reported that in people with diabetes cataract was the commonest contributor to visual loss (49%) followed by macular degeneration (29%) and diabetic maculopathy (15%). Conditions may co-exist. The proportionate causes vary with age, with DMO accounting for 28% of visual impairment in people with diabetes in the 5th and 6th decades.

Klein 199812 also reported that DMO was the commonest diabetic cause of blindness in diabetes.

The prevalence of DMO increases with increasing duration of diabetes. In type 1 diabetes, the prevalence of CSMO is very low in the first few years after diagnosis, but rises to over 20% after 20 years, though that figure is based on data from data from the 1980s and 1990s,13 and there is some evidence that better management of type 1 diabetes is reducing or postponing retinopathy. However the recent global meta-analysis concluded that prevalence of DMO under 10 years duration of diabetes was 3.15%; at 10-19 years, 13%; and after 20 years, 20%.14

The risk of DMO is increased by smoking, by poor glycaemic control and by hypertension.
In the global review by the Meta-analysis for eye disease (META-EYE) study group prevalence amongst people with normal blood pressure was 5.5% compared to 10.6% in those with hypertension (BP >140/90 or already on anti-hypertensive medications).\textsuperscript{14} There was a strong link between poor glycaemic control and prevalence;

<table>
<thead>
<tr>
<th>HbA1c</th>
<th>Prevalence of DMO</th>
</tr>
</thead>
<tbody>
<tr>
<td>7.0% or less</td>
<td>3.6%</td>
</tr>
<tr>
<td>7.1 to 8.0%</td>
<td>6.3%</td>
</tr>
<tr>
<td>8.1 to 9.0%</td>
<td>7.7%</td>
</tr>
<tr>
<td>Over 9.0%</td>
<td>12.5%</td>
</tr>
</tbody>
</table>

In the DCCT/EDIC study the group that received intensive treatment during the trial phase, still had less retinopathy 10 years after the trial ended.\textsuperscript{15}

**Hence good control of blood glucose and blood pressure should reduce the number of people developing DMO.**

Among people with type 2 diabetes, 3% have been found to have the condition five years after being diagnosed with diabetes, rising to 28% among people who have had diabetes for twenty years.\textsuperscript{16}

A recent study by Minassian and colleagues\textsuperscript{17} has estimated the prevalence of DMO in England. Based on an expected population of around 2.3 million people in England with diabetes (the NICE scope suggested 2.5 million and the YHPO estimate is now 3.3 million, prevalence 7.9%, but YHPO include undiagnosed diabetes), and an expected prevalence of DMO of 7.12% in one or both eyes, they estimated that there would be almost 65,000 people with clinically significant DMO with varying degrees of visual impairment. Their estimates were based on the excellent data from the Diabetic Retinopathy Screening Service for Wales, based on many years of screening and a dataset from 27,178 screened people with diabetes.

The richness of the data meant that Minassian et al\textsuperscript{17} were able to subdivide people with DMO into groups of varying severity, as shown in Table 1. Figures rounded to one decimal place.
Table 1. Estimated number of people with varying severity of DMO in England

<table>
<thead>
<tr>
<th>Description</th>
<th>Prevalence % of all people with diabetes</th>
<th>Expected number in England</th>
</tr>
</thead>
<tbody>
<tr>
<td>All DMO</td>
<td>7.1%</td>
<td>166,325</td>
</tr>
<tr>
<td>In one eye only</td>
<td>4.7%</td>
<td></td>
</tr>
<tr>
<td>In both eyes</td>
<td>2.3%</td>
<td></td>
</tr>
<tr>
<td>Slight sight loss</td>
<td>2.8%</td>
<td>64,725</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>2.6%</td>
<td>62,083</td>
</tr>
<tr>
<td>Blindness</td>
<td>0.1%</td>
<td>2642</td>
</tr>
<tr>
<td>Partial sight</td>
<td>0.2%</td>
<td>5240</td>
</tr>
</tbody>
</table>

The prevalence of DMO is dependent on how well diabetes is controlled, and access to (and take up of) preventive services which include screening for diabetic retinopathy, and laser photocoagulation. The aim of screening is to detect retinopathy at an early stage. Screening services are well-developed in England and Wales. The annual report for the Diabetic Retinopathy Programme, year 2010/2011, states that 2.5 million people had been identified as having diabetes, of whom 2.3 million had been offered screening, with an uptake of 85%. (Note that around 200,000 people were excluded for various reasons, such as having already been diagnosed and under ophthalmic care, and so not needing to be screened.)

Screening and early treatment is reducing the incidence of blindness due to diabetes. A recent study from Newcastle, where organised screening for retinopathy started in 1986, reported that diabetes was no longer the commonest cause of blindness in the working age population in Newcastle.


Approximately 33-35% of DMO cases may resolve after six months if untreated.
2.4 Mortality in people with diabetic retinopathy

In a previous DMO appraisal, of ranibizumab, assumptions about mortality had a significant effect on ICERs, of up to £4,660 per QALY. If people get benefit from treatment of DMO, the total QALY gain depends on, inter alia, how long they live for.

Mortality is increased amongst people with diabetes, and further amongst those with diabetes and retinopathy. The Mulnier study from the UK estimated that people with type 2 diabetes had a relative risk of dying of 1.93 (compared to the general population).\(^20\) Hirai and colleagues estimated that the excess risk in those diagnosed over the age of 30 (i.e. mostly type 2) with DMO to be 1.27, which combined gives those with diabetes and DMO a RR of 2.45.\(^21\)

The RR of 1.93 in the Mulnier study (which was of high quality) was for all ages.\(^20\) However people having treatment for DMO are older than the average in the Mulnier study. The RRs for the age range 55-64 in the Mulnier study were 2.21 for men and 3.28 for women. The overall RR of 1.93 is affected by the much lower RRs seen in the over 75 age groups.

As mentioned above, caveats are necessary when applying mortality rates from older studies, to present day modelling. The cohort in the Mulnier study was recruited on 1\(^{st}\) January 1992. No details on duration of diabetes are given in the paper, but most would have had diabetes for some years. Mortality was based on deaths in the years 1992 to 1998. The reported prevalence of diabetes was only 1.5% - much less than now. It is possible that diabetes care may have improved since then, for example with more use of the statins in diabetes, and better control of blood pressure. So mortality may be lower now. Gulliford and Charlton using General Practice Research Database (GPRD) data, showed that the RR for overall mortality declined from 1.38 in 1997 to 1.27 in 2006 in men, and from 1.62 to 1.44 in women.\(^22\) In Scotland, the Scottish Diabetes Research Network\(^23\) reports RRs in type 2 diabetes of 1.4 in men and 1.7 in women.

Targher and colleagues followed up a cohort of 2103 people with type 2 diabetes in Italy.\(^24\) All were initially free of diagnosed cardiovascular disease. The cohort had similarities to the patients in the FAME study,\(^25\) reported later;

<table>
<thead>
<tr>
<th></th>
<th>Targher(^{24})</th>
<th>FAME(^{25})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2</td>
<td>100%</td>
<td>91%</td>
</tr>
<tr>
<td>Mean age</td>
<td>60</td>
<td>63.5</td>
</tr>
<tr>
<td>HbA1c</td>
<td>7.2</td>
<td>7.8 (whole FAME group)</td>
</tr>
<tr>
<td>Duration diabetes</td>
<td>16</td>
<td>16 (T2 only)</td>
</tr>
</tbody>
</table>

The risk of new CVD was higher in those with retinopathy, especially in those who had more advanced retinopathy such as proliferative or previously laser treated. The RRs for those with
advanced retinopathy were 3.75 for men and 3.81 for women. Even after adjustment for a range of other variables, RRs remained high at 2.08 for men and 2.41 for women.

Other studies have also reported increased mortality amongst people with advanced retinopathy. Juutilainen et al reported that patients with proliferative retinopathy had (after adjustment for a range of variables) a RR of 3.06 (p<0.001) for all-cause mortality, relative to those with no retinopathy.26

Rajala et al compared mortality in several groups. People with visual impairment due to diabetic retinopathy had a RR compared to the general non-diabetic population of 5.1.27

In type 1 diabetes, van Hecke et al28 reported an adjusted hazard ratio in patients with proliferative retinopathy of 4.2, compared to those without retinopathy at baseline. The increased mortality was mainly explained by cardiovascular risk factors. Patients with proliferative retinopathy also had much more hypertension (38% vs. 5% in diabetic people without retinopathy) and prior CVD. At 8 year follow-up, 10% of the group with proliferative retinopathy had died compared to 1.5% of the group with no retinopathy.

In a Danish cohort of patients with type 1 diabetes, Grauslund et al reported that 55% of all patients survived to a 25-year follow-up, but that amongst those with proliferative retinopathy and proteinuria, only 22% survived for 10 years.29

From the Beijing Eye Study, Xu and colleagues reported that the presence of retinopathy doubled the mortality rate.30

Cusick and colleagues (ETDRS 27) reported that severe non-proliferative diabetic retinopathy conferred a 1.7 (crude) or 1.48 (adjusted) relative risk of mortality compared to those with no or only mild background retinopathy.31

The association between retinopathy and mortality is because cardiovascular risk factors are also risk factors for the development of retinopathy.28

Hence a range of studies suggest that;

- Mortality is higher in people with diabetes, compared to the general population
- In those with diabetes, mortality is much higher in those with advanced retinopathy, with RRs in the range 3 to 4.
One problem is that many studies report associations with proliferative retinopathy, rather than macular oedema. This is usually because they rely on 2-dimensional retinal photographs which cannot detect oedema. However there is a high correlation between DMO and proliferative retinopathy.

We could use the RR of 5.1 from the Rajala 2000 study, which compares mortality in people with visual impairment due to diabetic retinopathy, with that in the general non-diabetic population.

Or we could take the Cusick and Xu figures for the excess risk in those with more severe retinopathy, averaged to 1.75, and apply that to the excess risk amongst those with diabetes versus the general population – using the 2.3 from the AusDiab study or the 1.9 from Mulnier – to give the relative risk of mortality in those with DMO in the range 3.3 to 4.0.

The Alimera submission (Table B17, page 83) uses the RR of 2.45 as used in the ranibizumab appraisal, with a conservative estimate of 1.93 (which is the Mulnier RR for all people with diabetes, and is too low). In the ERG modelling, we will include a sensitivity analysis with RR 3.5.

2.5 Current treatments

Management of DMO involves both systemic and local treatments. Systemic treatments include glycaemic control, blood pressure control and lipid-lowering. Local treatments include laser photocoagulation, anti-VEGFs therapy, steroids, combinations of these, and vitrectomy.

Laser photocoagulation is used to prevent or delay progression and has been the mainstay of treatment for DMO for many years. The landmark Diabetic Retinopathy Study and the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated its clinical effectiveness. The ETDRS showed that laser treatment reduced the risk of moderate visual loss by 50% after three years of follow-up.

However, although laser photocoagulation was clearly effective in preserving vision, it was less successful in restoring it, once lost. Its main effect is stopping further visual loss rather than improving visual acuity. Vision is improved by 15 or more letters in only 17% of patients. By three years, 12% of treated eyes had lost >15 letters of VA.

Furthermore, patients with perifoveal ischaemia are not amenable to this form of therapy. Thus, although laser was shown to reduce the risk of moderate visual loss (a loss of 3 ETDRS lines) by 50%, visual acuity improved in only 3% of patients. Over the following decade it became apparent that certain patients suffered severe visual loss despite aggressive treatment. In addition, laser is not
without side effects. Foveal burns, visual field defects, retinal fibrosis and laser scars have been reported. Of the two types of DMO, diffuse and focal, laser has been said to be more effective in focal. Eyes with diffuse DMO respond less well to laser photocoagulation.

There has been a recent systematic review of the treatment of DMO by Ford et al (submitted for publication), and we draw on that here.

Two groups of drugs have been investigated in the past few years as possible alternatives for laser photocoagulation; others are in the pipeline. The first group is steroids, including triamcinolone, dexamethasone and fluocinolone. The second group is the inhibitors of vascular endothelial growth factor (VEGF) and include pegaptanib, bevacizumab, ranibizumab and VEGF Trap eye.

Intravitreal corticosteroids have potent anti-inflammatory effects. Triamcinolone (Kenalog) is not licensed for eye use but has been used to treat DMO for over ten years. Another form of triamcinolone, Trivaris, was licensed for eye use by the FDA but is no longer available. It was produced by Allergan, who now manufacture the longer-acting dexamethasone product, Ozurdex, an intravitreal implant that provides sustained release over several months. Dexamethasone has been recommended by NICE as an option for treating macular oedema following retinal vein occlusion.

The DRCR.net trial comparing intravitreal triamcinolone with laser photocoagulation reported that after two years follow-up, vision and macular oedema were improved among people treated by laser compared to those treated with steroids. Intravitreal steroid injection was associated with a higher chance of raised intraocular pressure and the development of cataracts. However in those with pseudophakic eyes at baseline, VA improvement in the triamcinolone + prompt laser group was better than in those phakic at baseline, and very similar to the results in those treated with ranibizumab, though raised IOP remained a risk.

Anti-VEGF agents have shown promise as potential alternatives to laser photocoagulation. Bevacizumab (Avastin, Genenetch /Roche) is a monoclonal antibody that targets all VEGF isoforms. Although being developed for colorectal cancer, it is widely used off-label, as an intravitreal treatment for macular oedema of different aetiologies. Ranibizumab (Lucentis, Genentech/Roche, but produced and marketed by Novartis in the UK) is a fragment of the bevacizumab antibody (molecular weight of ranibizumab 48.4 KDa compared with 149 KDa for bevacizumab). It was designed specifically for use in the eye. Ranibizumab is considerably more expensive than bevacizumab at around £760 per dose, compared to £50 -105 for bevacizumab. NICE did not approve ranibizumab for use in DMO.
Pegaptanib (Macugen, Eyetech Pharmaceuticals/Pfizer) is a PEGylated aptamer, with a high affinity to the VEGF isoform 165 and was approved for the treatment of exudative AMD in 2004. VEGF Trap eye (Regeneron/Bayer HealthCare) is a recent addition to the anti-VEGF class that targets all forms of VEGF-A and placental growth factor. Pegaptanib for DMO was in the NICE appraisal programme but that appraisal is currently suspended.43

**Vitrectomy**

Vitrectomy (removal of the vitreous within the eye) is used to treat diabetic eye disease. However, with respect to DMO, it has been stated: ‘Theoretically, vitrectomy should be beneficial in diabetic macular oedema ... but randomised trials have shown little effect. Vitreous traction (demonstrated by OCT) may be a contributing factor in a minority of patients with macular oedema. In this situation vitrectomy may be beneficial.’18

We review the evidence for other treatments in section 7, based on the Ford et al review.39

### 2.6 Critique of manufacturer’s description of the underlying health problem and current service provision.

The manufacturer’s description (sections 2.1 and 2.2) of diabetic macular oedema and its prevalence is brief but adequate.

The submission estimates that there are 2.8 million people with diabetes in England and Wales, of whom 6.6% have clinically significant DMO, giving a figure of 182,000. This is higher than the estimate by Minassian et al,17 but as noted above, the Minassian figure may be an under-estimate.

The Alimera description of current service provision makes a number of assertions. One is that; “The existing clinical pathway is highly individualised based on the progression of DMO, response and acceptability of the various treatments, the guidance of individual trusts, and the practices of each ophthalmologist”.

The ERG has no reason to doubt this. The submission also notes that laser photocoagulation therapy is the current standard of care. This is probably still correct but may be changing. However we are more dubious about the statement that;
“For patients who are insufficiently response (to laser), therapies available to retinal specialists vary. Some trusts allow only laser photocoagulation and with an insufficient response, provide support via low vision aids and blind registration. On rare occasions, in other trusts, insufficiently responsive patients are given therapies such as triamcinolone acetonide or bevacizumab on a case-by-case basis”.

The ERG view is that treatment with bevacizumab is no longer rare. Our impression is that many ophthalmologists are using bevacizumab if patients do not respond sufficiently to laser, and indeed some may be using it instead of laser. A rapid survey amongst Scottish retinal experts found that over 60% were using it regularly, with a few using it on an “exceptional” basis requiring submission of an exceptional case form to management.

During the pre-appraisal consultation, NICE observed that bevacizumab was used in DMO despite the lack of a marketing authorisation. The Commissioning Support Appraisals Service (CSAS) recommended that bevacizumab should be included as a comparator.

The report of a NICE workshop in July 2010 stated that; “Bevacizumab is regarded as an appropriate treatment option for AMD and non-AMD conditions”.

A useful outline of current treatment has been provided by Cunha-Vaz.

**Present view of DME Treatment**

![Diagram of DME treatment]

Figure 2. Present view of DMO treatment
2.7 Critique of comparators

A key point in the submission is that fluocinolone is intended to be used if laser treatment has not been sufficiently effective. The ERG assumes that fluocinolone would also be used when there were contraindications to laser, such as in ischaemic DMO.

The licence (May 20120 states that fluocinolone is indicated for chronic DMO. Section 4.1 does not give a duration, but section 5.1 implies 3 years. The licence also states that fluocinolone should be used when DMO is “insufficiently responsive to available therapies.”

Section 4.2 states that;
“Only patients who have been insufficiently responsive to prior treatment with laser photocoagulation or other available therapies for diabetic macular oedema should be treated with ILUVIEN.”

There is therefore an implication that all other available therapies should have been tried. The ERG assumes that these include systemic therapies, laser and the anti-VEGF drugs such as bevacizumab.

The ERG also note that section 4.2 says “laser or other available therapies” implying that laser need not be used, which is appropriate given that there are some contra-indications to laser.

A key issue is the definition of “insufficiently responsive”. Appendix 9 states that the FAME studies enrolled people who had received previous laser therapy but who had increased central retinal thickness and baseline VA ranging from 19 to 68 ETDRS letters.

The manufacturer states (p160);
“Since the FAc implant is not indicated as first line therapy in the context of the clinical pathway in the UK, the main comparator is optimised standard of care.”

And continues;
“optimised standard of care can broadly be defined as no treatment i.e. “watching and waiting” or registering for blindness services and low vision aids and when appropriate, with occasional maintenance laser treatments and in some cases intravitreal injections of triamcinolone or VEGF antibodies (typically bevacizumab).”

The manufacturer has not provided any information comparing fluocinolone against triamcinolone or the anti-VEGF drugs, bevacizumab and ranibizumab. This is contrary to the final scope from NICE, dated February 2012, which included other steroids and anti-VEGF therapy as comparators. However
if fluocinolone is to be positioned for use when other therapies have failed, or been contra-indicated, then the choice of comparator in the submission may be justified.

### 2.8 Critique of outcomes

The manufacturer aims to provide information on the following outcomes:

- Best corrected visual acuity
- Proportion of people receiving subsequent photocoagulation
- Central retinal thickness measured by OCT
- Adverse events

The NICE scope included mortality as an outcome. The manufacturer does not believe that mortality is an appropriate measure, and notes that it was not an outcome in the FAME trials.

The manufacturer does not provide data on quality of life directly from the FAME trials, but uses existing data on utility by VA.

The ERG does not regard macular thickness as an outcome of importance to patients. It is useful as a guide to management but cannot feed into cost-effectiveness analysis.

BCVA is presented in two main ways. Firstly, it is reported as proportions of patients who gain (or lose) significant amounts of vision, with gains of 15 or more letters being regarded as a good outcome. Secondly, BCVA is reported as changes in mean BCVA. The ERG regards the first approach as more useful, and based on previous appraisals, we would regard a gain of 10 letters as good.

The cost-effectiveness analysis is based on the distribution of patients across bands of vision, with each band having a utility value. This is a sound approach and has been used in previous appraisals. If treatment is effective, vision improves and quality of life/utility also improves. The gains can be expressed in QALY terms.

### 2.9 Equity

The manufacturer does not consider that there are any equity issues.

It is known that the prevalence of diabetes varies by ethnicity, being particularly high among individuals of South Asian, African and African-Caribbean descent. Furthermore, as reported by
Gulliford and colleagues, the prevalence of sight-threatening diabetes eye disease is higher in Africans (15.2%) and African-Caribbeans (14.7%) than in white Europeans (9.4%) because of a higher frequency of diabetic maculopathy.\textsuperscript{45}

The prevalence of type 2 diabetes varies by deprivation being more common among less affluent population, and their glycaemic control is generally poorer.\textsuperscript{46} In addition, Gulliford and colleagues have also reported that attendance for retinopathy is lower in deprived areas.\textsuperscript{45}

Therefore, people from some minority ethnic groups, and those living in our more deprived communities, are at particular risk of developing diabetes and its complications.

### 2.10 Summary of correspondence with NICE decision problem

The submission matches the NICE decision problem in most respects, the main omission being in comparators. However, the draft SPC states that (submission page 176) “Iluvien is indicated for the treatment of vision impairment associated with chronic diabetic macular oedema, considered insufficiently responsive to other available therapies”.

This could be read as saying that it is a treatment of last resort (apart from vitrectomy), in which case it would not be compared with drugs such as the anti-VEGF agents. It should be noted that although the anti-VEGFs are a significant advance, in the DRCR trial\textsuperscript{47} only half of the patients on ranibizumab got improvements of 10 or more letters. In the BOLT study using bevacizumab, 31% gained 10 or more letters.\textsuperscript{48} So many patients do not respond sufficiently to the anti-VEGFs, and we still need better treatments.

### 2.11 The FAME trial

The submission from Alimera refers to two FAME trials, FAME A and FAME B. However, as noted on page 32 of the submission, these were identical trials with a single protocol and registered under one NCT number (NCT00344968). They were done in 101 sites in North America, Europe and India, with FAME A being done in northern sites and FAME B in southern sites, in much the same countries. Several UK centres were involved - Bristol, Southampton and Wolverhampton.

In the published paper by Campochiaro and colleagues,\textsuperscript{25} and in the Alimera submission, they are treated as one trial, and the ERG regards them as one and no separate data will be presented.
It is common for large industry-sponsored trials to be divided into two identical ones and there have been precedents in previous NICE appraisals. This practice probably stems from FDA guidance where it states that;

"With regard to quantity, it has been the FDA’s position that Congress generally intended to require at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness."

The FDA does say that a single trial may sometimes be sufficient but adds;

“A conclusion based on two persuasive studies will always be more secure than a conclusion based on a single, comparably persuasive study.”

The FDA document mentions “independent substantiation” and the original desire may have been for substantiation to be independent of those who did the first trial – which clearly does not happen in most cases where the manufacturer runs both trials.

### 2.12 Dosages

The insert for which the license has been sought contains 0.19mg of fluocinolone, which is designed to release 0.2 µg/day. Three doses have been used in trials.

In the first trial, Pearson and colleagues compared the Retisert device containing 0.59 mg of fluocinolone with standard of care (SOC). Participants had persistent or recurrent DMO previously treated with laser therapy. The SOC group had either laser photocoagulation or observation as decided by the local investigator. The fluocinolone group could also have laser if required. The Retisert implant was designed to release 0.6 µg/day initially, decreasing to 0.3 - 0.4 µg/day after a month or so, lasting for about 30 months.

The primary outcome was the proportion gaining 15 or more letters. This was significantly higher for the fluocinolone group at most time points. At six months, 17% of the fluocinolone group and 1.4% of the SOC group achieved it. The difference was not significant at 12 or 15 months, partly because VA in the fluocinolone group declined, partly because the proportion achieving 15 letters in the SOC group rose. The fall in VA in the fluocinolone group was due to cataract development which had not occurred earlier. After removal, VA improved again. 91% of those phakic at baseline had had cataracts extracted by 4 years after enrolment, compared to 20% of phakic patients in the SOC group. By 3 years, there was no significant difference in VA, partly because the fluocinolone had run out, partly because the SOC group had improved. 41% of the SOC group and 16% of the fluocinolone one had laser therapy.
The most troublesome adverse event was raised intra-ocular pressure. IOPs of 30mm Hg or over were seen in 61% of implanted eyes, but only 6% of SOC eyes.

So the Retisert dose was effective but caused too many adverse effects. It was a different device, requiring surgical implantation, unlike the Iluvien product which is injected. An application for a European licence for use in uveitis was withdrawn in 2007. For the purposes of this report, Retisert can be forgotten.

In the FAME trial, two doses were used, aiming at 0.2 µg and 0.5 µg daily, being referred to as low dose and high dose inserts. There were little or no differences in VA gains, but the high dose was associated with more cataracts and more glaucoma. Surgery to relieve IOP was required in 8.1% of the high dose group, 3.7% of the low dose group and 0.5% of the sham group.

So the 0.5 µg/day dose has been consigned to history, and no details of results with that are included in this ERG report.

The Iluvien device is designed to release fluocinolone into the eye very slowly, after an initial burst. The diagram below is Figure 4 from the Alimera submission (Error! Reference source not found.). The data for the first year is in the public domain in the published paper by Campochiaro et al. The graph shows that after initially higher levels, there is a slow and steady release of fluocinolone.
3. CLINICAL EFFECTIVENESS; SUMMARY AND CRITIQUE OF MANUFACTURER’S SUBMISSION

The manufacturer based their clinical effectiveness section on the FAME trial.

Sources:
The main industry submission omitted a considerable amount of relevant data, and we used the following other sources in addition

- The main publication from the FAME trial by Campochiaro et al.,25. This did not report separately on the chronic DMO subgroup but provided useful background.
- The FAME clinical trial reports, condensed into two integrated documents, one on efficacy, one on safety. These were provided by Alimera.
- Alimera also provided a copy of their responses to queries raised by MHRA in an appendix to their “Specification of evidence” submission to NICE in October 2009, referred to hereafter as “Alimera Responses”.
- Alimera also provided responses to an unusually large number of clarification questions. As a result of some of the ERG’s questions, Alimera provided a new economic model, described later. We refer to the information from the responses to clarifications as “Alimera clarifications”. Clarifications were still being received late in the 8-week period in which the ERG report had to be produced.

3.1 Description of FAME trial

3.1.1 Design and quality

Two identical randomized, double-blinded, sham injection-controlled, parallel-group, multicenter studies known as Fluocinolone Acetonide for Macular Edema (FAME) studies (FAME A and FAME B) were conducted for over 36 months to study the efficacy and safety of intravitreal inserts releasing 0.2 µg/day (low dose) or 0.5 µg/day (high dose) fluocinolone acetonide in patients with diabetic macular oedema (DMO). The manufacturer submission only considered the 0.2 µg/day (low dose) of fluocinolone.

3.1.2 PICO

Population

The FAME studies were conducted at 101 sites in North America, India and the European Union. A total of 956 patients aged between 19 and 85 years with central retinal thickness of ≥250 µm despite at least one prior focal/grid macular laser photocoagulation treatment, and best corrected visual acuity (BCVA) in Early Treatment Diabetic Retinopathy Study (ETDRS) letter score between 19 and 68...
(Snellen equivalent range, 20/50 – 20/400) were recruited. Patients were randomized in a 2:2:1 ratio stratified by baseline BCVA (<49 and ≥49 ETDRS letters) and centre to 0.2 µg/day fluocinolone intravitreal insert (N=376), or 0.5 µg/day fluocinolone intravitreal insert (N=376) or sham injection (N=185).

The Alimera submission only considers a subgroup of patients with chronic DMO, defined as DMO diagnosed for ≥3 years and insufficiently responsive to available therapies. The manufacturer states that the subgroup analysis was pre-planned (though we note that the EU trial registration said that no sub-study was planned.”

A significant treatment effect was found in only those patients treated with the fluocinolone implant who had been diagnosed with DMO for ≥3 years. Therefore, the total number of patients with chronic DMO included in the submission was 321 (209 in 0.2 µg/day fluocinolone arm and 112 in sham arm).

In the manufacturer’s submission, details regarding baseline characteristics of the patients with chronic DMO are given in section 5.3.4 and Table B6. For convenience, Table B6 has been reproduced below as Table 2. Additional baseline characteristics of these patients were obtained from the clinical trial reports (CTRs) that were provided by the manufacturer on request and these are included in Table 2.
In the Alimera responses document, the manufacturer states that during protocol amendment, for a short period, patients who had not received prior laser therapy were allowed to participate in the trial. The manufacturer states that ‘Because few subjects in each group (N=5 in sham and N=15 in the 0.2 µg fluocinolone group) were enrolled without prior laser, the results are inconclusive; however, there is no indication that enrolment of these subjects inflated the visual outcomes for the overall study’. In the trial, overall 96.3% of patients received prior laser treatment. 91.7% of patients (sham: 91.9%; fluocinolone: 92.6%) had received prior focal/grid laser while 18.6% of patients (sham: 20.5%; fluocinolone: 16.5%) had received pan-retinal photocoagulation. In 3.9% of patients (sham: 3.8%;
fluocinolone: 1.9%) prior laser was unspecified. It is stated that ‘subjects could be counted in more than one category of prior laser treatment’.

The groups were well matched at baseline.

*Intervention:* the 0.2 µg/day fluocinolone intravitreal insert. Only one eye was treated. In 25 of cases, the better seeing eye was treated. The published paper reported that a standard procedure was used for injections that included ‘application of topical anaesthetic, insertion of a lid speculum, cleaning the conjunctiva with povidone-iodine, and pressure on the injection site for approximately 2 minutes with a povidone-iodine- and lidocaine-soaked cotton tip’. It is reported in the published paper that ‘the implant was inserted into the vitreous cavity through a 25-gauge needle in an outpatient clinic’.

*Comparator:* sham injection. The same standard procedure used to insert fluocinolone was followed. *The hub of a syringe was pressed against the conjunctiva to simulate administration of the insert.*

There were 18 visits over the 36 months period performed at week 1, week 3, week 6, month 3 and quarterly thereafter. Retreatment was permitted any time after the month 12 assessments provided the subject met retreatment criteria i.e. loss of vision of ≥5 letters or an increase in the CMT of ≥50 microns as compared to the subject’s best status in the previous 12 months. Laser photocoagulation was permitted as needed after week 6. Approximately 61% of the sham treated group and 41% of the fluocinolone treated group received laser during the study. No details are given of the exact form of laser given as rescue after treatment with fluocinolone. Patients also received other intravitreal off-protocol treatments (OPT) at the discretion of the investigators. Details of this will be discussed under results section.

*Outcomes:* The primary outcome was the proportion of patients with an improvement of 15 letters or more from baseline BCVA. Mean change in BCVA was a secondary outcome.

Other outcome measures included mean change in excess retinal thickness, % with 3 step worsening of ETDRS grade and % requiring laser. The change in retinal thickness is not an outcome relevant to patients or cost-effectiveness analysis and therefore will not be discussed further.

### 3.1.3 Quality assessment

The trial appeared to be of high quality, according to the Cochrane risk of bias table (Appendix 2).
One possibility is that the fluocinolone insert might be detected as a floater and thereby unmask patients in the fluocinolone group, but the frequency in the sham group probably removes this risk. Floaters were reported at any site in % of the sham group and % of the fluocinolone group in the CTR integrated safety section (page 1664), but in Table 12 figures are reported separately for study eye of % for fluocinolone and % for sham groups. The manufacturer also commented that floaters were common in people of the age group recruited, and in those with diabetic retinopathy.

3.2 Results

Some of the details given below are from the Alimera responses document.

3.2.1 Proportion of patients with chronic DMO with ≥15 letter increase from baseline BCVA

The manufacturer gives details of patients achieving an improvement of 15 letters or more in section 5.5.1, Figure B2 and Table B10 of the submission and Table 29 of the Alimera responses document. Table 3 is the simplified version of those given in the submission. For convenience, Figure B2 has been reproduced below as Figure 4.

Table 3. Proportion of patients with a DMO duration ≥3 years who had a ≥15 letter increase from baseline in BCVA

<table>
<thead>
<tr>
<th>% with ≥15 Letter Improvement in BCVA</th>
<th>0.2 μg/day fluocinolone (N=209)</th>
<th>Sham (N=112)</th>
<th>Difference* (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Month 24</td>
<td>34.4%</td>
<td>13.4%</td>
<td>21.1%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Month 36</td>
<td>34.0%</td>
<td>13.4%</td>
<td>20.6% (29.6, 11.6)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*0.2 μg/day fluocinolone minus sham

Highlighted figures are from the Alimera responses document.

The proportion of patients achieving ≥15 letter improvement was significantly higher with fluocinolone than with sham at all time periods (Table 3). The proportion of patients achieving an improvement of 15 letters or more with fluocinolone peaked at 30 months. (Table 3 and Figure 3). The 36 month lowering is not unexpected because the insert lasts for around 30 months, though there is no dramatic dropping off, suggesting that treatment may not need to be repeated at exactly 36 months, but might be based on BCVA. We raised this during the clarification process.

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Figure 3 below is taken from the industry submission, figure B2, and shows the percentages achieving 15 or more letters in each arm. (Please ignore the higher fluocinolone dose arm).

![Graph showing percentages of patients with ≥15 letter increase from baseline BCVA over time in different treatment groups.]

Figure 3. Percent (ASE) of Subjects with Chronic DMO with ≥15 Letter Increase from Baseline BCVA

As mentioned above, approximately **% of patients in the sham group and **% of patients in the fluocinolone group received laser therapy during the study. The proportion of patients with ≥15 letters improvements in BCVA by use of laser is given in Table 18 of the Alimera responses. For convenience, it has been reproduced below (Error! Reference source not found.)

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Some data from Aimera responses document.
The ERG wondered why patients would be treated with laser during the trial when they had apparently been insufficiently responsive to laser before entry. However Alimera clarified this by noting that recruits to the FAME trial were not required to be insufficiently responsive to laser, since the concept of “insufficiently responsive” arose from the subgroup analysis based on duration of DMO at randomisation.

As noted earlier, many patients had laser or other off-protocol treatments during the trial, and may have benefitted from those. Table 6 of the Alimera responses document has details regarding the proportions of patients with an improvement of 15 letters or more in those who had only received one study treatment, and without off-protocol treatments and/or laser. It has been reproduced below (Table 4).

Table 4. Comparison of the number (%) of patients with a ≥15 letters increase from baseline in BCVA (integrated duration of DME ≥3 year subgroup, observed cases, receiving only one fluocinolone treatment) (Source – Alimera responses)
3.2.2 Mean change BCVA in patients with chronic DMO

The findings on mean change in BCVA are given in section 5.5.1, Figure B3, Table B10 of the manufacturer submission and Table 30 of the Alimera response document. For convenience, those results have been summarised as Table 5 while Figure B3 has been reproduced below as Figure 4.

Table 5. Mean change from baseline BCVA in subjects with chronic DMO

<table>
<thead>
<tr>
<th>Mean Change in BCVA</th>
<th>0.2 μg/day fluocinolone (N=209)</th>
<th>Sham (N=112)</th>
<th>Difference, 95% CI (Figures in brackets are ERG subtractions)</th>
<th>P value</th>
</tr>
</thead>
</table>

The figures in column 4 in italics and brackets are the ERG calculations by simple subtraction. Alimera clarified the differences by reporting that the between treatment differences are derived from an analysis of variance model that include items such as baseline VA and other factors.

The mean change in BCVA was statistically significantly better with fluocinolone than sham at month 30 and 36. At 36 months, there was improvement of 7.6 letters with the fluocinolone implant compared to only 1.8 with sham. An improvement of 15 letters or more is regarded as a good result while a 10 letter improvement is regarded as clinically significant and worthwhile.
Those patients with an improvement of 5 letters or more were eligible for retreatment in the trial. 141 (~67%) patients in the fluocinolone group and 52 (~46%) patients receiving sham injection had improvements of at least 5 letters or more at month 36 (Error! Reference source not found.).

3.2.3 Off-protocol treatments

The details regarding off-protocol treatments are given in section 5.2.1, Table B1 and Table B2 of the manufacturer submission. Table B1 and Table B2 have been reproduced below as Table 6 and Table 7 respectively.

Figure 4. Mean (SEM) Change from Baseline BCVA in Subjects with Chronic DMO

(Source: Alimera responses Table 31)
Table 6. Summary of off-protocol treatments for DMO in subjects with chronic DMO (integrated FAME studies)

<table>
<thead>
<tr>
<th>Off-protocol Treatments</th>
<th>Treatment Group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (N = 112)</td>
<td>0.2 μg/day fluocinolone (N = 209)</td>
<td></td>
</tr>
<tr>
<td>Number of Off-protocol Treatments, n</td>
<td>117</td>
<td>48</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>1.0 (2.0)</td>
<td>0.2 (0.7)</td>
<td></td>
</tr>
<tr>
<td>Minimum, Maximum</td>
<td>0.0, 9.0</td>
<td>0.0, 4.0</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Subjects, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At Least 1 Treatment</td>
<td>39 (34.8)</td>
<td>28 (13.4)</td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number of Off-protocol Treatments by Frequency, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 Treatments</td>
<td>73 (65.2)</td>
<td>181 (86.6)</td>
<td></td>
</tr>
<tr>
<td>1 Treatments</td>
<td>15 (13.4)</td>
<td>16 (7.7)</td>
<td></td>
</tr>
<tr>
<td>2 Treatments</td>
<td>7 (6.3)</td>
<td>5 (2.4)</td>
<td></td>
</tr>
<tr>
<td>3 Treatments</td>
<td>7 (6.3)</td>
<td>6 (2.9)</td>
<td></td>
</tr>
<tr>
<td>4 or more</td>
<td>10 (9)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
</tbody>
</table>

Table 7. Summary of off-protocol treatments for DMO by type of therapy in subjects with chronic DMO (integrated FAME studies)

<table>
<thead>
<tr>
<th>Type of Therapy</th>
<th>Treatment Group</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (N = 112)</td>
<td>0.2 μg/day fluocinolone (N = 209)</td>
<td></td>
</tr>
<tr>
<td>Intravitreal steroids</td>
<td>27 (24.1)</td>
<td>17 (8.1)</td>
<td></td>
</tr>
<tr>
<td>P-value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Posterior sub-Tenon’s steroids</td>
<td>5 (4.5)</td>
<td>1 (0.5)</td>
<td></td>
</tr>
<tr>
<td>P-value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anti-VEGF therapy</td>
<td>17 (15.2)</td>
<td>7 (3.3)</td>
<td></td>
</tr>
<tr>
<td>P-value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vitrectomies</td>
<td>9 (8.0)</td>
<td>9 (4.3)</td>
<td></td>
</tr>
<tr>
<td>P-value&lt;sup&gt;1&lt;/sup&gt;</td>
<td>0.158</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>1</sup>P-value based on Cochran-Mantel-Haensel chi-square test stratified by baseline BCVA.

The number of off-protocol treatments was higher in the sham group than in the fluocinolone group (117 vs. 48). Approximately 35% of patients in the sham group and 13% of patients in the fluocinolone group received at least one off-protocol treatment. The off-protocol treatment included intravitreal steroids (triamcinolone and dexamethasone), anti-VEGF therapy, vitrectomies and posterior sub-tenon steroids (Table 7). In effect, the difference is another indication of the effectiveness of fluocinolone.

### 3.2.4 Re-treatments and rescue laser

Details regarding re-treatment of patients are given on page 61 of the industry submission, Table 33 of the Alimera responses document and the CTR. Table 33 has been reproduced below as Error!

Reference source not found.
Details regarding rescue laser therapies are given in section 5.3.3, Table B10, page 61-62 of the submission, Table 34 of the Alimera responses document and CTR. For convenience, all these have been summarised below as Table 8.

Table 8. Summary of any laser treatments for DMO in patients with DMO duration ≥3 years (Integrated FAME studies) (Source: Alimera responses)

<table>
<thead>
<tr>
<th>Laser treatments</th>
<th>Treatment group</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Sham (N=112)</td>
<td>0.2 µg/day fluocinolone (N=209)</td>
</tr>
<tr>
<td>Number of any laser treatments, n</td>
<td>160</td>
<td>167</td>
</tr>
<tr>
<td>Mean number per subject (SD)</td>
<td>1.4***</td>
<td>0.8***</td>
</tr>
<tr>
<td>Minimum, Maximum</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P-value</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Number of subjects, n (%)</td>
<td>At least 1 laser treatment</td>
<td>68 (60.7)</td>
</tr>
</tbody>
</table>

The mean numbers of any laser treatments in the sham arm and fluocinolone arm were 1.4 and 0.8 respectively. The proportion of patients receiving at least one laser treatment was greater in the sham arm than in the fluocinolone arm.
3.2.5 Quality of life

Quality of life measurement in the FAME trial

The Alimera submission notes (page 38) that the Visual Function Questionnaire-25 (VFQ-25) was used to assess health-related quality of life in FAME. However later in the submission (Table B16, page 75) it is stated that “Utility values were not measured in the trial but were obtained directly from the efficacy data using the method of Brown et al”.$^{53}$

The ERG wondered why the VFQ-25 data from the FAME trial had not been used and asked for the reason during the clarification process – see Box 1.

The VFQ-25 includes 25 questions on different aspects of visual function, with one general health subscale and 11 vision subscales. The latter cover functions such as near and distant vision, driving, social functioning, role difficulties, colour vision, and mental health issues related to vision. Results can be expressed as an overall score of 0 (worst) to 100 (best) or in terms of individual subscale results. For example, figure B12 of the Alimera submission shows the relationship between the overall score, and the driving difficult score, and severity of retinopathy.

A clinically important difference in the VFQ-25 has been reported to be around 4, by Suner et al,$^{54}$ using data from two ranibizumab trials, MARINA and ANCHOR. In those trials, an improvement in visual acuity of 15 letters was associated with improvements in the VFQ-25 overall score of 8.2 and 11.1, and clinically relevant changes were estimated to be 4.3 and 3.90.

In another trial-based analysis (Frick et al),$^{55}$ an improvement of one line (5 letter gain) in a better-seeing eye was associated with an increase in overall VFQ score of 3.65 points. Since an improvement of only 5 letters is not usually regarded as clinically important, this would suggest a clinically important difference in VFQ would have to be higher than 4. Loftus and colleagues$^{56}$ from the Macugen 1013 trial group (pegaptanib in DMO, sponsored by Pfizer, all authors from Pfizer) regarded a change of 5 or more in VFQ-25 as being clinically meaningful. In the Macugen 1013 trial, the mean change in VA, adjusted for placebo response, was 4.8 letters. At 102 weeks, there was small but statistically significant ($p < 0.05$) improvement in VFQ-25 overall score, but no significant difference in EQ-5D.$^{57}$ As Loftus and colleagues$^{56}$ note, it is difficult to show a significant different in vision-related quality of life if the eye treated is the WSE, because QoL depends mainly on the BSE.

It would be useful if we had VFQ-25 changes in people with a 10-letter change in VA. Alimera state that VFQ-25 was not suitable for use in the cost-effectiveness modelling in their submission because it measures overall visual function, which is driven by vision in the better-seeing eye (BSE). In FAME the majority of patients had the WSE treated.
The clinical trial reports, integrated efficacy analysis (page 1628, table ISE.72) provides data on VFQ-25 from the FAME DMO over 3 years group, as shown in **[chart]**.

These figures reflect overall visual function. It would have been useful if the results had been given separately from the patients who had the BSE treated.

**Box 1**

**Clarification question from ERG.** Due to the VFQ-25 having been collected during the FAME trials, and there being a reasonable balance between patients having the WSE and BSE treated within the FAME trials, there would appear to be a direct source of quality of life data available from the FAME trials. Mapping functions exist\(^1\) which could have enabled an exploration of this data and the HRQoL values implied by it. It is not clear why this was not undertaken. Please provide further justification for this lack of presentation and consideration of the trial based HRQoL data.

**Alimera response:**

At the time of initial generation of the model assessment review of the options for patient benefit assessment available to the Company was made. It was decided that there were two options available, namely:

- De novo generation of the data from a utility study of patients with DMO or an ophthalmology condition of similar impact;
- Use of data from peer reviewed publications in similar disease areas.

Given that data from a peer reviewed publication existed, which had been used in a submission to NICE, and the time and cost associated with a de novo exercise was not considered significantly additive to this information, the decision was made to use published data.

A mapping exercise was not considered, as it was recognized that there was not a universally accepted mapping process to convert NEI-VFQ data to utility scores.

\(^1\) e.g. Payakachat et al\(^58\) *Predicting EQ-5D utility scores from the 25-item National Eye Institute Vision*
Function Questionnaire (NEI-VFQ 25) in patients with age-related macular degeneration

The point made by Alimera about there not being a universally accepted mapping process may well be correct. The ERG has not had time to do a full literature review of this topic. We note one paper in diabetic retinopathy\textsuperscript{59} which reports a fairly low correlation between EQ-5D and VFQ-25 (Spearman’s $r = 0.27$). However another, by Frick and colleagues\textsuperscript{55} (from a trial of fluocinolone in uveitis) reports a correlation (Spearman’s rank) between EQ-5D and overall VFQ-25 of 0.52.

The general approach to assessing quality of life was similar to that used in previous NICE appraisals of treatment of eye disorders. If vision improves, so does quality of life. Each visual state (measured by BCVA) has a utility score, and a shift in distribution across vision states will be accompanied by a shift in overall utility. Improvement in vision results in a gain in QALYs.

Using the Brown data seems a reasonable approach, even though Brown and colleagues reported data from age-related macular degeneration. Brown and colleagues used two methods to assess utility, time-trade off (TTO) and standard gamble (SG). The TTO method gave lower scores (overall 0.72) than SG (overall 0.81) and a wider range, of 0.89 for normal or near-normal vision to 0.40 for severe visual loss. The corresponding SG figures were 0.96 and 0.55.

The Alimera submission uses the TTO data from Brown et al.\textsuperscript{53}

One issue which should be noted is that the Brown 2000 study\textsuperscript{53} reports utilities for different bands of visual acuity. VFQ-25 is a measure of visual functioning, and it has been reported that there is only a moderate correlation between visual function and visual acuity.\textsuperscript{55}

In the original Alimera submission, an uplift in utility of 25% is used when both eyes are treated, compared to when only one is treated. The reference cited for this is the second Novartis submission for the ranibizumab STA. However, as the ERG pointed out in the ranibizumab appraisal, no source or rationale was given for this 25% figure.

3.3 Safety

Cataracts

The lens in the eye is normally clear. Cataract is a condition in which it becomes opaque, thereby reducing vision.
Cataracts in diabetes typically present as posterior subcapsular cataracts. Cortical cataracts may also be seen, and less frequently, nuclear opacities. Less commonly, snowflake cortical opacities occur, which may resolve spontaneously or mature within a few days. Posterior subcapsular cataracts affect vision at an early stage.

A 5-year cohort study showed both the incidence of cortical and posterior subcapsular cataract and their progression were higher in people with diabetes. A recent population-based survey from Sweden by Olafsdottir et al., in people with type 2 diabetes, found that visually significant cortical, posterior subcapsular and nuclear cataracts were seen in 65.5%, 42.5% and 48% respectively. Prevalence increased with age. Posterior subcapsular cataract was associated with glycaemic control as reflected in HbA1c.

In type 1 diabetes, Grauslund et al. from Denmark reported that by 25 years after onset, 21% had had cataract surgery. People with type 1 diabetes had cataracts removed on average 20 years younger than non-diabetics. Those with maculopathy were almost twice as likely to require cataract surgery.

Formation of posterior subcapsular cataract is a well-known side effect of corticosteroids, whether administered by topical, systemic, or intravitreal route. Even one injection of a relatively short-acting intravitreal steroid (triamcinolone) can trigger cataract development. Surgical removal usually gives good results, but can have complications. Praveen et al. also showed that steroid-induced posterior subcapsular cataract was associated with a higher risk of developing posterior capsular opacification (PCO) after cataract surgery at the 1-year follow-up, which may require neodymium:YAG (Nd:YAG) laser capsulotomy, or on rare occasions, surgical removal. In the FAME groups, PCO was reported in 3.6% of sham group and 6.7% of fluocinolone group after cataract surgery (data from CTR, not in submission).

Surgical extraction is the only cure for diabetic cataract at present.

The standard surgical technique is now phacoemulsification. It is associated with less postoperative complications, inflammation and astigmatism, and rapid visual rehabilitation compared with extracapsular cataract surgery (ECCE). This is particularly important when earlier cataract surgery in people with diabetes is advisable before the cataract precludes detailed fundus examination.

Although the overall outcomes of cataract surgery are excellent, the Royal College of Ophthalmologists guidelines on cataract noted that patients with diabetes may have poorer vision outcomes than those without diabetes. Cataract surgery in diabetes is associated with a higher incidence of post-operative complications, including higher risk of infection, posterior capsule
opacity, worsening of retinopathy, fibrinous uveitis, induced rubeosis and macular oedema. Stein recently reviewed the literature on adverse events after cataract surgery, and concluded that recent studies showed fewer adverse events, but that people with diabetic retinopathy had a 33% greater risk of complications than those without. Patients with pre-existing proliferative diabetic retinopathy had a 62% increased risk of severe complications. The worst outcomes may occur in operated eyes with severe retinopathy and/or pre-existing macular oedema.

One of the most serious complications after cataract surgery is retinal detachment, which occurs in about 0.7%, mostly within the first two years after cataract removal. In the safety data from the FAME trial, it was reported in patients from the sham group who had cataract removed, and in patients in the fluocinolone group. In Table B13 of the submission, it was reported that no patients in either arm had retinal detachment. It is no more common in people with diabetes, but if more cataracts are induced by steroids and more surgery is required, the absolute number of people with complications will rise.

There have been reports of worsening of macular oedema after phacoemulsification, mainly in those with pre-existing retinopathy. There have also been reports that macular oedema after phacoemulsification resolves spontaneously, but that happens mainly in patients who did not have DMO pre-operatively. In those with pre-operative DMO, spontaneous recovery is rare.

**Glaucoma**

Glaucoma is characterised by increased pressure inside the eye – increased intraocular pressure, usually defined as IOP of 21 mm Hg or more. However some people may have signs of damage at lower pressure. The pressure rises because the normal drainage of aqueous fluid is impaired.

The increased pressure can cause progressive damage to the optic nerve, leading to impaired vision and blindness if not treated. Because of the way in which the nerve fibres are damaged, peripheral vision is lost first, with central vision being affected later. There may be no symptoms in the early stages.

Glaucoma is treated by lowering the IOP. Treatment is initially by eye drops, sometimes using several different drugs, but these are not always sufficient and some people will require surgery. Patients in whom IOP rises and in whom surgery is required, will need frequent follow-up visits, perhaps 10 visits in the first year, reducing to 3 visits in year 2 and then 6-monthly. Those at risk of glaucoma due to raised IOP are monitored less frequently, at six monthly intervals, adjusted for their risk of developing glaucoma. However since patients with DMO would be followed up regularly, so not all these visits would be additional.
The main types of glaucoma surgery are trabeculoplasty and trabeculectomy. (NB Not everyone regards trabeculoplasty as surgery.)

Trabeculectomy is the creation of a small hole in the eye to allow fluid to escape in order to reduce raised IOP, in those in whom it cannot be controlled by eye drops, even with two or three types of drops being used. 70% of patients can stop using drops after trabeculectomy. The operation takes about 60 minutes. Frequent visits are required afterwards, weekly at first, to monitor IOP, which can stay too high or fall too low.

Trabeculectomy increases the risk of cataract – about 10% of patients develop one by 3 years. Serious side-effects are rare, and include severe visual loss (about 1 in 1000). Other complications include endophthalmitis (infection in the eye) which can occur years later because the hole remains open, suprachoroidal haemorrhage, and cystoid macular oedema, usually transient. The RCO audit of trabeculectomy\textsuperscript{74} reported early complications in 47% and late complications in 42%. However the most frequent late complication was cataract in 20%, which would not apply in the DMO population because so many have had cataracts removed or are going to.

If trabeculectomy fails, other forms of surgery such as tube drainage are required. For details see Cochrane review by Burr.\textsuperscript{75}

Trabeculoplasty is a much simpler procedure where a laser is applied to the natural drainage system within the eye, leading to an increase in the outflow of aqueous humour. It is an outpatient procedure taking only minutes, though 2-3 hours of post-procedural monitoring is required. It may need to be repeated, perhaps a few years later.\textsuperscript{76}

We have relied on the clinical trial report for safety data because data in the main submission was rather sparse.

It was not clear from the submission how raised IOP was defined in the FAME trial, so Alimera were asked to clarify. Box 2 shows their response
ERG query
A16. There is a statement on page 170 of the manufacturer’s submission that “The rate of IOP ‘elevation considered an adverse event’ (including adverse event reports of ocular hypertension and IOP increased) rose from ****% at Year 2 to ****% at Year 3 in the low dose group”. Please clarify what is meant by ocular hypertension and increased IOP. Is it threshold over 21 mm Hg as used in the exclusion criteria?

Alimera response:
The adverse event terms of ‘ocular hypertension’ and ‘IOP elevation’ were based on the investigator’s judgement. No criterion was established defining an adverse event of IOP increased or ocular hypertension.

Table 9 shows that the prevalence of cataract in this population is high. At the beginning of the study 41.4% of the sham and 45.5% of the 0.2 µg/day fluocinolone group were pseudophakic i.e. had already had an operation for cataract removal and had been fitted with an intraocular lens to replace the natural crystalline lens.

The term “phakic” means that people still have their natural lens.

Table 9. Baseline data for duration of diabetic macular oedema ≥ 3 years

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Sham</th>
<th>0.2 µg/day fluocinolone</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N=112</td>
<td>N=209</td>
</tr>
<tr>
<td>Study eye lens status, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pseudophakic</td>
<td>46 (41.4%)</td>
<td>95 (45.5%)</td>
</tr>
<tr>
<td>Phakic</td>
<td>66 (58.9%)</td>
<td>114 (54.5%)</td>
</tr>
<tr>
<td>Missing</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Pre-existing cataract at baseline, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>47 (42.0%)</td>
<td>88 (42.1%)</td>
</tr>
<tr>
<td>No</td>
<td>14 (12.5%)</td>
<td>25 (12.0%)</td>
</tr>
<tr>
<td>Cannot grade or not applicable *</td>
<td>51 (45.5%)</td>
<td>96 (45.9%)</td>
</tr>
<tr>
<td>Percentage of phakic patients who had a pre-existing cataract at baseline</td>
<td>77.0%</td>
<td>77.9%</td>
</tr>
<tr>
<td>Baseline IOP (mmHg)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>15.2 (2.77)</td>
<td>15.0 (2.03)</td>
</tr>
<tr>
<td>Median</td>
<td>15</td>
<td>15</td>
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<tr>
<td>Minimum, Maximum</td>
<td>(10.0, 21.0)</td>
<td>(8.0, 22.0)</td>
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*Most of these patients have already had cataracts removed.

Of those who were phakic at baseline, 77.0% and 77.9% of the sham and fluocinolone groups respectively had a pre-existing cataract.

The overall mean baseline for IOP pressure was 15.2 mm Hg, and the range was from 8.00 to 22.0 mm Hg.
Error! Reference source not found. presents data extracted from the adverse events listed in the clinical study report for patients with a duration of DMO $\geq$ 3 years. It can be seen that the percentage
of glaucoma reported as an adverse event in the study eye was higher in the fluocinolone group (\textbullet\ in the sham group). Trabeculoplasty or trabeculectomy was reported in \textbullet\% of the fluocinolone group and 0\% in the sham group. Posterior capsule opacification in the study eye was reported in \textbullet\ in the fluocinolone group, compared to \textbullet\ in the sham group study eye, and to 2.7\% in non-study eye.

Myodesopsia (floaters) in the study eye was also increased by \textbullet\ in the fluocinolone group (\textbullet\ vs. \textbullet\ in sham).

There was only one case (\textbullet\ of endophthalmitis reported in the study eye in the fluocinolone group and \textbullet\ in the sham group.

Increased intraocular pressure in the study eye was reported in \textbullet\ of the fluocinolone group compared to \textbullet\ in the sham group. A prior vitrectomy was an exclusion criteria for the trial, but \textbullet\ of patients in the sham arm and \textbullet\ in the fluocinolone arm experienced one during the trial.

New cataracts were reported as an adverse event in the study eye in \textbullet\ patients in the fluocinolone group and \textbullet\ in the sham group (see Table 14). However Table 10 below (also taken from the CTR), shows the cataract related events in phakic subjects, and the numbers reporting ‘any cataract’ in the study eye were higher i.e. \textbullet\ but the numbers in the sham group were the same in both tables. (We do not know the reason for this discrepancy, although it may be due to the difference between the definition of ‘cataract’ and ‘any cataract’).

<table>
<thead>
<tr>
<th></th>
<th>Sham N=66</th>
<th>Fluocinolone 0.2 µg/day N=114</th>
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Table 10 shows that the incidence of any cataract in the study eye in phakic subjects was ??? in the fluocinolone group, compared to ??? in the sham group. The non-study eyes also had an incidence of ??? ??? respectively. Also, ??? of the phakic fluocinolone group had a cataract operation in the study eye, versus ??? in the sham group.

The mean time to cataract reported as an adverse event in phakic subjects in the fluocinolone group was ??? ??? in the sham group. Similarly, the mean time to cataract extraction was less in the fluocinolone group was shorter i.e. ??? ??? versus ??? ??? in the sham group. The reasons are not clear, but one possibility is that the type of cataract induced by fluocinolone is post-capsular which causes symptoms at an early stage.

The distribution of IOP changes from baseline at 12 months are shown in Figure 5. The fluocinolone arm had larger increases

Figure 5. IOP changes from baseline

The mean IOP changes from baseline are shown in Figure 6.

56
It can be seen that the maximum change in the fluocinolone group is much higher than the sham group at all time points, and peaks at 12 months and thereafter gradually declines. The drop after 12 months will be partly due to removal of cataracts and intra-ocular lens implantation. A review by Berdahl\(^7\) reported that cataract removal lowered IOP by, on average, 2-4 mm Hg and that this was sustained for five years. However the reduction is greater in those with higher pre-operative IOP.

A recent study by Mansberger\(^7\) (not included in Berdahl review) also reported a reduction in IOP of 4 mm Hg after cataract removal, sustained for at least 3 years, and greater in those with higher pre-operative IOP.
Table 11. Frequency distribution of patients requiring IOP lowering medications in the study eye

<table>
<thead>
<tr>
<th>IOP lowering medications in study eye</th>
<th>Sham N= 112</th>
<th>0.2 µg/day fluocinolone N=209</th>
</tr>
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[1] for a minimum of 7 days  
[2] Medications must be concurrent usage for a minimum of 14 days

Table 11 above shows the more than twofold use of any IOP lowering medication in the study eye in the fluocinolone group i.e. 36% compared to 15% in the sham group. Also, 18.6% of the fluocinolone group used 2 or more IOP lowering medications compared to 4.5% in the sham group.

At 36 months the mean IOPs were 16.3 mmHg in the fluocinolone group and 15.1 mmHg in the sham group, with an overall change from baseline of 1.5 mmHg and 0 mmHg respectively.

Figure 7 below shows the association between the percentage of patients using IOP medications and a 15 letter improvement in BCVA at any time in the fluocinolone arm. It would appear that the use of IOP lowering medication does not affect the response to fluocinolone for this outcome.
Figure 7. Association between percentage of patients with any use of IOP lowering medications and 15 letter improvement in BCVA at any time in 0.2 µg/day fluocinolone arm

Table 12 shows the IOP related adverse events. It can be seen that elevated IOP was considered as an adverse event in the study eye in ****% of the fluocinolone group compared to **** in the sham group; also ****% of the fluocinolone group had a surgical procedure to reduce elevated IOP, compared to 0% in the sham group.

An elevated IOP in the study eye to over 25mmHg and 30 mmHg was experienced by ****% and ****% respectively in the fluocinolone group, whereas the equivalent figures for the sham group were much lower at ****% and ****% respectively.
Table 12. IOP related events for duration of diabetic macular oedema ≥ 3 years

<table>
<thead>
<tr>
<th>Any report of cataract operation</th>
<th>Sham N=112</th>
<th>0.2 µg/day fluocinolone N=209</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 letter improvement at any time in BCVA</td>
<td>n (%)</td>
<td>n (%)</td>
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</table>

Table 13 and Figure 8 below show the association between any report of cataract operation and a 15 letter improvement in BCVA at any time. The data show that patients in the fluocinolone group who had a cataract operation had better results than those who did not have a cataract operation. An improvement in DMO may not improve vision if the main impairment of vision is due to cataract.

Table 13. Association between any report of a cataract operation and improvement in BCVA at any time.
Cerebrovascular events
The incidence of cerebrovascular events was the same for sham and the FA group.

Conclusions on safety
As expected with any intravitreal steroid (and indeed with systemic steroids) the incidence of cataract is increased. However diabetes itself increases cataract risk, and many patients had had cataracts removed before entry to the trial. Others had cataract at baseline and would have needed extraction at some time, so the fluocinolone only accelerated the process.

Results of cataract surgery are usually very good, but less so in diabetes than non-diabetics, and complications can occur.

There may be a particular niche for fluocinolone in people with DMO who have already had cataracts removed, or in those in whom removal is clearly going to be required at some time. In the latter group, insertion of fluocinolone at the time of cataract surgery may be an option.
Glaucoma is a less frequent but more serious problem. In most patients, it can be controlled with eye drops but a small percentage will require surgery.

Safety monitoring arrangements.
A number of measures have been agreed by the manufacturer and the regulator, as detailed in the extracts below. (Source: Alimera responses document)

3.4 Patients with duration of DMO less than three years.
The Alimera submission includes only patients with duration of DMO of 3 years or more. The licence states that fluocinolone is indicated for chronic DMO but does not define chronic in section 4.1.
However section 5.1 of the marketing authorisation implies that the cut-off is at three years, based on the subgroup in the FAME trial.

We expect that ophthalmologists will define chronic long before 3 years, possibly as centre thickening for longer than 6 months, with nearly all ophthalmologists considering DMO to be chronic by 12 months. Once other treatments have failed, they will wish to try fluocinolone. Hence there may be a mismatch between the marketing authorisation and clinical practice.

All the patients in the FAME trial had had DMO for more than 3 years. The subgroup with duration under 3 years had had DMO for a mean of years, median years, minimum year. So in effect, the subgroup with duration 12 to 35 months may be more akin to those who would be treated in routine care. Table 14 and Error! Reference source not found. What these data cannot tell us is whether there are variations within the short duration group. For example, would fluocinolone be more effective and cost-effective in those with duration of 24-35 months? There are no data in the published paper or the CTRs to answer that question. As far as we know, the manufacturer has not done any analysis of cost-effectiveness of fluocinolone in patients who have had DMO for 24-35 months.

The likely reason for the difference is that in many patients, DMO will resolve spontaneously, and in those in whom it does not, progression to visual impairment is slow. However since Alimera will have the data, it would be worth doing further sub-group analysis, since clinical practice is likely to lead to treatment earlier than 3 years.

Table 14. Number (%) of Subjects with a ≥15-Letter Increase from Baseline in BCVA

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<tr>
<th></th>
<th>Full population</th>
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<tr>
<td>Sham 0.2</td>
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<td></td>
<td></td>
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<tr>
<td>µg/day</td>
<td>N=185 N=376</td>
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<tr>
<td>Month 18</td>
<td>13% 21.3% 8.3%</td>
<td>0.027</td>
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<td></td>
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<td></td>
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<tr>
<td>Month 24</td>
<td>16.2% 28.7% 12.5%</td>
<td>0.002</td>
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<tr>
<td>Month 30</td>
<td>15.1% 31.4% 16.2%</td>
<td>&lt;0.001</td>
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<tr>
<td>Month 36</td>
<td>18.9% 28.7% 9.8%</td>
<td>0.018</td>
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The ERG wondered how the duration of DMO was determined in the FAME trial. Extracts from the Alimera response are shown in Box 3.
In the analyses submitted to Health Authorities to support the registration of the fluocinolone implant an algorithm was employed to calculate the duration of DMO at entry into the phase III clinical trial. This algorithm used the date of diagnosis, provided by the investigator upon randomising a subject into the trial, and the date of randomisation into the trial. Based on these two dates, the duration of DMO at baseline was determined as:

Year of Randomisation minus Year of Diagnosis plus One

This algorithm addresses two goals, which have significant regulatory importance. First, it includes all subjects randomised, where, even if a subject were randomised in the same year as their diagnosis, the duration of DMO would still be one year. Therefore, the duration of disease would not be zero, and the subject would be included in the dataset. Secondly, it creates bias only toward longer duration disease.

While there is a significant amount of evidence linking severity of diabetic disease with duration of disease, it is not possible to definitively point to a specific time where the “balance” in the microenvironment shifts. That is, as the role of inflammation grows, one would expect that a point may be reached where “harm or damage” begins to accumulate in the microenvironment. This point will be different for every patient. Once the balance has been tipped, the accumulation of damage will be such that new factors become important for consideration in the treatment of the disease which may not have been as important earlier in the disease.

**Efficacy Analysis Using an Alternate Method of Calculation of Duration of DMO**

With this perspective regarding the algorithm employed to support the marketing application, it is relevant to consider another algorithm as the use of the FAc implant in clinical practice is initiated. This algorithm most closely reflects the exact date reported by retina specialists, and serves as a sensitivity analysis to the effects of methodology for assessing duration of disease.

Thus, based on this method, which accounts for every subject enrolled in the FAME studies, the median duration of diagnosis of DMO was 3 years.

Using the original method, the median duration of DMO was 3 years, with 416 subjects having a duration < the median, and 536 subjects having a duration ≥ the median. Based on the new approach, 475 subjects fall below the median and 477 subjects fall above or equal to the median. A concordance/discordance analysis of subjects above and below the median using these two methods is presented in the table below.

Kappa is a measure of agreement ranging from -1 (complete discordance) to +1 (complete concordance). A value of 0.8508 represents very high agreement. The p-value confirms that we can reject the null hypothesis of no agreement, i.e., there is agreement. A significant number of subjects stayed in their original category. This indicates that the assignment to DMO subgroup is fairly insensitive to the method used in calculating the duration of DMO.

| Concordance/Discordance Analysis of Subjects Above and Below the Median by Method of Calculation of Duration |
|---|---|
| Original Method | New Method |
| < 3 years | □ | □ |
| ≥ 3 years | □ | □ |
| kappa | □ | □ |
Using this method for analysis of the primary outcomes in FAME A and FAME B, the relationships between sham and the fluocinolone implant groups for subjects with duration of **[blank]** at randomisation are the same as those found for using the initial method for calculation of duration of DMO.

Hence dating of DMO was left to individual investigators. This could have been based on date of first diagnosis of DMO, or date when symptoms were first noted by patients.

However, although different methods can be used to estimate the duration of DMO can be used, the results are similar. It would be unrealistic to assign precise dates unless frequent OCT was carried out.

The Alimera methods seem acceptable to the ERG.

Some key points regarding duration are;

- The marketing authorisation does not specify a duration at which DMO becomes chronic.
- Clinical opinion is that it would be wrong to wait for three years.
- Fluocinolone would be used after other treatments had failed to achieve a sufficient response, which would take time.
- The alternative system of estimating duration gives a [blank] Using that as the cut-off gives similar results to the original analysis, with those having durations under [blank] years showing no benefit from fluocinolone over sham, largely because the short-duration sham group had much better results than the longer duration sham group.
- NICE might wish to consider applying a short duration of DMO than the 3 years in the original submission, of, say 2 years.
- It would be useful if Alimera could provide ICERS for durations in bands of six months: 12 to 17; 18-23; 24-29; 30-35, for the original analysis, so that the threshold of cost-effectiveness by duration could be determined.

3.5 Conclusions

As shown above the patients in the sham group received other therapies, and the term used to describe their care in the manufacturer’s submission is “standard of care” (SOC).

Almost 52% of patients in the fluocinolone group had gains of 10 or more letters compared to just under 30% in the SOC group. 34% of the fluocinolone group and 13% of the SOC group achieved the primary outcome of a gain of 15 or more letters. The second outcome of mean BCVA showed little change in the sham group (1.8 letters) but improved by 76 letters in the fluocinolone group. The apparent inconsistency in these results (over 13% gaining over 15 letters with sham but little change...
in mean VA) is explained by the number of sham patients who lost vision – 26% lost 5 or more letters.

So fluocinolone is clinically effective in this group of patients, though it has to be noted that almost half had no clinically significant gain in VA (defining clinically significant as 10 letters).

**Commentary on responses to clarification from Alimera**

One of the most important responses was in the opening paragraph from Alimera (See Box 4).

**Box 4**

As a result of addressing the questions posed by the ERG, an important finding emerged related to the population eligible for treatment with the FAc implant. Namely, as a result of addressing question A 20, it became clear that *** of the chronic DMO population has bilateral chronic DMO. In the original submission, we used the assumption of 35% bilateral involvement based on the NICE TA237 submission for ranibizumab for DMO.

This finding supports the chronic nature of the population eligible for treatment with the FAc implant and is an important aspect of any cost effectiveness assessment.

As part of addressing certain questions posed by the ERG, the original model was updated, and as part of this new finding, a new version of the model has been created. Based on these findings regarding bilateral involvement, we are proposing a new base case. The original base case (Version A) and the new base case (Version B) are presented in the table below:

<table>
<thead>
<tr>
<th>Version A – required changes per NICE comments</th>
<th>Version B – all potential changes based on NICE comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fixed programming error in mortality calculation (B7)</td>
<td>Fixed programming error in mortality calculation (B7)</td>
</tr>
<tr>
<td>New methodology for mortality calculation (presented as sensitivity analysis in B8)</td>
<td>New methodology for mortality calculation (presented as sensitivity analysis in B8)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Per initial base case</th>
<th>35% bilateral treatment</th>
<th>**** bilateral treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>25% HRQL uplift for bilateral Tx</td>
<td>HRQL uplift of 10% for bilateral Tx (currently presented as sensitivity analysis in B4 – note that this is based on **** bilateral Tx, not 35%)</td>
<td></td>
</tr>
<tr>
<td>Retreatment based on 5 letter gain</td>
<td>Retreatment based on 10 letter gain</td>
<td></td>
</tr>
<tr>
<td>Utilities from Brown</td>
<td>Weighted average Heintz utilities</td>
<td></td>
</tr>
</tbody>
</table>

The re-treatment based on 10-letter gain was requested by the ERG on the basis that a gain of only 5 letters might not be regarded as clinically significant. The key new issue in the second model is the proportion having bilateral treatment. The ERG has therefore examined this in the next section.
**Bilateral treatment.**

In the FAME trial, fluocinolone was a novel and unproven treatment for DMO, and no patients had both eyes treated with fluocinolone. This would not apply in routine care. So for cost-effectiveness considerations, we need to consider what proportion of people might need both eyes treated.

The original Alimera submission (page 116) gives a figure of **40%** for bilateral treatment in the fluocinolone arm (shaded as CiC) and 35% in control arm. Of the three references cited, two are incorrect – Hirai and Mulnier are mortality studies. The third is TA 237. In that, NICE assumed, based on expert advice, that 25-30% of patients would need both eyes treated.

The second model from Alimera assumes that **50%** of patients will require bilateral treatment. This appears to be based on an assumption that all patients with DMO will require treatment. We think this is incorrect, because only patients with visual impairment (VI) will be treated.

Experience with previous appraisals, and expert opinion, suggest that the proportion requiring bilateral treatment will be less than **30%**. However trials used in previous appraisals did not give details of duration of DMO, and the focus on the chronic DMO subgroup, insufficiently responsive to previous therapies, in the Alimera submission means that extrapolation from earlier trials in broader groups, may not be appropriate. Nevertheless we know from FAME that cataract at baseline was common, and so not all of the visual impairment (VI) would have been due to DMO.

**ERG estimates of numbers requiring bilateral treatment.**

Table 15, produced by the ERG from Alimera data, shows the numbers in different BCVA bands from the four groups at baseline. VI is taken as VA <75 letters.
Table 15. Bilateral visual impairment based on BCVA in untreated eyes

<table>
<thead>
<tr>
<th>BCVA untreated eye</th>
<th>Fluocinolone, WSE treated</th>
<th>Sham, WSE treated</th>
<th>Fluocinolone, BSE treated</th>
<th>Sham, BSE treated</th>
</tr>
</thead>
<tbody>
<tr>
<td>75 and over</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>70-74</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>65-69</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>60-64</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
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<tr>
<td>55-59</td>
<td>![ ]</td>
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<td>![ ]</td>
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<tr>
<td>50-54</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
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<tr>
<td>45-49</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>40-44</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>35-39</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>30-34</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>25-29</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>20-25</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>&lt;20</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>Total</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
<tr>
<td>VI</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
<td>![ ]</td>
</tr>
</tbody>
</table>

Hence ** of the ** patients have some degree of VI in the untreated eye – **%. However the proportion requiring bilateral treatment for DMO would be less, for two reasons. Firstly, those who had their BSE treated had some reason why the WSE was not treated with fluocinolone. The reasons (provided by Alimera during the clarification process, in response to question A22) included:

- WSE had BCVA less than 19 letters at baseline
- WSE had macular thickness less than the BSE at baseline
- WSE had elevated IOP prior to enrolment
- Anatomical factors (such as retinal hole) suggested to the Investigator that the WSE could not improve
- WSE had concurrent disease such as retinal or choroidal neovascularisation due to macular degeneration
- WSE had ocular surgery within 12 weeks of screening
- WSE had had vitrectomy
Some of these would be permanent reasons for not treating with fluocinolone but others such as recent cataract surgery would be temporary. Another group could be those who had had laser therapy within 12 weeks of entry were excluded from FAME but would also become eligible over time.

The ERG asked Alimera for a breakdown of numbers excluded for each reason, but that information is not available because it had not been provided to Alimera by local investigators.

Assumption 1. In absence of data, the ERG assumes that most of the WSE’s not treated at baseline will remain excluded, but that some will not. We will assume that one in six will become eligible for bilateral treatment – so 4% of the

Secondly, as noted, not all VI is due to DMO.

Assumption 2. We will assume that 20% of those with VI have that because of DMO.

Another assumption is required. In some studies, about a third of eyes with DMO recover spontaneously over a 6-month period but in those whose DMO has become chronic, lasting more than 3 years, we are assuming that recovery does not occur without treatment.

Assumption 3: in this group, there will be no spontaneous recovery

A further complication is raised IOP. Patients who develop glaucoma in the eye first treated are likely to develop it in the second. However we need to differentiate between glaucoma (IOP high enough to cause visual field loss) and raised IOP. Increased IOP controlled with medication (which was what happened in the majority of patients in the FAME trial) would not necessarily deter ophthalmologists from treating DMO with fluocinolone, especially in the group whose DMO has not resolved after other treatments – i.e. the group expected by Alimera to be those receiving fluocinolone.

If we assume that only those requiring 3 or more IOP-lowering medications, or surgery, after fluocinolone in the first eye, are excluded from fluocinolone for the second eye, then about 15% are excluded.

Assumption 4: 15% of patients will not receive bilateral treatment because of concern about glaucoma risk, based on experience in the first eye.

One problem is that in the Alimera data, we have proportions of untreated eyes with DMO, and proportions of untreated eyes with visual impairment, but not the proportion of untreated eyes with VI due to DMO.
However, the ERG has tried to estimate proportions, based on Table 20 which is derived from data provided by Alimera during the clarification process (in response to questions A17 and A18, and on the flow chart provided in response to clarification question A20.

From Table 15, we know that 68%, 218 patients, had VI in the untreated eye at baseline. All of those who had their BSE treated had VI in the WSE – 73 patients.

So 145 of those who had the WSE treated at baseline, must have had VI in their BSE.

Applying assumption 2 on causes of VI means 116 would have VI due to DMO, and be considered for bilateral treatment.

Applying assumption 4 on IOP, reduces that number by 15%, to 99.

The data from the flowchart on page 35 of the clarification responses provides data on chronicity of DMO in untreated eyes. Some of the untreated eyes did not at baseline have DMO for the 3 years or more, defined as chronic, and would not be treated at that stage. However over time, assuming as above that there will be no spontaneous recovery, at least some will become eligible for treatment. From the flow diagram, we can calculate that 54 of those who had their WSE treated at baseline, will have had DMO for less than 3 years. Some may have VI – we cannot calculate that from the available data. But because of their duration, we can say that they will not be treated at baseline, but there is a strong likelihood that some will need treatment as time passes.

We can also calculate that 41 had no DMO in their untreated BSE.

So for bilateral treatment considerations, we can summarise the estimates as follows (Table 16).

Table 16. Summary of estimate of bilateral treatment

<table>
<thead>
<tr>
<th>Proportion of total group (321 patients)</th>
<th>Bilateral treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSE treated at baseline</td>
<td></td>
</tr>
<tr>
<td>WSE at baseline (240)</td>
<td></td>
</tr>
<tr>
<td>VI due to DMO in BSE (116)</td>
<td>36%</td>
</tr>
<tr>
<td>VI due to other causes (29)</td>
<td>9%</td>
</tr>
<tr>
<td>No DMO in other eye (41)</td>
<td>13%</td>
</tr>
<tr>
<td>DMO less than 3 years in other eye</td>
<td>17%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>0 at baseline; ? over time</th>
</tr>
</thead>
</table>

So the above estimates are inevitably broad indications not precise figures. However we can assume at least 40% will be considered for bilateral treatment at baseline, reduced to 34% after exclusion because of IOP concerns (assumption 4). In addition, some of the 17% with non-chronic DMO at
baseline will progress to chronic with VI. And of the 9% with VI due to other causes, some may also have DMO that progresses, so that after cataract removal, they may develop VI due to DMO.

It should also be noted that in the fluocinolone arm of FAME, by 36 months, the treated WSE had become the BSE in 21% of patients.
4. CRITIQUE OF INDIRECT COMPARISON

Sources: DCRR Protocol B 2008\textsuperscript{41}; Jansen 2011\textsuperscript{79}; industry submission

In the Alimera’s submission, details regarding indirect comparison are given in section 5.7, Table B11 and Table B12.

The manufacturer explains that in designing their indirect comparison two key points were taken into consideration: 1) definition of the comparator arm and 2) the target population in which the comparator was used. Based on UK clinical practice, the manufacturer thinks observation is the best comparator however lack of data meant it could not be used in an economic analysis. The manufacturer also mentions that ‘in the absence of other suitable comparators there was no requirement for blending data from multiple sources by mixed treatment methodology’. Therefore the manufacturer states that indirect comparison against laser photocoagulation monotherapy would probably reflect UK clinical practice best. The target population are patients with chronic DMO insufficiently responsive to available therapies.

The manufacturer then conducted a literature search to find randomised controlled trials that included patients with chronic DMO treated with laser for at least 2 years. The studies were included if one of the outcomes explored was proportion of patients with $\geq 15$ letter improvement from BCVA in the intent-to-treat population.

The manufacturer’s search strategy for RCT evidence (Appendix 9.2.4) did not use MeSH terms and could have been run in EMBASE in addition to PubMed. Despite this it did not miss any useful references that a more comprehensive search would have retrieved. The search strategy for comparator RCT studies (Appendix 9.4.4) also did not use MeSH terms and could have been run in EMBASE. A further criticism is that in order to limit the search to studies which met the inclusion criteria of ‘trials that ran for a minimum of 2 years’, ‘2 years’ was input (line 4) as a free text term. This would miss studies that ran for more than 2 years or indicated the trial length in months (e.g. 24 months).

Only one study (DCRR Protocol B 2008)\textsuperscript{41} met their inclusion criteria and was included in their indirect comparison.

This was a phase 3, multicentre, randomised clinical trial conducted in the United States to evaluate the efficacy and safety of 1 mg and 4 mg doses of intravitreal triamcinolone against focal/grid
photocoagulation in patients with DMO. Eligibility criteria included a) BC electronic-ETDRS VA letter score between 73 and 24 (Snellen equivalent 20/40 and 20/320); b) definite retinal thickening due to DMO on clinical examination involving the centre of the macula assessed to be the main cause of visual loss; c) retinal thickness ≥250 microns in the central subfield and d) no expectation for scatter photocoagulation within the next 4 months. Both eyes of a patient could be eligible for study and therefore a single patient may have two study eyes in the trial. Those assigned to triamcinolone were not allowed to receive laser unless they met specific failure criteria. Primary outcome measure included VA at 2 years. Other outcomes included OCT measured retinal thickness, and safety.

The manufacturer states that the laser arm of the DRCR study was ‘the most relevant and credible laser monotherapy comparator data available’. However, there were approximately 40% laser naïve patients in the trial and randomisation was not done according to duration of DMO. The manufacturer notes that the severity of DMO in the trial population was not severe as compared to FAME studies. In the submission, the manufacturer summarised the trials used to conduct the indirect comparison as Table B11. For convenience, it has been reproduced below as Table 17.

Table 17. Summary of the trials used to conduct the indirect comparison

<table>
<thead>
<tr>
<th>No. trials</th>
<th>References of trials</th>
<th>Intervention</th>
<th>Comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>DRCR Protocol B (DRCR 2008)</td>
<td>Triamcinolone</td>
<td>Sham + Prompt Laser</td>
<td></td>
</tr>
<tr>
<td>FAME Study (FAME Study ISE)</td>
<td>fluocinolone implant</td>
<td>Sham injection and laser as required</td>
<td></td>
</tr>
</tbody>
</table>

The manufacturer compared the following outcomes: the percentage of patients with ≥15 letters increase from baseline BCVA, mean change from baseline BCVA and mean number of laser treatments. In the submission, the summary of these outcomes are given in Table B12. It has been reproduced below as Table 18.
Table 18. Summary of Outcomes for Subjects with Chronic DMO in FAME A+B Compared to DRCR Protocol B – from Alimera submission.

<table>
<thead>
<tr>
<th></th>
<th>DRCR Protocol B Month 24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser photocoagulation arm</td>
<td></td>
</tr>
<tr>
<td>% with ≥15 Letter Improvement in BCVA</td>
<td></td>
</tr>
<tr>
<td>n (%)</td>
<td>N=115</td>
</tr>
<tr>
<td>18%</td>
<td></td>
</tr>
<tr>
<td>Mean Change in BCVA</td>
<td>N=209</td>
</tr>
<tr>
<td>n (%)</td>
<td></td>
</tr>
<tr>
<td>Observed n (SD)</td>
<td>N.A.</td>
</tr>
<tr>
<td>Change n (SD)</td>
<td>59.8 (19.18)</td>
</tr>
<tr>
<td>Mean Number of Laser Treatments</td>
<td></td>
</tr>
<tr>
<td>N=272 (completers)</td>
<td>N=209</td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>2.9 (1.4)</td>
</tr>
</tbody>
</table>

The manufacturer states that no statistical assessment of heterogeneity was undertaken as the data set for the DRCR Protocol B was not published.

The ERG notes that the 3-year results of DRCR were published in 2009 and that there was no need to use extrapolation to get 3-year DRCR data.

The manufacturer states that the fluocinolone implant led to a higher proportion of patients with ≥15 letters improvement from baseline BCVA (34% vs. 18%) than laser photocoagulation. However the proportion in DRCR with 15 or more letters gained was 26% at 3 years, not 18%.

The ERG notes that the 3-year results of DRCR were published in 2009 and that there was no need to use extrapolation to get 3-year DRCR data.

The manufacturer states that the mean change in BCVA from baseline was better in the fluocinolone group than in the laser photocoagulation group (7 letters vs. 1 letter). The correct figure for DRCR at 3 years was a mean gain of 5 letters, not one.

**ERG critique of the manufacturer’s indirect comparison**

The usual reason for undertaking in indirect comparisons is absence of direct head to head trial of the treatments of interest. However in order to conduct these analyses, all the included studies should have a common comparator arm – that can be either placebo or an active treatment. For example, if we wish to compare treatment B and treatment C, then AB and AC trials can be included provided A is a common comparator.

If there is no common arm, then indirect comparison of single arms of different trials may be done. This is referred to by experts in the field as “a naive approach”, and is said to be “a highly unpredictable method for making indirect comparisons, with a very high frequency of statistically significant discrepancies from direct estimates”.80
The ERG believes that the methods used in Alimera’s indirect comparison are not appropriate. There is no common comparator arm to link these trials together. In the DRCR study, there were three treatment groups – 1 mg triamcinolone, 4 mg triamcinolone and laser photoagulation. In the FAME studies, fluocinolone implant was compared against sham + laser. 40% of the patients in the laser arm of the DRCR study were laser naïve whereas patients in the sham arm of the FAME study had chronic DMO unresponsive to available therapies including laser. Patients also received off-protocol treatments including intravitreal steroids (triamcinolone, dexamethasone), anti-VEGF (ranibizumab, bevacizumab) and surgery (vitrectomies). Therefore because of these reasons, indirect comparison of the fluocinolone arm of the FAME study and the control arm of the DRCR study is what is referred to by the experts as a naïve approach.

The ISPOR Good Practice guideline on indirect treatment comparisons suggests that important characteristics of patients and included studies should be provided in a table format. The guideline states that this will help in determining differences across trials and help reduce bias. The manufacturer has provided details of patient or study characteristics in a table format (Table B15). It has been reproduced below.

Table 19. Baseline characteristics of fluocinolone implant treated FAME patients and laser treated patients from the DRCR Protocol B trial

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>FAC implant treated chronic DMO population (FAME)</th>
<th>Laser monotherapy treated population (DRCR Protocol B)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA score (ETDRS)</td>
<td>Between 68 and 19</td>
<td>Between 73 and 24</td>
</tr>
<tr>
<td>Location of disease</td>
<td>Centre involved DMO</td>
<td>Definite retinal thickening resulting from DMO involving the centre of the macula assessed to be the main cause of vision loss</td>
</tr>
<tr>
<td>Prior photocoagulation for DMO</td>
<td>100%</td>
<td>60%</td>
</tr>
<tr>
<td>Duration of diabetes (years)</td>
<td>Mean: 17.9 (SD: 8.3)</td>
<td>15 (median); (25th percentile: 9; 75th percentile: 21)</td>
</tr>
<tr>
<td>Duration of DMO</td>
<td>Mean: 5.1 (SD: 3.12)</td>
<td>Not reported</td>
</tr>
<tr>
<td>Centre point thickness on OCT (µm)</td>
<td>Mean: 456.2 (SD: 165.89)</td>
<td>398 (median) (25th percentile: 329; 75th percentile: 505)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Mean: 63.7 (SD: 8.9)</td>
<td>63 (median) (25th percentile: 58; 75th percentile: 69)</td>
</tr>
</tbody>
</table>

The main differences are in prior laser treatments and duration of DMO. It is worth noting that both these factors would suggest that results might be better in the laser arm, whereas in this indirect comparison, patients did better on fluocinolone.

**Conclusion**

The ERG believes that the indirect comparison undertaken by the manufacturer is of limited value.
5. COST EFFECTIVENESS

In the light of the ERG clarification questions the manufacturer submitted an extensively revised set of model inputs within the same overall modelling framework of the original submission. The manufacturer asks for this analysis to be considered as the new base case.

The ERG report reviews the original submission as the base case. The original submission also contains a number of sensitivity analyses, which are considered in section 5.2.10 below. The extensively revised set of model inputs submitted in the light of the ERG clarification questions is also considered as a further multivariate sensitivity analysis. But given the extent of this it is reviewed within the dedicated section 5.2.11 below.

In places the submission is quite scant, to the extent that some model inputs and assumptions can only be derived from the electronic copy of the model. As a consequence, the ERG review tabulates model inputs and model formula more than would usually be the case.

5.1 ERG commentary on manufacturer’s review of cost-effectiveness evidence

The manufacturer carried out a search for cost-effectiveness studies using appropriate databases (see figure B7 for details), including Medline and Embase, but found no studies suitable for inclusion. There is therefore no review of cost-effectiveness studies of the use of fluocinolone in DMO.

The search strategies for cost-effectiveness (Appendix 9.10.4) and quality-of-life (Appendix 9.12.4) were appropriate although did not report using the British spelling of edema in the MEDLINE/MEDLINE-in-process strategies (oedema).

5.2 Summary and critique of manufacturer’s submitted economic evaluation by the ERG

5.2.1 NICE reference case checklist

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Reference case and TA Methods guidance</th>
<th>Does the de novo economic evaluation match the reference case</th>
</tr>
</thead>
<tbody>
<tr>
<td>Comparator(s)</td>
<td>Therapies routinely used in the NHS, including technologies regarded as current best practice</td>
<td>The model compares fluocinolone with the sham arm of the fluocinolone trial through a direct head to head comparison, and with laser through an indirect comparison. The ERG views the comparison with sham as the more relevant to the NHS. As reviewed in the</td>
</tr>
<tr>
<td><strong>Patient group</strong></td>
<td>As per NICE scope. “Adults with visual impairment due to chronic diabetic macular oedema”</td>
<td>Yes.</td>
</tr>
<tr>
<td><strong>Perspective costs</strong></td>
<td>NHS &amp; Personal Social Services</td>
<td>Yes.</td>
</tr>
<tr>
<td><strong>Perspective benefits</strong></td>
<td>All health effects on individuals</td>
<td>Yes.</td>
</tr>
<tr>
<td><strong>Form of economic evaluation</strong></td>
<td>Cost-effectiveness analysis</td>
<td>Cost-utility</td>
</tr>
<tr>
<td><strong>Time horizon</strong></td>
<td>Sufficient to capture differences in costs and outcomes</td>
<td>A 15 year time horizon is adopted. Given the baseline age of 63 and the 2.45 DMO SMR the model suggests that 58% will remain alive at the end of the time horizon. This may be optimistic (Zhou et al)(^8) The extrapolation assumptions imply that the BCVA continuously evolves over the time horizon.</td>
</tr>
<tr>
<td><strong>Synthesis of evidence on outcomes</strong></td>
<td>Systematic review</td>
<td>Yes.</td>
</tr>
<tr>
<td><strong>Outcome measure</strong></td>
<td>Quality adjusted life years</td>
<td>Yes.</td>
</tr>
<tr>
<td><strong>Health states for QALY</strong></td>
<td>Described using a standardised and validated instrument</td>
<td>No.</td>
</tr>
<tr>
<td><strong>Benefit valuation</strong></td>
<td>Time-trade off or standard gamble</td>
<td>Time trade off. The base case uses estimates derived through a direct time trade off exercise conducted among 72 US patients with AMD and an average age of 74. The values used relate to the BCVA of the best seeing eye.</td>
</tr>
<tr>
<td><strong>Source of preference data for valuation of changes in HRQL</strong></td>
<td>Representative sample of the public</td>
<td>No.</td>
</tr>
<tr>
<td><strong>Discount rate</strong></td>
<td>An annual rate of 3.5% on both costs and health effects</td>
<td>Yes.</td>
</tr>
<tr>
<td><strong>Equity</strong></td>
<td>An additional QALY has the same weight regardless of the other characteristics of the individuals receiving the health benefit</td>
<td>Yes.</td>
</tr>
<tr>
<td><strong>Probabilistic modelling</strong></td>
<td>Probabilistic modelling</td>
<td>No probabilistic cost effectiveness estimates are submitted by the manufacturer. The model contains the facility</td>
</tr>
</tbody>
</table>
for probabilistic modelling. The scatter plot and CEACs are presented for the base case pairwise comparisons.

| Sensitivity analysis | A range of univariate and multivariate sensitivity analyses. |

### 5.2.2 Model structure

The model has 13 health states which are defined by 5 ETDRS letter bands of the BCVA in the treated eye, plus a 14th of death. Within the model structure no distinction is made for whether the BSE is being treated or the WSE is being treated. The model has a 15 year horizon and a quarterly cycle length.

The model has a mixed structure. For the first 3 years or 12 cycles the distribution between health states is drawn directly from the pooled FAME trials’ data. For extrapolation beyond the 3 year point a markov model structure is adopted with transition probability matrices (TPMs) being applied.

The base case assumes that only one fluocinolone administration will occur every 3 years. Retreatment at the 3 year point requires that patients satisfy a responder rule of having improved by at least 5 letters between baseline and month 36. Based upon LOCF of chronic DMO fluocinolone patients satisfied this responder rule. Given the health state distribution in the fluocinolone arm at month 36, the model assumes an equal likelihood of response for each health state.

But of chronic DMO fluocinolone patients had also dropped out of follow-up by month 36. Assuming that drop-outs are also equally likely across all the health states, the responder rate is adjusted by the drop-out rate to yield an estimate of of chronic DMO fluocinolone patients receiving a second treatment. Given the health state distribution in the fluocinolone arm at month 36, this retreatment rate is applied equally to each health state.

Beyond 36 months, those remaining on fluocinolone treatment have a TPM applied to the health state distribution which assumes that 5% of the patients in each health state will improve by 5 letters, and so transfer up to the adjacent better health state every quarter. Subsequent fluocinolone treatments are further conditioned by the baseline to month 36 drop-out rate of to yield fluocinolone treatment estimates 39.1%, 29.7% and 22.6% at years 6, 9 and 12 among those surviving. The patients modelled as discontinuing fluocinolone treatment at years 6, 9 and 12 do not incur the costs of fluocinolone or its adverse events. But they are assumed to continue to receive its benefits in terms of the 5% improving by one health state each quarter.
Beyond 36 months, those discontinuing fluocinolone treatment at 36 months have a TPM applied to
the health state distribution which assumes that of the patients in each health state will worsen by
5 letters, and so transfer down to the adjacent worse health state every quarter.

Beyond 36 months, those in the sham arm also have a TPM applied to the health state distribution
which assumes that 3% of the patients in each health state will worsen by 5 letters, and so transfer
down to the adjacent worse health state every quarter.

All the above is conditioned by age specific probabilities of death, which are applied equally across
the arms and the health states. These are derived from all-cause mortality data, coupled with a 2.45
relative risk of death amongst patients with diabetes and DMO.

The total costs in each arm are estimated on the basis of one eye being treated, as above. These are
then qualified by a 35% bilateral treatment rate. Due to around 15% of patients in the fluocinolone
arm having a raised IOP, the bilateral treatment rate in the fluocinolone arm is reduced to .

A 25% bilateral treatment QALY uplift is also applied to the aggregate QALYs estimated in each
arm, qualified by the 35% and proportions assumed to receive bilateral treatment in the sham arm
and the fluocinolone arm respectively.

5.2.3 Population
The population modelled is patients with visual impairment and chronic DMO.

5.2.4 Interventions and comparators
The manufacturer model compares the fluocinolone arm of the FAME trials with the sham arm of the
FAME trials. The ERG views the comparison between fluocinolone and sham as the main comparison
of interest within the submission.

An additional comparison is made with laser photocoagulation for which data is drawn from the
DRCR41 and an indirect comparison performed. As reviewed in the clinical effectiveness section the
ERG views the indirect comparison with laser to be of poor quality, and the comparison with laser to
be of secondary interest.

5.2.5 Perspective, time horizon and discounting
The model perspective is in line with the NICE reference case with costs being from the NHS and
PSS perspective and benefits being from the patient perspective.
A 15 year time horizon is adopted, with costs and benefits both being discounted at 3.5%.

5.2.6 Treatment effectiveness and extrapolation
Clinical effectiveness estimates for the first 3 years
For the comparison of fluocinolone with sham, for the first three years of the model the patient
distribution is drawn directly from the following trial data (Error! Reference source not found. and
Error! Reference source not found.).
Note that in the above the baseline patient distributions differ slightly between the arms.

For the comparison with laser, data is drawn from the DRCR 2008\textsuperscript{41} with the following changes in BCVA at the four monthly follow up points (Table 20).

Table 20. DRCR clinical effectiveness data ETDRS letters change from baseline

<table>
<thead>
<tr>
<th></th>
<th>Worse by</th>
<th>Same</th>
<th>Better by</th>
</tr>
</thead>
<tbody>
<tr>
<td>15- plus</td>
<td>10- to 14-</td>
<td>5- to 9-</td>
<td>5- to 5+</td>
</tr>
<tr>
<td>4 mth</td>
<td>9%</td>
<td>8%</td>
<td>7%</td>
</tr>
<tr>
<td>8 mth</td>
<td>12%</td>
<td>5%</td>
<td>12%</td>
</tr>
<tr>
<td>12 mth</td>
<td>14%</td>
<td>3%</td>
<td>9%</td>
</tr>
<tr>
<td>16 mth</td>
<td>13%</td>
<td>5%</td>
<td>10%</td>
</tr>
<tr>
<td>20 mth</td>
<td>10%</td>
<td>5%</td>
<td>9%</td>
</tr>
<tr>
<td>24 mth</td>
<td>13%</td>
<td>6%</td>
<td>9%</td>
</tr>
</tbody>
</table>

These percentage changes are applied to the baseline patient distribution drawn from the fluocinolone arm, These are coupled with the DCRC time points of

- 4 months being applied to the 3 month point of the model
- 8 months being applied to the 6 and 9 month points of the model
- 16 months being applied to the 15 and 18 month points of the model
- 20 months being applied to the 21 month point of the model
- 24 months being applied to the 28, 32 and 36 month points of the model

This results in the following (Table 21):
Table 21. Patient distribution for laser to 36 months

<table>
<thead>
<tr>
<th>Year</th>
<th>HS01</th>
<th>HS02</th>
<th>HS03</th>
<th>HS04</th>
<th>HS05</th>
<th>HS06</th>
<th>HS07</th>
<th>HS08</th>
<th>HS09</th>
<th>HS10</th>
<th>HS11</th>
<th>HS12</th>
<th>HS13</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0%</td>
<td>0%</td>
<td>19%</td>
<td>19%</td>
<td>16%</td>
<td>12%</td>
<td>9%</td>
<td>5%</td>
<td>4%</td>
<td>6%</td>
<td>7%</td>
<td>3%</td>
<td>0%</td>
</tr>
<tr>
<td>0.25</td>
<td>5%</td>
<td>7%</td>
<td>14%</td>
<td>14%</td>
<td>13%</td>
<td>12%</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>0.50</td>
<td>7%</td>
<td>7%</td>
<td>12%</td>
<td>13%</td>
<td>12%</td>
<td>11%</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>0.75</td>
<td>7%</td>
<td>7%</td>
<td>12%</td>
<td>13%</td>
<td>12%</td>
<td>11%</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>1.00</td>
<td>8%</td>
<td>8%</td>
<td>13%</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>1.25</td>
<td>8%</td>
<td>8%</td>
<td>12%</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>1.50</td>
<td>8%</td>
<td>8%</td>
<td>12%</td>
<td>13%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>4%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>1.75</td>
<td>9%</td>
<td>10%</td>
<td>13%</td>
<td>13%</td>
<td>11%</td>
<td>10%</td>
<td>8%</td>
<td>7%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>2%</td>
</tr>
<tr>
<td>2.00</td>
<td>10%</td>
<td>9%</td>
<td>12%</td>
<td>12%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>2.25</td>
<td>10%</td>
<td>9%</td>
<td>12%</td>
<td>12%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>2.50</td>
<td>10%</td>
<td>9%</td>
<td>12%</td>
<td>12%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>2.75</td>
<td>10%</td>
<td>9%</td>
<td>12%</td>
<td>12%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
<tr>
<td>3.00</td>
<td>10%</td>
<td>9%</td>
<td>12%</td>
<td>12%</td>
<td>11%</td>
<td>11%</td>
<td>9%</td>
<td>8%</td>
<td>6%</td>
<td>5%</td>
<td>3%</td>
<td>2%</td>
<td>3%</td>
</tr>
</tbody>
</table>

**Clinical effectiveness estimates for extrapolation beyond the first 3 years**

The changes beyond year three are extrapolated from the FAME trial data. This splits the patient data set by arm into responders, those achieving at least a 5 letter improvement between baseline and 36 months, and non-responders. This results in ********* and ********* in the fluocinolone arm, and ********* and ********* in the sham arm.

This data is then analysed on a quarterly basis to determine how many of these patients *********, how many changed by *********, and how many *********. Note that drop-outs within the data are retained through LOCF which may tend to overstate the percentages of patients experiencing no change. This results in the following patient percentages in the fluocinolone arm (Table 22).
And the following patient percentages in the sham arm² (Table 23)

² Note that there is an error within the table supplied by the manufacturer in response to ERG clarification question A23 in that the patient numbers supplied for non-responders in Q11 are 8, 46 and 9 which sums to 63.

³ ERG phrasing, the parallel to patient years
Similarly, among fluocinolone non-responders during the last four quarters of the “patient quarters” had an comparing to having a . These are netted out to yield an estimate of of fluocinolone non-responders worsening by one health state every quarter.

The sham arm data is disregarded and regardless of responder status. This assumption is also applied to the laser arm.

**Other treatments**

During the trial a number of other treatments were also administered. The model assumes that in the UK there will be no use of pegaptanib. The following rates are applied for the first three years as drawn from the clinical trial, with the assumption that thereafter there will be no further use of these treatments (Table 24).

Table 24. Other treatment rates

<table>
<thead>
<tr>
<th></th>
<th>Fluocinolone on treatment</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yr1</td>
<td>Yr2</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4.8%</td>
<td>4.1%</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.9%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

These rates are conditioned by survival in the model to provide the following undiscounted average number of administrations (Table 25). Note that this appears to be the annual average numbers of administrations per patient and not the percentages patients receiving what may be an ongoing treatment.

Table 25. Other treatment administrations

<table>
<thead>
<tr>
<th></th>
<th>Fluocinolone on treatment</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yr1</td>
<td>Yr2</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.9%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

*Rates of cataract extraction in the fluocinolone arm*
The rates of cataract extractions are based upon the rates measured with the FAME trial, extrapolated over the time horizon of the model. This extrapolation is based upon estimating the change in the number of treated eyes which are free of cataract extraction. The number of cataract extractions for a given quarter is the change in the estimated number of treated eyes which are free of cataract extraction during that quarter.

100% of treated eyes are assumed to be cataract free but at risk of cataract at baseline. (NB not as seen in the FAME trial). The number developing cataracts is calculated as the absolute percentage developing cataracts, e.g.: \( \frac{7.66\%}{4} = 1.92\% \) in the first quarter for fluocinolone, plus the absolute number of deaths during the quarter. There may be an argument for conditioning the percentage developing cataracts by the proportion surviving during the quarter, but adding the absolute number of deaths overestimates the number of cataract extractions. For instance, in the first three years the model inputs suggest 49.5% of fluocinolone patients have cataract extraction, while the model estimates 55.2%.

Also, among the chronic DMO patient group around 43% were pseudophakic at baseline, resulting in only 57% being at risk of cataract development. Not taking this into account overestimates the number of cataract extractions.

Also, within the modelling of the fluocinolone arm the rates of cataract extractions are based upon those measured in the fluocinolone arm of the FAME trials. During the extrapolation period every three years a proportion of fluocinolone patients are modelled as discontinuing fluocinolone treatment. For these patients it may be more reasonable to draw their rates of cataract extraction from the sham arm of the FAME trials, though it should be noted that one steroid injection can have a long term impact upon the risk of cataract.

*Rates of cataract extraction in the sham arm*

For the first three years of the model, the rates of cataract extraction are modelled as 7.1%, 8.3% and 7.1%. These are conditioned by survival to give undiscounted annual totals of 7.1%, 8.0% and 6.8% and a total of 21.9% over the first three years. Thereafter a 1.8% annual rate is assumed as drawn from Klein (1995). As in the fluocinolone arm, this rate is conditioned by the declining proportion of patients who are modelled as being free of cataract, coupled with the assumption that 100% are cataract free at baseline.

*Rates of endophthalmitis and retinal detachment surgery*

Rates of endophthalmitis and retinal detachment surgery are calculated on the basis of a rate per intravitreal injection rather than as a rate per arm. A rate of 0.19% for endophthalmitis and 1.03% for
retinal detachment is applied to the number of injections as drawn from trial data. This appears to result in the following rates (Table 26).

Table 26. Rates of endophthalmitis and retinal detachment

<table>
<thead>
<tr>
<th></th>
<th>Fluocinolone on treatment</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yr1</td>
<td>Yr2</td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>4.7%</td>
<td>3.9%</td>
</tr>
<tr>
<td>Ranibizumab</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>1.9%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Dexamethasone</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td>N injections</td>
<td>106%</td>
<td>4.9%</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Detachments</td>
<td>1.1%</td>
<td>0.1%</td>
</tr>
</tbody>
</table>

This results in a modelled 3 yearly rate, without adjusting for survival, of retinal detachment of 1.2% in the fluocinolone arm and 0.9% in the sham arm. During the extrapolation period the 1.03% rate is applied to the proportion modelled as receiving a fluocinolone injection.

Other adverse events

Chapter 6 of the submission does not detail the adverse event rates, but refers the reader to section 5.9.2 of the submission. The adverse event rates applied within the model are as below (Table 27).

Table 27. Adverse event rates

<table>
<thead>
<tr>
<th></th>
<th>Fluocinolone on treatment</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yr1</td>
<td>Yr2</td>
</tr>
<tr>
<td>Glaucoma</td>
<td>0.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Detachments</td>
<td>1.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>IOP med.</td>
<td>25.8%</td>
<td>13.2%</td>
</tr>
</tbody>
</table>

During the extrapolation period the annual rate of glaucoma is 2.64% for those on fluocinolone treatment. A source for this is not given but it corresponds with the annual average within the fluocinolone arm during the trial. The annual rate of glaucoma of 1.18% for those in the sham arm is sourced from Klein et al. Adjusting these rates for survival, and for the 54.1% modelled as remaining on fluocinolone treatment, results in the following undiscounted totals being modelled (Table 28).
Table 28. Other adverse events as modelled

<table>
<thead>
<tr>
<th></th>
<th>Flucinolone on treatment</th>
<th>Sham</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Yr1</td>
<td>Yr2</td>
</tr>
<tr>
<td>Glaucoma surgery</td>
<td>0.5%</td>
<td>2.0%</td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0.2%</td>
<td>0.0%</td>
</tr>
<tr>
<td>Detachments</td>
<td>1.1%</td>
<td>0.1%</td>
</tr>
<tr>
<td>IOP med.</td>
<td>25.7%</td>
<td>12.8%</td>
</tr>
</tbody>
</table>

The above values have been derived from the electronic model and there may be errors in the ERG derivation of these. The figures above differ from those in table B13 of the submission. For example, IOP medications are given in Table B13 as 35.9% and 15.2%. Table B13 says there were no cases of endophthalmitis in the sham group.

**Mortality**

There is limited detail of the treatment of mortality within section 6.3.8.7 of the submission. This notes that the all-cause mortality data is derived from the ONS and that a 2.45 SMR for DMO compared to general population all-cause mortality is derived from coupling the estimates of Mulnier et al\(^\text{20}\) and Hirai et al\(^\text{21}\), as in the NICE STA of ranibizumab for DMO (TA237).

The electronic copy of the model outlines that two exponential annual all-cause mortality risk functions are derived from the all-cause mortality data banded into eight 10 year ranges, stretching from age 14 to 24 up to age 85+. The data underlying these bands is not presented or clearly referenced, but this results in male and female mortality risk functions of:

- Male annual mortality risk \(= 0.00006085 \times \exp(\text{Age}\times0.0853)\)
- Female annual mortality risk \(= 0.00006325 \times \exp(\text{Age}\times0.0762)\)

The intention is that these are pooled in proportion to the male to female split within the trial to give an estimate of the baseline all-cause mortality risk for the baseline average age of 63 years. The SMR for DMO is then applied to this, with the subsequent extrapolation of the mortality risk relying upon a pooled exponential function. Given the baseline age of 63 years this results in 58% of the patient population being modelled as surviving to the end of the 15 year time horizon of the model.

**Bilateral treatment**
A rate of bilateral chronic DMO involvement requiring bilateral treatment of 35% is drawn from the NICE STA of ranibizumab for DMO, as is a 25% uplift to patient benefits for bilateral treatment. These are applied in the sham arm: the total costs with the exception of blindness and monitoring costs are increased by 35% and the total QALYs are increased by 25% of 35%; i.e. by 8.75%.

In the fluocinolone arm of patients experienced raised IOP. In the light of this the rate of bilateral treatment is adjusted to . This rate is applied in the fluocinolone arm: the total costs with the exception of blindness and monitoring costs are increased by and the total QALYs are increased by i.e. by 5.2.7 Health related quality of life

The health related quality of life data of the FAME trials collected using the VFQ-25 is not presented within the submission. The manufacturer draws HRQoL values from Brown et al. Brown et al measured utility through both time trade off and standard gamble among 72 US patients with AMD, the average age of whom was 74 years. Respondents were divided into 5 groups according to the visual acuity in the BSE. For the time trade off exercise patients were asked how long they expected to live, and how much of this survival they would trade for permanent perfect bilateral vision. For the standard gamble, patients were asked what the higher risk of death they would be willing to accept in return for permanent perfect bilateral vision. The values estimated by Brown et al and the values used within the model are as below (Table 29).
Table 29. HRQoL values from Brown et al and used within the model

<table>
<thead>
<tr>
<th>Snellen</th>
<th>TTO</th>
<th>SG</th>
<th>Health State</th>
<th>ETDRS</th>
<th>Snellen</th>
<th>Value used</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/20-20/25</td>
<td>0.890</td>
<td>0.960</td>
<td>HS01</td>
<td>≥ 75</td>
<td>≥ 20/32</td>
<td>0.890</td>
</tr>
<tr>
<td>20/30-20/50</td>
<td>0.810</td>
<td>0.880</td>
<td>HS02</td>
<td>≥ 70 to &lt; 75</td>
<td>20/32-23/40</td>
<td>0.810</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS03</td>
<td>≥ 65 to &lt; 70</td>
<td>20/40-20/50</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS04</td>
<td>≥ 60 to &lt; 65</td>
<td>20/50-20/63</td>
<td></td>
</tr>
<tr>
<td>20/60-20/100</td>
<td>0.570</td>
<td>0.690</td>
<td>HS05</td>
<td>≥ 55 to &lt; 60</td>
<td>20/63-20/80</td>
<td>0.570</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS06</td>
<td>≥ 50 to &lt; 55</td>
<td>20/80-20/100</td>
<td></td>
</tr>
<tr>
<td>n.a.</td>
<td>n.a.</td>
<td>n.a.</td>
<td>HS07</td>
<td>≥ 45 to &lt; 50</td>
<td>20/100-20/125</td>
<td>0.545</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS08</td>
<td>≥ 40 to &lt; 45</td>
<td>20/125-20/160</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS09</td>
<td>≥ 35 to &lt; 40</td>
<td>20/160-20/200</td>
<td></td>
</tr>
<tr>
<td>20/200-20/400</td>
<td>0.520</td>
<td>0.710</td>
<td>HS10</td>
<td>≥ 30 to &lt; 35</td>
<td>20/200-20/250</td>
<td>0.520</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS11</td>
<td>≥ 25 to &lt; 30</td>
<td>20/250-20/320</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>HS12</td>
<td>≥ 20 to &lt; 25</td>
<td>20/320-20/400</td>
<td></td>
</tr>
<tr>
<td>counting fingers</td>
<td>0.400</td>
<td>0.550</td>
<td>HS13</td>
<td>&lt; 70</td>
<td>&lt; 20/400</td>
<td>0.400</td>
</tr>
</tbody>
</table>

The HRQoL value of 0.545 for HS07, HS08 and HS09 is the average of the adjacent HRQoL values of 0.570 and 0.520 values.

No quality of life detriments are applied for adverse events. The assumption is that the HRQoL impact of adverse events is reflected in the BCVA of the treated eye. This does not take into account the disutilities from having to have operations, procedures and attendances.

5.2.8 Resources and costs

Treatment and monitoring

The manufacturer assumes the following treatment and monitoring schedule for the fluocinolone arm and the sham arm (Table 30).
Table 30. Direct drug, administration and monitoring schedule and costs

<table>
<thead>
<tr>
<th></th>
<th>Year 1</th>
<th>Year 2</th>
<th>Year 3</th>
<th>Total Yr1-3</th>
<th>Unit cost</th>
<th>Total Yr1-3</th>
<th>Year 4+</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Fluocinolone on Tx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone injections</td>
<td>1.00</td>
<td>0.00</td>
<td>0.00</td>
<td>1.00</td>
<td>£5,650*</td>
<td>£5,650</td>
<td></td>
</tr>
<tr>
<td>Laser administrations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine OP visit</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>12</td>
<td>£73</td>
<td>£876</td>
<td>4</td>
</tr>
<tr>
<td>OCT</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>12</td>
<td>£53</td>
<td>£636</td>
<td>4</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>£332</td>
<td>£0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Fluocinolone off Tx</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser administrations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine OP visit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OCT</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sham</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Laser administrations</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£150</td>
<td>£340.50</td>
<td>0</td>
</tr>
<tr>
<td>Monitoring</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Routine OP visit</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>12</td>
<td>£73</td>
<td>£876</td>
<td>4</td>
</tr>
<tr>
<td>OCT</td>
<td>4</td>
<td>4</td>
<td>4</td>
<td>12</td>
<td>£53</td>
<td>£636</td>
<td>4</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>3</td>
<td>£332</td>
<td>£996</td>
<td>0</td>
</tr>
</tbody>
</table>

* Includes £150 for administration

**Note that the number of laser treatments exceeds that observed in the FAME trial (1.4).

Within the above table the total costs for years 1 to 3 are undiscounted and not adjusted for survival. The model adjusts these for survival and correctly discounts. Most of the monitoring costs net out between the arms, with the exception of the fluorescein angiography applied over years 1 to 3 in the sham arm which totals £996. Note also that moving off fluocinolone and presumably onto sham does not involve the years 1 to 3 costs that are applied in the sham arm.

Both fluocinolone administration and laser administration are assumed to require one outpatient visit, which is costed at £150 from NHS reference cost BZ23Z – Vitreous Retinal Procedure Category 1. Routine quarterly outpatient monitoring is assumed, which is costed at £73 from NHS reference cost B130 Ophthalmology consultant led follow up face to face. Quarterly OCT is costed at £53 from NHS reference cost RA23Z – Diagnostic imaging ultrasound scan of less than 20 minutes.
The manufacturer draws a unit cost for fluorescein angiography of £278 in 2005 prices from Cruess et al.\textsuperscript{83} This is inflated at an annual 3% to arrive at a unit cost of £332 in 2011-12 prices. The annual indexation at 3% is closely aligned with the PSSRU HSCS over the same period. Coupled with the assumption that all sham arm patients but no fluocinolone arm patients would receive an annual fluorescein angiography during the first three years, this provides an overall cost offset of £924 within the modelling once discounting and survival have been taken into account.

Cruess et al\textsuperscript{84} is a study of the overall economic burden of neo-vascular AMD across a number of countries, with the authorship including a representative from the Southampton Eye Unit. The relevant UK unit costs are reportedly sourced using PSSRU Unit Costs of Health and Social Care (2004)\textsuperscript{84} plus additional medication costs being costed using the BNF, with these being inflated to 2005 costs using an unspecified inflation rate. The £278 is specific to fluorescein angiography, but for current purposes this has to be read alongside OCT being costed at £272, which if applied within the modelling would be inflated to £325. The unit cost of £272 was also applied by Cruess et al\textsuperscript{84} to the following: verteporfin in one eye; verteporfin in both eyes simultaneously; IVT corticosteroids per eye; photodynamic therapy with IVT corticosteroids per eye; and, other specialist visit for treatment for depression.

\textit{Other treatments}

As far as the ERG can determine, the unit cost of the other therapies is as below (Table 31). It appears that no additional administration or monitoring costs were associated with these therapies.

### Table 31. Unit costs of other treatments

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Unit cost</th>
<th>Basis (from electronic model)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triamcinolone (40mg/1ml)</td>
<td>£7</td>
<td>Single injection of 0.1ml</td>
</tr>
<tr>
<td>Ranibizumab (0.5mg/0.05ml)</td>
<td>£742</td>
<td>Single injection of 0.5mg/0.05ml</td>
</tr>
<tr>
<td>Bevacizumab (25 mg/ml, 4ml)</td>
<td>£105</td>
<td>Single injection of 1.25 mg</td>
</tr>
<tr>
<td>Dexamethasone (700 μg)</td>
<td>£870</td>
<td>Single injection of 700 μg</td>
</tr>
</tbody>
</table>

\textit{Adverse events}

Section 6.5.7 of the submission states that the resource use associated with adverse events is based upon previous NICE submissions in DMO but does not reference these, resulting in the following unit costs (Table 32).
Table 32. Adverse event unit costs

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Unit cost</th>
<th>Basis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Raised IOP</td>
<td>£26</td>
<td>3 month treatment with 50% beta blockers, 25% Xalatan and 25% generic latanoprost</td>
</tr>
<tr>
<td>Cataract surgery</td>
<td>£796</td>
<td>BZ02Z - Phakoemulsification cataract extraction and lens implant: Daycase £789 + 2 week dose average cost of antibiotics + NSAID</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>£1,783</td>
<td>BZ23Z - Vitreous Retinal Procedures Cat 1: Non-elective long stay</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>£1,339</td>
<td>BZ22Z - Vitreous Retinal Procedures Cat 2: Non-elective long stay</td>
</tr>
<tr>
<td>Glaucoma procedure</td>
<td>£1,128</td>
<td>BZ17Z - Glaucoma procedure Cat 3</td>
</tr>
<tr>
<td>Vitrectomy</td>
<td>£1,261</td>
<td>BZ22Z - Vitreous retinal procedures Cat 2</td>
</tr>
</tbody>
</table>

For the adverse events requiring a procedure, it is assumed that no further dedicated follow-up visits are required beyond the routine quarterly monitoring assumed for all patients.

The costs of blindness
An annual cost of blindness of £6,298 is apparently based upon a figure of £5,871 for the ongoing costs of blindness applied within the NICE STA of ranibizumab for DMO, though the referencing within the submission is not clear whether this is the ranibizumab manufacturer estimate or the ERG estimate. This is applied to the proportion of patients whose treated eye BCVA falls below 35 letters, which is equivalent to less than 20/200.

5.2.9 Cost effectiveness results
The deterministic base case cost effectiveness results are as below (Table 33 and Table 34):

Table 33. Base case deterministic model results: fluocinolone versus sham

<table>
<thead>
<tr>
<th></th>
<th>QALYs</th>
<th>Cost</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>7.016</td>
<td>£8,939</td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>7.516</td>
<td>£20,270</td>
<td>£11,331</td>
</tr>
</tbody>
</table>
Table 34. Base case deterministic model results: fluocinolone versus laser

<table>
<thead>
<tr>
<th></th>
<th>QALYs</th>
<th>Cost</th>
<th>Net</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laser</td>
<td>6.849</td>
<td>£9,283</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>7.516</td>
<td>0.667</td>
<td>£20,270</td>
<td>£10,987</td>
</tr>
</tbody>
</table>

The above also suggested that sham dominates laser, though as already noted the ERG does not view the indirect comparison with laser as robust.

The probabilistic base case cost effectiveness results are not presented within the submission, but from the model submitted by the manufacturer for the comparison of fluocinolone with sham it appears to be as below (Table 35). Note that as confirmed by the manufacturer response to ERG clarification question B16 within these probabilistic estimates the clinical effectiveness parameters are treated deterministically.

Table 35. Base case PSA treating clinical effectiveness estimates deterministically

<table>
<thead>
<tr>
<th></th>
<th>QALYs</th>
<th>Cost</th>
<th>Net</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>6.124</td>
<td>£15,673</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>7.070</td>
<td>0.946</td>
<td>£39,457</td>
<td>£23,784</td>
</tr>
</tbody>
</table>

The manufacturer also reports the estimates of the probabilities of fluocinolone being cost effective within the pairwise comparisons (Table 36):

Table 36. Probability of cost effectiveness treating clinical effectiveness estimates deterministically

<table>
<thead>
<tr>
<th></th>
<th>Versus sham</th>
<th>Versus laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>WTP per QALY</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

But as in response to ERG clarification question B15 the manufacturer urges caution in interpreting the probabilistic analyses, noting that:

“The particular type of data and assumptions in the model are not ideally suited for use in a PSA and are more suited to deterministic techniques which were the focus of the analysis supporting the submission. This is because the distributions of key parameters such as the number of FAc injections which form the majority of the model costs, but are restricted by the clinical considerations of the submission, will in effect skew PSA sensitivity work. This leads to the values obtained via PSA being inherently different and unreliable compare to those obtained by simpler deterministic techniques. Whilst PSA techniques are typically used in evaluations of models to determine the impact of

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uncertainty in model assumptions, in the case of the adoption of FAc implant it is felt that deterministic is more appropriate."

This may also be the justification for not presenting probabilistic modelling for the revised analyses submitted in the light of the ERG clarification questions.

5.2.10 Sensitivity analyses: original submission

The manufacturer submission presents a range of sensitivity analyses in tables B33 and B34. In the view of the ERG the sensitivity analyses of principal interest are as below (Table 37). Where required, the fluocinolone arm is referred to as fluo, the sham arm as sham, those within the fluocinolone arm remaining on fluocinolone treatment as fluoOnTx and those not receiving fluocinolone due to either having discontinued it or being in the sham arm as OffTx

Table 37. Manufacturer sensitivity analyses

<table>
<thead>
<tr>
<th></th>
<th>Base case</th>
<th>Sensitivity analysis</th>
<th>vs sham</th>
<th>vs laser</th>
</tr>
</thead>
<tbody>
<tr>
<td>SA01 DMO SMR</td>
<td>.</td>
<td>.</td>
<td>£22,655</td>
<td>£16,465</td>
</tr>
<tr>
<td>SA02 Bilateral treatments</td>
<td>2.45</td>
<td>1.93</td>
<td>£21,900</td>
<td>£15,962</td>
</tr>
<tr>
<td>SA03 Bilateral QALY uplift</td>
<td>fluo: sham: 35%</td>
<td>fluo: 35%, sham: 35%</td>
<td>£19,934</td>
<td>£15,173</td>
</tr>
<tr>
<td>SA04 Cost of blindness</td>
<td>£6,298</td>
<td>-20%</td>
<td>£23,505</td>
<td>£17,243</td>
</tr>
<tr>
<td>SA05 Extrapolation</td>
<td>fluoOnTx: +5%, OffTx: -3%</td>
<td>fluoOnTx: 0%, OffTx: -3%</td>
<td>£31,323</td>
<td>£20,785</td>
</tr>
<tr>
<td>SA06 Extrapolation</td>
<td>fluoOnTx: +5%, OffTx: -3%</td>
<td>fluoOnTx: 0%, OffTx: 0%</td>
<td>£46,192</td>
<td>£25,245</td>
</tr>
<tr>
<td>SA07 Extrapolation</td>
<td>fluoOnTx: +5%, OffTx: 0%</td>
<td>fluoOnTx: +5%, OffTx: 0%</td>
<td>£29,580</td>
<td>£19,177</td>
</tr>
<tr>
<td>SA08 Extrapolation</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>£25,465</td>
<td>£17,306</td>
</tr>
<tr>
<td>SA09 Extrapolation</td>
<td>fluoOnTx: +8%, OffTx: -3%</td>
<td>fluoOnTx: +8%, OffTx: -3%</td>
<td>£20,149</td>
<td>£15,056</td>
</tr>
<tr>
<td>SA10 Extrapolation</td>
<td>fluoOnTx: +8%, OffTx: -5%</td>
<td>fluoOnTx: +8%, OffTx: -5%</td>
<td>£18,090</td>
<td>£13,909</td>
</tr>
<tr>
<td>SA11 Extrapolation</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>£25,535</td>
<td>£17,596</td>
</tr>
<tr>
<td>SA12 Extrapolation</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>£25,535</td>
<td>£17,596</td>
</tr>
<tr>
<td>SA13 Extrapolation</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>fluoOnTx: +8%, OffTx: 0%</td>
<td>£25,535</td>
<td>£17,596</td>
</tr>
<tr>
<td>SA14 Fluo drop-out rate</td>
<td>0%</td>
<td>0%</td>
<td>£30,102</td>
<td>£22,869</td>
</tr>
<tr>
<td>SA15 Fluo treatments</td>
<td>100% yr1, 0% yr2, 0% yr3</td>
<td>100% yr1, 21% yr2, 11% yr3</td>
<td>£26,809</td>
<td>£19,757</td>
</tr>
<tr>
<td>SA16 Fluo treatments</td>
<td>100% yr1, 0% yr2, 0% yr3</td>
<td>100% yr1, 21% yr2, 11% yr3</td>
<td>£26,809</td>
<td>£19,757</td>
</tr>
<tr>
<td>SA17 Fluo treatments</td>
<td>100% yr1, 0% yr2, 0% yr3</td>
<td>100% yr1, 21% yr2, 11% yr3</td>
<td>£26,809</td>
<td>£19,757</td>
</tr>
<tr>
<td>SA18 Fluo treatments</td>
<td>100% yr1, 0% yr2, 0% yr3</td>
<td>100% yr1, 21% yr2, 11% yr3</td>
<td>£26,809</td>
<td>£19,757</td>
</tr>
<tr>
<td>SA19 Fluo treatments</td>
<td>100% yr1, 0% yr2, 0% yr3</td>
<td>100% yr1, 21% yr2, 11% yr3</td>
<td>£26,809</td>
<td>£19,757</td>
</tr>
<tr>
<td>SA20 Fluo treatments</td>
<td>100% yr1, 0% yr2, 0% yr3</td>
<td>100% yr1, 21% yr2, 11% yr3</td>
<td>£26,809</td>
<td>£19,757</td>
</tr>
</tbody>
</table>
Within the sensitivity analyses presented by the manufacturer the cost effectiveness estimates are most sensitive to: the extrapolation assumptions; the drop-out rate among fluocinolone responders; the HRQoL values; and, the number of fluocinolone treatments during the first three years.

5.2.11 Sensitivity analyses: in response to ERG clarification questions
As noted in the introduction to this chapter, while the ERG clarification questions did not request that a new model be submitted the manufacturer has submitted a revised model Version_B in response to the ERG questions. This Version_B revises the following model structural elements:

- The averaging between male and female all-cause annual mortality
- The calculation of the quarterly all-cause mortality rate from the annual all-cause mortality rate
- The quality of life uplift for bilateral treatment

and the following data inputs:

- Male and female mortality rates to revise the pooled annual all-cause annual mortality risk at baseline from 0.77% to 1.90%
- The proportion with bilateral chronic DMO requiring bilateral treatment from 35% to ***
- The percentage of those requiring bilateral treatment receiving bilateral fluocinolone treatment from 82.9% to 85.3% due to raised IOP in the initially treated eye, while retaining 100% for the comparator arm
- The quality of life uplift from bilateral treatment from 25% to 10%
- The response rate in the fluocinolone arm from ********************************
- The utility values for the health states being based upon Heintz et al rather than Brown et al

These changes are presented in more detail below. Their overall impact is to revise the base case cost effectiveness estimate for fluocinolone compared to sham from the £22,655 per QALY of the submission to £19,268 per QALY, and for fluocinolone compared to laser from £16,463 per QALY to £17,171 per QALY.

**Structural change 1: Estimating the pooled baseline all-cause annual mortality risk**
The original submission is in effect based upon the 0.77% baseline all-cause mortality risk for a female 63 year old. This ignores the 1.31% baseline all-cause mortality risk for a male 63 year old. Averaging between these based upon 55.6% of the baseline population being male results in a baseline all-cause mortality risk of 1.09%.

**Structural change 2: Estimating the quarterly pooled baseline all-cause mortality risk**
Due to the quarterly model cycle, the original model estimates the quarterly baseline mortality risk as $1 - ((1 - X\%)^{(1/4)})$ where $X\%$ is the pooled annual all-cause mortality risk. In addition to the correction for averaging between male and female all-cause mortality, the Version_B model also changes this calculation to $X\%/4$. This slightly reduces the quarterly all-cause mortality estimate, but the effect is small.

*Structural change 3: Application of the uplift for bilateral treatment*

Within the original model the uplifts to costs and QALYs arising from bilateral treatment are applied in both the fluocinolone arm and the sham arm.

Within the Version_B model the uplifts to costs and QALYs for bilateral treatment are applied in the fluocinolone arm on the same basis as in the original model. But it appears that only the uplift to the costs for bilateral treatment is applied within the sham arm, with the uplift to QALYs being removed.

More specifically, within the CE_Outcomes worksheet of the original model the formulae for adjusting costs for bilateral treatment are of the form:

- $I_{20} = \text{Calc1!AA184*(1+Model Settings!I25)}$
- $K_{20} = \text{Calc2!Z115*(1+Model Settings!I26)}$

for the fluocinolone arm and the sham arm respectively, where cells I25 and I26 of the Model_Settings worksheet contain the relevant rates of bilateral treatment. Similar adjustments are made to the aggregate QALY calculations and are of the form:

- $I_{71} = \text{Calc1!X184*(1+(Model Settings!I25*Model Settings!I30))}$
- $K_{71} = \text{Calc2!V115*(1+(Model Settings!I26*Model Settings!I30))}$

for the fluocinolone arm and the sham arm respectively, where cell I30 of the Model_Settings worksheet contain the 25% QALY uplift for bilateral treatment.

Within the CE_Outcomes worksheet of the Version_B model the formulae for adjusting costs for bilateral treatment remain as above. But the formulae for adjusting QALYs for bilateral treatment are:

- $I_{71} = \text{Calc1!X184*(1+(Model Settings!I25*Model Settings!I30))}$
- $K_{71} = \text{Calc2!V115}$

for the fluocinolone arm and the sham arm respectively.

In other words, in contrast to the original model, the Version_B model suggests that there will be costs and benefits from bilateral treatment in the fluocinolone arm, and costs but no benefits from bilateral treatment in the sham arm.

*Data input change 1: All-cause mortality*
In response to the ERG clarification question B8 querying why life tables were not used, the manufacturer revises the male and female all-cause baseline mortality risks. For a 63 year old female this is revised from 0.77% to 1.90%, and for a 63 year old male this is revised from 1.31% to 3.16%. The impact of this is to increase the estimate of the annual baseline all-cause mortality risk from 0.77% to 1.90%.

Note that the combined effect of this data change and the structural change that corrects the averaging between male and female all-cause mortality increases the pooled baseline all-cause mortality risk from the 0.77% of the original submission to 2.64%.

**Data input change 2: Proportion with bilateral chronic-DMO**

In response to ERG clarification questions A19 and A20 the manufacturer has supplied the following data on the proportions of patients with chronic DMO in the fellow untreated eye split by which eye was treated at baseline (Table 38).
Table 38. Proportions with chronic DMO in the fellow untreated eye

<table>
<thead>
<tr>
<th></th>
<th>Fluocinolone</th>
<th>Sham</th>
<th>Pooled</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BSE untreated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N total</td>
<td>154</td>
<td>86</td>
<td>240</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye developed during trial</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye at some point during trial</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td><strong>WSE untreated</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N total</td>
<td>48</td>
<td>25</td>
<td>73</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye developed during trial</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye at some point during trial</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td><strong>All untreated eyes</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N total</td>
<td>202</td>
<td>111</td>
<td>313</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye at baseline</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye developed during trial</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td>Chronic DMO in untreated eye at some point during trial</td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>***</td>
<td>***</td>
<td>***</td>
</tr>
</tbody>
</table>

(Note: total numbers vary slightly amongst tables depending on how 8 patients with equal vision between eyes are distributed)

Note that the responses to ERG clarification questions A19 and A20 appear to also imply that of patients had their WSE treated and of patients had their BSE treated within the trial. As confirmed by the patient flowchart of the manufacturer response to the ERG clarification questions, the remaining of patients had the same BCVA in both eyes at baseline.

In the light of the above, the Version_B model revises the proportion with bilateral chronic DMO requiring treatment in both eyes from 35% to the pooled with bilateral chronic DMO at baseline.

Note that from the response to ERG clarification question A17 among the who had what was their WSE treated at baseline, the proportion of fellow eyes that were in HS01 and had no visual impairment at baseline was . By definition, among the who had what was their BSE treated at
baseline the proportion of fellow eyes that were in HS01 and had no visual impairment at baseline was 

**Data input change 3: Rate of treatment of bilateral chronic-DMO in the fluocinolone arm**
The Version_B model revises the proportion of those requiring bilateral treatment who receive bilateral fluocinolone treatment from 82.9% to 85.6%. The 85.6% corresponds more closely to the **% of the chronic DMO fluocinolone patients who experienced a raised IOP of more than 30mmHg.

**Data input change 4: QALY uplift for bilateral treatment**
The original QALY uplift for bilateral treatment of 25%, as drawn from the manufacturer submission for the NICE STA of ranibizumab for DMO, is revised to 10%. No justification for this revision is presented, though the manufacturer appears to acknowledge the uncertainty around it by presenting a range of sensitivity analyses in the response to ERG clarification question B4.

**Data input change 5: Responder rate in the fluocinolone arm**
In response to ERG clarification question A26 the manufacturer outlines that **** of fluocinolone patients improved by at least 5 letters between baseline and month 36, and **** of fluocinolone patients improved by at least 10 letters between baseline and month 36. The Version_B model applies the ****10 letter responder percentage.

As in the original submission, within the Version_B model this responder rate is coupled with the ****drop-out rate to result in fluocinolone retreatment rates of **** at year 3. This **** retreatment rate at year 3 is applied equally across the 13 BCVA health states. The rate of fluocinolone retreatment, drug costs and adverse events incurred continues to be conditioned by the drop-out rate, resulting in retreatment rates at years 6, 9 and 12 of **** respectively.

Note that despite the definition of the fluocinolone responders who remain on treatment being changed to a 10 letter responder rule the extrapolation assumptions applied for years 4 to 15 remains unchanged. These are still based upon the 5 letter response criterion, with 5% of those remaining within the fluocinolone on treatment group improving by one health state each quarter and 3% of those in the fluocinolone arm who are modelled as not receiving a second treatment worsening by one health state each quarter.

**Data input change 6: Source of HRQoL values**
In response to ERG clarification question B3, the manufacturer acknowledges that the Brown et al HRQoL values “may not apply to patients having their WSE treated, as occurred for some patients in
the FAME studies”. Coupled with the finding of significant bilateral chronic DMO involvement, the manufacturer revises the HRQoL values that are applied on the basis of a weighted average of the HRQoL values for WSEs and BSEs in Heintz et al.59

Heintz et al59 administered time trade off and EQ-5D by telephone among 152 adult Swedish diabetics. The EQ-5D was valued using the UK social tariff. Respondents were recruited through the Swedish diabetic eye screening programme, and for the more severely visually impaired through two low vision rehabilitation centres. One unadjusted model and two adjusted models were estimated, the adjusted models taking into account various patient characteristics including some of the complications of diabetes. The adjusted models’ EQ-5D results are reported below (Table 39).

Table 39. Heintz EQ-5D adjusted models results

<table>
<thead>
<tr>
<th>BCVA</th>
<th>WSE n</th>
<th>EQ-5D</th>
<th>95% CI</th>
<th>BSE n</th>
<th>EQ-5D</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/10-20/25</td>
<td>99</td>
<td>0.77</td>
<td>0.72-0.82</td>
<td>114</td>
<td>0.78</td>
<td>0.73-0.82</td>
</tr>
<tr>
<td>20/32-20/63</td>
<td>22</td>
<td>0.87</td>
<td>0.76-0.98</td>
<td>17</td>
<td>0.84</td>
<td>0.72-0.97</td>
</tr>
<tr>
<td>20/80-20/160</td>
<td>8</td>
<td>0.78</td>
<td>0.61-0.96</td>
<td>6</td>
<td>0.54</td>
<td>0.34-0.75</td>
</tr>
<tr>
<td>≤20/200</td>
<td>23</td>
<td>0.66</td>
<td>0.53-0.79</td>
<td>15</td>
<td>0.63</td>
<td>0.48-0.77</td>
</tr>
</tbody>
</table>

The manufacturer ignores the values for 20/10 -20/25 on the grounds of non-monotonicity, though it might also be noted that these values have the largest number of respondents and the narrowest confidence intervals. The manufacturer takes a weighted average of the remaining values according to the modelled % of fluocinolone patients that will receive bilateral treatment4: being applied to the WSE values and to the BSE values. This results in the following (Table 40).

---

4 being the proportion of the requiring bilateral treatment adjusted for raised IOP in the initially treated eye.
### Table 40. Heintz EQ-5D adjusted models results as applied within the Version_B model

<table>
<thead>
<tr>
<th>Health State</th>
<th>ETDRS</th>
<th>Snellen</th>
<th>Original</th>
<th>Heintz</th>
<th>Version_B</th>
</tr>
</thead>
<tbody>
<tr>
<td>HS01</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS02</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS03</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS04</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS05</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS06</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS07</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS08</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS09</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HS13</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The non-monotonic value for HS05, HS06, HS07 and HS08 is retained. This estimate is based upon the estimates from Heintz et al\(^9\) which rely upon very small respondent numbers: □ for the WSE and □ for the BSE.

Note that retaining the non-monotonic value for HS01 slightly worsens the ICER. Removing the non-monotonicity for HS05, HS06, HS07 and HS08 by averaging the adjacent values to yield an estimate of □ also worsens the ICER.

#### 5.2.12 Model validation and face validity check

The submission does not present any validation data, but by definition the distribution between health states in the fluocinolone and in the sham arm over the first three years of the model corresponds with that of the trial.

There might appear to be an issue around the original model simulating 6% of patients having died by the end of year 3, but this is actually in line with the 6% (19/321) drop-outs due to death over the period of the trial as reported in the manufacturer response to ERG clarification question A27. Correcting the averaging between female and male mortality increases the proportion modelled as dying during the first 3 years to a little less than 9%. More seriously, the Version_B model simulates 20% of patients having died by the end of year 3.

The face validity of the base case model is perhaps best assessed by presenting the modelled:
• Survival, common to all arms, when the model is corrected for the averaging between female and male mortality but without the data input revision of the Version_B model;
• Proportion in the fluocinolone arm remaining in the fluocinolone on treatment cohort;
• Proportion in the fluocinolone arm remaining on fluocinolone treatment;
• Distribution between health states in the fluocinolone on treatment cohort, of whom are assumed to improve each quarter in years 4 to 15; and,
• Distribution between health states in the sham cohort, of whom are assumed to worsen each quarter in years 4 to 15.

Note that for reasons of space this does not present the distribution between health states in the fluocinolone off treatment cohort, as these follow the same extrapolation assumption as the sham arm for years 4 to 15. For the following three figures, the horizontal axis is the time in years (Figure 11, Figure 12 and Figure 13).

Figure 11. Survival, proportion in fluocinolone onTx cohort and proportion on fluocinolone!

The cohort flows show the distribution between health states among those surviving. The health states are stacked from worst at the top to best at the bottom: the top checkerboard pattern is HS13 with a BCVA of less than 20 letters, while the bottom checkerboard pattern is HS01 with a BCVA of more than 75 letters.

---

5 Taken from the Calc1 worksheet cells T55:T114 for survival, the sum across columns E:Q for rows 55:114 for the proportion remaining in the fluocinolone onTx cohort and cells S55:S114 for the proportion receiving fluocinolone treatment
5.3 ERG cross checks and critique

5.3.1 Base case results

The base case deterministic estimates within the electronic model correspond with those of the submission: £22,655 per QALY when compared with sham and £16,463 per QALY when compared with laser.

Note that for these the application of bilateral treatment is implemented as below (Table 41). With the exception of monitoring costs and blindness costs, the costs in the fluocinolone arm are increased by **. Similarly, the costs in the sham arm are increased by 35%. The QALY uplift is applied to each arm separately as **25% in the fluocinolone arm and 35%*25% in the sham arm.
Table 41. Application of bilateral uplifts within the modelling: fluocinolone versus sham

<table>
<thead>
<tr>
<th></th>
<th>DMO drugs</th>
<th>Procedures</th>
<th>AEs</th>
<th>Monitoring</th>
<th>Blindness</th>
<th>Total Costs</th>
<th>QALYs</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>One eye treated</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>£10,831</td>
<td>£439</td>
<td>£980</td>
<td>£4,919</td>
<td>-£453</td>
<td>£16,717</td>
<td>7.008</td>
</tr>
<tr>
<td>Sham</td>
<td>£121</td>
<td>£476</td>
<td>£457</td>
<td>£5,844</td>
<td>£1,673</td>
<td>£8,570</td>
<td>6.452</td>
</tr>
<tr>
<td>net</td>
<td>£10,710</td>
<td>-£36</td>
<td>£523</td>
<td>-£924</td>
<td>-£2,126</td>
<td>£8,147</td>
<td>0.557</td>
</tr>
<tr>
<td><strong>Bilateral treatment uplifts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>£3,141</td>
<td>£127</td>
<td>£284</td>
<td></td>
<td></td>
<td>£3,553</td>
<td>0.508</td>
</tr>
<tr>
<td>Sham</td>
<td>£42</td>
<td>£166</td>
<td>£160</td>
<td></td>
<td></td>
<td>£369</td>
<td>0.565</td>
</tr>
<tr>
<td>net</td>
<td>£3,099</td>
<td>-£39</td>
<td>£124</td>
<td></td>
<td></td>
<td>£3,184</td>
<td>-0.056</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>£13,972</td>
<td>£567</td>
<td>£1,264</td>
<td>£4,919</td>
<td>-£453</td>
<td>£20,270</td>
<td>7.516</td>
</tr>
<tr>
<td>Sham</td>
<td>£163</td>
<td>£642</td>
<td>£617</td>
<td>£5,844</td>
<td>£1,673</td>
<td>£8,939</td>
<td>7.016</td>
</tr>
<tr>
<td>net</td>
<td>£13,809</td>
<td>-£75</td>
<td>£647</td>
<td>-£924</td>
<td>-£2,126</td>
<td>£11,331</td>
<td>0.500</td>
</tr>
<tr>
<td><strong>ICER</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>£22,655</td>
</tr>
</tbody>
</table>

In the above, though the uplift to benefits per bilaterally treated patients is 1.752 QALYs in the fluocinolone arm and 1.613 QALYs in the sham arm, due to only 35% in the fluocinolone arm being assumed to be treated bilaterally compared to 35% the average bilateral treatment benefits is smaller in the fluocinolone arm than the sham arm: 0.508 QALYs and 0.565 QALYs respectively.

Taking the electronic model as submitted, revising the treatment of the clinical effectiveness parameters to be probabilistic and running the PSA over 10,000 iterations results in the following for the comparison of fluocinolone with sham (Table 42):

Table 42. Base case PSA treating clinical effectiveness probabilistically

<table>
<thead>
<tr>
<th></th>
<th>QALYs</th>
<th>net</th>
<th>Cost</th>
<th>net</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>6.206</td>
<td></td>
<td>£16,028</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>7.181</td>
<td>0.975</td>
<td>£39,876</td>
<td>£23,848</td>
<td>£24,467</td>
</tr>
</tbody>
</table>
The estimated probabilities of fluocinolone being cost effective at willingness to pay values of £20k, £30k and £40k per QALY are ***, *** and *** respectively (Figure 14). These differ from those reported in table B32 of the submission due to the clinical effectiveness parameters being treated probabilistically.

The ERG has rebuilt the deterministic model structure as a cross check of the submitted electronic model structure. Within this, adopting the manufacturer base case assumptions results in a cost effectiveness estimate for fluocinolone compared to sham of £22,241 per QALY which is a very good correspondence with the manufacturer base case of £22,655. QALY estimates are in line with those of the manufacturer, and what discrepancies there are mainly arise from the estimates of the fluocinolone drug cost being £74 higher and the net cataract and adverse event costs being around £100 lower in the ERG cross check rebuild.

5.3.2 Data Inputs: Correspondence between written submission and sources cited

- Quarterly percentage of patients changing by at least 5 letters

The ERG cross check of table B18 of the submission coupled with the data supplied in response to ERG clarification question A24 suggests that for the third year average the manufacturer may have averaged the last 5 quarters rather than the last four quarters. The results for the fluocinolone arm are as below (Table 43).
The parallel calculations for the sham arm suggest the following\(^6\) (Table 44).

- **DRCR data**

  The ERG cross-check of the DRCR suggests that at two years 18% of the laser group had gained 15 or more letters and 13% had gained 10-14, while 14% were worse by 15 or more letters and 5% were worse by 10-14. These are similar to the manufacturer figures.

- **Mortality**

  The base case estimates rely upon the baseline all-cause annual mortality risk of 0.77% for a 63 year old woman. Correcting the averaging between female and male mortality gives a 1.09% annual mortality risk.

---

\(^6\) Note that there is an error within the table supplied by the manufacturer in response to ERG clarification question A23 in that the patient numbers supplied for non-responders in Q11 are 8, 46 and 9 which sums to 63. This cannot be corrected by the ERG and the approach adopted has been to average over the “patient quarters” reported: e.g. 60+60+63+60 for Q9-12.
baseline all-cause risk of mortality. This is similar to the averaged $q_x$ of the interim 2008-10 UK life table of 0.97%\(^7\).

But Version\(_B\) of the model applies a baseline all-cause mortality risk of 2.64%. Due to the extent of the work required for this submission, the ERG has not had time to source and replicate this estimate. The manufacturer cites official sources\(^8\).

- **Treatment and monitoring unit costs**

Both fluocinolone administration and laser administration are assumed to require one outpatient visit, which is costed at £150 from NHS reference cost BZ23Z Vitreous Retinal Procedure Category 1. Routine quarterly outpatient monitoring is assumed, which is costed at £73 from NHS reference cost B130 Ophthalmology consultant led follow up face to face. Quarterly OCT is costed at £53 from NHS reference cost RA23Z Diagnostic imaging ultrasound scan of less than 20 minutes.

It appears that these values have been drawn from the NICE STA of ranibizumab of DMO. The 2010-11 NHS references costs revise these from £150 to £141 and £73 to £77 with the ultrasound scan remaining at £53. These values would make no material difference to the model results.

- **Other treatments’ unit costs**

BNF 63 gives a direct drug cost for triamcinolone in the form of Kenalog of £1.49 per 1ml 40mg/ml vial compared to the £7.00 applied by the manufacturer. BNF 63 lists £742 for ranibizumab and £870 for dexamethasone which are in line with those applied by the manufacturer.

- **Adverse events’ unit costs**

The ERG has not been able to source the NHS reference costs cited for adverse events (Table 45).

### Table 45. Adverse event unit costs ERG cross check

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Basis</th>
<th>Submission</th>
<th>Model(^9)</th>
</tr>
</thead>
</table>


\(^9\) Costs worksheet cells F9:F33, with the cataract cost of £789 being cell F17 excluding the costs of medication outlined in table B23 of the submission.
Cataract surgery | BZ02Z: Daycase | £789 | £789
Endophthalmitis | BZ23Z: NE IP Long stay | £1,783 | £1,783
Retinal detachment | BZ22Z: NE IP Short stay | £1,339 | £1,339
Vitrectomy | BZ22Z: NE IP Short stay | £1,339 | £1,261
Glaucoma procedure | BZ17Z | £1,128 | £1,128

The 2009-10 and 2010-11 combined NHS trusts and PCT reference costs give average costs for BZ02Z as a daycase of £794 and £820 respectively.

The 2009-10 and 2010-11 combined NHS trusts and PCT reference costs also supply the following for day case, non-elective inpatient short stay and non-elective inpatient long stay (Table 46).

Table 46. NSRC04 average cost data

<table>
<thead>
<tr>
<th>HRG</th>
<th>Description</th>
<th>2009-10</th>
<th>2010-11</th>
<th>2009-10</th>
<th>2010-11</th>
<th>2009-10</th>
<th>2010-11</th>
</tr>
</thead>
<tbody>
<tr>
<td>BZ17Z</td>
<td>Glaucoma - cat 3</td>
<td>£1,330</td>
<td>£1,404</td>
<td>£1,245</td>
<td>£1,151</td>
<td>£1,654</td>
<td>£2,915</td>
</tr>
<tr>
<td>BZ18Z</td>
<td>Glaucoma - cat 2</td>
<td>£949</td>
<td>£1,009</td>
<td>£994</td>
<td>£1,118</td>
<td>£1,335</td>
<td>£1,733</td>
</tr>
<tr>
<td>BZ19Z</td>
<td>Glaucoma - cat 1</td>
<td>£443</td>
<td>£414</td>
<td>£802</td>
<td>£956</td>
<td>£1,862</td>
<td>£2,315</td>
</tr>
<tr>
<td>BZ20Z</td>
<td>Vitreous Retinal Procedures - cat 4</td>
<td>£1,503</td>
<td>£1,754</td>
<td>£2,147</td>
<td>£2,433</td>
<td>£2,838</td>
<td>£3,059</td>
</tr>
<tr>
<td>BZ21Z</td>
<td>Vitreous Retinal Procedures - cat 3</td>
<td>£1,261</td>
<td>£1,401</td>
<td>£2,128</td>
<td>£2,287</td>
<td>£2,189</td>
<td>£2,350</td>
</tr>
<tr>
<td>BZ22Z</td>
<td>Vitreous Retinal Procedures - cat 2</td>
<td>£903</td>
<td>£1,057</td>
<td>£1,845</td>
<td>£1,938</td>
<td>£2,635</td>
<td>£2,833</td>
</tr>
<tr>
<td>BZ23Z</td>
<td>Vitreous Retinal Procedures - cat 1</td>
<td>£550</td>
<td>£427</td>
<td>£917</td>
<td>£909</td>
<td>£1,626</td>
<td>£2,242</td>
</tr>
</tbody>
</table>

There appears to be limited correspondence between the unit costs applied and cited non-elective inpatient reference costs data. The ERG assumption from the manufacturer footnote to table B23 is that the manufacturer intention is for endophthalmitis to be costed as a long stay which would suggest a unit cost of £2,242, but for the other adverse events coded in the above table to be costed as short stays which would suggest a unit cost of £1,938 for retinal detachment and vitrectomy and a unit cost of £1,151 for glaucoma.

The adverse event costs applied by the manufacturer also do not appear to be in line with the NICE STA of ranibizumab for DMO.

- The costs of blindness

The 2009 annual cost of blindness of £5,871 taken from the ranibizumab for DMO STA appears to be drawn from an ERG correction the manufacturer estimate as in table 26 of the ranibizumab ERG.
report\(^\text{10}\). But section 5.6.2 of the ranibizumab ERG report provides an extensive review of the costs of blindness estimates within the literature and the ranibizumab manufacturer submission, and appears to suggest an ERG estimate of £5,461. This would inflate to £5,794 compared to the £6,298 of the manufacturer base case.

5.3.3 Data Inputs: Correspondence between written submission and electronic model

- Laser administrations

The total numbers of laser administrations reported in table B10 of the written submission are in line with the CSR table ISE.18. When coupled with the manufacturer response to ERG question A27 this suggests the following (Table 47).

The Costs worksheet of the electronic model suggests the following (Table 48).

Note that in the above two tables, conditioning the annual number of laser administrations by the number at risk increases the number of laser administrations by a very similar percentage in both arms and the consequences of this largely net out. The model also conditions these by survival which reduces this effect.

But within the cost calculation of the Calc2 worksheet of the electronic model the number of laser administrations in year 1 refers to cell H534 of the SA_Inputs worksheet. In contrast to cells H535 and H536 which refer to the correct entries in the Costs worksheet for years 1 and 2, cell H534 of the SA_Inputs worksheet has been set to an absolute value of **** (Table 49).

\(^{10}\) http://www.nice.org.uk/nicemedia/live/13125/53408/53408.pdf
This marked increase is not explained anywhere and would increase the costs in the control arm.

### 5.3.4 Possible errors within the electronic model

It appears that there may be a number of errors within the submitted electronic model structure.

- **Mortality**

As highlighted in the ERG clarification question B7 when averaging between the age 18 female mortality in cell D41 and the male mortality in cell F41 in cell H41 of the *Mortality_Calc* worksheet this is correctly calculated as:

\[
H41 = D41 \times (1 - 'SA Inputs'!$H$437) + F41 \times 'SA Inputs'!$H$437
\]

where the absolute reference to 'SA Inputs'!$H$437 is the proportion of male patients at baseline.

But during model construction the absolute referencing to 'SA Inputs'!$H$437 in cell H41 was somehow revised to a relative referencing such that cells H42 and below are of the form:

\[
H42 = D42 \times (1 - 'SA Inputs'!H438) + F42 \times 'SA Inputs'!H438
\]

where the relative referencing to 'SA Inputs'!H438 increases to 'SA Inputs'!H439 for the calculation of cell H43, and so on down the column. The impact of correcting this is to increase the estimate of the baseline annual all-cause mortality risk from 0.77% to 1.09%.

Correcting this error increases the base case cost effectiveness estimate for fluocinolone versus sham from £22,655 per QALY to £24,184 per QALY.

- **Fluocinolone drop-outs in years 6, 9 and 12**

The cohort flow for the fluocinolone arm is split into two cohorts: those on treatment and those off treatment. This split is modelling as occurring at the end of year three, at which point the combined effect from the % dropout rate and the 3 year responder rate results in of fluocinolone patients being modelled as continuing with fluocinolone treatment. These patients are modelling as continually improving, with transferring up to the neighbouring better health state each cycle. The
of those off treatment are modelling as continually worsening, with transferring down to the neighbouring worse health state each cycle. This is correctly implemented for the next three years.

But at the six year point, and every three years thereafter the intention is that the % drop out rate should be applied. This serves to reduce the fluocinolone retreatment costs over the model time horizon: among those patients surviving at year 12 only are modelling as being retreated with fluocinolone.

But the three yearly % drop out rate does not appear to have been implemented within the cohort flow cells of the Calc1 worksheet upon which the QALYs are based. In the opinion of the ERG the cohort flow should reflect those on treatment and those off treatment, with those modelled as being off treatment having the off treatment TPM applied to them. It should also reflect that the balance between the health states of those transferring from fluocinolone to being off treatment at year six will not be the same as the balance between the health states at year six of those who transferred to being off treatment at year three.

This suggests revising the formulae in cells E79:Q79, E91:Q91 and E103:Q103 from being along the lines of:

\[
E79 = \text{MMULT}(\text{E78:Q78},D38:D50) \times (1 - \text{IF}(T78 < 0.0001,0,W78/T78))
\]

to being along the lines of:

\[
E79 = \text{MMULT}((1-D16) \times \text{E78:Q78},D38:D50) \times (1 - \text{IF}(T78 < 0.0001,0,W78/T78))
\]

Paralleling this, the formulae in cells E145:Q145, E157:Q157 and E169:Q169 should be revised from being along the lines of:

\[
E145 = \text{MMULT}(\text{E144:Q144},\text{Calc2!D36:D48}) \times (1 - \text{IF}(T144 < 0.0001,0,W144/T144))
\]

to being along the lines of:

\[
E145 = \text{MMULT}((\text{E144:Q144}+(D16 \times \text{E78:Q78})),\text{Calc2!D36:D48}) \times (1 - \text{IF}(T144 < 0.0001,0,W144/T144))
\]

Correcting this error increases the base case cost effectiveness estimate for fluocinolone versus sham from £22,655 per QALY to £24,740 per QALY.

- The percentage remaining on fluocinolone treatment after year 9

\[11\] It might be more elegant to model this at a constant rate per cycle. Intuition suggests that this would reduce the aggregate QALYs further but the likely size of this has not been quantified by the ERG. While conjecture it could also be argued that even among those dropping out between fluocinolone treatments, some on-going benefits would occur throughout the three year period; i.e. it is better to consider the drop-out rate as the converse to the fluocinolone re-treatment rate.
There may be a minor error in the *Calc1* worksheet in the calculation of the proportion of patients remaining on treatment within cells S55:S114 between each three yearly point for years 6, 9 and 12 in cells S79, S91 and S103. When dropouts are being modelled at these three yearly points, it appears that the calculation only applies the drop-out rate of cell D16 to the proportion from the previous cycle and does not attribute an additional proportion of the overall deaths occurring during the cycle; e.g. for those continuing treatment at year 6 rather than:

\[ S79 = S78 * (1 - D16) \]

the cell formula should perhaps read:

\[ S79 = (S78 - (W78 * (T78 - U78) / T78)) * (1 - D16) \]

where column T is the number surviving, column U is the number of those not on treatment and column W is the number of deaths during that cycle.

But further examination of cells S55:S114 of the *Calc1* worksheet suggests another error which is more difficult to account for. For the calculation of the evolution of the proportion of patients remaining on fluocinolone treatment up to year 9 the basis of the calculation is to apply

- The responder rate at year 3
- The drop-out rate at years 3, 6, 9
- The overall death rate in proportion to the percentage of patients remaining on treatment

With regards to the last bullet point this results in the typical formula:

\[ S68 = S67 - (W67 * (T67 - U67) / T67) \]

where W67 is the total number of deaths, T67 the patients remaining alive and U67 the proportion off treatment. This formula is correct and is applied in cells S68:S78 and S80:S90.

But for reasons that are not obvious this calculation is revised for cells S92:S102 to:

\[ S92 = S91 - (W91 * (1 - (T91 - U91) / T91)) \]

This applies the overall death rate in proportion to the percentage of patients off treatment to the percentage of patients remaining on treatment. By this point in the modelling the percentage of patients off treatment is large, and as a consequence too large a number of deaths are being applied to these patients. This applies to the extent that for cells S104:S114 the formula has to be further conditioned to prevent the patient numbers in this group turning negative:

\[ S104 = \text{Max}(0, S103 - (W103 * (1 - (T103 - U103) / T103))) \]

The calculations in cells S55:S114 only affect the costs, including not only the direct drug and administration costs but also the costs of adverse events associated with treatment. This error does not
affect the calculation of QALYs because this is based upon the cohort flow in cells E55:Q114. There is not a parallel to this error in the comparator arm calculations.

The correction of these two errors offset one another, but the joint effect is to slightly increase the base case cost effectiveness estimate for fluocinolone versus sham from £22,655 per QALY to £22,823 per QALY.

- Cumulative impact of errors upon the cost effectiveness estimate for fluocinolone versus sham

In the light of the above three bullets the ERG is of the opinion that the intended manufacturer model structure results the base case estimate for fluocinolone versus sham being revised from £22,655 per QALY to £26,526 per QALY.

- Treatment of the DCRC data within the laser arm

ERG cross check of the cohort flow within the laser arm corresponds with that of the manufacturer model with the exception of HS1, HS2, HS3, HS11, HS12 and HS13. For HS1 and HS13 these absorb more transitions that the other health states due to ceiling and floor effects. For instance within the *Laser_Estim* worksheet for cell H121 the original formula is:

$$H121 = (F121 \times (H15 + H14 + H13 + H12)) + (F122 \times H14) + (F123 \times H13) + (F124 \times H12)$$

In the opinion of the ERG it should read:

$$H121 = (F121 \times (H15 + H14 + H13 + H12)) + (F122 \times (H14 + H13 + H12)) + (F123 \times (H13 + H12)) + (F124 \times H12)$$

In addition, for the cell H122 the original formula is:

$$H122 = (F122 \times (H15 + H14 + H13 + H12)) + (F123 \times H14) + (F124 \times H13) + (F125 \times H12) + (F121 \times H16)$$

In the opinion of the ERG it should read:

$$H122 = (F122 \times H15) + (F123 \times H14) + (F124 \times H13) + (F125 \times H12) + (F121 \times H16)$$

Similarly, in the opinion of the ERG the formulae for the cells H123, H131, H132 and H133 should be:

$$H123 = (F123 \times H15) + (F124 \times H14) + (F125 \times H13) + (F126 \times H12) + (F122 \times H16) + (F121 \times H17)$$

$$H131 = (F131 \times H15) + (F132 \times H14) + (F133 \times H13) + (F130 \times H16) + (F129 \times H17) + (F128 \times H18)$$

$$H132 = (F132 \times H15) + (F133 \times H14) + (F131 \times H16) + (F130 \times H17) + (F129 \times H18)$$

$$H133 = (F133 \times (H15 + H16 + H17 + H18)) + (F132 \times (H16 + H17 + H18)) + (F131 \times (H17 + H18)) + (F130 \times H18)$$

Similar considerations may apply to the parallel cells in columns L, N, P, R, T, V, X, Z, AB, AD and AF.
Note that for month 24 to month 36, stable visual acuity is assumed and the month 24 patient
distribution is retained in the laser arm for the corresponding four model cycles.

If these corrections are accepted it mainly changes the proportions being in the best and the worst
health states. For instance, for the month 24 patient distribution of patients it would be revised from
the manufacturer estimate to the ERG estimate as below (Table 50):

<table>
<thead>
<tr>
<th>Table 50.</th>
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The manufacturer base case estimate for the cost effectiveness of fluocinolone compared to laser is
£16,462 per QALY. Addressing the errors concerning the modelling of the fluocinolone arm increases
this estimate to £18,745 per QALY. Further addressing the concern outlined above for the laser arm
results in a revised base case cost effectiveness estimate of £19,189 per QALY.

Note that the ERG revision results in a patient distribution for laser at 24 months that is not too
dissimilar from that observed in the sham arm at 24 months (Table 51). But also note that there may
be some continued improvement between 24 months and 36 months in the sham arm. Whether
something similar should be applied between 24 months and 36 months in the laser arm is a moot
point.

<table>
<thead>
<tr>
<th>Table 51.</th>
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</thead>
<tbody>
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<tr>
<td></td>
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</tbody>
</table>

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5.3.5 ERG commentary on model structure, assumptions and data inputs

- Half cycle correction

Table B16 of the submission states that the model employs half cycle correction. The manufacturer response to clarification question B9 states that it does not. In the light of this, it appears that the patient distributions drawn directly from the trial data for the first 13 cycles of the model are the baseline patient distributions followed by 12 end of quarter distributions. The ERG can confirm that subsequent to the first 13 cycles, the modelled cohort flow does not apply half cycle correction.

The ERG is of the opinion that any impact of this upon net QALYs, net costs and the ICER is likely to be slight, particularly when viewed against the other ERG concerns about the model structure and data inputs.

- Mortality

When the 0.77% baseline all-cause annual mortality risk is extrapolated it results in 58% of patients being simulated as surviving the end of the 15 years, and results in a cost effectiveness estimate for fluocinolone versus sham of £22,655 per QALY. When the averaging between female and male mortality is corrected to given a 1.09% annual baseline all-cause risk of mortality it results in 46% of patients being simulated as surviving to the end of the 15 years, and results in a cost effectiveness estimate for fluocinolone versus sham of £24,184 per QALY. When the Version_B 2.64% baseline all-cause annual mortality risk is extrapolated within the context of the original model it results in 15% of patients being simulated as surviving to the end of the 15 years, and results in a cost effectiveness estimate for fluocinolone versus sham of £32,717 per QALY.

The ERG cannot easily revise the manufacturer model structure to apply life table data through the period of the modelling. The interim 2008-10 UK life table suggests a baseline all-cause mortality risk of 0.97% which is quite similar to the 1.09% of the original model when the averaging between female and male mortality is corrected. Applying the DMO SMR to the annual all-cause risks of mortality suggests a survival of 45% at the end of the 15 years which is again very similar to the 46% of the original model when the averaging between female and male mortality is corrected.

But the baseline all-cause mortality risk used in the Version_B model appears to be too high, to the detriment of fluocinolone.

- VFQ-25 quality of life data

As reviewed in the clinical effectiveness section and repeated below, the quality of life data collected during the trial showed limited benefits in the fluocinolone arm compared to the sham arm (Table 52).

Table 52. Trial data on HRQoL by VFQ-25

<table>
<thead>
<tr>
<th>VFQ-25 mean values (s.d.)</th>
<th>Sham</th>
<th>Fluocinolone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Month 36</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

On the assumption that the VFQ-25 is at least as sensitive to changes in the BCVA as the EQ-5D, the above coupled with **** of patients having their baseline WSE treated may underline that quality of life is mainly determined by changes in the BCVA of the BSE. As reviewed below, any modelling of bilateral treatment is likely to imply that a majority of patients will have their BSE treated either in isolation of as part of bilateral treatment.

In the light of this and the manufacturer response to ERG clarification question A21, there may be a case for analysing the trial based VFQ-25 HRQoL mean changes between baseline and month 36 data alongside the BCVA of the treated eye mean change between baseline and month 36 data by arm and pooled across the arms:

- across all patients; and
- split by:
  - those having their baseline BSE treated: **** of the pooled patient population
  - those having their baseline WSE treated the BCVA of which did not rise above the baseline BCVA of the BSE during the course of the trial: **** of the pooled patient population
  - those having their baseline WSE treated which became their BSE during the course of the trial: **** of the pooled patient population

Note that the above percentages are presented on an ITT basis. It might be anticipated that drop-outs would affect these percentages, but this appears to be not particularly the case. On an observed patient basis the proportion having their baseline WSE treated that remained their WSE and the proportion having their WSE treated that became their BSE are apparently **** and **** respectively.

The manufacturer in response to ERG clarification questions B5 and B6 notes that there is not a universally accepted mapping function from VQ-25 to EQ-5D or EQ-5D utilities, and that “a decision was made not to commit the significant financial or human resources that would be required for de novo generation of utilities.” The ERG is of the opinion that in comparison to the effort expended
collecting the VFQ-25 data, the effort required to present: a review of the VFQ-25 data, a review of the feasibility of applying any mapping functions that exist in the literature; and, the impact of applying any such mapping functions, is relatively minor.

The ERG has identified one paper within the literature, Payakachat et al,\textsuperscript{58} that estimates a function for mapping from the VFQ-25 to EQ-5D utilities estimated using the standard UK social tariff. Payakachat et al\textsuperscript{58} map from the VFQ-25 to EQ-5D utilities using data drawn from AMD patients, with 151 observations being used for estimation and 393 for validation. The relevance of the Payakachat et al\textsuperscript{58} data which had an average age of 78 to the chronic DMO patients of the trial would appear to be limited to the same degree as the Brown et al\textsuperscript{53} paper from which the manufacturer sources the base case HRQoL values. Brown et al\textsuperscript{53} also relates to AMD patients, though with an average age of 74 years. This may also have to be read alongside Brown et al (2002),\textsuperscript{85} who conclude that “At similar levels of visual acuity loss, that associated with diabetic retinopathy causes a similar reduction in quality of life to that associated with ARMD.”

Payakachat et al\textsuperscript{58} provide a very clear recommendation to use their CLAD short form model. This requires only the two main domains of the VFQ-25, the general health and the composite score, and appears to be simple to apply to VFQ-25 data.

- Extrapolation percentages

There is no obvious justification for ignoring the data from the sham arm for extrapolation. Based upon the 5 letter responder rule the data from the FAME trials can be pooled across all patients to yield the following (Table 53).

<table>
<thead>
<tr>
<th>Table 53.</th>
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The data from the last year of the FAME trials can be similarly pooled across all patients to yield the following (Table 54).
Given the model structure, for the sham arm there is no need to differentiate between responders and non-responders. Adopting the manufacturer approach for the sham arm would appear to suggest broadly the same quarterly proportion of patients improving and worsening over both the period of the trial and during the last year of the trial. This should also be read alongside figure B3 of the manufacturer submission which suggests that within the sham arm, after an improvement during the first three months of the trial, the mean BCVA in the treated eye remains roughly constant.

It is only in the fluocinolone arm that there is the need for this differentiation. Among fluocinolone patients satisfying the 5 letter responder rule the above suggests an average improving and an average worsening per quarter: a slightly larger difference than the manufacturer estimates of improving and worsening which appears to be based upon averaging over Q8-12.

The above also suggests that fluocinolone non-responders do slightly worse than the average experience within the sham arm as might be anticipated, though there still appears to be a reasonable balance between the percentage of quarterly improvements and the percentage of quarterly worsenings, particularly during the last year of the trial.

There is no obvious requirement to net out the percentages improving and worsening to arrive at a single percentage, as in the manufacturer base case where of those responding to fluocinolone at month 36 are anticipated to improve by one health state every quarter for the remainder of the model. The data supplied by the manufacturer in response to ERG clarification question A23 coupled with the final month 36 patient distribution appears to suggest that there may be an element of churn within the data.
Applying the estimates of improving and worsening\textsuperscript{13} for fluocinolone responders within the original submitted model results in the cost effectiveness estimate for fluocinolone versus sham worsening from £22,655 per QALY to £25,524 per QALY. This occurs despite the difference between them being larger than the manufacturer base case netted out figure of.

Applying a common improving and worsening\textsuperscript{14} for fluocinolone non-responders and sham as being reasonably representative of the above data worsens the cost effectiveness estimate for fluocinolone versus sham from £22,655 per QALY to £27,733 per QALY.

Applying the above changes to the extrapolation percentages for fluocinolone responders, fluocinolone non-responders and sham simultaneously worsens the cost effectiveness estimate for fluocinolone versus sham from £22,655 per QALY to £32,148 per QALY.

Note that by definition the pooled estimates for sham apply regardless of the fluocinolone responder rule. But as clarified within the manufacturer response to ERG clarification questions A24 and A26 for a responder rule of 10 letters between baseline and month 36 the estimates change (Table 55).

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</table>

There are small discrepancies between the pooled rates in the above table and that based upon pooling rates in the fluocinolone arm based upon the 5 letter responder rule. The reasons for this are not clear to the ERG.

ERG expert opinion notes: The percentage of treated eyes with a 15 letter gain increased steadily in the trial up to month 30. With repeat treatments the BCVA may continue to improve with further drying out of the retina, and some further settlement of the previously distorted retinal anatomy. But

\textsuperscript{13} Implemented in the \textit{Efficacy-Past Year_3} worksheet by setting F19=17.9%, F20=70.4%, F21=11.7% and H21=F21. Note that setting F21=11.7% creates a circular cell referencing warning within excel. The source of this is not apparent, but the \textit{Calc1} worksheet TPM for extrapolation in D38:P50 appears to remain correctly calculated and the rows still sum to 100%.

\textsuperscript{14} Implemented in the \textit{Efficacy-Past Year_3} worksheet by setting F19=13.0%, F20=74.0%, F21=13.0% and H19=F19.
continuous improvement may tail off at some point and anticipating the same rate of improvement after the third implant may be optimistic. But for sham, while some eyes may continue to deteriorate, these patients are not being left untreated and progressive deterioration should not be assumed for all. This applies with particular force given the proportion of patients recording more than 15 letters gain in the treated eye at month 36.

- The modelled drop-out rate versus the actual drop-out rate

The model applies a constant drop-out rate of ***% every third year among responders in the fluocinolone arm, regardless of the responder rule.

With regards to the drop-out rate that should be applied at year 3 to fluocinolone responders, for the base case it might be more reasonable estimate a drop-out rate applicable to fluocinolone responders. By definition, there are issues around ITT versus observed cases, but it may be that the drop-out rate among those doing well and responding is lower than the drop-out rate across the fluocinolone arm as a whole. Given the ***% 5 letter responder rate and *** 10 letter responder rate, conditioning these by the overall ***% drop-out rate may tend to underestimate the number of patients that will receive a second fluocinolone administration at year 3. It may be more appropriate for the base case to estimate the drop-out rate specific to fluocinolone responders: the percentage of responders relying upon LOCF at 36 months to show a response divided by the overall response rate including these patients.

Or perhaps to estimate the proportion remaining on fluocinolone treatment and the distribution among them more simply as the health state distribution at 36 months among those followed up to this point and satisfying the responder rule.

With regards to the drop-out rate that should be applied at years 6, 9 and 12 to fluocinolone responders remaining on treatment, it might be anticipated that those receiving a second fluocinolone administration would also tend to go on to receive further fluocinolone administrations because they are by definition fluocinolone responders. Among those receiving a second fluocinolone administration, there may be grounds for anticipating a subsequent 3 yearly drop-out rate that is lower than the overall drop-out rate measured within the fluocinolone arm of the trial.

Lastly, the manufacturer response to ERG clarification question A27 outlines that of the *** discontinuations among chronic DMO patients in the fluocinolone arm, *** were deaths. The model separately accounts for deaths. Given the modelling approach adopted and where required LOCF determining the health state distribution at month 36, taking this into account during the trial period within the model would be complicated. But during the extrapolation period it may not be reasonable
to both explicitly model deaths and apply a drop-out rate that includes deaths. This suggests revising the fluocinolone drop-out rate to

- Fluocinolone responders, non-responders and discontinuations at 36 months

As per the manufacturer response to clarification question A28, [redacted] patients out of a total [redacted] patients who were assessed among the [redacted] remaining on fluocinolone treatment at month 36 improved by at least 5 letters from baseline and were classified as responders. The base case assumes [redacted]% were responders based upon LOCF and couples this with a drop-out rate of [redacted]% to arrive at the 54.1% assumed to continue with fluocinolone treatment. It could be argued that a more reasonable estimate of the number of those likely to continue treatment given a responder rule of 5 letters might be \((121\times(159/157))/209 = \) [redacted] While the two figures are not that dissimilar, results are quite sensitive to this variable.

Given the baseline patient distribution in the fluocinolone arm, assuming a common [redacted] split between responders and non-responders across all health states cannot be correct. All those remaining on treatment and in HS1 state at 36 months will be responders, and virtually all those remaining on treatment and in HS2 at 36 months will be responders. Similarly, all those in HS13 will be non-responders.

The actual distribution of fluocinolone responders remaining on treatment at the end of the trial could have been drawn from trial data. Without access to this data the ERG cannot determine whether the modelled distribution of fluocinolone responders remaining on treatment at 36 months results in a more or less favourable ICER compared with the alternative of having used the actual distribution of fluocinolone responders remaining on treatment at the end of the trial. The expectation is that it will improve the ICER, but this is then conditioned by the reasonableness of the discontinuation rate being applied within the submitted model. Ceiling and floor effects will also come into play.

- The impact of drawing this distribution directly from the trial data may be reduced by ceiling effects. Extrapolation beyond 36 months for those modelled as being responders and remaining on fluocinolone treatment assumes [redacted] improve by one health state every quarter. Ceiling effects apply to this [redacted] quarterly improvement. If the responders remaining on fluocinolone treatment tend to be at the upper end of the health state distribution these ceiling effects will be more marked. This would tend to lessen the extent of any improvement in the ICER.

- The reverse may apply in terms of floor effects. Extrapolation beyond 36 months for those modelled as discontinuing fluocinolone assumes [redacted] worsen by one health state every quarter. Floor effects apply to this [redacted] quarterly worsening. If the non-responders discontinuing
fluocinolone treatment tend to be at the lower end of the health state distribution these floor effects will similarly be more marked, but with the opposite effect of limiting any worsening in the ICER.

The impact of the above may also tend to be larger for a 10 letter responder rule than for a 5 letter responder rule.

- Rate of bilateral treatment

Given the available data, the ERG cannot accurately estimate the appropriate rate of bilateral retreatment that should be applied within the modelling, as noted in the bilateral treatment section at the end of the previous chapter. The manufacturer could not provide a breakdown of the numbers of patients whose WSE was excluded for each reason, but it is safe to conclude that for most but not all cases the reason would mean permanent exclusion from bilateral treatment. In the absence of other data it seems reasonable to assume that 20% who had their baseline BSE treated during the trial are permanently excluded from treatment in their WSE and that these patients should not be modelled as receiving bilateral treatment.

Among the of patients who had their baseline WSE treated, the manufacturer response to the ERG clarification question A19 suggests that had had chronic DMO in their fellow BSE at baseline. A further had had DMO for less than 3 years in what was their BSE fellow eye at baseline but joined the chronic DMO group over the period of the trial. The and correspond with and of the overall trial population.

Note that in some studies, about a third of eyes with DMO recover spontaneously within 6 months (e.g. Romero-Aroco 2010). But among those with chronic DMO the most reasonable assumption may be that none recover spontaneously.

The manufacturer response to the ERG clarification question A17 suggests that of those who had their baseline WSE treated had a BCVA in the untreated eye of less than 75 letters at baseline. These could be assumed to all have chronic DMO at baseline in that eye, but not all visual impairment will be due to DMO. A reasonable percentage to assume might be around , with the rest having VI for other reasons, mainly cataract. The rate of development of visual impairment in the of fellow BSEs with chronic DMO at baseline is a matter of conjecture, but any assumption on this point should at a minimum tie in with any assumptions made for extrapolation elsewhere in the model. Similarly, an assumption would have to be made about the rate of development of visual impairment among the developing chronic DMO in what was their BSE fellow eye at baseline over the 3 year duration of the trial (Table 56).
The above suggests a baseline bilateral treatment rate of *** of presenting patients, or around *** as presented in the clinical effectiveness section. Increasing the proportion of those with chronic DMO in their fellow BSE subsequently developing visual impairment in this eye to ***, ***, and ***, increases the bilateral treatment rate to ***, ***, and *** respectively.

Given the above bilateral treatment percentages, if these are applied a majority of patients will be modelled as having their BSE treated: between ** and ***. In the light of this it may be more reasonable to apply HRQoL values which have been derived from EQ-5D or time trade off data relating to the BSE.

But a problem arises. The distribution of health states within the model is still determined by the evolution of the distribution of the BCVA of eyes that were treated at baseline within the trial, of which were the WSE. Given the modelling approach adopted by the manufacturer, the most reasonable approach may be to rely upon the evolution of the BCVA of the subset of BSEs that were treated at baseline within the trial. This applies with particular force if the manufacturer base case extrapolation assumptions are retained.

- Bilateral treatment cost and QALY uplifts

As tabulated for the base case results of the original model, for the 35% of patients requiring bilateral treatment the rate of bilateral treatment in the fluocinolone arm is adjusted downwards by the
proportion experiencing a raised IOP in their initially treated eye to result in only **being treated bilaterally. This results in a bilateral treatment uplift of 0.508 QALYs in the fluocinolone arm and 0.565 QALYs in the sham arm.

It does not seem reasonable for the bilateral treatment uplift to QALYs to be smaller in the fluocinolone arm than in the sham arm. The 6% of patients originally treated with fluocinolone in one eye requiring bilateral treatment but rendered ineligible for bilateral fluocinolone treatment due to raised IOP would presumably receive the equivalent of sham in the other eye. For this 6% it seems reasonable to apply the absolute cost uplift and the absolute QALY uplift as modelled for a patient receiving bilateral treatment in the sham arm.

For the originally submitted model for the fluocinolone arm this revision changes the total cost from £20,270 to £20,332 and the total QALYs from 7.516 QALYs to 7.613 QALYs, and compared to sham results in net costs of £11,393 and a net gain of 0.597 QALYs. This results in the base case cost effectiveness estimate for fluocinolone compared to sham being revised from £22,655 per QALY to £19,086 per QALY.

With these changes to the model, the method of applying the cost uplift for bilateral treatment seems a reasonable approximation to modelling a patient with two eyes. The method of applying the QALY uplift is more questionable and seems less likely to be a reasonable approximation to modelling a patient with two eyes. The bilaterally treated fellow eye will often be the BSE. The distribution of the BCVAs of these fellow eyes is likely to differ from the baseline distribution of treated eyes in the trial. The clinical effectiveness of fluocinolone as measured in the trial and as assumed for extrapolation may differ for these eyes, if only due to ceiling effects.

- Fluorescein angiography rates and unit cost

ERG expert opinion suggests that some ophthalmologists may not always undertake fluorescein angiography, but that ETDRS guidelines suggest undertaking a fluorescein angiography prior to laser therapy. But this rate of one fluorescein angiography prior to each laser therapy should be applied equally to both arms.

The ERG has not been able to source the Cruess et al\(^\text{83}\) figure of £278 for fluorescein angiography from within the PSSRU Unit Costs of Health and Social Care (2004).\(^\text{84}\) The ERG has also

\(^{15}\) Implemented within the **CE_Outcomes** worksheet by revising cell I47=SUM(I17,I26,I28,I34,I45)+('Model Settings!'I26-'Model Settings!'I25)*((K47-K45-K26-K41)/(1+'Model Settings!'I26)) and cell I71=Calc1!X184*(1+('Model Settings!'I25*'Model Settings!'I30)+('Model Settings!'I26-'Model Settings!'I25)*'Model Settings!'I30*(K71/(1+('Model Settings!'I26*'Model Settings!'I30)))
unsuccessfully searched for the parallel unit cost of £272 for OCT and various other elements within Cruess et al,\textsuperscript{83} since it appears that this may be the basis for the £278 fluorescein angiography unit cost. This is complicated by Cruess et al\textsuperscript{83} not having specified the inflation rate applied to arrive at the £272 from 2004 costs, though the HSCS published subsequently suggests the 2004 cost would be around £263.

ERG expert opinion suggests that the NHS charges manufacturers around £250 for a fluorescein angiography in the context of a clinical trial. This may tend to be more than the cost to the NHS, and the ERG is currently trying to confirm an appropriate unit cost for this.

Note that the manufacturer submission for the NICE STA of ranibizumab for DMO applied a common monitoring cost to both the ranibizumab arm and the comparator laser therapy arm of £126. This was based upon reference costs of £73 for B130-Ophthalmology Consultant Led: Follow up Attendance Non-Admitted Face to Face plus £53 for OCT based upon RA23Z-Diagnostic Imaging code: Ultrasound Scan less than 20 minutes.

- The costs of blindness

As noted in the section 5.9 of the ERG report of NICE STA of ranibizumab for DMO “The costs of severe visual impairment have been applied when the treated eye falls below 36 letters. These costs only apply when both eyes fall below 36 letters”.\textsuperscript{86} A similar concern applies within the current STA.

In response to the ERG clarification question B2 the manufacturer notes that the Version_B model revises the rate of bilateral treatment to \_\_\_ and “it is felt that in these subjects it is highly likely to have a similar VA deterioration in both eyes. Thus, for this patient group, the deterioration of one eye can be held as a proxy for both eyes being severely impacted and the patients overall visual status being designated as blind in the absence of a bilateral BCVA value”. But the manufacturer implicitly suggests that this argument only applies to the proportion having, or eligible for, bilateral treatment.

Data provided in response to the ERG clarification question A17 gives the following health state distributions among the \_\_\_ treated in their WSE at baseline (Table 57).
As would be expected, relatively few of those who had their WSE treated at baseline had the same BCVA in their baseline BSE. But the great majority of patients who had their WSE treated at baseline had a BCVA in their baseline BSE that was at least 2 health states or on average 10 letters better: *** in total. The proportion of these BSEs that were 3, 4 and 5 or more health states better than the WSE at baseline were *** and *** respectively. This data is drawn from all patients who had their WSE treated at baseline, and is not specific to the *** of these patients who had chronic DMO in their fellow eye at baseline. But it suggests the manufacturer assumption that patients with chronic DMO in both eyes are likely to have a similar BCVA in both eyes may not be realistic.

- **Probabilistic modelling**

The PSA of the original model as submitted treats the number of fluocinolone treatments, the number of laser administrations and the price of drugs as probabilistic with a triangular distribution. For consistency of approach and to limit the model revisions required of the ERG these can be treated deterministically \(^\text{16}\) and the PSA re-run. For example, for the original model submitted corrected for the averaging between male and female mortality the deterministic cost effectiveness estimate for fluocinolone compared to sham is £24,184 per QALY. The central probabilistic estimate over 10,000 iterations when administrations and drug prices are treated deterministically is £23,200 per QALY.

But for the Version_B model the deterministic cost effectiveness estimate for fluocinolone compared to sham is £19,269 per QALY, while the revised probabilistic estimate over 10,000 iterations when

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\(^{16}\) Implemented within the SA_Inputs worksheet by setting cells J499-J506=N, J534:J536=N and J577:J582=N

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Table 57.
administrations and drug prices are treated deterministically is £29,132 per QALY. This apparent strong non-linearity has not been confirmed with the manufacturer, and has not been investigated by the ERG due to time constraints.

- The NICE STA of ranibizumab for DMO

Given the manufacturer references to the NICE STA of ranibizumab for DMO, a brief summary of its elements is in order. It should also be borne in mind that the NICE STA of ranibizumab for DMO did not recommend its use. While this does not imply that NICE rejected all the modelling inputs, the converse that NICE accepted all the modelling inputs cannot be assumed.

  - Ranibizumab STA: Quality of life values

The ranibizumab manufacturer estimated quality of life values using EQ-5D data collected during pivotal ranibizumab trial. This was transformed into HRQoL values using the standard UK social tariff in line with NICE guidelines, with these values apparently being regressed on the BCVA in the treated eye, within an analysis that apparently corrected for repeat observations. This resulted in the following HRQoL estimates\(^{17}\) (Table 58).

\(^{17}\) Table 11 of the ERG report: [http://www.nice.org.uk/nicemedia/live/13125/53408/53408.pdf](http://www.nice.org.uk/nicemedia/live/13125/53408/53408.pdf), and repeated in section 6.4.7 of the fluocinolone submission.
Table 58. Utility values used within the ranibizumab and fluocinolone for DMO STA modelling

<table>
<thead>
<tr>
<th>Ranibizumab submission</th>
<th>Fluocinolone submission</th>
</tr>
</thead>
<tbody>
<tr>
<td>Health state</td>
<td>ETDRS</td>
</tr>
<tr>
<td>HS01 &amp; HS02</td>
<td>≥ 75</td>
</tr>
<tr>
<td>HS03</td>
<td>≥ 65 to &lt; 75</td>
</tr>
<tr>
<td>HS04</td>
<td>≥ 55 to &lt; 65</td>
</tr>
<tr>
<td>HS05</td>
<td>≥ 45 to &lt; 55</td>
</tr>
<tr>
<td>HS06</td>
<td>≥ 35 to &lt; 45</td>
</tr>
<tr>
<td>HS07</td>
<td>≥ 25 to &lt; 35</td>
</tr>
<tr>
<td>HS08</td>
<td>&lt; 25</td>
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<td></td>
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</table>

Unfortunately, within the publicly available documents the proportion of the ranibizumab patients who had their BSE treated is redacted, as are the rates of fellow eye DMO and fellow eye DMO with visual impairment at baseline.

The initial ERG commentary was concerned about the spread of utility values being too large if the BCVA tended to be correlated with the other complications of diabetes. The ERG commentary on the ranibizumab manufacturer response to the ACD was that the manufacturer had provided additional covariate analysis, which found none of the covariates to be significant.

The spread of utility values for the base case of the fluocinolone submission is larger than that of the ranibizumab submission.

- **Ranibizumab STA: Bilateral retreatment rate**

The ranibizumab manufacturer suggested that 35% of DMO patients might require bilateral treatment. The ERG commented that not taking bilateral treatment into account would have seriously underestimated overall treatment costs. The ERG commented that the original modelling of only the WSE would also overestimate the cost offsets arising from fewer patients falling into blindness.

A key difference within the fluocinolone submission is that the 35% rate of bilateral treatment in the sham arm is reduced to only [insert value] in the fluocinolone. This arises from the assumption that those...
experiencing raised IOP from fluocinolone in the initially treated eye will not be treated with fluocinolone in the fellow eye.

- **Ranibizumab STA: Bilateral QALY uplift**

For the quality of life uplift the ERG commentary was that the ranibizumab manufacturer presented an additional scenario analysis with “35% of patients requiring treatment in both eyes” and “assumes an additional incremental 25% utility gain”\(^{18}\). There was no justification presented for the assumed 25% utility gain.

It appears that the presentation of the results of this analysis was such that quite what had been changed within the modelling could not be determined by the ERG. But the wording suggests that the 25% utility gain might not have been applied to each arm but rather to the incremental gain estimated assuming no bilateral treatment.

The fluocinolone modelling applies the bilateral QALY uplift to each arm, conditioned by the rates of bilateral retreatment: 35% in the sham arm and [ ] in the fluocinolone arm. This results in a larger bilateral QALY uplift being applied within the sham arm than within the fluocinolone arm. The two methods are only equivalent if the same bilateral treatment rate is applied in both arms. Which if any method is most reasonable to apply is a moot point.

- Individual and overall impacts of the changes made for the Version_B model

For the comparison between fluocinolone and sham, the changes between the original model and the Version_B model revise the cost effectiveness estimate from £22,655 per QALY to £19,269 per QALY. The ERG has applied the changes individually and collectively to the original model to arrive at the Version_B model as tabled below.

Among the structural changes, the revised calculation of the quarterly all-cause mortality from the annual all-cause mortality has little impact: removing it only worsens the revised ICER from £19,269 per QALY to £19,334 per QALY. For this reason, the structural changes affecting the mortality calculation have been combined. The column headers apply:

- No structural changes to the original submission
- The structural changes around mortality, in effect allowing for the higher male mortality rate
- The structural change of only applying the QALY uplift for bilateral treatment within the fluocinolone arm
- The two bullets above combined

\(^{18}\) [Link to source](http://www.nice.org.uk/nicemedia/live/13125/55338/55338.pdf)
The individual impacts of the individual data input changes are applied, followed by the combined impact of all the data input changes. The revision to the mortality data inputs is then removed from the Version_B model as the ERG views this as unrealistic. This permits the percentage QALY uplift for bilateral treatment and the source of the HRQoL data to be selectively removed, to explore their contribution to the Version_B model outputs.

The following table reports the cost effectiveness estimates that result from these changes for the comparison of fluocinolone with sham (Table 59).

Table 59. Individual and overall impacts of the changes made for Version_B model: ICERs

<table>
<thead>
<tr>
<th>Data input changes</th>
<th>Structural changes</th>
</tr>
</thead>
<tbody>
<tr>
<td>None: the Original submission</td>
<td>£22,650&lt;sup&gt;19&lt;/sup&gt;</td>
</tr>
<tr>
<td>(1) All-cause mortality from 0.77% to 1.90%</td>
<td>£28,542</td>
</tr>
<tr>
<td>(2) Bilateral percentage from 35.0% to 35.3%</td>
<td>£37,961</td>
</tr>
<tr>
<td>(3) Flu. bilateral treatment from 82.9% to 85.6%</td>
<td>£22,144</td>
</tr>
<tr>
<td>(4) Bilateral QALY uplift from 25% to 10%</td>
<td>£21,214</td>
</tr>
<tr>
<td>(5) Responder percentage from 25% to 22%</td>
<td>£21,525</td>
</tr>
<tr>
<td>(6) HRQoL from Heintz rather than Brown</td>
<td>£32,617</td>
</tr>
<tr>
<td>All: the Version_B model</td>
<td>£50,800</td>
</tr>
<tr>
<td>All except (1)</td>
<td>£41,273</td>
</tr>
<tr>
<td>All except (1) and (4)</td>
<td>£55,463</td>
</tr>
<tr>
<td>All except (1) and (6)</td>
<td>£29,942</td>
</tr>
<tr>
<td>All except (1), (4) and (6)</td>
<td>£34,736</td>
</tr>
</tbody>
</table>

In terms of the structural changes, the main impact arises from only applying the QALY uplift for bilateral treatment within the fluocinolone arm. In terms of the data input changes, the revised mortality data has a reasonably large impact. But the main impacts arise from the increased percentage of bilateral treatment and the source of the HRQoL data.

If none of the structural changes are made, reducing the bilateral QALY uplift from 25% to 10% has little impact upon the cost effectiveness results and only reduces the cost effectiveness estimate from £22,650 per QALY to £21,214 per QALY. Excluding the revisions to the mortality input data, if the structural change to the QALY uplift for bilateral treatment is applied resulting in it only occurring within the fluocinolone arm, a 25% uplift rather than a 10% uplift greatly improves the cost.

<sup>19</sup> This differs very slightly from the £22,655 per QALY of the base case of the original submission for reasons that the ERG has not been able to identify.
effectiveness estimate from £14,870 per QALY to £7,963 per QALY. But if the structural change to the QALY uplift for bilateral treatment is not applied, and the uplift remains in both arms, a 25% uplift compared to a 10% uplift worsens the cost effectiveness estimate from £43,736 per QALY to £59,337 per QALY.

5.4 Conclusions of the cost effectiveness section

The detail of the economic modelling provided within the submission is poor. The ERG has a number of concerns with the modelling that can be broadly grouped under the following headings: modelling approach and structure; model implementation; model data inputs; and, model extrapolation. There is some unavoidable cross over between these headings.

Note that due to the opacity of the submission and the extent of the cross checking required, the ERG has not had time to double check all the elements that are quantified in this chapter. The ERG has tried to be explicit in the derivation of all these elements. The ERG recognises that the manufacturer has to thoroughly cross check these elements during the next stage of the assessment process, prior to the first assessment committee meeting. The ERG is happy to provide any further clarification of the derivation of these elements that the manufacturer may require.

- Modelling approach and structure
The over-riding issue is whether it would have been both more appropriate and feasible to model patients as having two eyes, rather than undertaking an ad hoc adjustment to the output of a model of patients having only one eye. The ERG is of the opinion that it would have been feasible. The trial underlying this submission had a reasonable proportion of patients that had their better seeing eye treated, and the rate of chronic DMO in the fellow eye at baseline and over the course of the trial was high. A patient level model might be required to model patients as having two eyes, coupled with assumptions about the rate of visual worsening in eyes with chronic DMO but no visual impairment. Transition probability matrices could be applied to the individual eyes, with a patient’s BCVA being genuinely bilateral and driven by the best seeing eye. This could be coupled with a base case assumption that the majority of the untreated WSEs are not eligible for treatment. Modelling patients as having two eyes would appear to be the most reasonable model structure. It would also help address data input issues around quality of life values and the costs of blindness.

The distribution between health states over the period of the trial is drawn directly from trial data, rather than the more usual modelling approach of using transition probability matrices. But the distribution between health states for both fluocinolone responders and fluocinolone non-responders at 36 months is modelled as being a constant percentage of the overall patient distribution at 36
months. This change of approach is not justified by the manufacturer and it may have led to bias against fluocinolone. Linked to this, the three yearly drop-out rate applied within the fluocinolone arm at year 3 is not obviously required. It may have been better to simply use the responder patient distribution remaining in the trial and followed up at 36 months.

The original model applies a fluocinolone responder rule of a minimum 5 letter improvement between baseline and 36 months. A more realistic responder rule might be a minimum 10 letter improvement between baseline and 36 months. The manufacturer has provided revised estimates based upon the 10 letter responder rule. But as per the above point, the only impact arising from this within the model is to increase the overall proportion of patients discontinuing fluocinolone treatment at year 3. It does not affect the health state distribution among the fluocinolone responders. Taking into account the health state distribution among the fluocinolone responders might significantly improve the cost effectiveness estimate for fluocinolone versus sham.

- Model implementation
The original electronic model contains a number of structural errors. It is difficult to see how the majority of these have arisen, if not by design. Addressing these to reflect what appears to be the intended manufacturer model structure as stated within the submission worsens the cost effectiveness estimate for fluocinolone versus sham by around 17%. Note that this does not revise the model to address the ERG concerns about the intended manufacturer model structure. It only revises the electronic model to be in line with the apparently intended manufacturer model structure.

The model anticipates quite large cost offsets from the fluorescein angiography costs arising from laser treatment, with all patients in the sham arm requiring 3 fluorescein angiographies during the first 3 years. ERG expert opinion suggests that these costs should be applied per laser administration, regardless of arm.

The original model applies the bilateral treatment uplift to increase costs and QALYs in the fluocinolone arm and in the sham arm. Of those eligible for bilateral treatment, around 15% fewer patients are modelled as receiving bilateral fluocinolone treatment due to raised IOP in the originally treated eye. Given the model implementation of the bilateral treatment QALY uplift, this penalises fluocinolone.

The Version_B model, which the manufacturer asks to be considered as the revised base case, removes the bilateral treatment QALY uplift from the sham arm. This has a large beneficial impact upon the cost effectiveness estimate. The manufacturer does not mention this structural change.
The manufacturer justification for not presenting the central probabilistic cost effectiveness estimates alongside the deterministic estimates for the base case is not valid.

- Model data inputs

The fluocinolone overall drop-out rate of **% from years 1 to 3 applied to fluocinolone responders at years 6, 9 and 12 should be corrected for deaths resulting in a ** estimate. It is also not clear that the fluocinolone overall drop-out rate should be applied to fluocinolone responders at years 6, 9 and 12.

The model does not take into account the proportion of patients who are pseudophakic at baseline. As a consequence, it overestimates the number of cataract extractions required to the probable detriment of fluocinolone.

Due to the model mainly simulating the BCVA of the worst seeing eye, there is considerable uncertainty around the appropriateness of the quality of life values. The original submission quality of life values relate to the better seeing eye. While the manufacturer has attempted to address this within the Version_B model, the revisions provide only three quality of life values over the 13 health states of the model. These are also non-monotonic.

The rates of adverse event applied within the modelling do not appear to cross check with those given within the submission. The costs applied to these also do not appear to cross check with the NHS reference costs cited.

The all-cause mortality data of the original model, when correctly averaged between female and male all-cause mortality, appears to be more reasonable that that applied within the Version_B model.

- Model extrapolation.

The original model divides the fluocinolone arm into responders at year 3 who do well and continue with fluocinolone treatment, and non-responders at year 3 who do not. Data from the fluocinolone responders is used by the manufacturer to extrapolate a net ** improving by one health state every quarter thereafter, which may be optimistic over the time horizon of 15 years. Applying the trial data of ** “patient quarter” improvements and ** “patient quarter” worsenings, a larger net difference of **, also worsens the cost effectiveness estimate for fluocinolone versus sham by around **.

Data from the fluocinolone non-responders is used by the manufacturer to extrapolate ** worsening by one health state every quarter thereafter. Whether this will apply to the fluocinolone non-
responders over the time horizon of 15 years is uncertain. But more serious is that this assumption is also applied across all patients in the sham arm. Data supplied by the manufacturer at clarification does not support this assumption. Applying an approximation of the trial data of “patient quarter” improvements and “patient quarter” worsenings to fluocinolone non responders and those in the sham arm worsens the cost effectiveness estimate for fluocinolone versus sham by around . Applying the above extrapolation changes to fluocinolone responders, fluocinolone non-responders and sham simultaneously worsens the cost effectiveness estimate for fluocinolone versus sham by around .
6. **IMPACT ON THE ICER OF ADDITIONAL CLINICAL AND ECONOMIC ANALYSES UNDERTAKEN BY THE ERG**

The ERG is bound by the model structure implemented by the manufacturer, and cannot implement what might be a preferable model approach and structure as summarised at the end of the previous chapter. The ERG can only revise the manufacturer model structure and data inputs within reasonable bounds. In the light of this, the ERG presents a revised baseline. This makes a number of changes.

- **Error correction**
  - Corrects the errors in the electronic model identified in section 5.3.4
  - Retains the mortality data inputs of the original submission
  - Assumes that a fluorescein angiography costing £250 will be required prior to each laser administration, with this applying in both the fluocinolone arm and the sham arm\(^{20}\). In the hospital of one of the ERG members, private patients are charged around £150 for fluorescein angiography, and this cost has been applied

- **Data inputs**
  - Corrects the laser administration rate in the sham arm for year 3 to be 0.68 as intended within the manufacturer model\(^{21}\)
  - Applies unit costs for adverse event procedures of £1,151 for glaucoma, £1,938 for vitrectomy, £1,938 for retinal detachment and £2,244 for endophthalmitis.\(^{22}\)
  - Retains the quality of life values of the original submission

- **Extrapolation**
  - Revises the quarterly extrapolation percentages for fluocinolone patients satisfying the 5 letter responder rule to improving and worsening\(^{23}\)
  - Revises the quarterly extrapolation percentages for fluocinolone patients satisfying the 10 letter responder rule to improving and worsening\(^{24}\)
  - Revises the quarterly extrapolation percentages for sham to improving and worsening\(^{25}\)

---

\(^{20}\) Implemented in the *Default Inputs* worksheet by setting cell F343=0 and adding a £150 cost per fluorescein angiography to the cost per laser administration by setting cell F307=£150+£150.

\(^{21}\) Implemented in the *SA Inputs* worksheet by setting H534=Costs!H78

\(^{22}\) Implemented in the *Default Inputs* worksheet by setting H280=£2,244, H281=£1,938, H282=£1,151 and H283=£1,938

\(^{23}\) As per Chapter 5

\(^{24}\) Implemented in the *Efficacy-Past Year_3* worksheet by setting F19=**, F20=**, F21=** and H21=F21. Note that as before in Chapter 5, setting F21=** creates a circular cell referencing warning within excel, which relates to cells P413:P415 of the *SA Inputs* worksheet. These cells are only used for the probabilistic model, and the deterministic model should be unaffected by this. The responder rate also has to be revised in the *Calc1* worksheet by setting D17=**

\(^{25}\) As per Chapter 5
- Revises the fluocinolone drop-out rate for years 6, 9 and 12 to control for deaths\textsuperscript{26}

**Bilateral treatment**
- Applies a bilateral treatment rate of 40\% in the sham arm\textsuperscript{27}
- Applies a bilateral treatment rate with fluocinolone of \textsuperscript{28} \% of the sham bilateral retreatment rate
- Applies a quality of life uplift of 10\% for bilateral treatment\textsuperscript{29}
- Applies a cost and quality of life uplift for those requiring bilateral treatment in the fluocinolone arm but not eligible for bilateral fluocinolone treatment drawn from the bilateral uplifts applied within the sham arm\textsuperscript{30}
- Applies the bilateral treatment rate in the sham arm to a £5,794 cost of blindness to result in an annual average cost of blindness of £2,318\textsuperscript{31}

Note that for those receiving bilateral fluocinolone treatment the revised method of applying the bilateral treatment QALY uplifts is equivalent to applying the bilateral treatment QALY uplift to the incremental QALY gain from fluocinolone over sham, as appeared to be the method of the ranibizumab manufacturer within the NICE STA of ranibizumab for DMO.

Note that these changes do not correct all the issues identified by the ERG within the submission and model. For instance, the rates of adverse events have not been addressed, or the costs of any possible additional follow up associated with their treatment. The rates of cataract extraction have also not been addressed, mainly because simply revising the baseline pseudophakic percentage to 43\% within the cohort flow worksheets causes downstream structural problems within the model.

The following cost effectiveness estimates are referred to as a baseline estimates rather than as base case estimates (Table 60 and Table 61). They only partially address the concerns around the model structure and model inputs, and are something to work from rather than rest upon.

\textsuperscript{26} Implemented in the Calc1 worksheet by setting D18=16.7\% and revising the references in cells E79:Q79, E91:Q91, E103:Q103, E145:Q145, E157:Q157, E169:Q169, S79, S91 and S103 to $D$16 to instead refer to $D$18
\textsuperscript{27} Implemented in the Default_Inputs worksheet by setting F35=40\%
\textsuperscript{28} Implemented in the Default_Inputs worksheet by setting J35=0.852*F35
\textsuperscript{29} As per Chapter 5
\textsuperscript{30} Implemented in the Default_Inputs worksheet by setting J37=10\%
\textsuperscript{31} Implemented in the Default_Inputs worksheet by setting F37=£2,318
Table 60. ERG baseline cost effectiveness estimates: 5 letter responder rule

<table>
<thead>
<tr>
<th></th>
<th>Cost net</th>
<th>QALYs net</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>£6,795</td>
<td>6.375</td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>£21,364</td>
<td>£14,569</td>
<td>6.761</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.386</td>
<td>£37,740</td>
</tr>
</tbody>
</table>

Table 61. ERG baseline cost effectiveness estimates: 10 letter responder rule

<table>
<thead>
<tr>
<th></th>
<th>Cost net</th>
<th>QALYs net</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham</td>
<td>£6,795</td>
<td>6.375</td>
<td></td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>£19,532</td>
<td>£12,736</td>
<td>6.730</td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.354</td>
<td>£35,940</td>
</tr>
</tbody>
</table>

The above could be taken to imply a cost effectiveness estimate of moving from a 10 letter responder rule to a 5 letter responder rule of £57,888 per QALY. But the ERG views this as beyond the capacity of the current model. It must be borne in mind that the current model applies the same distribution of fluocinolone responders between the health states regardless of the responder rule applied.

The following sensitivity analyses are also presented (Table 62).

1. Discontinuations among fluocinolone responders limited to year 3
2. A proportion requiring bilateral treatment of 52%, which also increases the average annual cost of blindness applied to £3,013
3. A quality of life uplift for bilateral treatment of 25%
4. Applying the manufacturer Version_B quality of life values
5. Applying the ranibizumab manufacturer quality of life values from the NICE STA of ranibizumab for DMO
6. Stable visual acuity in the fluocinolone on treatment arm from year 9
7. Reverting to the original manufacturer extrapolation assumptions
8. Reverting to the original fluorescein angiography cost of £332 and its implementation
9. Reverting to the original annual average cost of blindness of £6,298
10. Applying the all-cause mortality risk from the Version_B model
11. Applying a DMO SMR of 3.5, resulting in 33% being modelled as surviving to the end of the time horizon

---

32 Implemented within the Default_Inputs worksheet by setting F33=3.50
### Table 62. ERG sensitivity analyses

<table>
<thead>
<tr>
<th>Change made</th>
<th>ICERs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Revised baseline</td>
<td>5 letter responder rule</td>
</tr>
<tr>
<td></td>
<td>£37,740</td>
</tr>
<tr>
<td>SA1 Fluo. discontinuation only year 3</td>
<td>£40,534</td>
</tr>
<tr>
<td>SA2 Bilateral treatment 52%</td>
<td>£39,788</td>
</tr>
<tr>
<td>SA3 Bilateral treatment QALY uplift 25%</td>
<td>£35,963</td>
</tr>
<tr>
<td>SA4 Version_B quality of life values</td>
<td>£48,843</td>
</tr>
<tr>
<td>SA5 Ranibizumab DMO STA quality of life values</td>
<td>£145,866</td>
</tr>
<tr>
<td>SA6 Fluo. onTx stable BCVA from year 9</td>
<td>£38,306</td>
</tr>
<tr>
<td>SA7 Fluo. onTx 5% better, offTx 3% worse per cycle</td>
<td>£29,208</td>
</tr>
<tr>
<td>SA8 Manufacturer fluorescein angiography assump.</td>
<td>£35,690</td>
</tr>
<tr>
<td>SA9 Manufacturer cost of blindness £6,298</td>
<td>£34,356</td>
</tr>
<tr>
<td>SA10 Version_B model all-cause mortality</td>
<td>£46,647</td>
</tr>
<tr>
<td>SA11 DMO SMR 3.5</td>
<td>£40,328</td>
</tr>
</tbody>
</table>

Results show some sensitivity to the costs of blindness, the treatment of fluorescein angiography costs and are reasonably sensitive to both the extrapolation percentages assumed and mortality. But the main sensitivity is to the source of quality of life values.

The changes in the ICERs when the quality of life values from the manufacturer submission to the NICE STA of ranibizumab for DMO are applied are surprisingly large, to the extent that the ERG would much appreciate the manufacturer re-running these analyses during the formal factual error cross check prior to the first assessment committee meeting.
7. DISCUSSION AND RESEARCH NEEDS

What should be regarded as a clinically significant response and as an indication for further treatment?

The Alimera submission assumes that at 36 months, re-treatment with fluocinolone would be given in those with at least 5 letters gain. Using this rule, ** would be re-treated.

There are several issues to be considered.

Firstly, is a 5-letter gain sufficient? Should a gain of 10 or more letters be used instead?

Secondly, what about patients who gained 10 or more letters during the 3 years, but who had lost some by 5 years? Some patients may gain 10-15 letters at 2 to 2.5 years (peak effect) but then deteriorate. So we might define responders as those who gain at least 10 letters at any time.

Thirdly, how do we define unresponsiveness to laser? One laser treatment is not enough, because even after a modest response to first laser, further laser treatments may be worthwhile. In the FAME trial, it was stated that patients had to have had at least one previous laser treatment but have central retinal thickness over 250 microns. However, if before laser, CRT had been 400 and was now 251, that would be a very good response. So repeating laser therapy would be an option.

Combinations of treatment
The FAME trial recruited mainly people who had not done sufficiently well on laser treatment, but management of DMO is changing. Drugs such as the anti-VEGFs and fluocinolone could be used initially since they tend to reduce the amount of oedema quite quickly, and then laser could be used to “consolidate” the effects. Laser could then be applied with low power when the retinal thickness has decreased, with the aim of reducing the number of treatments needed. We need research to determine how well this would work.

Convenience
Fluocinolone involves treatment once every 3 years, albeit with intervening monitoring. This might be very attractive to some people for whom access to hospital clinics is difficult, because of distance or disability. Patients who do not like injections into the eye might also prefer a single injection every three years, even if it means compromising on outcomes.

Could raised IOP be predicted?
A previous study tried to use topical steroids to predict which patients would have marked rises in IOP with intravitreal steroids. This was not very successful with a negative predictive value of only 60% - i.e. 40% of patients who had no rise in IOP after topical steroids would have a rise after intravitreal steroids. The Iluvien insert releases fluocinolone for about 30 months, and once inserted, cannot easily be removed (it would need a vitrectomy). The ERG wondered if a trial of a shorter-lasting steroid such as dexamethasone (as Ozurdex) could be used – if there was no rise in IOP, treatment could be continued with fluocinolone. Ozurdex releases dexamethasone for under 3 months, with peak effect at 90 days. However it is possible that IOP may not rise with dexamethasone but rise with fluocinolone. It is also possible that even using the same steroid, there may be no rise with the first injection but a rise with a second one. So at present there is no sound evidence base for a trial of a shorter-acting steroid as a predictor of raised IOP with fluocinolone.

This might be an area for further research. It would also be useful to determine the factors that predict the need for glaucoma surgery.

**Should glaucoma be an absolute contraindication to fluocinolone?**

Patients with glaucoma were excluded from the FAME trial. However if other treatments for DMO have failed, and visual impairment is progressing, and if the IOP is controlled on eye drops, could there be a place for fluocinolone?

**Other drugs**

This section is based on the systematic review of treatment for DMO by Ford et al 2012.

**Other steroids**

Two other steroids have been used in DMO, triamcinolone and the long-acting form of dexamethasone, Ozurdex. All steroids will be associated with cataract and raised IOP.

The effects of dexamethasone (Ozurdex) appear to peak at three months. At six months there was no significant difference compared with laser. This might imply that earlier re-treatment is needed if the beneficial effect is to be maintained, but increasing the number of treatments would be likely to increase the associated complications, especially with the relatively large needle size. The addition of laser did not appear to add further benefit. There was no significant difference in cataract formation at six months with dexamethasone compared to observation but it is likely that a higher incidence of cataracts would be seen with longer follow-up. Significantly more patients suffered increased IOP in the dexamethasone group compared with observation. Ozurdex does not yet have a licence for DMO.
Triamcinolone is not licensed for use in the eye but has been widely used. Ford et al\textsuperscript{39} identified ten trials evaluating intravitreal triamcinolone. Two trials used Trivaris\textsuperscript{47,89}, two trials used Kenacort\textsuperscript{90,91}, one trial used Kenalog\textsuperscript{92}, one trial used Trimahexal\textsuperscript{93} and four trials did not report the type of triamcinolone used.\textsuperscript{94-97} Three doses were assessed in the included studies (1 mg, 4 mg and 8 mg) and triamcinolone has been combined with laser or bevacizumab. Trivaris is no longer available.

Ip and colleagues (n=840) were the only authors to evaluate triamcinolone 1 mg (Trivaris).\textsuperscript{41,89,98,99} They found a statistically significant improvement in mean BCVA at two years in the laser group compared with the triamcinolone group and no significant difference between 1 mg compared with 4 mg.

Several trials used 4 mg intravitreal triamcinolone. Ip and colleagues (n=840) found that laser therapy resulted in a greater improvement in mean BCVA at two years compared to 4 mg triamcinolone (Trivaris).\textsuperscript{41,89,98,99} Lam and colleagues (n=111), found no statistically significant difference between laser and triamcinolone at six months (triamcinolone type not reported).\textsuperscript{95} When these two trials were pooled through meta-analysis, the treatment effect favoured laser but differences were not statistically significant. Ockrim and colleagues (n=88) compared 4 mg intravitreal triamcinolone (Kenalog) with laser alone.\textsuperscript{92} At 12 months they found no statistically significant BCVA improvement between the triamcinolone and laser groups. Gillies and colleagues (n=69) compared 4 mg of triamcinolone (Kenacort) with sham injection.\textsuperscript{90} Mean BCVA improved statistically significantly with triamcinolone at 24 months compared with sham injection (3.1 letters gain compared with 2.9 letters loss, \(p = 0.01\)).

Lam and colleagues (n=111) compared triamcinolone 4 mg alone with 4 mg of triamcinolone plus laser or laser alone.\textsuperscript{95} At six months the authors found no difference in BCVA between any of the groups. Elman and colleagues (n=854) compared 4 mg of triamcinolone (Trivaris) plus laser with ranibizumab plus prompt (within 3-10 days) or deferred (more than 24 week) laser and laser alone.\textsuperscript{47} At two years they found a statistically significant difference in mean BCVA between ranibizumab plus prompt/deferred laser compared with laser alone (7 letters gain/9 letters gain compared with 3 letters gain), but no difference with triamcinolone plus laser compared with laser alone (2 letters gain compared with 3 letters gain). Oliveiro Neto and colleagues (n=120) compared 4 mg triamcinolone alone (triamcinolone type not reported) with 4 mg plus 1.25 mg bevacizumab.\textsuperscript{96} At six months they found no statistically significant difference between groups.

The Elman and Lam studies were suitable for meta-analysis, which showed non-statistically significant improvements in mean BCVA and the proportions of patients with more or equal than 15 letter gain in the triamcinolone plus laser group compared with laser alone.
Triamcinolone was associated with consistently higher incidences of IOP increase and cataracts. Gilles and colleagues reported a cataract rate of over 50% by three years in patients treated with triamcinolone.

The anti-VEGF drugs
These are bevacizumab, ranibizumab and pegaptanib. They are not relevant to this appraisal because fluocinolone is indicated when other treatments have been tried. However, given the once in every three years fluocinolone regimen, there could be an argument for selective earlier use of fluocinolone instead of the anti-VEGF drugs in patients with problems with access problems, especially if they have had cataracts removed. Bevacizumab and ranibizumab have to be given much more frequently, perhaps 8-9 times in the first year, reducing to 2-3 a year thereafter.

Although the anti-VEGFs are clinically effective and a major step forward in the management of DMO, it has to be noted that they have little effect in the majority of patients. Generally speaking, the proportion of patients who have demonstrated 10 or more letter gain is between 30-50% in the trials that demonstrate greatest effectiveness. Most of these patients would not achieve the 20/40 visual acuity required for driving. More effective treatments, or combinations of treatments, are required.

Other treatments
It should be remembered that better control of blood glucose, blood pressure and blood lipids reduces the risk of DMO and the other complications of diabetes.

A variety of other treatments have been tried. One study assessed diclofenac but follow-up was for only 12 weeks and the study had only 32 patients. Patients were randomised to intravitreal diclofenac or triamcinolone. Both diclofenac and triamcinolone reduced CMT, but a statistically significant visual improvement was observed only in the triamcinolone group.

Sfikakis and colleagues undertook a small (11 patients) 30-week randomised crossover trial comparing infliximab and placebo. They found that infliximab resulted in a 28.6% improvement in vision compared with 4.3% with placebo.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial was primarily a study to see if the lipid-lowering agent fenofibrate, could reduce macrovascular and microvascular events in type 2 diabetes. However a substudy within FIELD recruited 1012 patients to a retinopathy study. The primary outcome in the main study was need for laser therapy (3.4% on fenofibrate versus 4.9% on placebo) but the substudy used retinal photography to assess progression of retinopathy or
development of macular oedema. The hazard ratio at six years for DMO was 0.69 (95%CI 0.54 to 0.87) in the fenofibrate group compared to placebo.

One small trial by Gupta et al\textsuperscript{103} and a small case series reported by Panagiotoglou et al\textsuperscript{104} suggested that lipid-lowering with atorvastatin might also be useful in DMO.

Ruboxistaurin is another oral agent which has been assessed for the treatment of DMO. Aiello and colleagues randomised 686 patients to receive placebo or one of three doses of ruboxistaurin.\textsuperscript{105,106} There was no statistically significant difference in delay to sight-threatening DMO in any ruboxistaurin group compared to placebo. The authors suggest that differences in laser treatment between groups may have contributed to the non-significant finding.

**Mortality**
The importance of mortality rates is that the longer people live after gaining vision from treatment, the more time they have to gain QALYs.

In their submission, Alimera used a relative risk of 2.45 for mortality, for people with diabetes and DMO, relative to the general non-diabetic population. They noted (paragraph 6.3.8.7) that this had been used in the NICE appraisal of ranibizumab.

That figure was provided by Novartis in a post-ACD submission following a minded no. It was derived from two studies, one that provided the relative risk of people with diabetes compared to the general population, of 1.93 (Mulnier), and one that provided the relative risk of people with diabetes and DMO compared to people with diabetes but no DMO, of 1.27 (Hirai). The 2.45 is 1.93 x 1.27. However the 1.93 was for men only, with type 2 diabetes. The RR for women was 1.77.

The ranibizumab ERG noted problems with getting up to date mortality data, and noted that the figure of 2.45 seemed reasonable. In the time available, the ranibizumab ERG did not have time to do a systematic review of mortality studies. The remit of an ERG in the STA system is to critique the manufacturer’s submission. They are not resourced to do literature reviews.

However, for this submission, the fluocinolone ERG has done a rapid search for mortality studies, and has obtained more than were available for the ranibizumab STA. As outlined in a previous section, we believe that the figure of 2.45 could be too low.

In their submission, Alimera provide a sensitivity analysis using a RR of 1.9, which the ERG thinks is far too low. They did not carry out any SAs with higher RRs. In their model version B, they did
examine the effect of there being only 15% of patients being alive at the end of 15 years. If this figure is used in the manufacturer model (corrected for errors), the ICER goes from £26,526 to £35,384. As reported in the previous chapter, using a RR of 3.5 as a sensitivity analysis increases the ICER by about 7%, from baseline £35940 to £38467 (assuming 10 letter re-treatment threshold).

**Indirect comparison**

Could a proper indirect comparison have been done?

The ERG constructed a possible network diagram (Figure 15).

Figure 15. Possible network diagram

IVP: intravitreal pegaptanib; IVR: intravitreal ranibizumab; IVT: intravitreal triamcinolone

References available on request. We thank Dr John Ford for helpful discussions on NMAs

The feasibility of such as comparison would depend on their being reasonable similarities in the common comparator arms, in:

- Previous laser treatments
- Duration of DMO
- Length of follow-up
Treatment in sham arms.
A major problem would be that as mentioned in this report, the sham arm in FAME was a “standard of care” arm with 60% receiving laser treatment, but some receiving other therapies. In some other studies, the sham group did not receive other treatments.

The ERG has not had time to fully explore the possibility of doing a network meta-analysis, but given differences amongst what would be the common comparator arm (sham with rescue laser), we are doubtful that the FAME trial could be included in a NMA.

Research needs
Studies comparing dexamethasone and fluocinolone are needed to ascertain the most cost-effective steroid. We suspect that on the basis of duration of action, number of inserts required, and size of needle, that fluocinolone will be preferable on clinical effectiveness grounds.

There is a lack of evidence for the use of anti-VEGF drugs or steroids in patients with macular ischemia secondary to DMO. A number of trials excluded patients with macular ischemia. The RESTORE trial included patients with macular ischemia and undertook a subgroup analysis. The authors compared patients with (n=34) and without (n=35) macular ischemia at baseline. They found that those without macular ischemia responded better to ranibizumab (mean average change in BCVA at 12 months 7.2 letters gain compared with 6.3 letters). Larger trials are needed to assess the use of anti-VEGF drugs and steroids in patients with macular ischemia.

There is also the question of assessing and treating peripheral retinal ischaemia. What is the value of laser treatment to such areas in reducing VEGF levels and hence improving DMO?

Conclusions
On clinical effectiveness grounds, fluocinolone appears to be a useful addition to the therapeutic armentarium for DMO, and to be the steroid of choice. Because of the very high cost and the adverse effects, its place remains to be determined. It may be that as Alimera have argued, it should be used in chronic DMO after laser photocoagulation and anti-VEGF treatment has failed. However the 3-year or more interval between inserts may make it suitable for selective earlier use when only laser has failed, particularly for patients for whom frequent attendance for anti-VEGF injections would be problematic.

There may be a particular niche for fluocinolone in patients who have already had cataracts removed, or who are developing cataracts that will need removal.
Better treatments for DMO are still required because many patients do not get a satisfactory response to any of the current treatments. It should be remembered that better control of blood glucose, blood pressure and blood lipids would reduce the frequency of DMO.
REFERENCES


58. Payakachat N, Summers KH, Pleil AM, Murawski MM, Thomas J, III, Jennings K et al. Predicting EQ-5D utility scores from the 25-item National Eye Institute Vision Function


APPENDICES

Appendix 1. Searches for diabetic retinopathy and risk of mortality

Searches for diabetic retinopathy and risk of mortality - run in Medline (Ovid) 1946 – to May 18th 2012

1. "diabet*".m_titl.
2. retinopathy.tw.
3. (macular edema or macular oedema).tw.
4. 2 or 3
5. 1 and 4
7. 5 and 6
8. limit 7 to english language

Searches for diabetic retinopathy and nephropathy - run in Medline (Ovid) 1946 – to May 21st 2012
1. (diabet* and (retinopathy or macular edema or macular oedema)).m_titl.
2. (nephropathy or microalbuminuria or proteinuria).m_titl.
3. 1 and 2
4. (prevalence or association or associated).tw.
5. 3 and 4
6. limit 5 to english language
Appendix 2. Risk of bias table for FAME study

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Description</th>
<th>Judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adequate sequence generation</td>
<td>Patients were randomized in a 1:2:2 ratio stratified by baseline BCVA and site. Patients were enrolled in the study using a computer generated schedule and an integrated voice recognition system.</td>
<td>Yes</td>
</tr>
<tr>
<td>Allocation concealment</td>
<td>Patients were enrolled in the study using a computer generated schedule and an integrated voice recognition system. Injectors and packaging identical.</td>
<td>Yes</td>
</tr>
<tr>
<td>Masking</td>
<td>Double-blinding. To preserve masking, two investigators were used. One investigator performed the treatments and the other masked investigator performed all assessments and determined retreatment eligibility.</td>
<td>Yes</td>
</tr>
<tr>
<td>Incomplete outcome data addressed</td>
<td>Intention to treatment analysis was used for the primary endpoint and missing data were imputed by last observation carried forward. Adequate description of loss to follow-up, withdrawals and adverse events.</td>
<td>Yes</td>
</tr>
<tr>
<td>Free of selective reporting</td>
<td>All pre-specified outcomes were reported</td>
<td>Yes</td>
</tr>
<tr>
<td>Groups comparable at baseline</td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Sample size calculation</td>
<td>180:180:90 subjects were expected to provide 89% power to detect a difference of 16% including a projected 10% dropout rate.</td>
<td>Yes</td>
</tr>
</tbody>
</table>