Clinical effectiveness and cost utility of photodynamic therapy for wet age-related macular degeneration

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ABOUT “HOME UNIT”

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Chris Hyde Main editor, conclusion, advice on conduct of systematic review of effectiveness

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SUMMARY

• Description of proposed service
Photodynamic therapy (PDT) is the new intervention to be evaluated. It uses photosensitive drugs and a specially developed low-powered laser. PDT is intended to treat patients with new neovascular membranes in wet AMD who still retain some visual acuity. Its aim is to stop leaking from the membranes and so halt further loss of vision. It is not intended to restore vision already lost. This systematic review examines the clinical effectiveness and cost utility of PDT for the neovascular form of wet AMD.

• Epidemiology and background
The vast majority of AMD occurs in people over 60 years of age and the incidence and prevalence of AMD and its wet form is very dependent on age. Women and men probably have similar rates. The prevalence of wet AMD has been estimated at 3 per 1000 at age 60-64 and 117 per 1000 at age 90+. There are two forms of neovascular membranes in wet AMD – classic and occult. There will be roughly 50 new cases of classic neovascular membranes per year in a typical health authority of population ~ 500,000.

The result of AMD is a painless loss of central, sharply defined vision (decreased visual acuity) often noticed as difficulty in reading fine print or threading a needle. Visual impairment for an elderly person can have a severely disabling impact. When a person quickly loses their sight, they have to adapt their activities of daily living. For an older person this can be very difficult and the visual impairment may come at a time when they may be less able to adapt.

• Number and quality of studies, and direction of evidence
In the TAP trial there was consistent evidence at both 1 & 2 years that verteporfin PDT results in less deterioration in visual acuity in the randomised eye than placebo. The relative risk for loss of 15 letters (3 lines) or more at 2 years was 0.75 (95% CI 0.65, 0.88). This effect is both statistically significant and clinically important. The VIP trial showed a similar result. There is an increase in adverse events associated with verteporfin PDT. Most are minor. Sudden visual loss occurs in 1 to 4.4% of verteporfin PDT patients and is an effect that patients should be aware of.

• Summary of benefits
The balance of beneficial and disbeneficial effects measured in the included RCTs appears to favour verteporfin PDT. However, avoiding deterioration in visual acuity, does not equate directly with improving patient function and quality of life. Also, function is dependent on vision in both eyes, not just the impact of wet AMD on one eye and this needs to be taken into account. Lack of heterogeneity between the results of TAP and VIP challenges the assumption that the nature of the wet AMD neovascular lesions has as much influence on the relative effect of verteporfin PDT as is predicted on the basis of an assessment of clinical heterogeneity. Further investigation suggests the results of sub group analyses should be treated with extreme caution and at best should be regarded as generating hypotheses requiring more research. The impact of reduced deterioration in visual acuity should be based on whole trial estimates of effect.
• Costs
The cost of one vial of verteporfin, the drug used for PDT is currently £850. The current treatment costs for PDT treatment were estimated at £1181 per treatment. The net cost impact of implementing verteporfin PDT to the NHS for its currently licensed indication is somewhere between £16.4-£41.3 million per annum by the third year of the service being introduced. This figure could increase to £63.4 million by the third year if the licence was extended to all wet AMD neovascular lesions. These figures do not include the costs of training and likely need for increased numbers of consultant ophthalmologists and other trained staff.

• Cost/QALY
There is uncertainty about the cost-utility of verteporfin PDT. Cost effectiveness studies reviewed estimated that the cost per QALY at two years ranged from £60k to £122k. The economic model developed as part of this report obtained a base-case estimate of between £151k-£182k. The sensitivity analyses ranged from the best scenario of £47,000 to a worst scenario of £342k. All of the estimates at 2 years are at best at the margins of what is generally considered to be an efficient use of health care resources. None of them take into account that wet AMD can occur in the worse seeing eye and that this would increase the cost utility still further. More favourable estimates of cost-utility have only been obtained in models extrapolating beyond two years, the limit of RCT data.

• Need for further research
Our belief is that the best way to resolve many of uncertainties identified would be to conduct a large, multicentre, publicly funded pragmatic double-blind RCT with parallel health economic evaluation, assessing not just impact on visual acuity and adverse events, but also directly measured global quality of life and survival. There is no indication of the relationship between benefits and costs where wet AMD affects the worse seeing eye first. Treatment of wet AMD, with verteporfin, other types of PDT, and other new technologies is an area under very active investigation, so this technology should be kept under close review.
## ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>AA</td>
<td>Attendance allowance</td>
</tr>
<tr>
<td>AE</td>
<td>Adverse event</td>
</tr>
<tr>
<td>AMD</td>
<td>Age related macular degeneration</td>
</tr>
<tr>
<td>ARM</td>
<td>Age related maculopathy</td>
</tr>
<tr>
<td>ARVO</td>
<td>Association for Research in Vision and Ophthalmology</td>
</tr>
<tr>
<td>AUS/Aus$</td>
<td>Australia/Australian dollar</td>
</tr>
<tr>
<td>BD8</td>
<td>Registration form for blindness or partial sight</td>
</tr>
<tr>
<td>BNF</td>
<td>British National Formulary</td>
</tr>
<tr>
<td>BSC</td>
<td>Best supportive care</td>
</tr>
<tr>
<td>CCOHTA</td>
<td>Canadian Co-ordinating Office for Health Technology Assessment</td>
</tr>
<tr>
<td>CI</td>
<td>Confidence interval</td>
</tr>
<tr>
<td>cm</td>
<td>Centimetres</td>
</tr>
<tr>
<td>CNPTRG</td>
<td>Choroidal Neovascularisation Prevention Trial Research Group</td>
</tr>
<tr>
<td>CNV</td>
<td>Choroidal Neovascularisation (also CRN, CRNV, SRN, SRNV)</td>
</tr>
<tr>
<td>DARE</td>
<td>Database of Abstracts of Reviews of Effectiveness</td>
</tr>
<tr>
<td>DIHTA</td>
<td>Danish Institute for Health Technology Assessment</td>
</tr>
<tr>
<td>DLA</td>
<td>Disability living allowance</td>
</tr>
<tr>
<td>EDTRS</td>
<td>Early Treatment Diabetic Retinopathy Study</td>
</tr>
<tr>
<td>EUROQOL</td>
<td>European Quality Of Life – generic quality of life measure</td>
</tr>
<tr>
<td>GB</td>
<td>Great Britain</td>
</tr>
<tr>
<td>GHQ</td>
<td>General health questionnaire, (mental health)</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>Human immunodeficiency virus/acquired immunodeficiency syndrome</td>
</tr>
<tr>
<td>HTA</td>
<td>Health Technology Assessment</td>
</tr>
<tr>
<td>ICD-10</td>
<td>International classification of diseases, 10th revision</td>
</tr>
<tr>
<td>ICER</td>
<td>Incremental cost effectiveness ratio</td>
</tr>
<tr>
<td>INAHTA</td>
<td>International Association for Health Technology Assessment</td>
</tr>
<tr>
<td>LogMAR</td>
<td>Logarithm of the minimum angle of resolution</td>
</tr>
<tr>
<td>Lu-Tex</td>
<td>Lutetium texaphyrin</td>
</tr>
<tr>
<td>LVA</td>
<td>Low vision aids</td>
</tr>
<tr>
<td>m/m/m/m/mm</td>
<td>metres/milligrams/millilitres/millimetres</td>
</tr>
<tr>
<td>MPS</td>
<td>Macular Photocoagulation Study</td>
</tr>
<tr>
<td>N/A</td>
<td>Not applicable</td>
</tr>
<tr>
<td>NHS</td>
<td>National Health Service</td>
</tr>
<tr>
<td>NHSC</td>
<td>National Horizon Scanning Centre</td>
</tr>
<tr>
<td>NHSCRD</td>
<td>National Health Service Centre for Reviews and Dissemination</td>
</tr>
<tr>
<td>NHS EED</td>
<td>Database of economic studies</td>
</tr>
<tr>
<td>NICE</td>
<td>National Institute for Clinical Excellence</td>
</tr>
<tr>
<td>NL</td>
<td>Netherlands</td>
</tr>
<tr>
<td>NNT</td>
<td>Number needed to treat</td>
</tr>
<tr>
<td>no</td>
<td>Number</td>
</tr>
<tr>
<td>NPL</td>
<td>No perception of light</td>
</tr>
<tr>
<td>NSF</td>
<td>National Service Framework (for older people)</td>
</tr>
<tr>
<td>PDT</td>
<td>Photodynamic therapy</td>
</tr>
<tr>
<td>Abbreviation</td>
<td>Description</td>
</tr>
<tr>
<td>--------------</td>
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</tr>
<tr>
<td>PED</td>
<td>Pigment epithelial detachments</td>
</tr>
<tr>
<td>QALY</td>
<td>Quality adjusted life year</td>
</tr>
<tr>
<td>RCOphth</td>
<td>Royal College of Ophthalmologists</td>
</tr>
<tr>
<td>RCT</td>
<td>Randomised controlled trial</td>
</tr>
<tr>
<td>RNIB</td>
<td>Royal National Institute for the Blind</td>
</tr>
<tr>
<td>RPE</td>
<td>Retinal pigment epithelium</td>
</tr>
<tr>
<td>RPI</td>
<td>Retail price index</td>
</tr>
<tr>
<td>RR</td>
<td>Relative risk</td>
</tr>
<tr>
<td>SMM</td>
<td>Norwegian Centre for Health Technology Assessment</td>
</tr>
<tr>
<td>SnET2</td>
<td>Tin ethyl etiopurpurin</td>
</tr>
<tr>
<td>SOE</td>
<td>European Society of Ophthalmology</td>
</tr>
<tr>
<td>TAP</td>
<td>Treatment of age related macular degeneration with photodynamic therapy (trial)</td>
</tr>
<tr>
<td>TTO</td>
<td>Time trade off</td>
</tr>
<tr>
<td>TTT</td>
<td>Transpupillary thermotherapy</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>USA</td>
<td>United States of America</td>
</tr>
<tr>
<td>VA</td>
<td>Visual acuity</td>
</tr>
<tr>
<td>VF-14</td>
<td>Visual Function 14 – vision specific quality of life measure</td>
</tr>
<tr>
<td>VIM</td>
<td>Visudyne® in minimally classic CNV (trial)</td>
</tr>
<tr>
<td>VIO</td>
<td>Visudyne® in occult CNV (trial)</td>
</tr>
<tr>
<td>VIP</td>
<td>Verteporfin in photodynamic therapy (trial)</td>
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## DEFINITIONS OF TERMS

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Age related macular degeneration (AMD)</td>
<td>Loss of the photoreceptors in the macula region of the retina resulting in decreased central vision and eventually central blindness. Occurs mainly in people over the age of 60. There are two main types: wet AMD and dry AMD (see below)</td>
</tr>
<tr>
<td>Age related maculopathy</td>
<td>Early stage of age related macular degeneration</td>
</tr>
<tr>
<td>Amsler Grid</td>
<td>A hand held chart with black horizontal and vertical lines on a white background, used to test for central visual field defects.</td>
</tr>
<tr>
<td>Blindness</td>
<td>Various definitions but usual standard is VA of 6/60 (20/200) or worse in the better eye or a visual field &lt; 20° in the better eye</td>
</tr>
<tr>
<td>Choroid</td>
<td>Layer of the eye containing the blood supply to the outer retina</td>
</tr>
<tr>
<td>Classic neovascular membranes/lesions</td>
<td>Neovascular membranes which are clearly delineated on fluorescein angiography and leak fluorescein uniformly</td>
</tr>
<tr>
<td>Drusen</td>
<td>Subretinal amorphous deposits, often age related</td>
</tr>
<tr>
<td>Dry AMD</td>
<td>More benign of the two forms of AMD in which neovascular membranes do not occur</td>
</tr>
<tr>
<td>Extrafoveal area</td>
<td>The area of the macula excluding the fovea</td>
</tr>
<tr>
<td>Fovea</td>
<td>Small area of the retina, lying within the macula, where light is focused to give sharpest central vision</td>
</tr>
<tr>
<td>Juxtafoveal area</td>
<td>The remainder of the foveal area, excluding the subfovea</td>
</tr>
<tr>
<td>Laser photocoagulation</td>
<td>Technique whereby new neovascular membranes are removed by laser ‘burns’ which concurrently damage overlying retina</td>
</tr>
<tr>
<td>Macula</td>
<td>Small area of the retina used for central vision, divided into three – subfoveal, juxtafoveal and extrafoveal</td>
</tr>
<tr>
<td>Neovascularisation</td>
<td>The formation of new blood vessels, often fragile and inappropriate to location, underneath or in the the retina</td>
</tr>
<tr>
<td>Neovascular AMD</td>
<td>Alternative name for wet AMD. Avoided wherever possible throughout report because it gives impression that wet AMD is always associated with neovascular membranes, which is false</td>
</tr>
<tr>
<td>Neovascular membranes</td>
<td>New blood vessels formed by the process of neovascularisation</td>
</tr>
<tr>
<td>Occult neovascular membranes/lesions</td>
<td>Neovascular membranes which are hard to detect on fluorescein angiography and where fluorescein leakage is patchy</td>
</tr>
<tr>
<td>Photodynamic therapy (PDT)</td>
<td>Injection of photosensitive dye then application of laser, intended to treat neovascular membranes</td>
</tr>
<tr>
<td>Pigment epithelial detachment or RPE detachment</td>
<td>The separation of the neural tissue of the retina including the pigmented epithelium layer from the blood supply. Results in loss of vision in the detached area</td>
</tr>
<tr>
<td>Retinal pigment epithelium</td>
<td>A layer of epithelial cells lying between the photoreceptors of the retina and the choroidal blood supply</td>
</tr>
<tr>
<td>Photoreceptors</td>
<td>The rods and cones in the retina that are sensitive to light</td>
</tr>
<tr>
<td>Scotoma</td>
<td>An area of partial or complete vision loss surrounded by an area of...</td>
</tr>
<tr>
<td><strong>Subfoveal area</strong></td>
<td>Area of the macula less than 1 µm from the foveal centre</td>
</tr>
<tr>
<td>--------------------</td>
<td>------------------------------------------------------</td>
</tr>
<tr>
<td><strong>Tin ethyl etiopurpurin (SnET2)</strong></td>
<td>One of the two main types of dyes used in PDT for wet AMD.</td>
</tr>
<tr>
<td><strong>Verteporfin</strong></td>
<td>One of the two main types of dyes used in PDT.</td>
</tr>
<tr>
<td><strong>Visudyne® (Novartis Ophthalmics AG; Switzerland)</strong></td>
<td>Specific formulation of verteporfin. The only licensed dye for PDT of wet AMD. Generally referred to throughout this report by its generic name, verteporfin, as it is the only commercially available version of verteporfin.</td>
</tr>
<tr>
<td><strong>Visual acuity</strong></td>
<td>The clearness of vision which depends on the sharpness of the retinal image, the finest of details that an eye can distinguish.</td>
</tr>
<tr>
<td><strong>Visual field</strong></td>
<td>The area or extent of space visible to an eye in a given position of gaze.</td>
</tr>
<tr>
<td><strong>Wet AMD</strong></td>
<td>Type of AMD characterised by neovascular membranes, haemorrhage and exudates. Also sometimes known as neovascular AMD. Wet AMD is the preferred term throughout this report, because neovascular membranes (see above) are not always a feature.</td>
</tr>
<tr>
<td><strong>Wet AMD – classic type</strong></td>
<td>Wet AMD with classic neovascular membranes/lesions (see appendix 1)</td>
</tr>
<tr>
<td><strong>Wet AMD – occult type</strong></td>
<td>Wet AMD with occult neovascular membranes/lesions (see appendix 1)</td>
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1. **AIM OF THE REVIEW**

Age related macular degeneration (AMD) is a form of blindness that usually occurs in people over the age of 50 years. There are two forms: wet and dry AMD. An important, but variable feature of wet AMD is that new blood vessels (neovascular membranes) grow beneath the central retina. These are prone to leakage and bleeding, causing in turn disruption of the overlying retina. The aim of photodynamic therapy (PDT) is to destroy the blood vessels and thereby halt the resulting vision loss.

**Objective:** To establish the clinical and cost-effectiveness of PDT for the neovascular form of AMD relative to current practice and in relation to the current licensed indications, in order to produce guidance to the NHS in England and Wales.

2. **BACKGROUND**

2.1 **Description of underlying health problem**

2.1.1 **Nature of AMD**

AMD is the most common cause of blindness in people registered blind over the age of 65. The condition is usually described as having an early form – age related maculopathy (ARM) and a late form causing blindness (AMD). The late form has two versions – dry AMD and wet AMD. Wet AMD is associated with several pathological features – pigment epithelial detachments (PED), neovascular membranes, retinal scarring, haemorrhages and exudates. Of these neovascular membranes are particularly important in relation to possible applications of PDT. They can develop directly under the centre of the fovea (subfoveal), in the remainder of the fovea (juxtafoveal) or in the rest of the macula excluding the fovea (extrafoveal). Neovascular membranes can have features that define them as classic or occult. For a fuller classification and description of the condition, see Appendix 1.

AMD causes a painless loss of central vision resulting in sufferers being unable to read, recognise faces and drive a vehicle. If neovascular membranes develop there can also be distortion of vision so that straight lines appear wavy. None of these visual symptoms are specific to AMD and diagnosis is by retinal examination. For an explanation of how visual acuity is measured and recorded, see Appendix 2.

Dry AMD is associated with a very gradual loss of vision, often with foveal sparing until late in the disease and can take 10 years from onset to legal blindness. The wet form has a variable course but tends to progress much more quickly and visual acuity can change from normal vision to legal blindness within weeks. Classic neovascular membranes are associated with faster progression to legal blindness than occult neovascular membranes. Annually, classic neovascular membranes develop in up to 50% of occult lesions.

A key issue concerning natural history of wet AMD is that developing the disease in one eye is highly predictive of disease developing in the other.
2.1.2 Aetiology

The cause of wet AMD and AMD in general is unknown. There have been several risk factors linked to development of AMD including family history of the disorder, cigarette smoking, low dietary intake or plasma concentrations of antioxidant vitamins and zinc and white race (in wet AMD only). Other factors linked in some studies, but not consistently, with risk of developing AMD include female gender, light coloured iris, cardiovascular disease and increased exposure to sunlight. It is unlikely that primary prevention of wet AMD will be possible in the near future.

2.1.3 Epidemiology

The vast majority of AMD occurs in people over 60 years of age. However, pathological changes (presence of drusen, RPE depigmentation, increased retinal pigment) without visual defects can be seen at an earlier age. This section will focus on AMD causing visual disturbance or legal blindness.

The ICD-10 classification of degeneration of the macula and posterior pole of the eye (H35.3) includes features not exclusively associated with AMD. The category includes ‘angioid streaks, cysts, drusen (degenerative), holes, puckering, Kuhnt-Julius degeneration, senile macular degeneration and toxic maculopathy (drug induced)’. Therefore routine UK health data cannot supply prevalence and incidence of AMD. Published surveys of representative populations are used instead.

The prevalence of AMD and its wet form are very dependent on age. A recent survey of prevalence studies gives age specific prevalence per 1000 population (with 95% confidence intervals) according to visual impairment and type of AMD. Women and men probably have similar prevalence rates. There is no evidence to suggest that the prevalence varies by geographical region.

<table>
<thead>
<tr>
<th>Age group</th>
<th>Sample number</th>
<th>Partially sighted (95%CI)</th>
<th>Blind (95%CI)</th>
<th>Sample number</th>
<th>Wet AMD (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;50</td>
<td>840</td>
<td>0 (0-4)</td>
<td>0 (0-4)</td>
<td>835</td>
<td>0 (0-4)</td>
</tr>
<tr>
<td>50-54</td>
<td>675</td>
<td>0 (0-5)</td>
<td>0 (0-5)</td>
<td>668</td>
<td>1 (0-8)</td>
</tr>
<tr>
<td>55-59</td>
<td>1759</td>
<td>0 (0-2)</td>
<td>1 (0-3)</td>
<td>1762</td>
<td>1 (0-3)</td>
</tr>
<tr>
<td>60-64</td>
<td>2254</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>2241</td>
<td>3 (1-6)</td>
</tr>
<tr>
<td>65-69</td>
<td>2179</td>
<td>0 (0-2)</td>
<td>0 (0-2)</td>
<td>2165</td>
<td>2 (1-5)</td>
</tr>
<tr>
<td>70-74</td>
<td>1882</td>
<td>1 (0-3)</td>
<td>1 (0-3)</td>
<td>1868</td>
<td>10 (6-16)</td>
</tr>
<tr>
<td>75-79</td>
<td>1500</td>
<td>3 (1-7)</td>
<td>4 (1-9)</td>
<td>1475</td>
<td>20 (13-28)</td>
</tr>
<tr>
<td>80-84</td>
<td>793</td>
<td>9 (4-18)</td>
<td>9 (4-18)</td>
<td>756</td>
<td>49 (34-67)</td>
</tr>
<tr>
<td>85-89</td>
<td>285</td>
<td>11 (2-31)</td>
<td>35 (17-65)</td>
<td>274</td>
<td>55 (31-90)</td>
</tr>
<tr>
<td>90+</td>
<td>94</td>
<td>32 (7-93)</td>
<td>43 (12-109)</td>
<td>94</td>
<td>117 (58-209)</td>
</tr>
</tbody>
</table>


AMD as a cause of blindness appears to have increased by about 30-40% per age adjusted head of population over the last 40 years.
As the aim of treatment for AMD is to prevent deterioration in vision, incidence rates will give a better indication of the number of people who could benefit from treatment over time. Table 2 shows the incidence of all AMD, dry AMD and wet AMD. As with prevalence, the age specific incidence rates rise quickly so study results will vary depending on the age profile of the population used. In the Blue Mountains Eye Study the five-year incidence of AMD was 0.9% at 60-69 yrs, 2.6% at 70-79 yrs and 6.8% at 80+ yrs. In the Beaver Dam Eye Study, the five-year incidence rates for wet AMD were 0% at age <55 and 3.2% in those aged 75+.

### Table 2 Incidence of AMD in either eye

<table>
<thead>
<tr>
<th>Study</th>
<th>Number in survey followed up</th>
<th>Definition</th>
<th>Incidence (range)</th>
<th>mean age (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Avon (GB) 14</td>
<td>N=942,000</td>
<td>Registered blind from AMD</td>
<td>0.06% /2yrs</td>
<td>(all ages)</td>
</tr>
<tr>
<td>Blue Mountain (AUS) 13</td>
<td>N=2323</td>
<td>AMD</td>
<td>1.3% /5yrs</td>
<td>(49-90+)</td>
</tr>
<tr>
<td>Beaver Dam (USA) 15</td>
<td>N=3684</td>
<td>Wet</td>
<td>0.6% /5yrs</td>
<td>(43-84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry</td>
<td>0.3% /5yrs</td>
<td></td>
</tr>
<tr>
<td>Melton Mowbray (GB) 16</td>
<td>N=88</td>
<td>Wet</td>
<td>1.3% /7yrs</td>
<td>80 (77-90)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Dry</td>
<td>1.3% /7yrs</td>
<td></td>
</tr>
<tr>
<td>(Denmark) 17</td>
<td>N=Population of Denmark as at 1/1/1994</td>
<td>Registered blind from AMD</td>
<td>0.1% /5yrs</td>
<td>(60-99)</td>
</tr>
<tr>
<td>Rotterdam (NL) 18</td>
<td>N=5095</td>
<td>AMD</td>
<td>0.24% /2yrs</td>
<td>(55-85+)</td>
</tr>
</tbody>
</table>

#### 2.1.4 Prevalence and/or incidence in an average health authority ~ 500,000

From Table 1, the prevalence of wet AMD in an average health authority of population 500,000 would be approximately 1,946 people.

Estimates of one-year incidence figures for all AMD and wet AMD for a typical health authority are shown in Table 3. These use age and sex specific incidence rates from the Beaver Dam Eye Study, age specific incidence rates from the Blue Mountains Eye Study and Rotterdam Study and census population estimates for England.
Table 3 Estimates of annual incidence of AMD and wet AMD in a typical health authority of population ~ 500,000

<table>
<thead>
<tr>
<th></th>
<th>1 yr incidence</th>
<th>Wet AMD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any AMD</td>
<td></td>
</tr>
<tr>
<td>Beaver Dam(^{15})</td>
<td>529</td>
<td>158</td>
</tr>
<tr>
<td>Blue Mountains(^{13})</td>
<td>537</td>
<td></td>
</tr>
<tr>
<td>Rotterdam(^{18})</td>
<td>186</td>
<td>103</td>
</tr>
</tbody>
</table>

The wet AMD category in the Beaver Dam study\(^{15}\) included pigment epithelial detachments but did not mention the percentage of people with these but no neovascular membranes. Other studies have indicated that the proportion of AMD patients with pigment epithelial detachments but no neovascular membranes varies from 3.7%\(^{21}\) to 10%\(^{22}\). Thus effectively, the majority of people with wet AMD have neovascular membranes. The ratio of people presenting with subfoveal compared to juxtafoveal and extrafoveal neovascular AMD is approximately 5:1\(^{23}\). Finally, approximately half of those registered blind have two or more causes of blindness, such as glaucoma and cataract, in addition to AMD.\(^{2}\) So taking all these into account, the approximate number of uncomplicated new cases of AMD with neovascular membranes in an average health authority would be approximately halved to 75 persons per year. This is likely to be an underestimate of those eligible for treatment because having a second condition does not preclude eligibility for treatment of AMD. There is little information available regarding the proportion with AMD who would be eligible so it is acknowledged that the above estimate is approximate.

There are two forms of neovascular membranes – classic and occult (see Appendix 1). This distinction is important when considering the outcomes of trials for AMD. Although the evidence available is limited, a ratio of wet AMD with some classic neovascular membranes to those with occult only can be estimated from the largest study available\(^{23}\) and is approximately 2:1 (see Table 4). Therefore, there will be roughly 50 new cases of uncomplicated wet AMD with some classic neovascular membranes per year in a typical health authority of population ~ 500,000. This equates to approximately new 5,000 cases in England and Wales.

Table 4 Estimate of ratio of classic to occult neovascular membranes

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of classic</th>
<th>Number of occult</th>
<th>Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNPTRG(^{24})</td>
<td>1 (classic only)</td>
<td>17 (whole or part occult)</td>
<td>1:17</td>
</tr>
<tr>
<td>Margherio(^{23})</td>
<td>256 (classic with occult)</td>
<td>136 (occult only)</td>
<td>1:0.53</td>
</tr>
<tr>
<td>Sunness(^{25})</td>
<td>4 (classic + classic with occult)</td>
<td>8 (occult only)</td>
<td>1:2</td>
</tr>
</tbody>
</table>

This figure agrees well with a recent UK estimate of 5,000 people with classic AMD requiring treatment in England and Wales per year.\(^{26}\) From a different case study of 1,000 patients with any AMD attending a US retinal practice, 171 were found to be indicated for
PDT, using the predominantly classic criteria.\textsuperscript{23} If this rate is applied to a typical health authority of population \(\sim 500,000\) there would be 90 new cases and 9,000 in England and Wales. However this sample may have had more wet AMD than dry, as dry AMD is not treatable and there would be less need for referral to a specialist service.

Putting wet AMD as a cause of blindness into perspective, it is important to realise that total number of individuals who might become blind (all causes) in any year in an average health authority is approximately 1,350, with 1,800 registering as partially sighted.\textsuperscript{27}

### 2.1.5 Significance in terms of ill-health (burden of disease)

Visual impairment for an elderly person can have a severely disabling impact. When a person quickly loses their sight, they have to adapt their activities of daily living. For an older person this can be very difficult and the visual impairment may come at a time when they may be less able to adapt. A recent editorial\textsuperscript{28} presents a common scenario where an elderly person who lives alone, develops wet AMD in her better eye. At six months she has sustained a fall and broken her hip and as a result is receiving long term care. Older people who develop visual impairment often have other disabilities as well\textsuperscript{29,30} and there is significantly more visual impairment between those patients admitted to hospital with falls and those admitted with other medical problems.\textsuperscript{31} The prevalence of low vision (6/60 (20/200) or worse in better eye) in residential care homes has been estimated at 19.6\%\textsuperscript{32} and 32\%\textsuperscript{33} whereas in the community of a similar age profile, the prevalence has been estimated at 6.6\%.\textsuperscript{34} People with rapidly deteriorating vision also tend to suffer more depression and anxiety due to their loss of vision and reduction in independence\textsuperscript{35-39}

Studies have shown that average quality of life drops as a function of binocular visual loss in AMD\textsuperscript{40,41}. Where visual acuity is near normal (20/20-20/25) the utility is 0.89 (95\% CI 0.82-0.96) whereas when the visual acuity drops to 20/200-20/400 the utility is 0.52 (95\% CI 0.38-0.66) as measured by the time trade off technique (TTO)\textsuperscript{40}. However, where this vision loss is only in one eye, this loss of utility is not demonstrated.\textsuperscript{42}

Although vision loss can be severely disabling to an elderly person, visual acuity may not correlate well with functional ability.\textsuperscript{43,44} A person with a visual acuity of 20/40 may feel totally incapacitated whereas another with 20/200 may have adapted well and have few problems with daily tasks.\textsuperscript{44} The two main aspects of rehabilitation for people with visual acuity loss caused by AMD are reading skills and activities for daily living. AMD causes central vision loss so people need to be taught eccentric fixation techniques, where the eye is focused away from the fovea.\textsuperscript{38,44} Together with appropriate magnification, reading standard sized newsprint is possible for up to 90\% of those referred to a specialist low vision clinic.\textsuperscript{45,46} There are many other modified appliances that can help around the home such as liquid level indicators, talking clocks and scales, special marking clips etc. Vision rehabilitation includes training in their use, so that people can continue to cook meals and tell the time. Good visual rehabilitation can help people with AMD make the most of the sight that they still have and help them maintain an active life.\textsuperscript{47} Unfortunately, the provision of low vision rehabilitation around the country is patchy.\textsuperscript{47}

Beyond adaptation to vision loss a further issue which makes the relationship between vision and functionality more complex is the fact that most people have two eyes. In general terms function is probably determined by vision in the better seeing eye. Thus if the worse seeing
eye is affected by AMD function may be little altered. Conversely if the better seeing eye is affected, function may be dramatically affected. Further complexity is added in that developing AMD in one eye strongly predicts the likelihood that disease will develop in the other eye.

2.2 Current service provision

Numerous treatments have been tried in order to halt or reverse the damage caused by neovascular membranes in wet AMD, many with little success. Experimental treatments tried include ionising radiation, antiangiogenic agents (including interferon, vascular endothelial growth factor, integrins and thalidomide) and surgical interventions (including retinal excision and implantation). No RCTs on these interventions have shown significant benefit to the patient.

A recent RCT of anti-oxidant vitamin and mineral supplements (Vitamin C, E, beta carotene and zinc) has indicated that this combination may delay progression of AMD.

For most patients, as with dry AMD, management consists of social support, visual rehabilitation and provision of low vision aids.

One of the few treatments for neovascular membranes that has been shown to have some beneficial effect is laser photocoagulation. Well defined, ‘classic’ extrafoveal lesions can be treated by an argon, krypton or diode laser. The result of this treatment is a dark scotoma causing a visual field defect. The laser treatment is intended to halt the rapid vision loss caused by progression of the neovascular membrane.

If subfoveal lesions are treated with laser photocoagulation, there is an immediate loss of visual acuity but long term follow up has shown some benefit in patients with small new vessel complexes and already poor visual acuity. Visual rehabilitation for these patients can be difficult.

The main disadvantages of laser photocoagulation are:

- Not more than 10-15% of all wet AMD lesions are sufficiently small and clearly delineated enough to be eligible.
- Most presenting lesions are subfoveal.
- The immediate visual acuity loss means that this treatment is rarely used. This immediate visual loss is purported not to be well accepted, in spite of some research evidence to the contrary.
- There is approximately a 50% chance that leakage will recur during the two years after treatment.
- There is a small risk (0.5% - 2%) of a RPE tear occurring which will lead to profound loss of vision.

2.3 Description of new intervention

2.3.1 Identification of patients

Patients with AMD are diagnosed by clinical signs visible on ophthalmoscopic examination of the retina rather than by visual function. If records of the fundal images need to be kept,
colour photographic film or digital cameras are used. Fundal images can be greatly enhanced by the use of angiography and two main angiographic media are used – fluorescein and more recently indocyanine green. Angiography is used for both lesion diagnosis and classification (subfoveal/juxtafoveal/extrafoveal lesions, classic/occult and other features such as haemorrhage/pigment epithelial detachment). Diagnosis of AMD and its wet form is not straightforward, particularly for ophthalmologists who are not retinal specialists.

Neovascular membranes can be classified as classic or occult according to their appearance on fluorescein angiography. Classic lesions are clearly delineated and leak fluorescein uniformly whereas occult lesions are hard to detect and fluorescein leakage is patchy. Occult lesions can be distinguished from pigment epithelial detachments angiographically if there are irregular hyperfluorescence areas and spots of intense hyperfluorescence. Comparison of the two types of angiographic media are also used for diagnosis. There is no information available on the sensitivity and specificity of these tests.

### 2.3.2 Criteria for treatment

PDT is intended to treat patients with new neovascular membranes in wet AMD who still retain some visual acuity. The aim is to stop leaking from the membranes and so halt further loss of vision. It is not intended to restore vision already lost but results from trials suggest that vision can improve in a small percentage of people. The causal mechanism for this is unclear.

### 2.3.3 Intervention - PDT

PDT is the new intervention to be evaluated. It uses photosensitive drugs and a specially developed low-power laser.

Photosensitive drugs as a group all work in a similar way. An inert substance, usually a benzoporphyrin derivative, is injected into the peripheral bloodstream. After a length of time (minutes or hours) the substance enters or attaches to all cells of the body. It is cleared from most cells but preferentially remains with proliferative cells (such as new blood vessels). A low-powered laser calibrated to a specific wavelength then activates the photosensitive drug to form peroxides. The result is cell death by apoptosis, mitochondrial or cell membrane destruction, vascular thrombosis or immune system destruction. The laser is not powerful enough to cause any damage on its own. Photodynamic therapy results in proliferative cells being selectively targeted and destroyed with other cells being left alive.

Photosensitive treatments are under investigation for a variety of conditions such as cancers, HIV/AIDS, transplant rejection, bone marrow infection, psoriasis and arthritis. For this report, the two relevant photosensitive substances currently undergoing randomised controlled trials for AMD are verteporfin (Visudyne® (Novartis Ophthalmics AG, Switzerland)) and tin ethyl etiopurpurin (SnET2), now called rostaporfirin (trade name was Purlytin® (Pharmacia and Upjohn, USA and Sweden, Miravant, USA)). Other photosensitive substances being investigated in preliminary trials on humans are motexafin lutetium which is also called lutetium texaphyrin (trade names Lu-Tex® and Optrin® (Alcon Laboratories, USA)) and indocyanine green (which is also used in retinal angiography).
The laser/photosensitive drug combination means that, as long as the doses are correct, no damage occurs to the retinal cells next to the neovascular membranes. Unlike laser photocoagulation, there is no sudden vision loss (except in a small minority who suffer a choroidal infarction (Personal communication, Professor Bird, Moorfields Eye Hospital, 2000). For the remaining patients there may be some slight visual disturbance for a few days after treatment only. Single treatment is possible but the new blood vessels can and often do return so retreatment may be needed, sometimes several times before no further growth of new vessels is seen. Photodynamic therapy is relatively painless and can be undertaken in the outpatient department. However, there are a number of disadvantages.

- The treatment may only be effective on some patients with wet AMD and not others. It may be tried several times for up to a year before this is known. This could have adverse psychological consequences and visual rehabilitation will be delayed
- The photosensitive drug remains in the body for various durations, depending on the substance (verteporfin 24-48 hours, tin ethyl etiopurpurin 2-4wks, lutetium texaphyrin 1-2wks). As a result, patients are required to avoid direct sunlight and intense halogen light until the drug has cleared from the body.
- There can be adverse events from injection of the dye, such as short-term visual disturbance, back pain and hypersensitivity and pain around the injection site, in addition to the photosensitivity reactions mentioned above.
- The long-term effects in humans of PDT for wet AMD are unknown.
- The treatment does not influence the underlying pathological process which leads to the development of neovascular membranes so recurrence is very possible.
- Overdose of drug and/or laser dose can result in permanent irreversible vision loss.
- If used on patients with pigment epithelial detachments, it is liable to cause severe loss of vision.

### 2.3.4 Verteporfin PDT

Verteporfin is currently the only photosensitive agent licensed for use in PDT for wet AMD. Currently, the licence only allows the treatment of AMD in patients with predominantly classic subfoveal choroidal neovascularisation. This precludes treatment of wet AMD with either no neovascular membranes or where most neovascular membranes are of an occult type and wet AMD where lesions are juxtafoveal or extrafoveal irrespective of their type. However, following the two-year results of the VIP trial, there is an intention to seek to extend the licence to treat people with occult subfoveal lesions. Application has been made to the Canadian and European licensing authorities for this extension.

Verteporfin is contra-indicated in patients with porphyria, severe liver impairment or known hypersensitivity to verteporfin or any other component of the infusion, including egg proteins. It is produced from porcine hemin as a starting material so vegetarians and people of Muslim and Jewish faiths should be notified. It should not be used in people with uncontrolled high blood pressure, unstable cardiovascular disease, active hepatitis or

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*Throughout this report the generic name, verteporfin is generally used in preference to the trade name Visudyne® (Novartis Ophthalmics AG, Switzerland). At the time of writing the report the two are synonymous with respect to PDT for wet AMD as there is only one commercially available formulation of verteporfin.*
moderate to severe liver disease. Concomitant medications that reduce the effectiveness of liver catabolism may prolong systemic photosensitivity.

“Verteporfin can cause severe pain, inflammation, swelling and discolouration of the injection site”\textsuperscript{73} If this occurs the manufacturers recommend that the infusion is discontinued, cold compresses and/or ice is applied immediately and that the arm be elevated for 1 day when possible.\textsuperscript{73} Bearing in mind that the average age of recipients is 75 years old, extravasation is fairly common, happening in approximately 3% of cases.\textsuperscript{61,62}

The entry for verteporfin in the British National Formulary (BNF)\textsuperscript{76} is shown in Table 5.

### Table 5 British National Formulary entry for verteporfin

<table>
<thead>
<tr>
<th>SUBFOVEAL CHOROIDAL NEOVASCULARISATION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verteporfin is licensed for use in the photodynamic treatment of subfoveal choroidal neovascularisation associated with age-related macular degeneration or with pathological myopia. Following intravenous infusion, verteporfin is activated by local irradiation using non-thermal red light to produce cytotoxic derivatives. Only specialists experienced in the management of these conditions should use it.</td>
</tr>
</tbody>
</table>

**Verteporfin**

**Indications:** see notes above – specialist use only.

**Cautions:** photosensitivity – avoid exposure of unprotected skin and eyes to bright light during infusion and for 48 hours afterwards; hepatic impairment (avoid if severe), biliary obstruction; avoid extravasation; pregnancy.

**Contra-indications:** porphyria; breast-feeding.

**Side-effects:** visual disturbances (including blurred vision, flashing lights, visual-field defects), nausea, back pain, asthenia, pruritis, hypercholesterolaemia, hypertension, chest pain, syncope, fever; rarely lacrimation disorder, subretinal or vitreous haemorrhage; injection site reactions including pain, oedema, inflammation, haemorrhage, discolouration.

**Dose:** by intravenous infusion over 10 minutes, 6 mg/m\textsuperscript{2} Visudyne\textregistered (Novartis Ophthalmics)

**Injection, powder for reconstitution, verteporfin, net price 15 mg vial = £850.00**

**Method of preparation:** Reconstitute each 15mg with 7ml water for injections to produce a 2 mg/ml solution then dilute requisite dose with infusion fluid (5% dextrose) to a final volume of 30mL and give over 10 minutes; protect from light and administer within 4 hours of reconstitution. Incompatible with sodium chloride infusion.

*Note that one vial is sufficient to treat one person for one infusion only.

### 2.3.5 Personnel involved, equipment and setting

Verteporfin must be administered under the supervision of an ophthalmologist who is specially trained in PDT. Also needed is a doctor or nurse to prepare, administer and monitor the infusion and to provide patient education (all patients must be warned about photosensitivity reactions and precautions they must take).\textsuperscript{77}

The equipment and supplies needed are
- Angiographic photography system
- Syringe or infusion pump, needles for injection

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\textsuperscript{61,62}
• Diode laser system that is specially made for this application and can be used with a variety of ophthalmological slit lamps.
• Vials of photodynamic drug for injection
• Infusion kits, sterile water for injection, 5% dextrose solution
• Patient weighing machine and height chart
• Ice packs, cold compresses in case of extravasation
• Patient labels for warnings about photosensitivity reactions.

PDT with verteporfin can be carried out in a standard out-patient department clinic.

Requirements for PDT with other photosensitive agents especially SnET2, cannot be stated with complete confidence, but appear to be similar. It should however again be emphasised that these other agents are not currently licensed for PDT in wet AMD.

2.3.6 Length of treatment and follow up required
Before PDT is undertaken, the patient needs to be assessed for treatment. This requires measurement of best corrected visual acuity, fundus biomicroscopy via a dilated pupil, fluorescein angiography, an explanation of the procedure and informed consent. Next the body surface area and hence dose is calculated from the patient’s height and weight using a nomogram. The required amount of verteporfin is withdrawn from the vial, the remainder usually being discarded. The drug is made up to the required strength in 30ml water for injection and given to the patient intravenously over 10 minutes, using an infusion pump. Then 15 minutes after the start of the infusion, the patient is sat at a modified slit lamp and a specific dose of red laser light is applied to the back of the eye for 83 seconds. The laser is set at 689 nanometres wavelength and the dose is 50Joules/cm² at an intensity of 600mWatts/cm² using a spot size with a diameter 1mm larger than the greatest linear dimension of the lesion. After this, assuming no problems, the patient is free to go as long as they take suitable precautions to protect against photosensitivity reactions. Patients are advised to protect themselves from direct sunlight and bright halogen light for 5 days or for 2 days after treatment.

As this treatment may not be effective in a single dose, retreatment is recommended at 3 monthly intervals. Retreatment is recommended where there is further evidence on angiography of leakage from neovascular membranes. As the treatment doesn’t affect the underlying pathological process, long term follow up may be required.

2.3.7 Degree of diffusion
Photodynamic therapy for AMD is not currently freely available in the NHS. It is available in only a few health authorities in England and Wales.

Data from Novartis separate from industry submission suggests that there is ‘equipment to perform PDT at 75 NHS eye units, 23 private hospitals and 2 private rooms’ (unknown definition of private room). There is ‘some verteporfin use at 28 NHS eye units, 12 private hospitals and 1 private room’. There is ‘regular verteporfin use at 12 NHS eye units, 7 private hospitals and 1 private room’. ‘(Please note that NHS eye units all have private wings)’. Of the 20 units regularly treating with PDT, only 12 are NHS eye units (Industry submission
Novartis estimate that the number of new patients currently receiving PDT at NHS expense each year is 500 (Industry submission p44).

2.3.8 Costs

The costs of the two main components of PDT for wet AMD are:

- Verteporfin - £850 per 15 mg vial (sufficient to treat most adults at a dose of 6mg/m²)\(^76\)
- Specially made diode laser system – purchase cost £14,750, servicing and warranty £500 per year. (Industry submission spreadsheet)

The true cost of PDT for wet AMD needs however to take into account other costs associated with investigation and administration (including the need for repeated administration), costs associated with any adverse events and costs off-set by avoidance of vision loss. These are considered in detail in the economic evaluation.

2.4 Other new approaches to the treatment of wet AMD

Research into treatment of wet AMD appears to be an extremely dynamic area. Not only are several types of PDT being actively investigated and developed, but new approaches are under investigation too. Two of the most important are angiostatic steroids (Anecortave Acetate\(^80\)) and transpupillary thermotherapy (TTT\(^81\)). TTT is a laser therapy where a low powered laser is used to ‘cook’ rather than ‘burn’ neovascular membranes and so occlude them without damaging other cells. Another treatment being investigated is vascular endothelial growth factor (VEGF) (Personal Communication, Mr R Wormald, Moorfields Eye Hospital, 2002)

2.5 Summary

Condition:
- AMD is a major cause of blindness, affecting the central portion of the retina (the macula)
- There are several types, but wet AMD is the most problematic
- A key, but variable component of wet AMD is the formation of neovascular membranes. Through leakage and bleeding of these fragile blood vessels, the retina is disturbed leading to visual loss, which is irreversible
- Neovascularisation may be of two types – classic and occult, giving rise to a further important sub-categorisation of wet AMD. Wet AMD with classic neovascular membranes are generally more threatening to sight than wet AMD with occult neovascular membranes
- Occult lesions frequently develop into classic lesions
- Both classic wet AMD and occult wet AMD may be further divided by the location of the lesions into subfoveal, juxtafoveal and extrafoveal. Subfoveal locations (under the centre of the macula - the fovea) however, are by far the most common in wet AMD
- An important feature of the natural history is that development of wet AMD in one eye is highly predictive of the fellow eye becoming affected
Epidemiology:
- The vast majority of AMD occurs in persons over 60 years of age
- Incidence and prevalence figures for wet AMD are available from epidemiological studies
- These suggest that for an average health authority of 500,000 persons the annual number of:
  - New cases of wet AMD is approximately 150
  - New cases of wet AMD not co-existing with other sight impairing conditions like cataracts and glaucoma (uncomplicated wet AMD) is 75
  - New cases of uncomplicated wet AMD with some classic neovascular membranes is 50, in most of which the lesions would be subfoveal in location
  - New cases of uncomplicated wet AMD with just occult neovascular membranes is 25, in most of which the lesions would be subfoveal in location
- Putting this in context, an average health authority of 500,000 persons would expect to have 1350 new cases of blindness (all causes) each year

Burden of disease:
- The consequences to the individual may be severe
- Quality of life measures confirm the potential magnitude of the impact on individuals who lose binocular vision
- Not only is vision compromised or lost, but as wet AMD predominantly affects older persons, function may be greatly compromised, either directly or indirectly resulting from falls and injuries sustained as a result
- The association between vision loss and loss of function is complex
- Rehabilitation can be successful
- The fact that function is dependent on vision in both eyes, not just the impact of wet AMD on one eye needs to be taken into account

Existing treatment:
- There are no strategies for primary prevention as too little is known about the aetiology of the disease
- The mainstay of existing treatment is social support, visual rehabilitation and provision of low vision aids
- Unfortunately there is some evidence that the level of such support is often sub-optimal
- For wet AMD where neovascular membranes are located outside the fovea (extrafoveal and juxtafoveal) laser photocoagulation may halt the progression of the disease
- Laser photocoagulation has important limitations, not least of which is that most neovascular lesions are subfoveal

Proposed treatment:
- The new intervention of interest is PDT
- PDT has two components; injection of a photosensitive agent followed by directing a low energy laser onto the affected areas of the retina
- Like laser photocoagulation, the purpose of PDT is prevention of further loss of vision by halting progression of neovascular membranes.
- Several photosensitive agents are being developed and tested for use in PDT of wet AMD
- Of these verteporfin is the only one to have received a licence so far
- The current licence is for the treatment of AMD in patients with predominantly classic subfoveal choroidal neovascularisation
• An extension of this licence to occult subfoveal choroidal neovascularisation is being sought
• Verteporfin is recommended only for use by specialists
• Photosensitivity is a caution; patients should avoid exposure of unprotected skin and eyes to bright light during infusion and for 48 hours afterwards
• The cost of verteporfin is £850 per person per treatment
• The costs of laser treatment, investigation, retreatments, adverse effects and costs off-set are important and need to be considered carefully

3. EFFECTIVENESS

3.1 Methods for reviewing effectiveness

3.1.1 Search strategy
As the authors had completed a systematic review on the same subject within the previous year, no formal scoping search was undertaken. This systematic review was used as the basis for the protocol for this technology assessment, which was undertaken in accordance with the pre-defined protocol (see Appendix 3). There were no major departures from this protocol.

The following sources were searched:
• Bibliographic databases: Cochrane Library 2001 Issue 3; MEDLINE (Ovid) 1993 – Aug 2001; EMBASE (Ovid) 1993 – Aug 2001; Science Citation Index (Web of Science) 1993 – Sept 2001; National Research Register and MRC current controlled trials register - September 2001
• National and international HTA sites – (INAHTA, NHSC, CCOHTA, DIHTA, SMM, July 2001)
• Internet sites (Novartis, Visudyne® (Novartis Ophthalmics, Switzerland))
• Citations of all relevant articles found and the data outline sent to us by Novartis separately from the industry submission.

For database search strategies on clinical effectiveness, see Appendix 4.

3.1.2 Inclusion and exclusion criteria
One reviewer, using explicit predetermined criteria, made the inclusion and exclusion decisions. These were checked by a second reviewer. Inclusion and exclusion decisions were made independently of the inspection of trial results.

Trials and studies were only included if they met the following criteria;

Study design: Randomised controlled trials.
Population: Adults with wet AMD.
Intervention: PDT using any photosensitive drug.
Comparator: Either no treatment (best supportive care) for subfoveal lesions or laser photocoagulation for juxtafoveal or extrafoveal lesions.
Reporting: Only trials where recruitment had closed and which reported follow up results for all or nearly all recruited patients were included.

The exclusion criteria were:
1. RCTs that had not finished recruiting. (A separate list of ongoing RCTs found during the searches was made, see section 3.2.1)
2. RCTs that had published only baseline characteristics or follow up results for a small proportion of the trial participants.
3. Studies carried out on animals.

Although items 1, 2 and 3 above were excluded from the analysis of clinical effectiveness, their presence was noted as essential background to the review. Note that although new treatments (anecortave acetate and TTT) are potential comparators to PDT, it was considered that their development is at too early a stage to merit listing in the inclusion criteria.

3.1.3 Data extraction and quality assessment strategies
Two researchers independently extracted the effectiveness and quality assessment data from all included studies, using predefined criteria. Any discrepancies were recorded and resolved by discussion. The quality of the included studies was assessed using the Jadad scale.\(^{83}\)

3.1.4 Synthesis of results
The main method of synthesis was qualitative, supplemented by further quantitative analysis and synthesis where appropriate using Review Manager software version 4.1.
3.2 Results

3.2.1 Number of studies identified

The clinical effectiveness searches identified 417 references. Six RCTs of PDT in wet AMD were ultimately found of which four are ongoing and two completed. These six were considered as included for the purposes of demonstrating coverage of areas relevant to current and future assessment of the effectiveness of PDT in wet AMD. Only the two completed were considered as included for the purposes of analysing the current evidence on effectiveness of PDT for wet AMD.

3.2.2 Coverage of completed and ongoing RCTs identified

The following is a list of RCTs of PDT in wet AMD found (completed and ongoing), or not found, described according to category.

Possible comparisons:
A. PDT compared to placebo – 6 RCTs (2 completed; 4 ongoing)
   A1. Verteporfin vs placebo - 5 RCTs (2 completed; 3 ongoing)
   A2. SnET2 vs placebo – 1 RCT (0 completed; 1 ongoing)
B. PDT compared to laser photocoagulation – no RCTs
C. PDT + usual visual rehabilitation compared to optimised visual rehabilitation – no RCTs
D. PDT compared to new approaches eg TTT– no RCTs
E. One type of PDT compared to another – no RCTs

For the comparison of PDT to placebo (categories A1 plus A2) the possible comparisons are either:
   a) Single treatment– 1 RCT ongoing found
   b) Multiple treatment - 2 RCTs completed and 3 RCTs ongoing found

b) For multiple treatment RCTs, the possible lesion locations and types are:
   • Subfoveal, juxtafoveal or extrafoveal
   • No neovascular lesions, mainly classic neovascular lesions, mainly occult neovascular lesions or combinations of classic and occult.

For comparison b), this gives 12 possible combinations (see Table 6), although it is acknowledged that the rationale for use of PDT where there are no neovascular lesions is unclear and it is hence not surprising that there are no RCTs. It is included for completeness and to remind readers that there is a proportion of wet AMD where there are no neovascular lesions.
### Table 6 Multiple treatment RCTs of PDT in wet AMD found (ongoing RCTs in brackets)

<table>
<thead>
<tr>
<th></th>
<th>Subfoveal</th>
<th>Juxtafoveal</th>
<th>Extrafoveal</th>
</tr>
</thead>
<tbody>
<tr>
<td>No neovascular lesions</td>
<td>None found</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>Classic neovascular lesions only</td>
<td>TAP, (SnET2)</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td></td>
<td>VIP if VA&gt; 70 letters</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>Combined classic and occult</td>
<td>TAP, VIP, (VIM)</td>
<td>None found</td>
<td>None found</td>
</tr>
<tr>
<td>Occult neovascular lesions only</td>
<td>VIP, (VIO)</td>
<td>None found</td>
<td>None found</td>
</tr>
</tbody>
</table>

#### 3.2.3 Number and type of studies excluded from analysis of effectiveness

From the 417 references, 159 were excluded because of being duplicates from the different databases and 230 were excluded because of obvious irrelevance on the basis of their title and abstract (ie reviews, case-series or animal studies). This left 28 references which required further consideration. 10 studies were excluded on scrutiny of the full text (6 because the trial design was not RCT, 3 because they weren’t RCTs of PDT but of anecortave acetate and one because it was a review) and 13 because they were duplicate reports of the 5 RCTs already found in the searches. (The sixth RCT found was from a conference not from the searches). Of the 13 duplicate reports from the 5 RCTs, 7 were from the TAP RCT, 4 from the VIP RCT and 2 from Thomas et al (see below).

Of the six on-going or completed RCTs of PDT in wet AMD identified, the four on-going studies were excluded from the analysis of current evidence on effectiveness, because the data were incomplete. Details of these four ongoing studies are as follows:

**Gierek-Lapinska et al 2001**

This is a single treatment RCT using verteporfin. It may also be the only trial found which is independent of drug company sponsorship. Details of this RCT are from one poster and one abstract. Follow up is presented for 19 patients and for 33 patients respectively. Therefore it is unclear as to whether follow up is complete. Attempts were made to contact the first author, but no further information was obtained. Therefore, it was decided to regard this trial as not completed and not to present any results.

**Thomas et al 2000**

This is a multiple treatment RCT. It was started in 1999 and compares SnET2 in two doses to placebo and uses a different laser setting to the TAP trials. Recruitment finished in approximately June 2000 and 933 patients were randomised. The 2 year follow up has been completed on approximately 1/3rd of these (as of June 2001). Follow up should be complete on the remainder in early 2002. 86% of patients had wet AMD with some classic neovascularisation (and the remainder had occult neovascular lesions) (Presentation at SOE conference, Istanbul, 2001). A recent press release (Miravant, 13/1/02) suggests that ‘the trial did not meet the primary efficacy endpoint’.
VIM
The VIM trial (Visudyne® (Novartis Ophthalmics AG, Switzerland) in minimally classic CNV) is another multiple treatment RCT but has only recently started and is still in the recruitment phase. It compares a standard dose of verteporfin (6mg/m²) to placebo, with standard or reduced laser settings. To date (as of June 2001) approximately 270 patients have been randomised (Presentation at SOE conference, Istanbul, 2001). We have no information on the target number of patients.

VIO
The final ongoing multiple treatment RCT is VIO trial (Visudyne® (Novartis Ophthalmics AG, Switzerland) in occult CNV). Again it has only recently started and is in the recruitment phase. It compares verteporfin to placebo with standard laser settings in patients with occult only wet AMD. We have no information on the target number of patients.

3.2.4 Characteristics of included studies
The two RCTs were the TAP trial and the VIP trial. Both had 2 year follow up results published. The TAP trial 1-year results were also published.

Data was extracted for these two trials as per the methods section. Overall out of 74 items for each trial, the data extractors were in complete agreement on 71 items for each. The reasons for the three disagreements in each of the trials generally related to the characteristics of the studies (as opposed to study quality or trial results) and are listed in Appendix 6.

The TAP trial was carried out by the TAP study group. Two trials were carried out simultaneously in 22 clinical centres in Europe and North America, using identical protocols. Ten of the centres were prospectively assigned to one study and the remainder to the other and the results of both trials have been presented together. It is debatable whether the TAP RCT is one trial or two. For the purposes of this systematic review it was treated as one.

The VIP trial was carried out by the VIP study group. Many of the VIP authors were also involved in the TAP trial. Both RCTs were industry sponsored.

The photosensitive substance used in both trials was verteporfin (which is a green colour) given at 6mg per m² body surface area diluted to 30ml and the placebo was 30ml of uncoloured 5% dextrose in water. Both solutions were infused over 10 minutes using a syringe pump. The laser used was a diode laser at 689 nanometres wavelength, delivering 50 Joules per cm² at an intensity of 600 milliWatts per cm² over 83 seconds, using a spot size 1mm greater than the largest dimension of the lesion. The laser was applied at 15 minutes after the start of the infusion and the same laser dose schedule was used for all patients (i.e. intervention and placebo). No information is given in either RCT as to the nature and extent of visual rehabilitation offered where the wet AMD progressed. It seems reasonable to assume that whatever the level it was equal in both treatment and control arms.

In both trials there was one treatment group and one placebo group but patients were allocated so that there were twice as many receiving treatment than placebo. Only one eye per patient was included in both trials. There were no stipulations about the visual acuity in the fellow eye. Follow up was at 3 months after each treatment episode for two years, i.e. at
3, 6, 9, 12, 15 18, 21 and 24 months. Re-treatment with the same treatment only at each follow up visit was permitted. The mean visual acuity in the study eye at baseline was approximately 53 letters in the TAP trial and 66 letters in the VIP trial. In the fellow eye it was approximately 50 letters in the TAP trial and 46 letters in the VIP trial. The patient inclusion criteria are shown in Table 7.

### Table 7 Included RCT inclusion criteria.

<table>
<thead>
<tr>
<th></th>
<th>TAP</th>
<th>VIP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion location and size</td>
<td>Angiographic evidence of subfoveal neovascular membranes caused by AMD ≤ 5.4mm in the greatest linear dimension</td>
<td>Angiographic evidence of subfoveal neovascular membranes caused by AMD ≤ 5.4mm in the greatest linear dimension</td>
</tr>
<tr>
<td>Allowable extras</td>
<td>Patients could also have haemorrhage, angiographic hypofluorescence or pigment epithelial detachment but these other obscuring features should occupy less than 50% of the total lesion.</td>
<td>Area of choroidal neovascularisation at least 50% of the area of the total lesion.</td>
</tr>
<tr>
<td>Lesion type</td>
<td>Classic only or classic plus occult</td>
<td>Occult only or evidence of classic if VA &gt; 70 letters</td>
</tr>
<tr>
<td>Visual acuity (using a modified LogMAR chart)</td>
<td>73 to 34 letters (20/40 to 20/200 at 2m)</td>
<td>(a, \geq 50) letter (20/100 or better (occult only) (b, &gt; 70) letters (any classic)</td>
</tr>
<tr>
<td>Recent deterioration</td>
<td>Not specified</td>
<td>If occult only – presumed recent disease progression (visual or anatomical) within previous 3 months or haemorrhage.</td>
</tr>
<tr>
<td>Age</td>
<td>50 years or more</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

The exclusion criteria for both trials were:
- Tear (rip) of pigment epithelium.
- Any significant eye diseases that affected or could affect vision in the study eye which would confound the primary outcome measure.
- Inability to obtain fluorescein angiograms, including where it is due to poor venous access.
- History of treatment for neovascular membranes in the study eye (except for nonfoveal laser photocoagulation). During the first 7 months of the TAP trial, patients with subfoveal lesions eligible for laser photocoagulation were excluded but after this the laser treatment guidelines were changed to enable patients to chose this trial and forego laser treatment.
- Participation in another ophthalmic clinical trial or use of other new drugs within 12 weeks prior to the start of the trial, prior photodynamic therapy for neovascular membranes.
- Surgery inside the study eye in the previous 2 months or capsulotomy (cataract surgery) in the previous month.
- Active hepatitis, clinically significant liver disease, porphyria or porphyrin sensitivity.
An additional exclusion criterion for VIP was features of any condition other than AMD (eg pathological myopia) associated with choroidal neovascular membranes in the study eye. A different branch of the VIP trial included patients with neovascular membranes caused by pathological myopia.

The characteristics of the patients entered in the RCTs are shown in Table 8. They corroborate the nature of the group to whom the results of the RCTs can be generalised, as suggested by the inclusion/exclusion criteria. From the viewpoint of generalisability, it is notable that in both RCTs the vast majority of patients were white. A further interesting observation which is only deducible from the baseline characteristics of the TAP trial is that in at least 36% of patients the treated eye visual acuity was worse than in the fellow eye. So visual function of these patients was unlikely to be influenced by the success or failure of PDT. Finally, although in theory the VIP trial might contribute information on the value of PDT in patients with wet AMD with classic neovascular lesions where baseline visual acuity in the treated eye was relatively good (>70 letters), the vast majority of the patients in the trial (77%) had occult with no classic neovascular lesions.

### Table 8 Included RCT participant characteristics and follow up

<table>
<thead>
<tr>
<th></th>
<th>TAP</th>
<th></th>
<th>VIP</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Intervention</td>
<td>Control</td>
<td>Intervention</td>
<td>Control</td>
</tr>
<tr>
<td>N =</td>
<td>402</td>
<td>207</td>
<td>225</td>
<td>114</td>
</tr>
<tr>
<td>Mean age</td>
<td>74.9</td>
<td>76.0</td>
<td>75</td>
<td>74</td>
</tr>
<tr>
<td>% women</td>
<td>53.2%</td>
<td>62.8%</td>
<td>58%</td>
<td>62%</td>
</tr>
<tr>
<td>% white</td>
<td>98.5%</td>
<td>98.1%</td>
<td>99%</td>
<td>98%</td>
</tr>
<tr>
<td>Mean VA in treated eye</td>
<td>52.8 letters</td>
<td>52.6 letters</td>
<td>66 letters</td>
<td>65 letters</td>
</tr>
<tr>
<td>Mean VA in fellow eye</td>
<td>48.9 letters</td>
<td>51.8 letters</td>
<td>44 letters</td>
<td>48 letters</td>
</tr>
<tr>
<td>Proportion with VA&gt;73 letters in fellow eye</td>
<td>36.3%</td>
<td>38.2%</td>
<td>27%</td>
<td>29%</td>
</tr>
<tr>
<td>Lesion area subfoveal</td>
<td>89.1%</td>
<td>90.3%</td>
<td>85%</td>
<td>81%</td>
</tr>
<tr>
<td>Some classic component</td>
<td>89.8%</td>
<td>90.4%</td>
<td>24%</td>
<td>19%</td>
</tr>
<tr>
<td>Some occult component</td>
<td>75.9%</td>
<td>75.8%</td>
<td>93%</td>
<td>96%</td>
</tr>
<tr>
<td>% followed up at 12 months</td>
<td>94.3%</td>
<td>93.7%</td>
<td>93.3%</td>
<td>91.2%</td>
</tr>
<tr>
<td>% followed up at 24 months</td>
<td>87.3%</td>
<td>86.0%</td>
<td>85.8%</td>
<td>86.8%</td>
</tr>
<tr>
<td>Mean no treatments per patient (1\textsuperscript{st} year)</td>
<td>3.4</td>
<td>3.7</td>
<td>3.14</td>
<td>3.55</td>
</tr>
<tr>
<td>Mean no treatments per patient (2\textsuperscript{nd} year)</td>
<td>2.2</td>
<td>2.8</td>
<td>1.81</td>
<td>2.36</td>
</tr>
<tr>
<td>Mean no angiographies per patient</td>
<td>Not given</td>
<td>Not given</td>
<td>Not given</td>
<td>Not given</td>
</tr>
</tbody>
</table>

The outcomes measured in the two trials were:

- **Visual acuity**
  - Number of people who lost 15 or more letters compared to baseline
  - Number of people who lost 30 or more letters compared to baseline
  - Mean visual acuity
  - Mean change in visual acuity
- **Contrast sensitivity**
Mean change in contrast threshold (number of contrast sensitivity letters lost)

- Angiographic
  - Progression of neovascular lesion
  - Size of lesion

In addition, the VIP trial measured the proportion who progressed to a VA of <34 letters (20/200) but did not report this outcome in the trial report. The TAP trial did not state this as an outcome but did report it. In both trials the unit of analysis was eyes not binocular vision, i.e., the visual acuity change was for the single treated eye not taking into account any changes in the fellow eye.

Both trials measured a variety of adverse events including mortality, adverse event considered by the ophthalmologist to be associated with treatment, adverse event serious enough to warrant stopping treatment, allergic reactions, subjective visual disturbance, and severe loss of VA.

Neither of the RCTs directly measured the impact of treatment on function (such as Nottingham Health Profile) on generic quality of life (such as EUROQOL) or vision specific quality of life (such as VF-14).

### 3.2.5 Quality of included studies

There was complete agreement between both reviewers for all elements of the Jadad score for the two included RCTs.

The method of randomisation was by sealed envelope organised by a central department of QLT PhotoTherapeutics Inc. for the TAP trial and by Statprobe for the VIP trial. Randomisation was stratified by participating centre (TAP and VIP) and by baseline visual acuity (categories of 20/40 to 20/80 and 20/100 to 20/200) (TAP) using separate groups of colour coded envelopes. There was no stratification by type of lesion (classic/occult). Randomisation took place after eligibility was confirmed and patient consent was obtained. The randomisation procedure appeared to be successful except that in the TAP trial four patients were randomised according to the wrong visual acuity category. Their results were included in the group to which they were originally assigned.

Masking of allocation to intervention or placebo was carried out in several ways. In the TAP trial the randomisation log with opened and unopened randomisation envelopes was kept in a locked cabinet at each clinical centre. Only the study co-ordinator and the technicians making up the verteporfin or placebo infusions had access to this log. These personnel were trained to make every reasonable attempt to maintain masking of the ophthalmologists, patients, vision examiners and the people reading the fundus photographs. Although the two infusions were different colours (green v. clear) all tubing used was covered in foil, which must have presented some practical problems. The fundus appearance apparently does not change during infusion of verteporfin so the ophthalmologist administering the laser could not tell group assignment. In the VIP trial masking procedures were the same as in the TAP trial.

For both trials, the intervention and placebo groups appear to have been treated similarly during follow up. During the course of the TAP trial, six ophthalmologists and two patients became unmasked to treatment allocation. This was because of leaking infusions,
angiographic fundus appearance after one week or prior to a surgical procedure for subretinal haemorrhage. In the VIP trial there were no major protocol deviations.

Overall both trials appear to have been well conducted and they obtained a Jadad score of 5 (the maximum possible score). Random assignment seems to have been carried out effectively. Groups were treated similarly apart from the intervention and outcomes were assessed blind to treatment allocation. Relatively complete follow up was achieved. However, there was no mention of the number of patients eligible to take part in the trials compared to those randomised or of any withdrawals before or after randomisation.

Visual acuity data from people who dropped out was included in the results using the method of last observation carried forward.

The only other source of concern about the conduct of the two trials was imbalance in baseline characteristics, suggesting that the randomisation process may not have been as random or well concealed as it might at first appear. In the TAP trial, the 21 recorded baseline characteristics of the two groups were similar except that there were significantly more women in the placebo group and more past and current smokers in the intervention group. In the VIP trial very similar baseline characteristics were recorded but no significance tests given.

3.2.6 Main results of included studies

There was complete agreement between the reviewers about the results data abstracted from the included trials.

A priori and based on detailed analysis of the characteristics of the TAP and VIP RCTs, we did not believe it would be reasonable to combine their results. This was principally because the spectrum of neovascular lesions in TAP (majority of participants had lesions with some classic component) was so different from VIP (minority of participants had lesions with some classic component). For this reason their results are presented separately.

TAP Trial (majority of participants have some classic neovascular lesions)

The main results are summarised in Table 9.

### Table 9 TAP; clinical and angiographic results at 1 & 2 years

<table>
<thead>
<tr>
<th></th>
<th>TAP – 1 year</th>
<th>TAP – 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verteporfin PDT</td>
<td>Placebo PDT</td>
</tr>
<tr>
<td>Total patients</td>
<td>402</td>
<td>207</td>
</tr>
<tr>
<td>Lost 15 or more letters</td>
<td>156 (38.8%)</td>
<td>111 (53.6%)</td>
</tr>
<tr>
<td>Lost 30 or more letters</td>
<td>59 (14.7%)</td>
<td>49 (23.7%)</td>
</tr>
<tr>
<td>Mean VA (no letters)</td>
<td>42</td>
<td>35</td>
</tr>
<tr>
<td>Mean change in VA (lines)</td>
<td>-2.2</td>
<td>-3.5</td>
</tr>
<tr>
<td>Mean number contrast sensitivity</td>
<td>-1.3</td>
<td>-4.5</td>
</tr>
</tbody>
</table>
These results make clear that irrespective of the measure used or the time at which it was measured, visual acuity in the randomised eye deteriorated less in the verteporfin PDT group than the placebo PDT group. For those measures where a relative risk could be calculated, the 95% CI indicate clearly that these results are statistically significant. Statistical tests could not be recalculated on the mean values reported because no measures of dispersion were provided. For the verteporfin PDT group the mean visual acuity was 52.8 letters at baseline and this dropped to 39.4 letters by the 2-year follow up. In the placebo group the equivalents were 52.6 and 32.9 (with respect to the corresponding figures in Table 9, note that 5 letters is approximately equivalent to 1 line of visual acuity).

For contrast sensitivity, the placebo group had significantly more mean number of contrast sensitivity letters lost than the intervention group at the two year follow up but not the one year follow up.

There was no significant difference in mortality for the two groups in the trial although it should be noted that the trial was not powered to detect any difference in this outcome. (see Section 3.2.9 on adverse events)

VIP (minority of participants have some classic neovascular lesions)

The main results are summarised in Table 10

Table 10 VIP; clinical and angiographic results at 1 & 2 years

<table>
<thead>
<tr>
<th></th>
<th>VIP – 1 year</th>
<th></th>
<th>VIP – 2 years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verteporfin PDT</td>
<td>Placebo PDT</td>
<td>Relative risk</td>
<td>Verteporfin PDT</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% CI)*</td>
<td></td>
</tr>
<tr>
<td>Total patients</td>
<td>225</td>
<td>114</td>
<td>0.93 (0.75, 1.15)</td>
<td>225</td>
</tr>
<tr>
<td>Lost 15 or more</td>
<td>114 (51%)</td>
<td>62 (54%)</td>
<td>Not reported</td>
<td>121 (54%)</td>
</tr>
<tr>
<td>letters</td>
<td></td>
<td></td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Lost 30 or more</td>
<td>Not reported</td>
<td>Not reported</td>
<td>N/A</td>
<td>67 (30%)</td>
</tr>
<tr>
<td>letters</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean VA (no letters)</td>
<td>Not reported</td>
<td>Not reported</td>
<td>N/A</td>
<td>Not Reported</td>
</tr>
<tr>
<td>Mean change in</td>
<td>Not reported</td>
<td>Not reported</td>
<td>N/A</td>
<td>Not Reported</td>
</tr>
<tr>
<td>VA (lines)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean number</td>
<td>Not reported</td>
<td>Not reported</td>
<td>N/A</td>
<td>Not Reported</td>
</tr>
<tr>
<td>contrast sensitivity</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>letters lost</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
The reported data for the whole trial population are much more scant than for TAP (even though the protocols for VIP and TAP were said to be similar). For the trial’s primary outcome of loss of 15 letters of visual acuity or more at 1 and 2 years, the results favour verteporfin PDT. The results at 2 years are statistically significant. The impression that verteporfin PDT is beneficial in patients with wet AMD in occult neovascular lesions is reinforced by the fact that at 2 years the number of patients losing 30 letters of visual acuity or more is statistically significantly smaller in the verteporfin group relative to placebo. Like TAP, in VIP it should be noted that the less marked deterioration in visual acuity in the verteporfin PDT group refers to individually randomised eyes (one eye per person). It seems likely that in a substantial proportion of participants the treated eye had worse VA than its non-randomised fellow.

Contrast sensitivity was not reported, even though mentioned in the methods section of the trial report.

There was no significant difference in mortality for the two groups in the VIP trial although it should be noted that the trial was not powered to detect any difference in this outcome. (See Section 3.2.9 on adverse events)

3.2.7 Heterogeneity between the results of TAP and VIP

As stated above, it was our prior assumption that there was clinical heterogeneity between the two included RCTs and hence likely to be heterogeneity between their results. In order to test this assumption we undertook some exploratory meta-analyses to measure the heterogeneity between the results of VIP and TAP. The forest plots are presented in Figure 1 below:
Surprisingly, there is little heterogeneity between the results of the two trials for the three outcomes on which information is provided by both. This is particularly true for the outcomes measured at 2 years. This must to some extent challenge the assumption that there is truly important clinical heterogeneity between the trials, i.e., that the spectrum of types of neovascular lesions does not actually have a great impact on the relative effectiveness of verteporfin PDT. However, both the limited numbers of studies contributing to the meta-analysis and the known lack of power of tests for heterogeneity means that this is only an observation. It is certainly not conclusive, and we certainly do not believe at this stage that it is appropriate to use the summary measures provided by the meta-analyses above to represent the effectiveness of verteporfin PDT in wet AMD.

3.2.8 Subgroup analyses for main results of included studies

Both the TAP and VIP trials carried out numerous subgroup analyses. In the TAP trial, 12 subgroup analyses are reported for all trial participants. A similar pattern is seen in the reporting of the VIP trial with 10 subgroup analyses reported for the subgroup of trial participants with no classic neovascular wet AMD lesions.

The results of the TAP trial subgroup analyses are presented in Appendix 7. These results relate to the outcome loss of <15 letters of visual acuity in the randomised eyes, and are hence the inverse of the results presented in Table 9 (i.e., loss of 15 or more letters). 12 subgroup analyses are reported. It is not completely clear how many, if any, of these were...
prespecified in the protocol, as we have not been able to obtain a copy of the protocol despite requests, or whether any other analyses were carried out but not reported.

Two of these analyses reported significant tests for interaction; % lesion area composed of classic CNV (p=0.02) and evidence of occult CNV (p<0.001). Figure 2 illustrates the impact on the estimate of effectiveness by restricting analysis to the predominantly classic component in the first sub-group analysis, and the no occult component in the second sub-group analysis. By comparison, the effect size in the whole trial was RR=0.75 (95%CI 0.65, 0.88):

Figure 2 Claimed sub-group effects in TAP

<table>
<thead>
<tr>
<th>Comparison: 6% subgroup</th>
<th>Outcome: 1% predominantly classic CNV</th>
<th>2% occult only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study</td>
<td>verteporfin n/N</td>
<td>placebo n/N</td>
</tr>
<tr>
<td>01 predominantly classic</td>
<td>65 / 159</td>
<td>57 / 63</td>
</tr>
<tr>
<td>02 occult only</td>
<td>105 / 202</td>
<td>58 / 104</td>
</tr>
</tbody>
</table>

This subgroup analysis by % lesion area composed of classic CNV suggests that the benefit of verteporfin PDT may be confined to eyes with predominantly (>50%) classic CNV. The analysis by whether or not there was evidence of occult CNV suggests that there may be little or no benefit in the relatively large proportion of eyes with evidence of occult CNV. However, the statistical evidence for these possible interactions is weak. Subgroup analyses are prone to false positive findings, and with such a large number of subgroup analyses performed, it would be surprising if at least one interaction was not significant at the conventional 5% level (p<0.05).

Further, it is important to note that, although there are two significant results reported here, they are not independent of each other. That is, whatever the underlying truth, we might expect these two analyses to show similar results simply because the presence of occult disease and the % lesion composed of classic disease will tend to group patients in similar ways.

A corollary of the frailty of the sub-group results presented is that the results of the VIP trial do not lend any support to the subgroup findings from TAP. 94% of patients in VIP had evidence of occult disease, with 76% having occult disease with no classic disease at all. 75 patients (22%) had classic disease that could be graded, and the majority of these (56/75) had minimally (<50%) classic disease. Thus this trial consisted almost entirely of patients who would be predicted to obtain minimal benefit from verteporfin PDT if the conclusions from the subgroup analysis of TAP were correct. The results of VIP presented in the preceding
sections clearly show that there is benefit of the same level at 2 years as that obtained in the TAP trial.

There is therefore no strong evidence that there are subgroups of patients who benefit more or less from verteporfin PDT. The sub-group analyses may be a useful starting point for further hypotheses requiring testing, but we do not believe they should be used to portray the likely effectiveness of verteporfin PDT. To do so would be likely to overestimate its impact. The most reliable estimates of effectiveness should therefore be obtained using whole trial data.

3.2.9 Adverse events in included studies

The first year and cumulative two-year safety and adverse event (AE) data are shown in Table 11 and Table 12.

Table 11 1st year safety and adverse events for TAP and VIP trial

<table>
<thead>
<tr>
<th></th>
<th>TAP</th>
<th>VIP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Verteporfin</td>
<td>Placebo</td>
</tr>
<tr>
<td></td>
<td>Verteporfin</td>
<td>Placebo</td>
</tr>
<tr>
<td>Total number patients</td>
<td>402</td>
<td>207</td>
</tr>
<tr>
<td></td>
<td>225</td>
<td>114</td>
</tr>
<tr>
<td>Mortality</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Severe VA loss within 1 week (loss 20 letters)</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>71 (17.7%)</td>
<td>24 (11.6%)</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>AE associated with treatment</td>
<td>185 (46%)</td>
<td>74 (36%)</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Stopped treatment from AE</td>
<td>7 (1.7%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Injection site AEs</td>
<td>54 (13.4%)</td>
<td>7 (3.4%)</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>5 (1.2%)</td>
<td>7 (3.4%)</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>Photosensitivity reactions</td>
<td>12 (3.0%)</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
Table 12 Cumulative 2 year safety and adverse events for TAP and VIP trial

<table>
<thead>
<tr>
<th></th>
<th>Verteporfin</th>
<th>Placebo</th>
<th>RR® (95%CI)</th>
<th>Verteporfin</th>
<th>Placebo</th>
<th>RR® (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number patients</td>
<td>402</td>
<td>207</td>
<td></td>
<td>225</td>
<td>114</td>
<td></td>
</tr>
<tr>
<td>Mortality</td>
<td>13 (3.2%)</td>
<td>8 (3.9%)</td>
<td>0.84 (0.35-1.99)</td>
<td>4 (1.8%)</td>
<td>3 (2.6%)</td>
<td>0.68 (0.15-2.97)</td>
</tr>
<tr>
<td>Severe VA loss within 1 week (loss 20 letters)</td>
<td>3 (1%)#</td>
<td>0#</td>
<td>0.84 (0.19-69.62)</td>
<td>10 (4.4%)</td>
<td>0</td>
<td>10.69 (0.63-108.75)</td>
</tr>
<tr>
<td>Visual disturbance</td>
<td>89 (22.1%)</td>
<td>32 (15.5%)</td>
<td>1.43 (0.99-2.07)</td>
<td>94 (42%)</td>
<td>26 (23%)</td>
<td>1.83 (1.26-2.66)</td>
</tr>
<tr>
<td>AE associated with treatment</td>
<td>192 (47.8%)</td>
<td>70 (33.8%)</td>
<td>1.41 (1.14-1.75)</td>
<td>96 (43%)</td>
<td>21 (18%)</td>
<td>2.32 (1.53-3.51)</td>
</tr>
<tr>
<td>Stopped treatment from AE</td>
<td>7 (1.7%)</td>
<td>0</td>
<td>7.74 (0.44-134.90)</td>
<td>8 or 9</td>
<td>0 or 1</td>
<td>9.67 (0.57-164.65)</td>
</tr>
<tr>
<td>Injection site AEs</td>
<td>64 (15.9%)</td>
<td>12 (5.8%)</td>
<td>2.75 (1.52-4.97)</td>
<td>18 (8%)</td>
<td>6 (5%)</td>
<td>1.52 (0.62-3.72)</td>
</tr>
<tr>
<td>Allergic reactions</td>
<td>8 (2.0%)</td>
<td>3 (3.9%)</td>
<td>1.37 (0.37-5.12)</td>
<td>3 (1%)</td>
<td>3 (3%)</td>
<td>0.51 (0.10-2.47)</td>
</tr>
<tr>
<td>Photosensitivity reactions</td>
<td>14 (3.5%)</td>
<td>0</td>
<td>14.97 (0.90-249.68)</td>
<td>1 (0.5%)</td>
<td>1 (1%)</td>
<td>0.51 (0.03-8.03)</td>
</tr>
</tbody>
</table>

# TAP trial data mentioned in VIP trial report discussion section.
* Unclear from VIP trial report whether one patient was in the treatment or placebo arm
@ calculated using Review Manager software version 4.1

In general there seem to be increases in all adverse events anticipated and reported in the treatment arm compared to placebo in both trials, with the exception of allergic reactions. Of concern are the statistically significant increases in AEs associated with treatment (TAP and VIP) and visual disturbance (VIP) (Relative risks calculated using Review Manager software version 4.1). One adverse event of particular concern is severe visual acuity loss within 1 week (loss 20 letters). Although this is relatively rare (1%-4.4%) it only seems to occur in the intervention groups and causes a dramatic drop in vision for those affected. Although this may have little effect on the overall effectiveness of verteporfin PDT, it is clearly a potential consequence of the treatment that patients should be aware of.

3.3 Discussion and assessment of effectiveness

One of the objectives of the systematic review of effectiveness is to give an indication not just of the individual effects of verteporfin PDT but an assessment of the overall effectiveness, taking into account the balance between beneficial and disbeneficial outcomes identified. What ultimately needs to be influenced is the quantity and quality of life for patients. In the case of this intervention, quantity of life may not be a key issue, but quality of life is, particularly as reflected by a person’s ability to carry out their normal daily activities. In this respect, unfortunately, the included RCTs provide no direct information, such as might be obtained from instruments measuring QoL such as the SF36 or EQ-5D or vision specific quality of life instruments such as VF-14.
In lieu of this, the included RCTs provide good quality information on the impact on visual acuity in the single eye randomised to the studies. The results clearly show that in patients with wet AMD with classic neovascular lesions (the indication for which verteporfin PDT is licensed) the deterioration in visual acuity in the randomised eye is markedly less. In the TAP trial the RR was 0.75 (95% CI 0.65, 0.88) for loss of 15 letters of visual acuity or more at 2 years. Such an effect is both statistically significant and would seem to be clinically important. It is equivalent to an NNT to avoid one person losing 15 letters (3 lines) of visual acuity over 2 years of 7 (95%CI 4 to 14). This NNT only applies to the circumstances prevailing in the TAP trial. The effect on reducing loss of visual acuity also seems to apply in patients with wet AMD where the majority of participants have occult neovascular lesions, although verteporfin PDT is currently not licensed for this indication. These beneficial effects seem to be offset to some degree by adverse events. However, with the exception of immediate severe visual loss, which would be incorporated in the main results above, most of these adverse events seem to be of a minor nature. Concerning immediate visual loss, we reiterate that it is important that patients who might receive verteporfin PDT are made aware that this might occur.

Going beyond this statement of the main beneficial and disbeneficial effects is however problematic. As noted in the background, the link between visual acuity changes resulting from wet AMD and a patient’s ability to function is complex. Thus, translating the undeniable reduction in deterioration in sight attributable to verteporfin PDT into improved QoL and function is not straightforward. A key issue identified is that the results relate to the improvement in vision in single eyes, whereas function is dependent on the combined vision in both eyes. A further key issue concerning the interpretation of the included RCT results is that certainly in TAP, and probably in VIP, the randomised eye is the “worse seeing eye” at the outset of the trial in many participants. In these participants we would expect any reduction in deterioration of visual acuity to have less impact on function than if the randomised eye was the “better seeing eye” at the start of the RCT. Unfortunately there are no simple answers as to how to deal with this two-eye problem. We highlight it here as a major challenge in estimating cost-effectiveness, and cost-utility in particular, considered in the next section.

What this problem indicates for the future is that research needs to address directly, not just the impact on visual acuity in the randomised eye, but on the global function and QoL of the patient. There is no evidence that such outcomes are being measured in the ongoing trials identified.

With respect to ongoing trials it needs to be noted that further RCT evidence should be forthcoming on the use of verteporfin PDT in wet AMD where classic neovascular lesions are in a minority or absent (ie pure occult neovascular lesions) and on the effects of SnET2 PDT. It is also apparent the there are many areas of potential importance where no research appears to be planned.

Another issue is that we believe that the sub-group analyses offered in the original reports of the included RCTs only provide weak evidence for the existence of important differences in the effect on visual acuity deterioration depending on the nature of the neovascular lesions occurring in wet AMD. Estimates of effect should be based on whole trial results, not estimates arising from sub-group analyses. Using sub-group estimates of effect on loss of 15 letters or more of visual acuity potentially inflates the estimate of effect based on the whole
trial data by 100% ie results in an approximate doubling of the absolute risk reduction or halving of the NNT. This is again an issue to which we will return in the section on economic evaluation. The absence of any believable sub-group effect also has implications for rational targeting verteporfin PDT.

The last proviso concerning the evidence on effectiveness is that the assessment of effects is restricted to 609 patients in the TAP trial and 339 in the VIP trial and both of these trials are industry sponsored. Publication bias is an ever-present threat to the conclusions of any systematic review. If it were to be operating in this condition, the fact that the conclusions above are based on a relatively small number of patients, means that the potential for small unpublished studies to erode the size of effect demonstrated is greater. However, a comprehensive search was instituted and no unpublished studies were identified. Therefore we have no greater reason to suspect that publication bias might be operating here than in any other systematic review of this type.

This assessment of effectiveness agrees with other systematic reviews done on this topic in some respects and disagrees with others. There were 4 other completed systematic reviews found on PDT. One reviewed the one and two year TAP trial results and the remaining three reviewed the first year results of the TAP trial only. Two were very positive about PDT and did not echo our concerns regarding quality of life, the impact of the second eye, the weak evidence on predominantly classic lesions from the subgroup analyses and basing treatment decisions on the small amount of good quality research available. The Cochrane review did mention impact on quality of life and the impact of the second eye. They also echoed our concerns re the weak evidence from the subgroup analysis of percentage of lesion comprising classic CNV and its ‘somewhat surprising result’ and that further, independent RCTs were required. The fourth systematic review stated that ‘It is not known whether this benefit (of PDT) leads to a real improvement in daily life activities’. They also mention that the retrospective sub group analyses provide only weak evidence and that further trials are needed.

3.4 Summary

Methods:
- A systematic review of evidence of clinical effectiveness of PDT in wet AMD was undertaken according to pre-defined protocol and there were no major departures

Quantity of studies found:
- 417 potentially relevant citations were initially identified from the searches
- 28 required detailed scrutiny to include/exclude
- 23 were excluded; the main reasons for which were not RCTs (7), not RCTs of PDT (3) and duplicate reports of RCTs found (13).
- 6 RCTs were identified (5 from the searches, 1 from a conference), but 4 of these were on-going and the results were not analysed
- The two included RCTs (TAP and VIP) address the effectiveness of verteporfin relative to placebo in patients with wet AMD with neovascular lesions in the subfoveal region
- The four on-going trials address the effects of a single treatment of verteporfin (Gierek-Lapinska et al), a different photosensitive drug – SnET2 (Thomas et al), verteporfin in minimally classic AMD (VIM) and verteporfin in occult only AMD (VIO).
• There seem to be no RCTs completed or on-going in the following important areas of wet AMD
  • Non-neovascular lesions (although given the rationale for use of PDT, the absence of RCTs is understandable)
  • Juxtafoveal/extrafoveal neovascular lesions
  • Direct comparison of PDT with laser photocoagulation (which would be particularly relevant to the above)
  • Direct comparison of PDT + visual rehabilitation with optimised visual rehabilitation in any type of wet AMD
  • Direct comparison of PDT with other new treatments for wet AMD
  • Direct comparison of one type of PDT with another in any type of wet AMD

Trial design:
• TAP randomised 609 patients (402 verteporfin PDT; 207 placebo PDT); VIP randomised 339 (225 verteporfin PDT; 114 placebo PDT)
• TAP mainly addresses the effectiveness of verteporfin in patients with wet AMD with classic neovascular lesions; approximately 24% had only classic lesions; 66% had a mixture of classic and occult lesions; and 10% had only occult lesions
• VIP mainly addresses the effectiveness of verteporfin in patients with wet AMD with occult neovascular lesions; approximately 4% had only classic lesions; 20% had a mixture of classic and occult lesions; and 76% had only occult lesions
• Both studies investigated the effects of multiple verteporfin PDT treatment
• In both studies eyes were randomised; certainly for the TAP trial and probably VIP, in a considerable number of patients the randomised eye had worse vision at baseline than the fellow eye
• In both studies the main outcome was change in visual acuity in the randomised eye measured up to two years post-treatment
• Neither trial reported direct impact on patient function or quality of life

Trial quality:
• Both RCTs were well conducted and received Jadad scores of 5
• As TAP and VIP examine purportedly markedly different spectra of wet AMD with respect to the type of neovascular lesions included, it was not felt reasonable at first to combine their results

Results:
• In TAP (majority have classic neovascular lesions) there was consistent evidence at both 1 & 2 years that verteporfin PDT results in less deterioration in visual acuity in the randomised eye than placebo. The relative risk for loss of 15 letters (3 lines) or more at 2 years was 0.75 (95% CI 0.65, 0.88). This effect is both statistically significant and clinically important.
• In VIP (minority have classic neovascular lesions), the results are similar, particularly at 2 years.
• Lack of statistical heterogeneity between the results of TAP and VIP challenges the assumption that the nature of the wet AMD neovascular lesions has as much influence on the relative effect of verteporfin PDT as is predicted on the basis of an assessment of clinical heterogeneity
• Nonetheless, at this stage, there are not sufficient grounds for using a summary estimate of effect obtained by combining the results of TAP and VIP
• Extensive sub-group analyses are presented for both trials. Further investigation suggests the results of these should be treated with extreme caution and at best should be regarded as generating hypotheses requiring more research. The whole trial estimates of effect should be those on which the effect size of impact on reduced deterioration in visual acuity is based.
• There is an increase in adverse events associated with verteporfin PDT. Most are minor. Sudden visual loss occurs in 1 to 4.4% of verteporfin PDT patients and is an effect that patients should be aware of.
• The balance of beneficial and disbeneficial effects measured in the included RCTs appears to favour verteporfin PDT.
• However, avoiding deterioration in visual acuity, does not equate directly with improving patient function and quality of life.

Discussion:
• Important issues concerning the conduct of cost-effectiveness and cost-utility analyses are raised by the above.
• Important issues concerning future research are also raised.
4. ECONOMIC ANALYSIS

4.1 Methods for economic analysis

4.1.1 Costs and cost effectiveness review

A systematic review of the literature on costs, health economic impact and generic quality of life outcomes of PDT for AMD was carried out. Costs studies include studies reporting primary research on the costs and utilisation of care and cost studies that discuss economic aspects of care and contain useful primary or secondary cost or utilisation data.

The review of economic studies followed the method of Mugford\textsuperscript{91} and has subsequently been established in other reviews\textsuperscript{92}.

Search

A specific search strategy for information on costs, cost effectiveness and quality of life involved searches of:

\begin{itemize}
\item Bibliographic databases: MEDLINE (Ovid) 1993 – Aug 2001; NHS Economic Evaluation Database (NHS EED) and the NHS Database of Reviews of Effectiveness
\item DARE
\item Internet sites of national economics units
\end{itemize}

Details of the search terms used are given in Appendix 5. Relevant information found during the clinical effectiveness searches was also used. Any economic analysis submitted as part of the Industry submission to NICE could also potentially be included.

The search was broadened to find information to inform the economic model. Searches focused on finding relevant economic information on laser photocoagulation and other possible treatments for AMD, the natural course of wet AMD without treatment and of the consequences of blindness.

Inclusion and exclusion criteria, data extraction and quality assessment

One reviewer, using explicit predetermined criteria, made the inclusion and exclusion decisions for the cost effectiveness review and this was checked by a second researcher. Studies were only included if they met the following criteria:

\begin{itemize}
\item Study design: Any study type.
\item Population: Adults with any AMD.
\item Intervention: PDT using any photosensitive drug.
\item Outcomes: Costs, cost consequences, cost utility, cost effectiveness or any generic quality of life.
\end{itemize}

One researcher extracted data from the included studies and a second researcher again checked this.
There were 3 stages used for the review of cost and economic studies. In Stage 1 each study was categorised by one of the investigators on the basis of its title and abstract where available, according to five classification criteria. Studies that were categorised into the relevant classification for this review proceeded to Stage 2. In Stage 2 all potentially relevant studies were read in full and further classified. All papers confirmed as being relevant to this review proceeded to Stage 3. In Stage 3 all relevant articles were assessed according to predetermined quality criteria. The quality of the economic evaluations was assessed according to the criteria outlined in Drummond 93. The quality of the cost studies was assessed using criteria which have been used in a previous published review by one of the current authors 92.

Analysis
This was qualitative. Conclusions were based on clearly tabulated data from included studies.

4.1.2 Economic evaluation
A cost utility analysis was undertaken by a health economist. The perspective that has been adopted for this is of direct costs to the NHS and local and central government. A simple decision tree was developed, using information from the RCTs on PDT for AMD found during the clinical effectiveness searches. Best supportive care only (BSC) was used as the comparator because this is currently the most usual mode of care for wet AMD. Thus the model compares the benefits and costs of verteporfin PDT + BSC with BSC alone. Although a small percentage of people with wet AMD receive laser photocoagulation, this treatment is not widely used and no evidence on which to base an economic evaluation of PDT against laser photocoagulation was identified.

The starting point for estimation of net benefits was the TAP trial one and two year results. The VIP trial was not considered, both because it deals with an indication for verteporfin PDT which is not currently licensed and because the findings from the effectiveness review was that the results were not greatly dissimilar from TAP. Utilities from the published literature for levels of visual acuity were applied to the TAP trial data. Survival was not included in the model. The costs of blindness to the NHS and to other local and central government funded agencies in the first and subsequent years were estimated from a variety of published and unpublished sources. Sensitivity analysis was carried out on these estimates.

The time frame for the cost utility analysis is 2 years as this is the limit of follow up for the TAP trial. All costs are reported in year 2000 prices. Modelling of subsequent years was not undertaken because of insufficient evidence and concerns about the validity of the extrapolation.

4.2 Results

4.2.1 Review of past studies of cost, cost-effectiveness and cost-utility
Full details of the three stage review process and the results are presented in Appendix 8. In brief the search identified 64 (plus 7 duplicates) articles that were potentially relevant to this review. Five papers were identified by other means such as personal communications. Only two economic evaluations reached Stage 3 of the review. Both passed the quality assessment and are included. Four cost studies were identified initially but only 3 reached
Stage 3 of the review and none of them passed the quality assessment stage. Details of these three studies are given in Appendix 9.

Thus two studies were included, to which was added the economic analysis Section of the Industry submission to NICE. These three studies are discussed below.


Description: The evaluation took the form of a cost utility analysis which compared verteporfin and placebo based on an outcome of improved vision. The study assessed the direct costs of PDT to the NHS. It also considered separately the societal perspective by taking into account the costs of rapidly deteriorating vision. The effectiveness evidence used in the evaluation was taken from the TAP trial. Other published studies were used to link the visual acuity estimates of patients in the TAP trial at follow up to utility values using the time trade off technique. The costs of PDT were disaggregated into the costs of one typical treatment. The cost of the drug was £850 in year 2000 prices. The cost data were taken from one main published source (National Schedule for Reference Costs) and where possible a local NHS Trust (University Hospital Birmingham) costs were provided as a comparison. The total cost for one verteporfin PDT treatment was estimated to be £1181. Assuming each patient receives 3.4 treatments in the first year, the average cost of treatment per patient in the first year was estimated to be £4015. The utility values were combined with the cost data in a decision analysis framework to estimate incremental cost utility ratios. The incremental cost per QALY of treatment compared to the placebo was £137,000. When taking the cost of blindness into account the incremental cost per QALY was £120,000.

Comment: This economic evaluation satisfied all the points listed used to assess its overall quality and it appeared to be carried out well using the best available data. A sensitivity analysis was carried out which focussed on the two main areas of uncertainty namely the translation of health states into utilities and costs both of the intervention and of blindness. Given the range of estimates provided as a result of the sensitivity analysis and the authors’ own concerns, the results of this economic evaluation should be viewed with some caution until better data on costs are available.


Description: The evaluation took the form of a cost utility analysis. It assessed PDT for the treatment of subfoveal choroidal neovascularisation in patients with disciform degeneration in one eye (ie end stage wet AMD causing blindness) and whose second better seeing eye develops visual loss secondary to predominantly classic subfoveal choroidal neovascularisation. The analysis adopted the perspective of a for-profit third party insurer. The analysis used Markov models within a decision analysis software package to determine the cost effectiveness of PDT compared to placebo for two years and 11 years. There were two Markov states included in the model, namely the development or non-development of a
three line vision loss. The effectiveness data used in the models was taken from the TAP trial. The authors have a track record of published studies which derive patient based utilities linked to visual acuity, which have also provided the source of the utility estimates in this paper. A Delphi panel was used to assign utilities to a number of complications associated with PDT. Relevant cost data were obtained from published 1999 Medicare reimbursement data. Only variable incremental costs were included in the model, other costs such as capital expenditure etc were not included because they were considered to be equivalent in both arms of the TAP trial. Sensitivity analyses were performed on the estimates of efficacy (from the TAP Trial) and on the utilities. The authors cite Laupacis et al and the recommendation that health care technologies are considered cost-effective if they cost less than $20,000/QALY, moderately cost effective if they cost between $20,000 and $100,000, and cost ineffective if they are more costly than $100,000.

Two base case scenarios were presented. Base Case 1 referred to the hypothetical patient whose second and better seeing eye becomes affected and who has 20/40 vision and Base Case 2 which is the same but where the patient has 20/200 vision at baseline.

In Base Case 1, for the 2 year model, presenting visual acuity of 20/40 in the second and better-seeing eye, the expected overall utility assuming an annual discount rate of 3% for a patient with predominantly classic neovascular membranes who received PDT was 1.3243. This compares to a utility of 1.1959 for a patient who received the placebo therapy. Thus, treatment with PDT was found to confer a relative increase in patient quality of life of 10.73%. The Base Case scenario 1’s cost /QALY for PDT treatment was $86,721.

In Base Case 2, for the 2 year model, presenting visual acuity of 20/200 in the eye to receive treatment, the expected overall utility assuming an annual discount rate of 3% for a patient with predominantly classic CNVM who received PDT was 0.8816. This compares to a utility of 0.8176 for a patient who received the placebo therapy. Thus, treatment with PDT was found to confer a relative increase in patient quality of life by 7.82%. The Base Case scenario 2’s cost /QALY for PDT treatment was $173,984.

The authors conclude that within the recommendations of Laupacis et al, the treatment would be of only modest or poor cost effectiveness for AMD patient with good vision and cost –ineffective for a patient with a visual acuity of 20/200.

Comment: This study was the only other economic valuation to pass all the pre-determined quality criteria for both economic evaluations and for cost studies. This study appeared to be very comprehensive, well conducted and clearly presented. In this model the authors appear to have discounted costs and benefits at the same rate of 3%. Some sensitivity analysis around these discount rates would have been useful. The authors conclude that PDT will cost a third-party insurer $86,721 for an AMD patient with 20/40 vision in the better seeing eye to obtain one QALY and $173,984 for an AMD patient with 20/200 vision in the better seeing eye to obtain one QALY. Also, the authors noted that their 11-year model is based on treatment assumptions that are unproven and which may be unreliable. The authors were cautious in their recommendation of PDT for AMD.

To assist with the interpretation of this paper in the UK context, UK £ (2000) equivalent values for those presented in the paper by Sharma et al are provided in Table 13.
Table 13 Sharma et al costs associated with PDT in US $ for year 2000 and converted into £ for year 2000

<table>
<thead>
<tr>
<th>Cost per visit</th>
<th>US$</th>
<th>£</th>
</tr>
</thead>
<tbody>
<tr>
<td>Visit</td>
<td>162</td>
<td>114</td>
</tr>
<tr>
<td>Fluorescein</td>
<td>380</td>
<td>267</td>
</tr>
<tr>
<td>Angiography photography</td>
<td>75</td>
<td>53</td>
</tr>
<tr>
<td>Visudyne cost</td>
<td>1,453</td>
<td>1,021</td>
</tr>
<tr>
<td>Laser fee</td>
<td>544</td>
<td>382</td>
</tr>
<tr>
<td>Total</td>
<td>2,702</td>
<td>1,899</td>
</tr>
<tr>
<td>Incremental cost of treatment</td>
<td>1,822</td>
<td>1,281</td>
</tr>
</tbody>
</table>

Cost per QALY for PDT (Initial VA=20/40)

<table>
<thead>
<tr>
<th></th>
<th>2 year model</th>
<th>11 year model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>86,721</td>
<td>60,954</td>
</tr>
<tr>
<td></td>
<td>43,547</td>
<td>30,608</td>
</tr>
</tbody>
</table>

Cost per QALY for PDT (Initial VA=20/200)

<table>
<thead>
<tr>
<th></th>
<th>2 year model</th>
<th>11 year model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>173,984</td>
<td>122,288</td>
</tr>
<tr>
<td></td>
<td>87,197</td>
<td>61,288</td>
</tr>
</tbody>
</table>

Novartis submission to NICE, October 2001. Section 1.4: Economic Burden of AMD (and Novartis Appendix 2, Care pathways)

Description: This section of our discussion of the industry submission draws on the care pathway for AMD presented in Novartis Appendix 2 for the identification of the costs associated with AMD identification and diagnosis. This economic evaluation has been carried out by the University of Sheffield School of Health and Related Research, sponsored by the drug company.

In Novartis Appendix 2, a flow diagram is presented which makes explicit the diagnosis and treatment decisions, which leads to a typical patient pathway for any individual patient and these are accompanied by a commentary. The identification of the disease for a typical patient is most likely to involve a visit to an optometrist at a cost of £15.52 and a GP consultation at a cost of £18.00. Thus the total cost of identification for a typical patient was estimated to be £33.52. The diagnosis of wet AMD is confirmed by fluorescein angiography, which also provides the basis for the management of the disease by establishing the presence of CNV and defining the precise location of CNV with a 50%, or greater, classic component. The mean cost of fluorescein angiography was estimated to be £108 (range for 50% of NHS trust was £63 to £149). The total cost of identification and diagnosis is not explicit in Novartis Appendix 2, but it is implied by the costs that are presented to be approximately £141.52 (£33.52 + £108).

However, in Section 1.4, the annual UK cost for identification and diagnosis of wet AMD is estimated by the industry to be £2.6 million. This estimate is arrived at by multiplying the annual number of new cases of AMD of 21,000 (Section 1.3) by £123.77. It is not clear where the figure of £123.77 comes from, as it is not presented anywhere in the identification and diagnosis sections of Novartis Appendix 2.
In Novartis Appendix 2 the treatment protocols for both laser photocoagulation and PDT is described. However, it is also pointed out that there is very little overlap in the patient groups eligible for photocoagulation and PDT because photocoagulation of subfoveal lesions is limited to small lesions in patients with a visual acuity of < 6/24. For PDT, using evidence based on the TAP studies, after the first verteporfin treatment a patient will see the consultant ophthalmologist every three months making a total of 12 visits over three years. Fluorescein angiography is conducted at each visit and, if there is any new leakage, the patient is given repeat PDT with visudyne. Patients in the TAP study receive an average of seven doses in 3 years. The expected cost of a 3 year treatment course is presented as shown in Table 14. The average annual cost of PDT with verteporfin is shown to be £2,435. It is stated that it is unlikely that a patient will see a consultant ophthalmologist again on account of their AMD unless the fellow eye becomes affected. It would have been helpful to have been given some estimate of the probability of the fellow eye becoming affected. It is estimated elsewhere that the occurrence rate for the fellow eye is 42% at 5 years\(^8\).

### Table 14. Cost of 3 year verteporfin PDT treatment course (from Novartis Appendix 2)

<table>
<thead>
<tr>
<th>Resource</th>
<th>Cost estimate</th>
<th>Units consumed</th>
<th>Total cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluorescein angiography (digital)</td>
<td>£63</td>
<td>12</td>
<td>£756</td>
</tr>
<tr>
<td>Verteporfin</td>
<td>£850</td>
<td>7</td>
<td>£5,950</td>
</tr>
<tr>
<td>Consultant ophthalmologist</td>
<td>£54.50</td>
<td>7</td>
<td>£381.5</td>
</tr>
<tr>
<td>Staff nurse (day ward) (40 minutes)</td>
<td>£20.67</td>
<td>7</td>
<td>£144.69</td>
</tr>
<tr>
<td>Laser</td>
<td>£5.96</td>
<td>7</td>
<td>£41.72</td>
</tr>
<tr>
<td>Total over 3 years</td>
<td></td>
<td></td>
<td>£7,304</td>
</tr>
<tr>
<td>Average annual cost of PDT with verteporfin</td>
<td></td>
<td></td>
<td>£2,435</td>
</tr>
</tbody>
</table>

In Section 5 of Appendix 2 ‘Best supportive care’ is discussed, in terms of visual rehabilitation, the provision of low vision aids and the strategies that are provided for training and coping with having a chronic visual disability. The effect of individuals having a visual disability and being registered blind or partially sighted in terms of the impact on social services is also discussed. The benefits available and concessions from the department of Social Security in terms of The Disability Living Allowance (DLA) and Attendance Allowance (AA) are discussed and presented in detail. Some assumptions are made about the number of individuals who are registered blind or partially sighted and some assumptions are made about what benefits AMD sufferers are likely to be eligible for. If the assumptions here are wrong it could overstate or understate the saving to the Department of Social Security as a result of verteporfin therefore some sensitivity analyses should be carried out on some of the resultant estimates.
The assumptions made regarding the numbers of individuals who will register blind or partially sighted ultimately lead to two important tables (page 14) which present a breakdown of the relevant costs to the Department of Social Security. Although the constituent parts of both these tables are explained in Section 5, the final estimated mean cost per person of developing partial sight of £109.77 and the final estimated mean costs per person of going blind of £152.80 do not follow from the breakdown of unit costs presented. In other words the sums in the tables do not add up from the figures presented. These unexplained calculations cast doubt over the final figures of the mean cost per person of going blind and the mean cost per person of developing partial sight. Consequently, the annual cost of blind and partial sight registration for wet AMD of £1.7 million which is presented in Section 1.4 of the report is unsupported as it is based on the doubtful calculations of the care pathways in section 5 of Novartis Appendix 2.

**Comment:** Much of the cost evidence presented in Section 1.4 of the report is based on the care pathways of Novartis Appendix 2 and is unsupported by the calculations which have been presented there because they are unclear.

In the treatment protocols, no reference is made to the extra NHS resources that would be needed to treat any increase in the number of patients who may receive PDT in terms of extra ophthalmologists or other staff or retraining existing staff.

**Novartis submission to NICE, October 2001. Section 3: Cost effectiveness of Visudyne therapy for predominantly classic subfoveal CNV due to AMD (and Appendix 7, which presents a working model used for the economic evaluation)**
In the results section, the overall treatment and other costs for the base case scenario for both verteporfin treated patients and the untreated patients are presented for 5 different time horizons: 2 years, 5 years, 7 years, 10 years and lifetime. Similar results are presented for outcomes for the same 5 time periods, both in terms of vision years and QALYs. These are reproduced in Table 15.

---

\footnote{Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence}
Table 15 The cost effectiveness ratios for verteporfin vs placebo as presented in Novartis Industry Submission to NICE

<table>
<thead>
<tr>
<th></th>
<th>2 year</th>
<th>5 year</th>
<th>7 year</th>
<th>10 year</th>
<th>Lifetime</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marginal cost per vision year</td>
<td>£13,096</td>
<td>£6,044</td>
<td>£4,547</td>
<td>£4,174</td>
<td>£2,996</td>
</tr>
<tr>
<td>Marginal cost per QALY</td>
<td>£70,492</td>
<td>£33,137</td>
<td>£24,986</td>
<td>£19,516</td>
<td>£14,754</td>
</tr>
</tbody>
</table>

§ Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
** Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
Discussion of review of cost effectiveness studies

There are some vague similarities in the cost per QALY of PDT across the different studies, but these should be considered with caution because the patient groups in the comparison may not be appropriate for comparison. For instance, the cost per QALY for PDT of £137,000 in the report by Meads and Moore is in a similar ballpark to the cost per QALY for the two year model, for an initial visual acuity of 20/200, of £122,288 in the study by Sharma et al. But the study by Meads and Moore did not specify the initial visual acuity score.

In their two year model with an initial visual acuity of 20/40, Sharma et al estimate the cost per QALY to be approximately £60,954. This is similar to the estimate of the industry submission of £70,492 per QALY although an initial visual acuity is not specified in the Industry submission.

The comparison of these estimates should be made with caution because the impact of visual acuity starting point of the individuals in each study may have a significant effect. A superficial comparison of the estimates as presented above is unlikely to be valid as we may not be comparing like with like. Furthermore, for the purposes of comparison the cost data in the study by Sharma et al has been converted to UK currency. But international comparisons may not be appropriate, as many resource components, such as staff costs etc, can be valued differently in different countries.

The study by Sharma et al and the Industry Submission both model outcomes beyond the end points of the two year TAP trials. For the projections beyond two years the discounting of the costs and benefits will have an impact. In the study by Sharma et al both costs and benefits have been discounted at the same rate of 3% as recommended by the Washington Panel for the Unites States of America. 

†† Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence

‡‡ Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
4.2.2 Review of research on quality of life in AMD

As already stated there is no quality of life data available from the TAP or VIP trials. No other studies were identified which measured generic quality of life in PDT compared to placebo.

However, there are good quality studies which measure utility in AMD using time trade off and standard gamble techniques. One of these studies has been used to link visual acuity levels in the better seeing eye to utility score in a group of patients with mixed wet and dry AMD, using the time trade off technique. The utility values are reproduced in Table 16. (These same utility values are used in the Novartis industry submission and the two other cost utility analyses reviewed in this report)

Table 16. Utilities for given levels of visual acuity for the better seeing eye in AMD (inputs to HTAG model)

<table>
<thead>
<tr>
<th>VA (20/20-20/25)</th>
<th>Utility (TTO)</th>
<th>95% confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/20 – 20/25</td>
<td>0.89</td>
<td>0.82-0.96</td>
</tr>
<tr>
<td>20/30 – 20/50</td>
<td>0.81</td>
<td>0.73-0.89</td>
</tr>
<tr>
<td>20/60 – 20/100</td>
<td>0.57</td>
<td>0.47-0.67</td>
</tr>
<tr>
<td>20/200 – 20/400</td>
<td>0.52</td>
<td>0.38-0.66</td>
</tr>
<tr>
<td>Count fingers to light perception</td>
<td>0.40</td>
<td>0.29-0.50</td>
</tr>
</tbody>
</table>

Note that a decrease in visual acuity in the worse seeing eye does not appear to cause a drop in utility (see Section 2.1.5).

4.2.3 Review of cost data, and estimation of costs

No published studies were identified which had detailed investigations of costs for PDT compared to placebo. No cost data was available from the TAP and VIP trials.

Estimation has been made of the costs involved using published estimates of costs and resource use from the TAP trial and from other published sources.

Estimation of costs of verteporfin PDT treatment

The cost of a vial of verteporfin is £850. We estimate that the disposables, etc. using during the procedure (syringes, water for injection, drip set, needles, uses of syringe pump) would cost £10 per treatment. The cost of the laser treatment is £101.

Each person needs an angiogram one week before PDT in order to localise the lesion. The patients then return a week later in order to undergo the procedure if required. If the procedure is required or not, this assessment will have been made following the angiogram and a follow up appointment carried out. The costs for each of these elements are shown in Table 17. The total cost is £1181 for the first treatment. At subsequent treatments, the cost of a follow up outpatient appointment only is used giving a cost per cycle of £1113.
Table 17. Costs for verteporfin PDT treatment (inputs to HTAG model)

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verteporfin and disposables76</td>
<td>£860</td>
</tr>
<tr>
<td>Laser95</td>
<td>£101</td>
</tr>
<tr>
<td>Angiography95</td>
<td>£108</td>
</tr>
<tr>
<td>First O/P appointment for PDT95</td>
<td>£68</td>
</tr>
<tr>
<td>Follow up O/P appointment95</td>
<td>£44</td>
</tr>
</tbody>
</table>

In the TAP trial each patient received a PDT treatment at time 0 and then had an angiography session every 3 months until the 21st month and was followed up at the 24th month. If leakage from neovascular membranes was detected at one of these angiographies the patient received a further PDT treatment. If there was no leakage detected the patient was not treated. If the patient was not treated then the only costs involved were the cost of angiography plus assessment.

The TAP trial provides data on the number of PDT treatments received at each 3 monthly time point during the 2 year follow up. The minimum number of PDT treatments was one and the maximum was eight. The estimated probabilities for the number of PDT treatments are shown in Table 18.

Table 18. Costs and probability of PDT by number of treatments (inputs to HTAG model)

<table>
<thead>
<tr>
<th>Number of treatments</th>
<th>Probability</th>
<th>Undiscounted costs</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.045</td>
<td>£2245</td>
</tr>
<tr>
<td>2</td>
<td>0.072</td>
<td>£3206</td>
</tr>
<tr>
<td>3</td>
<td>0.102</td>
<td>£4167</td>
</tr>
<tr>
<td>4</td>
<td>0.085</td>
<td>£5128</td>
</tr>
<tr>
<td>5</td>
<td>0.144</td>
<td>£6089</td>
</tr>
<tr>
<td>6</td>
<td>0.127</td>
<td>£7050</td>
</tr>
<tr>
<td>7</td>
<td>0.137</td>
<td>£8011</td>
</tr>
<tr>
<td>8</td>
<td>0.288</td>
<td>£8972</td>
</tr>
</tbody>
</table>

From these, costs were calculated corresponding to each possible number of treatments. For example, the mean costs for a patient who had 2 treatments (and therefore 6 angiographies without treatment) is \((1 \times £1181) + (1 \times £1113) + (6 \times (£108 +£44)) = £3206\).

In the TAP trial there is no information on when, during the follow up, PDT treatments occurred. This is except for the first one which occurred at time 0 or if a patient had 8 treatments. Therefore if more than 1 and less than 8 treatments were received by a patient, it was assumed that the treatments were received at consecutive 3 monthly intervals starting from time 1. As there was only 2 years of follow up, costs were not discounted.
Sensitivity analysis around treatment costs
This was undertaken to incorporate the observed uncertainty around high and low combined costs of laser, angiography, assessment and outpatient appointment for PDT. The high and low estimates are the minimum and maximum ranges for 50% of NHS trusts and are presented in Table 19.

Table 19. Sensitivity analysis on costs of verteporfin PDT treatment (inputs to HTAG model)

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost</th>
<th>High estimate</th>
<th>Low estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verteporfin and disposables</td>
<td>£860</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Laser</td>
<td>£101</td>
<td>£102</td>
<td>£52</td>
</tr>
<tr>
<td>Angiography</td>
<td>£108</td>
<td>£149</td>
<td>£63</td>
</tr>
<tr>
<td>Assessment</td>
<td>£44</td>
<td>£54</td>
<td>£34</td>
</tr>
<tr>
<td>O/P appointment for PDT</td>
<td>£68</td>
<td>£84</td>
<td>£51</td>
</tr>
</tbody>
</table>

Potential savings from use of PDT
There is the potential that PDT could reduce the number of people becoming blind and that this would reduce the cost to the NHS and local and central government. Therefore the costs associated with blindness and rapidly deteriorating vision were investigated.

Costs of rapidly deteriorating vision:
One study was found which estimated the cost of blindness in the UK (Scotland in 1981-2). Their estimate of the cost per blind adult was £3,575 and included staffing costs of the Blind Welfare Service and from state benefits. Using the RPI (to December 2000) this equates to £7,433.

An Australian study estimated that the direct financial costs of blindness to the government and community of a pensioner (male over 65, female over 62) was Aus$14,686 (range Aus$9,749 to Aus$22,507). Using average 1999/00 exchange rates this converts to £5,795 (range £3,847 to £8,881). However, government benefits and the provision of services vary in different countries.

The potential costs borne by the NHS and by local and central government are listed below. The NHS alone funds some services, whereas for others such as blindness registration, there is joint funding by NHS and local government.

- Low vision clinic assessment, provision of low vision aids. Training in their use.
- Low vision rehabilitation in activities for daily living.
- Acute admission to geriatric ward for broken hip. Total hip replacement. Rehabilitation.
- Registration as blind or partially sighted.
- Admission into residential care.
- Community care – provision of a home care worker.
- Social security benefits, in particular attendance allowance.
- Blind person’s tax allowance.
- Treatment and support of an elderly person with depression.
Where costs are from literature published before 2000, the costs have been inflated to December 2000 using the RPI. Elderly people with low vision have a range of likelihoods of incurring each of these costs. Estimates of the costs and probabilities are shown in Table 20. Where available, more recent estimates have been given precedence.

No actual cost estimate for blindness registration was found. The cost shown is the doctor’s sessional fee for completion of the BD8 form plus the mean cost of a community occupational therapist for the initial assessment. These two elements represent the certification and registration elements of the process. The estimate of proportion with blind registration is taken from a comparison of the prevalence of AMD causing partial and blind sight given in a recent review of prevalence and the number of registered blind and partially sighted people. Frequently, the RNIB survey has been quoted, suggesting that only 50% of those eligible are actually registered. However, the prevalence estimate for vision impairment in this RNIB survey is well outside the 95% confidence intervals of the recent review (500,000 v. 312,000) which suggests that the earlier study is less accurate. A second RNIB survey, focused on older visually impaired people, gives a 93% registration rate.

The low vision aid cost was an assessment of hospital eye-service prescription forms in a District General Hospital. The cost of low vision rehabilitation is from a cost per care episode of a health authority community occupational therapist. The low vision rehabilitation proportion estimate comes from the RNIB survey. The housing benefit and council tax benefit is the annual average for Great Britain for those aged over 60. The social security cost is a year’s worth of attendance allowance at the lower rate. The tax allowance assumes payment of basic tax rate (22%). The cost of depression comes from a cost study of people with affective disorders who have been recently discharged from a long stay psychiatric hospital in the UK. The sample was small (n=28) with average age of 62 years. It is recognised that this sample will not mirror closely the population suffering visual loss in AMD but this has been used in lieu of any better estimates. The community care is the cost of a home care worker. The residential care is the cost of private residential care for elderly people, taking into account that approximately 30% of residents pay for themselves.

**Table 20. Estimate of costs of blindness (inputs to HTAG model)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Estimated cost</th>
<th>Estimate of the proportion with CNV and 20/200 visual acuity who would have this outcome in one year</th>
</tr>
</thead>
</table>
| Blind registration                           | £59.70 + £37.71      | 94.5%  
| Low vision aids                              | £136.33              | 33%  
| Low vision rehabilitation                    | £205.30              | 11%  
| Housing benefit and council tax benefit      | £2714.40             | 45%  
| Social security                              | £1,924               | 63%  
| Tax allowance                                | £319                 | 5%   
| Depression                                   | £391.97              | 38.6% 
| Hip replacement                              | £3,669               | 5%   
| Community care                               | £2,848.63            | 6%   
| Residential care                             | £15,904.41 (-30%)    | 30%  

Version 1 1 February, 2002
If the potential NHS, local and central government costs and the probabilities of occurrence are multiplied, this gives a very approximate cost of the first year of blindness of approximately £6,455. In the second and subsequent years of blindness this figure falls to £6,295 per annum.

This does not take into account all of the costs to the individual concerned, both financial and emotional.\textsuperscript{110}

**Sensitivity analysis around cost of rapidly deteriorating vision**

There is uncertainty about particular components of these costs. The issues are detailed in Appendix 10 and summarised in Table 21.

**Table 21 Sensitivity analysis on costs of blindness (inputs to HTAG model)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>High cost</th>
<th>Low cost</th>
<th>High % probability</th>
<th>Low % probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blind registration</td>
<td>£169.73\textsuperscript{99,103}</td>
<td>£40.10\textsuperscript{103}</td>
<td>94.5\textsuperscript{12}</td>
<td>50\textsuperscript{20}</td>
</tr>
<tr>
<td>Low vision aids</td>
<td>£136.33\textsuperscript{104}</td>
<td>£56.41\textsuperscript{104}</td>
<td>74\textsuperscript{29}</td>
<td>33\textsuperscript{46}</td>
</tr>
<tr>
<td>Low vision rehabilitation</td>
<td>£309\textsuperscript{152}</td>
<td>£125\textsuperscript{15}</td>
<td>11\textsuperscript{29}</td>
<td>11\textsuperscript{29}</td>
</tr>
<tr>
<td>Housing benefit and council tax benefit</td>
<td>£3588\textsuperscript{105}</td>
<td>£2412.80\textsuperscript{105}</td>
<td>73\textsuperscript{29}</td>
<td>21\textsuperscript{29}</td>
</tr>
<tr>
<td>Social security</td>
<td>£2875.60\textsuperscript{106}</td>
<td>£0</td>
<td>63\textsuperscript{30}</td>
<td>17\textsuperscript{29}</td>
</tr>
<tr>
<td>Tax allowance</td>
<td>£319\textsuperscript{107}</td>
<td>£145\textsuperscript{107}</td>
<td>18\textsuperscript{29}</td>
<td>5\textsuperscript{29}</td>
</tr>
<tr>
<td>Depression</td>
<td>£391.97\textsuperscript{108}</td>
<td>£391.97\textsuperscript{108}</td>
<td>50\textsuperscript{39}</td>
<td>6\textsuperscript{37}</td>
</tr>
<tr>
<td>Hip replacement</td>
<td>393\textsuperscript{39}</td>
<td>1177\textsuperscript{15}</td>
<td>24.7\textsuperscript{27,31,95}</td>
<td>0.5\textsuperscript{20,95}</td>
</tr>
<tr>
<td>Community care</td>
<td>£4,758.80\textsuperscript{97}</td>
<td>£1138.36\textsuperscript{97}</td>
<td>40\textsuperscript{29}</td>
<td>6\textsuperscript{30}</td>
</tr>
<tr>
<td>Residential care</td>
<td>£23,584.28\textsuperscript{97}</td>
<td>£7,843.27\textsuperscript{97}</td>
<td>56\textsuperscript{111}</td>
<td>13\textsuperscript{35}</td>
</tr>
</tbody>
</table>

If the potential NHS, local and central government costs and the probabilities of occurrence are multiplied for the sensitivity analysis, this gives a very approximate cost range for the first year of blindness of approximately £1,375 to £17,100. In the second and subsequent years of blindness this range falls to £1,325 to £16,800 per annum. The highest cost by far is the cost of residential care and the cost of blindness is most sensitive to the percentage of people with AMD who need this. Without a longitudinal study of people with AMD who subsequently enter residential care, this will continue to cause wide variation in the estimate of the cost of blindness.

**4.2.4 HTAG Economic model of cost-utility**

**HTAG Model details**

The model chosen for the cost utility analysis is a decision tree model. (There was insufficient information available to construct a Markov model). The software used was Treeage DATA\textsuperscript{TM} version 3.5. The decision tree has two policy branches – PDT (plus BSC) or BSC alone. At the end of the PDT there is a chance node with 8 branches representing the possible number of treatments over the 2-year follow up. At the end of each of the 8 branches
is a further chance node with 7 branches representing the 7 possible utility outcomes. At the end of the BSC arm there is a chance node with 7 branches representing the 7 possible utility outcomes. This relatively simple model was chosen because of lack of available information. It does not include the disutility of receiving PDT treatment because there is insufficient information on the change in QALYs that this might cause. The decision tree is shown in Figure 3:
Figure 3 Decision tree for HTAG economic model

Patient with AMD

Best Supportive Care

Photodynamic Therapy

0.324 cblind / utility6
0.126
0.062
0.038
0 / utility2
0.288
0.137
0.127
0.144
0.085
0.102
0 / utility1

0.15 0 / utility5
0.3
0.289
0.229
0.147 ctreat8 / utility4
0.065
0.182
0.289
0.229
0.147
0.065
0 / utility4

0.182 (ctreat7+cblind) / utility7
0.289
0.229
0.147
0.065
0 / utility3

0.182
0.289
0.229
0.147
0.065 ctreat7 / utility3

0.182
0.289
0.229
0.147
0.065 ctreat6 / utility2

0.182
0.289
0.229
0.147
0.065 ctreat6 / utility1

0.182
0.289
0.229
0.147
0.065 ctreat5 / utility5

0.182
0.289
0.229
0.147
0.065 ctreat5 / utility4

0.182
0.289
0.229
0.147
0.065 ctreat5 / utility3

0.182
0.289
0.229
0.147
0.065 ctreat5 / utility2

0.182
0.289
0.229
0.147
0.065 ctreat5 / utility1

0.182
0.289
0.229
0.147
0.065 ctreat4 / utility5

0.182
0.289
0.229
0.147
0.065 ctreat4 / utility4

0.182
0.289
0.229
0.147
0.065 ctreat4 / utility3

0.182
0.289
0.229
0.147
0.065 ctreat4 / utility2

0.182
0.289
0.229
0.147
0.065 ctreat4 / utility1

0.182
0.289
0.229
0.147
0.065 ctreat3 / utility5

0.182
0.289
0.229
0.147
0.065 ctreat3 / utility4

0.182
0.289
0.229
0.147
0.065 ctreat3 / utility3

0.182
0.289
0.229
0.147
0.065 ctreat3 / utility2

0.182
0.289
0.229
0.147
0.065 ctreat3 / utility1

0.182
0.289
0.229
0.147
0.065 ctreat2 / utility5

0.182
0.289
0.229
0.147
0.065 ctreat2 / utility4

0.182
0.289
0.229
0.147
0.065 ctreat2 / utility3

0.182
0.289
0.229
0.147
0.065 ctreat2 / utility2

0.182
0.289
0.229
0.147
0.065 ctreat2 / utility1

0.182
0.289
0.229
0.147
0.065 ctreat1 / utility5

0.182
0.289
0.229
0.147
0.065 ctreat1 / utility4

0.182
0.289
0.229
0.147
0.065 ctreat1 / utility3

0.182
0.289
0.229
0.147
0.065 ctreat1 / utility2

0.182
0.289
0.229
0.147
0.065 ctreat1 / utility1

0.182
0.289
0.229
0.147
0.065 (ctreat1+cblind) / utility7

0.182
0.289
0.229
0.147
0.065 (ctreat1+cblind) / utility6

0.182
0.289
0.229
0.147
0.065 (ctreat1+cblind) / utility5

0.182
0.289
0.229
0.147
0.065 (ctreat1+cblind) / utility4

0.182
0.289
0.229
0.147
0.065 (ctreat1+cblind) / utility3

0.182
0.289
0.229
0.147
0.065 (ctreat1+cblind) / utility2

0.182
0.289
0.229
0.147
0.065 (ctreat1+cblind) / utility1

0.182 (ctreat1+cblind) / utility7
0.289
0.229
0.147
0.065
0 / utility1

0.182 (ctreat1+cblind) / utility6
0.289
0.229
0.147
0.065
0 / utility2

0.182 (ctreat1+cblind) / utility5
0.289
0.229
0.147
0.065
0 / utility3

0.182 (ctreat1+cblind) / utility4
0.289
0.229
0.147
0.065
0 / utility4

0.182 (ctreat1+cblind) / utility3
0.289
0.229
0.147
0.065
0 / utility5

0.182 (ctreat1+cblind) / utility2
0.289
0.229
0.147
0.065
0 / utility6

0.182 (ctreat1+cblind) / utility1
0.289
0.229
0.147
0.065
0 / utility7

0.182 (ctreat1+cblind) / utility7
0.289
0.229
0.147
0.065
0 / utility8

0.182 (ctreat1+cblind) / utility6
0.289
0.229
0.147
0.065
0 / utility8

0.182 (ctreat1+cblind) / utility5
0.289
0.229
0.147
0.065
0 / utility8

0.182 (ctreat1+cblind) / utility4
0.289
0.229
0.147
0.065
0 / utility8

0.182 (ctreat1+cblind) / utility3
0.289
0.229
0.147
0.065
0 / utility8

0.182 (ctreat1+cblind) / utility2
0.289
0.229
0.147
0.065
0 / utility8

0.182 (ctreat1+cblind) / utility1
0.289
0.229
0.147
0.065
0 / utility8
There are 3 further assumptions used in the decision tree.

- The probabilities of each of the seven possible utility outcomes at the end of the 2-year follow up are the same irrespective of the number of PDT treatments received. We requested data from Novartis which would have enabled us to distinguish utility outcomes for different numbers of PDT treatments but these were not provided.

- The utilities reported are cumulative utilities over the two year period. This uses the assumption that the difference in utilities for the two groups at start is zero. Over the two year period the utility declines at a steady rate in both groups, but declines less in the PDT group than the placebo group. At two years the difference in utility between the two groups is the same as the cumulative difference over the two year period. (see Appendix 11)

- Blindness in the models was deemed to have occurred if a patient could read 38 letters or less. Normally legal blindness is deemed to have occurred at a visual acuity of 20/200 corresponding to 35 letters or less. 38 letters or less had to be used in the model because of the way that visual acuity scores were reported in the TAP trial.

Effectiveness data for the HTAG model

The effectiveness data are based on the whole trial results of TAP, not the sub-group analyses. The HTAG model does not include survival because the TAP (and VIP) trials were not powered for this outcome but there were no significant differences in deaths between PDT and placebo arms in the TAP (and VIP) trials.

In the TAP and VIP trials there are seven categories of changes in visual acuity –

- $\geq 6$ line increase,
- $\geq 3$ to $< 6$ line increase,
- $\geq 1$ line to $< 3$ line increase,
- no change,
- $\geq 1$ line to $< 3$ line decrease,
- $\geq 3$ line to $< 6$ line decrease and
- $\geq 6$ line decrease.

The number of lines was then converted to the number of letters by multiplying by 5 (there are 5 letters to a line in the EDTRS chart).

The mean baseline visual acuity in the TAP trial was 53 letters. The approximate visual acuity for the seven categories listed above was established by subtracting or adding the relevant number of letters from 53. The number of letters for each of the seven categories was then converted to a Snellen score using the Visual acuity conversion table in Appendix 2. The Snellen score for the seven categories above was then matched to the relevant utility score, using Table 16.

The result is shown in Table 22. This table also shows the probabilities of being in each of the seven categories for PDT and placebo groups.
Table 22. Utilities and probabilities for visual acuity at 24 months for PDT and BSC (inputs to HTAG model)

<table>
<thead>
<tr>
<th>Change in VA (lines)</th>
<th>Mean utility score</th>
<th>PDT probability</th>
<th>BSC probability</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 6 line increase</td>
<td>0.89</td>
<td>0.008</td>
<td>0</td>
</tr>
<tr>
<td>≥ 3 to &lt; 6 line increase</td>
<td>0.81</td>
<td>0.080</td>
<td>0.038</td>
</tr>
<tr>
<td>≥ 1 line to &lt; 3 line increase</td>
<td>0.81</td>
<td>0.065</td>
<td>0.062</td>
</tr>
<tr>
<td>no change</td>
<td>0.57</td>
<td>0.147</td>
<td>0.126</td>
</tr>
<tr>
<td>≥ 1 line to &lt; 3 line decrease</td>
<td>0.52</td>
<td>0.229</td>
<td>0.150</td>
</tr>
<tr>
<td>≥ 3 line to &lt; 6 line decrease</td>
<td>0.52</td>
<td>0.289</td>
<td>0.324</td>
</tr>
<tr>
<td>≥ 6 line decrease</td>
<td>0.40</td>
<td>0.182</td>
<td>0.300</td>
</tr>
</tbody>
</table>

Cost data for HTAG model
These were taken from our estimates of costs reported in 4.2.3.

Sensitivity analyses used in HTAG model
Sensitivity analyses (one-way only) around the base-case estimates of cost-utility were undertaken for the following parameters:

- Effectiveness – incorporating uncertainty due to both small sample size and only one trial around estimates of effectiveness for the impact of verteporfin PDT in achieving each of the seven visual end-states provided by the TAP trial. The method for achieving this is relatively complex and is detailed in Appendix 11.
- Utilities - The high and low utility scores from the published paper linking visual acuity to utility score were incorporated (see Table 16).
- Costs of verteporfin PDT (see Table 19).
- Using discounting at 6% or undiscounted costs of verteporfin PDT.
- Costs averted by avoidance of blindness (see Table 21).

The highest and lowest possible cost utility was also obtained by varying all of the relevant parameters at once.

We did not include extending the model to beyond 2 years as part of the sensitivity analysis, as we believe that this is an unacceptable extrapolation of the available data. In any event the effects of such an alteration are predictable, in that only costs are affected. The cost of PDT treatment is spread over a longer time period and the recurrent costs of blindness averted are magnified. Inevitably, rolling the 2 year trial results forward will thus lead to increasingly favourable ICERs the longer the model is projected beyond 2 years.

Nor, like all other economic models encountered, did we take into account the fact that patients have two eyes. On average, one would expect that wet AMD would develop in the better eye in 50% of patients and in the worse eye in 50% of patients. Therefore, as utilities are dependent on the affected eye being the better seeing eye\(^{30,41,94}\), the effectiveness estimates and corresponding utilities will only apply to 50% of the patients affected. As the other 50% will be little affected, their corresponding utility will not change much so the incremental cost utility of PDT will be far higher.
HTAG model results - Base Case

The base results are shown in the table below. There are, in effect, two base cases. The first is if blindness occurs in the second year (incurring 1 year of blindness costs) and the second is if blindness occurs in the first year (incurring 2 years of blindness costs).

Table 23. HTAG model Base Case results.

<table>
<thead>
<tr>
<th></th>
<th>1 year of blindness</th>
<th>2 years of blindness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incremental cost of PDT</td>
<td>£5,658</td>
<td>£4,695</td>
</tr>
<tr>
<td>QALYs gained</td>
<td>0.0311</td>
<td>0.0311</td>
</tr>
<tr>
<td>ICER</td>
<td>£182,188</td>
<td>£151,179</td>
</tr>
</tbody>
</table>

The results indicate that PDT is associated with a cost utility of between £151,000 to £182,000 over two years.

HTAG model results - Sensitivity analysis

All of the sensitivity analyses were carried out using the costs of blindness for one year only (except for varying the costs of blindness) so vary around the cost utility estimate of £182,188. For results see Table 24.

Before varying the estimate by best and worst case effectiveness scenarios (see Appendix 11), the fitted data for the base case model was compared to the trial effectiveness data. This effectiveness distribution reduced the cost utility estimate to £137,000. The fitted data of pessimistic assumptions on effectiveness increased the cost utility to £305,000. The fitted data of optimistic assumptions on effectiveness reduced the estimate to £83,000. Both of these estimates used fitted data for both PDT and placebo groups.

Varying the utilities had very little effect on the cost utility estimate. Both the high and low utility scores reduced the estimate to £179,000.

The high and low cost of PDT estimates did not vary the cost utility by as much as varying the effectiveness estimates. With high costs, the cost utility was £196,000 and with low costs it was £158,000. Discounting costs reduced the ICER by approximately 4%. However, varying the cost of blindness did have more impact. Using the lowest cost of blindness for one year only increased the cost utility to £207,000. Using the highest cost of blindness over two years reduced the cost utility to £130,000. This wider range may have more to do with the wider range of cost of blindness estimates compared to cost of treatment estimates, rather than the impact of blindness per se on the cost utility estimate.

Varying the parameters to achieve highest and lowest possible cost utility estimates resulted in a very wide range. The best scenario aimed to achieve the lowest possible cost utility estimate. The parameters used were optimistic fitted effectiveness data, high utility score, low net costs and highest possible cost of blindness. This resulted in a cost utility of £47,000. To get the highest possible cost utility estimate, the parameters used were the pessimistic fitted data, base case utility scores, high net costs and lowest possible cost of blindness. This
resulted in a cost utility estimate of £342,000. This is not much higher than the estimate of £304,000 from the pessimistic assumptions on effectiveness.

**Table 24. Results of sensitivity analysis, HTAG cost utility model.**

<table>
<thead>
<tr>
<th></th>
<th>Base Case</th>
<th>Upper variable</th>
<th>Lower variable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effectiveness</td>
<td>182,000</td>
<td>304,000</td>
<td>83,000</td>
</tr>
<tr>
<td></td>
<td>Trial data</td>
<td>Fitted data</td>
<td></td>
</tr>
<tr>
<td>Utility</td>
<td>182,000</td>
<td>179,000</td>
<td>179,000</td>
</tr>
<tr>
<td>Cost of PDT</td>
<td>182,000</td>
<td>196,000</td>
<td>158,000</td>
</tr>
<tr>
<td>Cost of blindness</td>
<td>182,000</td>
<td>129,000</td>
<td>207,000</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Worst case</td>
<td>Best case</td>
</tr>
<tr>
<td>All variables</td>
<td>182,000</td>
<td>342,000</td>
<td>47,000</td>
</tr>
</tbody>
</table>

**Limitations of the cost utility analysis (HTAG model) and comments**

The HTAG model is limited to 2 years because of lack of available data for the longer term. It is acknowledged that the benefits may extend longer than 2 years and that most of the costs of treatment are incurred in the first two years. If the follow up was for longer than 2 years, this would probably reduce the cost utility estimate but it is unknown by how much it would be reduced.

Several assumptions were made when building the model and these are listed in the methods section. If the data that was requested from Novartis had been forthcoming, the model could have been more accurate. It is unknown how much these assumptions may have affected the cost utility estimates.

The cost of blindness estimate has a very wide range due to lack of available information, particularly on the likelihood of entering residential care. Further research is needed on this. However, the results of our model suggest that PDT is more cost effective if the people who go blind incur more costs over the two years of follow up.

The most important factor to vary the cost utility is the effectiveness of PDT treatment.

**4.2.5 Estimation of net costs to the NHS**

The cost implications of treating neovascular membranes in wet AMD varies by the incidence estimates and the population to be treated, the number of treatments used and the cost of the PDT treatment itself. Our incidence estimates for England and Wales suggest that approximately 15,800 people will develop wet AMD in one year, 7,500 will have uncomplicated wet AMD and 5,000 will develop classic AMD. The numbers of treatments as per the TAP trial were 3.4 in the first year, 2.2 in the 2nd and 1.4 in the 3rd year. Our estimate of the cost of PDT is £1,181, with low and high estimates of £1,060-£1,249. This means that the first year’s cohort of classic AMD would cost £20.1million. As there will be a new cohort of 5,000 each year, by the third year the cost will rise to £41.3million (£37.1-£43.7million) per year. If the licensed indication for PDT is extended to occult (applications already in place in Europe and Canada74,75) then the costs will rise to £30.1million (£27.0-31.8million) in the first year and £62.0 (£55.6-£65.6million) per annum by the third year. If all people who present with wet AMD are treated with PDT it will cost £63.4million (£56.9-£67.1million) in the first year and £130.6million (£117.2-£138.1million) per annum by the third year.
Novartis estimate that the cost of verteporfin per person over 3 years would be £7,304 and the average annual cost would be £2,435. They estimate that 5,000 – 7,500 new cases could benefit from treatment and 4,000 would be treated each year. They estimate that the incremental expenditure would be £7.95million in the first year, rising to £16.64million per year by the third year, remaining at that level thereafter (Industry submission p44). This assumes that if 4000 people were treated, in the first year the cost per person would be £1,987.50 which gives an average of 2.12 treatments per year. However, their cost estimate is based on a number of assumptions, including:

1. Only 4000 people eligible for PDT per year,
2. The cost of angiography and clinician time to diagnose eligibility is ignored,
3. The proportion of non-responders to PDT who get 2 treatments in the first year and none thereafter is 26%
4. Any training needs are ignored. (Industry submission p44).

If we use data from Novartis’s industry submission, they estimate that there will be 21,000 new cases of wet AMD in the UK per annum and that 7,500 will have predominantly classic AMD eligible for treatment under the current licensed indication. They estimate that the cost of PDT is £931 (but this doesn’t include the cost of angiography of £108.00-their estimate). Using the same numbers of treatments as per the TAP trial, the cost of treating predominantly classic AMD would be £23.7million (£22.4-£23.9million) in the first year. By the third year it would rise to £48.9million (£46.1-£49.2million). If all people with new wet AMD were treated the first year costs would be £66.5million (£62.8-£67.0million) rising to £136.9million (£129.2-£137.9million) by the third year.

None of these cost estimates include the cost of training new staff to deliver the PDT service. The implications of this observation both in terms of cost and implementation are considered further in section 6.

By way of comparison, the National Service Framework for Older People has set aside a budget of £150million in 2000/1 rising to £405million in 2003/4 to pay for intermediate care intended, amongst other aims, to minimise dependence on long term care.

If, instead of PDT treatment, all people with new wet AMD were given low vision rehabilitation and provision of low vision aids, the cost in England and Wales (using our population estimate of 15,800) would be £5.4million (£2.9-£7.0million). Using Novartis’ estimate the cost in the UK would be £7.2million (£3.8-£9.4million).

### 4.3 Discussion and conclusions

Our estimate of cost utility at two years was between £151k-£182k whereas the Industry model estimate at 2 years was £70k. The reasons for the discrepancy may be more to do with the inputs to the model than the model structure per se. There are several differences between the models. These include;

§§

§§ Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
We chose to use a simple decision tree methodology, basing our models as closely as possible on the data provided by the TAP trial reports for the first and second years of the trial. Due to data limitations, we were forced to make simplifying assumptions which are somewhat questionable. For example, we had to assume that the probabilities of each of the 7 possible utility outcomes in our models at the end of the 2-year trial period were the same irrespective of the number of PDT treatments received over the 2-year period. On the whole, we tended to find that the ICERs for PDT plus BSC relative to BSC alone were quite high, a finding repeated when we used model structures not as dependent on the presence of additional data. We can conclude that unless the costs of blindness are indeed very high or the effectiveness is much higher than demonstrated in the TAP and VIP trials, PDT is unlikely to be a cost-effective alternative to BSC in terms of stabilising visual acuity.

***

*** Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
Further investigation of the source of the different estimates of cost-utility at two years through more detailed modelling would be useful. However, in the absence of this, we believe the difference most likely to account for more optimistic estimates of cost-utility is the use of sub-group effectiveness data. We have already argued this to be invalid, and thus believe that two year cost-utility estimates are likely to be well above £100k/QALY... It should again be noted that this cost-utility is for the more optimistic scenario of wet AMD affecting the best-seeing eye.

Irrespective of the model used, cost-utilities at two-years are universally unfavourable. More acceptable values only occur in models which extrapolate beyond two-years, often considerably so. The model presented in this report, did not extrapolate because we believe that in a population and disease where recurrence and comorbidity are highly likely, extrapolating in the absence of empirical data is highly dangerous and potentially misleading.

Further detailed modelling, with recourse to the full trial data, could help clarify the extent to which alternative extrapolation assumptions might affect cost-utility estimates. However, in the absence of this, considering all the economic models encountered and the most likely reasons for the variation in results, we believe that on balance the true cost-utility of verteporfin PDT relative to best-supportive care lies above accepted thresholds denoting efficient use of health care resources.

The estimation of net costs suggests that implementation of PDT into the NHS is likely to incur large costs. Also, the increased numbers coming for treatment may mean that there could well be insufficient staff to provide a good service. This would result in increased waiting times for treatment and the valuable window of opportunity in which to treat patients with wet AMD before they go blind would be lost. The importance of this has been confirmed by two peer reviewers (Mr Wormald, Professor Murray).

**4.4 Summary**

- Although none were perfect, all were sufficiently robust to deserve serious consideration
- All essentially compare verteporfin PDT + best supportive care with best supportive care alone

††† Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
• The cost-effectiveness and cost-utility of verteporfin PDT where wet AMD occurs in the worse seeing eye has thus not been examined. It should be, and this is an important recommendation for further research.
• However, it seems highly likely that the cost-effectiveness and cost-utility will be less favourable as patient function is less likely to be improved with the initial treatment, and further treatment in the fellow eye is likely to be required as wet AMD in one eye is highly predictive of developing AMD in the fellow eye.

At two years the values for cost per QALY were:
• £70k (Novartis Industry submission)
• £61k (where initial visual acuity is 20/40) or £122k (where visual acuity is 20/200) (Sharma et al)
• £120k (Meads & Moore)
• However, all these estimates are at best at the margins of what is generally considered to be an efficient use of health care resources
• More optimistic assessments of cost-utility only occur when models are extended beyond the two years, the limit of RCT data.

Our own model of cost utility also used the TAP trial effectiveness data, standard utility values and a range of published sources for costs of treatment and blindness. It extended

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§§§ Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
**** Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
for two years only and included effectiveness, utilities, costs of treatment (undiscounted and discounted at 6%) and costs of blindness in the sensitivity analyses

- The estimate of cost-utility was £151k-£182k
- The estimate was mostly sensitive to estimates of effectiveness, then the costs of blindness, costs of treatment and least to utilities and discounting

On balance we believe that the true value of the cost-utility of verteporfin PDT is highly likely to lie above the generally acknowledged threshold separating efficient from inefficient use of health resources

To emphasise, this statement does not consider the scenario where verteporfin PDT is applied where wet AMD develops in the worse seeing eye. The cost-utility of this is likely to be even less favourable but needs to be confirmed in further research

The only important proviso is that no models so far have considered the possibility that verteporfin PDT has an effect on survival. This is plausible given the age-group of the patients mainly affected and that the consequences of loss of visual acuity, especially falls and institutionalisation, do have substantial associated mortality. There is however, no empirical data (the mortality data in the TAP trial is totally insufficient for this purpose) to confirm or refute this possibility and if this possibility was thought to deserve further investigation such data should be sought.

The net cost impact of introducing verteporfin PDT for its currently licensed indication is somewhere between £16.4-£41.3 million per annum by the third year of the service being introduced.

This figure could increase to £63.4 million by the third year if the licence was extended to wet AMD with both classic and occult neovascular lesions

None of the figures on cost impact include the costs of training and likely need for increased numbers of consultant ophthalmologists and other trained staff

5. IMPLICATIONS FOR OTHER PARTIES

There are important implications to other parties from verteporfin PDT. Although the impact on funded personal social services are to some extent taken into account in the models of cost-utility it is worth emphasising that investing health care resources in providing verteporfin PDT may:

- Reduce requirement for personal social services funding (although the magnitude of this is highly uncertain)
- Reduce costs to individuals and their families

With respect to the latter it is worth reflecting that the burden of care placed on individuals, their partners and their families in the age group in question is enormous. Any measure which would reduce this burden, improve the quality of life in older persons and increase their ability to function independently for longer would be greatly welcomed. It is possible the value to individuals and their carers may not be completely captured by the evidence on effectiveness and cost-utility presented in this report, that we have used to draw our conclusions.

†††† Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
6. FACTORS RELEVANT TO NHS

6.1 Skills and personnel in the NHS needed to deliver PDT service

It is apparent that Novartis consider that no new facilities or staff will be required to implement PDT in the NHS.

“The skills necessary for administration of Visudyne therapy are similar to those for hot laser treatment and are already in place.” (Industry submission p44)

“The costs of the additional workload involved in offering Visudyne therapy to all eligible patients have been accounted for above (see previous sentence). However, it should be noted that one ophthalmologist/nurse team could treat between six and ten patients per NHS session. Offering Visudyne therapy to an annual new population of 4000 patients would therefore be consuming from 2,800 to 4,650 NHS sessions each year by the time uptake reached its peak at three years.” (Industry submission p45)

“The central figure for a single treatment with verteporfin is £931, with a range of £879-£938 depending on the amount of nurse and clinician time assumed and whether a consultant (central and high figures) or a registrar (low figure) does the procedure.

However, others are of different opinion. The National Horizon Scanning Centre suggest that there may be an increase in patients referred to specialist centres for PDT leading to an increased demand for diagnostic services and trained professionals. A recent Cochrane review states that

‘There are major implications for the health services, both in terms of potential expenditure and organisation, if PDT is to be introduced. Where referral to an ophthalmologist is through a primary care network, facilities for the recognition of this condition in its early stages are needed. There is potential for an enormous increase in referral of people with early ARM for assessment, in case an early treatable lesion is present. This could swamp the already overstretched facilities at the secondary care level. Extra resources will be required at the secondary care level to manage increased referrals, for the necessary technology to diagnose treatable lesions and to deliver treatment.’

Another recently published review by an ophthalmologist already using PDT states:

“If verteporfin PDT is to be established in the UK under the NHS the capacity of the hospital eye service will need to be expanded considerably. Stereoscopic angiography is essential to accurate lesion classification and so departments of medical illustration will need training and additional personnel. Ophthalmologists will require training in the interpretation of images to ensure accurate detection and measurement of occult and classic lesions and an increase in numbers of medical, nursing and other ancillary staff will be required.” These sentiments have been echoed by peer reviewers.

According to the Royal College of Ophthalmology guidelines of February 2001, Centres wishing to perform PDT must have:

1. Ophthalmologist with expertise in case selection and management of AMD. Eg. completed a medical retina fellowship or hold dedicated medical retina or macula clinics regularly as laid down by higher specialist training guidelines of the RCOphth.

Section of original report deleted as it relies on knowledge of the methods of the Industry health economic model which has been declared commercially in confidence
2. Facilities for standardised vision assessment by a suitably trained optometrist or technician.

3. Facilities for stereoscopic fluorescein angiography by a suitably trained photographer or technician.

Currently there are approximately 790 consultant ophthalmologists of which approximately 150-200 are medical retina specialists or consultants who do some medical retina work in the UK (Personal communication, Miss Hallendorf, RCOphth, 2001). Therefore to cover 2,800-4,650 sessions per year (see first paragraph above) will require that each one would have to do 14-31 sessions per year. Alternatively 16-26 specialists could cover the extra PDT sessions (assuming four outpatient sessions per week for 44 weeks per year. This would cost £1,181,216 - £1,919,476). (The salary for a medical consultant plus oncosts is £73,826.112)

This does not include the costs or consultant time required to assess people who probably won’t be suitable for treatment. If many more people come for assessment then the number of sessions will increase. If 21,000 are assessed at 8 per session then 2625 sessions will be required for this alone. This may result in each of the 150-200 medical retinal specialists devoting 1 day per week to PDT.

6.2 National targets

Care of older persons is a defined national target area. It is undeniable that implementation of verteporfin PDT would help address a major source of morbidity suffered by a small proportion of this group. However, as has already been mentioned the cost of implementation would constitute a considerable proportion of the development monies set aside for implementing the NSF.

6.3 Equity

Some issues of equity can be identified. First, interventions in older persons have historically been considered less favourably than those affecting younger persons because of perceptions that the individuals in question have reached a stage in life where health benefits are less likely to occur. Care needs to be taken that such a perception does not colour a decision on whether the benefits are worth the costs in verteporfin PDT. Second there is some evidence that this intervention is already being provided and that much but not all of it is privately funded. Hence, by definition, there is already inequitable access. Should a decision be made to support verteporfin PDT, the inequity within the NHS would need to be addressed.

7. DISCUSSION

7.1 Main results

- Wet AMD, particularly that associated with neovascular lesions, classic or occult, causes impairment of vision and blindness, and is responsible for a substantial amount of morbidity
- Although best supportive care can lead to adaptation and rehabilitation of the loss of central vision, a treatment that could avert this loss of would be of benefit
PDT may be such a treatment. This report mainly considers the effectiveness and cost-effectiveness of verteporfin PDT. It is the only type of PDT currently licenced and is restricted to wet AMD where classic neovascular lesions predominate.

Verteporfin PDT is effective in reducing the visual deterioration associated with wet AMD. An indication of the size of the effect, taken from the TAP trial is that relative risk of losing >15 letters (3 lines) of visual acuity at 2 years with verteporfin PDT relative to placebo PDT is 0.75 (95% CI 0.65 to 0.88). This effect is statistically significant and clinically important.

This benefit is achieved at some cost in terms of adverse events, but qualitatively at least, the balance between beneficial and harmful effects favours verteporfin PDT.

Unfortunately the cost of verteporfin PDT is very high at £1,181 per treatment and more than one treatment may be needed. Inevitably efficiency, particularly its cost-utility becomes an important issue.

There is uncertainty about the cost-utility of verteporfin PDT. Past estimates of cost per QALY at two years range from £60k to £122k. The economic model developed as part of this report obtained a base-case estimate of between £151k-£182k. The sensitivity analyses ranged from £342k to £47k.

Favourable estimates of cost-utility have been obtained in past economic evaluations, but only by modelling the cost-utility beyond two years (the length of follow-up in the two included RCTs) and by basing the results of effectiveness on sub-group analyses of the TAP trial.

On balance therefore we believe that the true value of cost per QALY is likely to be considerably in excess of £50k, and that verteporfin PDT is consequently an inefficient use of health care resources.

It should be clearly noted that these estimates of cost-utility assume that it is the better seeing eye which develops wet AMD first. The efficiency of verteporfin PDT in a situation where the worst seeing eye develops AMD cannot currently be considered but the efficiency of verteporfin PDT in this situation is likely to be even less favourable.

7.2 Limitations and uncertainties

The main factor limiting the conclusions of this report is the data available. Concerning the methods of the report itself readers can confirm that both with respect to the systematic review and economic evaluation the methods were pre-specified and conform to published standards for conducting such analyses. The review team have no conflicts of interest.

The main sources of uncertainty arising from the data are discussed in the following paragraphs.

7.2.1 Estimates of effects

There is some uncertainty about the benefit, particularly the size of effect that verteporfin PDT is likely to have on visual acuity. A particular issue is whether there is an important difference in impact on visual acuity depending on whether the neovascular lesions in wet AMD are classic or occult. This report takes the view that the whole trial data should be the basis of the estimate of effect on visual acuity, not that obtained from the sub-group analyses. If this view is not accepted, we may have underestimated the impact of verteporfin PDT.
The absence of information on impact on survival may also be an important source of uncertainty. It is plausible that in this patient group and given the nature of the consequences of sudden loss of vision, there may be important effects on survival. However, there is no empirical research to inform a judgement on this one way or another. If present however, a survival effect could dramatically change the balance between benefits and costs.

7.2.2 Estimation of overall effectiveness and impact on patient function

There is also uncertainty about how the benefits and disbenefits measured in the trials of verteporfin PDT translate into what ultimately needs to be influenced, ability to function and live independently. Quantifying the degree to which the beneficial effects (reduced deterioration in visual acuity) are offset by adverse events of verteporfin PDT is problematic where quality of life has not been measured directly. However it is reasonably clear that the balance between these favours verteporfin PDT.

Much more problematic is how reduction in deterioration of visual acuity attributable to verteporfin PDT translates into impact on patient function. Availability of data on impact on quality of life for changes in visual acuity in a person’s better seeing eye allows this to be modelled where wet AMD affects the better seeing eye first. Modelling of the impact where wet AMD affects the worse seeing eye first has not been possible by any group. Addressing this problem would require a major piece of research, involving new data collection. However, it may well be important because wet AMD affecting the worse seeing eye first is as likely as affecting the better seeing eye and the impact on a patient’s ability to function may be substantially different.

7.2.3 Estimation of costs

There seems relatively little uncertainty about the likely costs of verteporfin PDT, although there is concern that the treatment schedules used in TAP and VIP might be unnecessarily intense and that the benefits might be achieved at lower cost. There is great uncertainty about the magnitude of costs potentially averted associated with developing impaired vision or blindness. The greater one assesses these costs to be, the more favourable will be the assessment of verteporfin PDT. We, like most others, have acknowledged this uncertainty and included its effect as part of the assessment of cost-utility.

Although outside the main focus of the report, it is also worth noting with respect to costs that there is also uncertainty about whether there would be substantial implementation costs. Ours and others’ views are that they would be high. The Industry submission suggests that they would be minimal.

7.2.4 Estimation of efficiency and cost-utility

The variation in cost-utility estimates is marked and stems, in our view, from:

- Use of sub-group analyses to provide estimates of effect (see above)
- Variation in the magnitude of costs averted (see above)
- Extending the modelling beyond the two-year follow-up of the RCTs, raising uncertainty about whether the visual acuity state at two years is stable
7.3 Need for further research

Each of the above sources of uncertainty should ideally be reduced by further research. Thus concerning the effectiveness and cost-utility of verteporfin PDT for wet AMD, the implications for future research for each of the sources of uncertainty are:

- **Sub-group effect on visual acuity.** This issue is likely to be resolved by the results of further trials in progress. However, resolution of whether an important sub-group effect exists will be greatly enhanced if an individual patient data meta-analysis was conducted. Another possibility is a new RCT focusing on just 100% classic only or predominantly classic wet AMD may also be helpful. As indicated below, this should, incorporate quality of life outcomes and costs. Proper assessment of whether sub-group effects exist would also undoubtedly help inform decisions on targeting verteporfin PDT on those groups most likely to benefit, and where the relationship between benefits and costs is most favourable (see below). However, if such groups were identified, the numbers involved would have to be ascertained to predict impact on cost to the NHS. For instance, with respect to the possibility that patients with 100% classic lesions might be an appropriate target group, the proportion of wet AMD cases having this attribute is uncertain.

- **Absence of information on survival.** Debatably, an assessment should be made on whether there is an effect on survival. Preliminary modelling of the size of effect on survival required to make a major difference to the balance between the benefits and costs of verteporfin PDT may help in making an assessment of the priority for an RCT assessing this outcome.

- **No direct measures reported of impact of quality of life.** RCTs ideally ought to be repeated using such measures. Realistically, it should be insisted that future trials in this area assess such outcomes.

- **No indication of the relationship between benefits and costs where wet AMD affects the worse seeing eye first.** An economic evaluation, associated with primary data collection is likely to be required to address this uncertainty. Such an evaluation would also need to take into account the likelihood that wet AMD needing treatment would be required in the fellow eye.

- **Costs of blindness averted.** A cost study to measure these directly or model them would be required.

- **Impact on visual acuity beyond two years.** Further follow-up data from TAP and other existing trials should be sought if, as seems likely, more favourable estimates of efficiency depend on considering costs and benefits over time periods beyond that currently available on treatment and monitoring of the effects of PDT.

Independent of the sources of uncertainty identified, there is definitely a suggestion that the relationship between benefits and costs may vary depending on patient characteristics. Whether the wet AMD occurs first in the better seeing or worse seeing eye has already been raised above. However, the study by Sharma et al also suggests that this relationship may vary depending on initial visual acuity (verteporfin PDT being less effective in those with poorer initial visual acuities) although the TAP trial subgroup analyses suggested that the treatment effects are greater where there was a lower initial visual acuity. Further economic modelling could be employed to investigate this possibility further, although this would be dependent on data additional to that already published being made available from the existing trials.
Our belief is that the best way to resolve many of uncertainties identified would be to conduct a large, multicentre, publicly funded pragmatic double-blind RCT assessing not just impact on visual acuity and adverse events, but also directly measured global quality of life and survival. The study should compare verteporfin PDT + best supportive care versus placebo PDT + best supportive care (the nature of best supportive care being made explicit so that it being made equally available in each arm of the RCT can be confirmed). The study should be powered to detect important differences in patient function, rather than visual acuity. The need for follow-up for up to at least five years should be anticipated, and a health economic analysis should be conducted in parallel, with particular scrutiny being directed to the magnitude of potential costs averted by verteporfin PDT. As indicated above there may be an argument for restricting the study population to the target group where there is currently a belief that PDT offers greatest benefit, namely 100% or predominantly classic AMD. A major potential obstacle to such a trial, which would need to be tested, is whether there was sufficient equipoise. It should also be ensured that there are no trials in progress and we understand that relevant bids may have been recently submitted (Personal communication R. Wormald, 2002); further information on this is being sought.

Finally, beyond the specific requirements for research on the clinical and cost-effectiveness of verteporfin PDT versus placebo in wet AMD are concerned, the report also notes the importance of supporting research in related areas. Particularly:

- RCTs comparing the effectiveness of alternative verteporfin PDT treatment schedules
- Basic research on the aetiology of AMD, so that plausible strategies for primary prevention can be explored
- Research on the effectiveness and cost-effectiveness of optimal rehabilitation and support for wet AMD (ie best supportive care unconstrained by available resources)
- RCTs comparing PDT with laser photocoagulation for juxtafoveal and extrafoveal wet AMD neovascular lesions

In the more distant future, RCTs directly comparing verteporfin PDT with other types of PDT and other developing treatments for wet AMD ie TTT may be required too.

8. CONCLUSIONS
Verteporfin PDT is effective in reducing the visual deterioration associated with neovascular lesions in wet AMD. It should be noted that as far as treatment of wet AMD is concerned, verteporfin PDT is currently only licenced for those forms where classic neovascular lesions predominate. Whether this is an efficient use of health care resources is highly uncertain, but on balance we believe that it is inefficient.

Other issues concerning implications to other parties, national targets, implementation and equity were identified which may need to be considered in any decision on whether verteporfin PDT is funded by the NHS.

Sources of uncertainty concerning efficiency could be reduced, and suggestions for further research are made. Principle amongst these is a large publicly funded pragmatic RCT with parallel health economic evaluation. Treatment of wet AMD, with verteporfin, other types of PDT, and other new technologies is an area under very active investigation, so this technology should be kept under close review.
9. APPENDICES

Appendix 1 Classification of age related maculopathy and age related macular degeneration.

The early stage of disease of the macula is termed early age related maculopathy (also maculopathy or occasionally macular dystrophy). The late stages of age related maculopathy are called late age related maculopathy or age related macular degeneration (AMD). This condition was previously called senile macular degeneration but the name was changed to prevent confusion with senile dementia.\textsuperscript{114}

The International Age Related Maculopathy (ARM) epidemiological study group has produced a classification of age related maculopathy and age related macular degeneration.\textsuperscript{3,115} This classification depends on clinical signs visible on examination of the retina and does not include visual function. The international classification is not currently used universally\textsuperscript{116,117} and there are several alternative terms for a number of the pathological features seen in age related maculopathy. This systematic review uses the international classification terminology and alternative terms are included in parentheses where appropriate.

**Early age related maculopathy**

This is characterised by the development of drusen (singular – druse) which are discrete, round, yellow/white patches of deposits that accumulate between the retinal pigment epithelium and Bruch’s membrane and can be scattered throughout the macula. There are two types of drusen. Hard drusen are small and well defined, very commonly found in adults and associated with little visual loss. Soft drusen are large, ill-defined, less common and are thought to be associated with progression to the more severe forms of macular degeneration. Over time the drusen can increase in number, enlarge, join together and calcify.

The other main change in early age related maculopathy is that the pigment of the RPE may be disturbed, giving areas of hyper- and/or hypo-pigmentation.

The international classification\textsuperscript{3,115} defines early age related maculopathy in people aged over 50 years as having the following signs (in the absence of other diseases which may cause these lesions)

- Soft drusen > 63μm diameter
- Areas of increased pigment or hyperpigmentation (in the outer retina or choroid) associated with drusen
- Areas of depigmentation or hypopigmentation of the RPE, most often more sharply demarcated than drusen, without any visibility of choroidal vessels, associated with drusen.

Despite the damage visible on examination of the retina, early age related maculopathy is often not associated with much loss of central vision. The atrophic changes may stabilise or progress only slowly. Also one eye may be affected less than the other. However, early age related maculopathy can progress to AMD, resulting in gradually deteriorating sight.
Approximately 10% of people with early age related maculopathy in both eyes will go on to develop AMD within 5 years.\textsuperscript{15}

**Age related macular degeneration**

The result of AMD (late age related maculopathy) is a painless loss of central, sharply defined vision (decreased visual acuity) often noticed as difficulty in reading fine print or threading a needle. There can also be parts of central vision with opaque or dark patches (positive scotoma) and distortion of vision so that straight lines, outlines or printed letters appear bent or wavy (metamorphopsia). None of these visual symptoms are specific to AMD and diagnosis is by retinal examination.

The AMD disease category includes a broad spectrum of clinical and pathological findings. It is usually classified into two groups, which have different manifestations, prognoses and treatment strategies.

1. **Dry AMD (geographic atrophy or atrophic age related macular degeneration)**

Dry AMD is the more benign form where there is a discrete loss of RPE and overlying rods and cones, often in a horseshoe or ring shape around the fovea, causing a dense blind spot. Eventually the fovea can become atrophic, causing central blindness. In the international classification, dry AMD is defined as any sharply delineated roughly round or oval area of hypopigmentation or depigmentation or apparent absence of the RPE in which choroidal vessels are more visible than in surrounding areas, which must be at least 175\textmu m in diameter.\textsuperscript{3,115} Dry AMD can progress to wet AMD but the risk factors are largely unknown.\textsuperscript{8,25}

2. **Wet AMD (disciform, exudative or neovascular AMD)**

Wet AMD is associated with a variety of pathological changes in the macula.\textsuperscript{3,115} 

a. Pigment epithelial detachment (PED or RPE detachment). In this a lipid/protein filled space can develop between the retinal pigment epithelium and Bruch’s membrane.\textsuperscript{118} This can be associated with neurosensory retinal detachment.

b. Subretinal or sub-RPE neovascular membranes (subretinal neovascularization, choroidal neovascularisation, SRNV, SRN, CNV, CRNV or CRN lesions).

c. Retinal scarring – this can be epiretinal, intraretinal, subretinal or sub-pigment epithelial scars, glial tissue or fibrin-like deposits.

d. Subretinal haemorrhages that are not related to other retinal vascular disease. They may be nearly black, bright red or whitish-yellow and can extend into the retina.

e. Hard exudates (lipids) within the macular area related to any of the above and not related to other retinal vascular disease.

Neovascular membranes are new blood vessels that grow up from capillaries in the choriocapillaris and then spread under the retinal pigment epithelium or grow through it into the area between the retinal pigment epithelium and the photoreceptor cells of the retina (the sub-retinal space). They tend to leak fluid beneath and into the sensory retina, to bleed and to create a fibrovascular disciform scar in the macular region.\textsuperscript{5}
People with wet AMD can have pigment epithelial detachments only and no neovascular membranes.\textsuperscript{118} If the term neovascular AMD is used for wet AMD then this can cause some confusion.

Wet AMD can be subdivided into classic and occult. Classic neovascular membranes are clearly delineated on angiography\textsuperscript{57} and are the more aggressive form of the condition, usually causing rapid blindness.\textsuperscript{7} Occult lesions have poorly demarcated boundaries and are associated with less vision loss.\textsuperscript{7} However, classic lesions can develop in occult lesions to give a mixed picture.\textsuperscript{7} This conversion from occult to classic can happen after TTT.\textsuperscript{119}

AMD can be subdivided as per the diagram below.

![Venn diagram 1](https://example.com/venn_diagram1.png)

Also, there are various ways that neovascular membranes in wet AMD can be subdivided on the classic/occult continuum. There could be, at its simplest, classic only versus any occult, occult only versus any classic or the three categories shown in Venn Diagram 1.

Venn diagram 1

![Venn diagram 1](https://example.com/venn_diagram1.png)

Since the TAP trial\textsuperscript{61} there has been created a further subdivision where the classic plus occult group is cut in two to make a minimally classic group and a ‘mostly classic’ group. Then the ‘mostly’ classic and classic only results can be combined into one group called predominantly classic. This group contains all lesions having 50% or more classic lesions (everything to the right of the vertical line - see Venn Diagram 2)
All the above types, particularly those involving neovascular membrane formation may be further sub-classified according to where the lesions occur in relation to the fovea:

- Sub-foveal – lesions located behind the middle of the fovea
- Juxta-foveal – lesions locate behind fovea, but not the middle of it
- Extra-foveal – lesions located outside the fovea
Appendix 2 Measurement of vision and definition of blindness

Visual function consists of a number of aspects. Ways of assessment include visual acuity, contrast sensitivity and visual field measurement.

Visual acuity
Visual acuity is the ability to distinguish the details and shape of objects and is measured by the smallest angle at which the eye can distinguish fine detail. This threshold angle is called the minimum angle of resolution and is measured in minutes of arc. (One minute of arc is $1/60^{th}$ of a degree, 360 degrees in a circle). One minute of arc has been accepted as the normal human minimum angle of resolution.

A number of test charts are used to measure visual acuity including Snellen and Bailey-Lovie charts. Snellen charts have letters arranged in seven rows from largest at the top to smallest at the bottom. In each row of letters the width of the lines forming the letter subtends an angle of one minute of arc at a certain specific distance. For the largest letter the distance is 60 metres and for the smallest it is 4 metres. When a person’s visual acuity is tested, they are placed at 6 metres from the chart and the smallest line of letters correctly read is recorded. The result is expressed as a pseudofraction where the number above the line is the testing distance and the number below is the ‘size’ of the letter (as measured in distances as explained above). Normal vision is assumed to be 6/6. The line below the ‘normal vision’ line is 6/5. If, at 6 metres, a person can only read the largest letter on the chart their visual acuity is recorded as 6/60. If they are unable to read the largest letter at 6 metres then they are gradually brought closer to the Snellen chart, to a minimum distance of 1 metre. At this distance, if they can read the largest letter their visual acuity is 1/60. If not then the ability to count fingers is tested. If they cannot count fingers but can see a hand moving then the vision is recorded as hand movements. If they are unable to see a moving hand then a bright light is shone into the eye. If they can perceive this then their vision is recorded as perception of light. If they cannot see the bright light then their vision is recorded as no perception of light (stone blind).

Some countries use feet instead of metres to measure visual acuity. Six metres is equivalent to 20 feet so normal vision is recorded as 20/20 and 1/60 is equivalent to 3/200.

The Snellen chart is the most widely used test in clinical practice but there are a number of flaws which affect its accuracy as a test for visual performance:

- There are a different number of letters on each row so patients with poor acuity are required to read fewer letters than those with good acuity.
- The letters on the lower lines are more crowded which increases difficulty in reading.
- The spacing between each letter and each row of letters bears no systematic relation to the width or height of the letters so the task required of the patient changes as they read down the chart.
- Recording the results of a Snellen test is also problematic as patients seldom read all of one row and no letters on the row below. The endpoint can spread over 3 lines and there are no agreed standards for the exact notation in these situations.

Bailey-Lovie charts have been developed to overcome the difficulties with the Snellen charts. They have seven rows of letters like Snellen charts but have five letters on each row. The
spacing between each letter and each row is related to the width and the height of the letters respectively. Each row is a scaled down version of the previous row and the same amount of magnification will give the same number of extra rows for all patients, irrespective of their initial visual acuity.

Very similar to Bailey-Lovie charts are LogMAR charts (where LogMAR stands for the logarithm of the minimum angle of resolution) and ETDRS charts (Early Treatment Diabetic Retinopathy Study). For a diagram of these types of charts see appendix 1. (The diagram is of a LogMAR chart which has 14 rows of letters.)

The progression of letter sizes on these three types of charts is uniform, increasing at a constant ratio of 0.1 log unit steps from the bottom of the chart to the top. The result of the test is usually recorded as a LogMAR score so that 6/6 (normal vision) is equivalent to a LogMAR score of 0.0 (0.0 is log base 10 of 1). At the top line of the Bailey-Lovie chart, (5 lines up from 0.0) 0.50 is equivalent to 6/19 and at the bottom of the chart, (one line lower than 0.0) –0.10 is approximately equivalent to 6/5 (because log base 10 of any number less than 1 is negative). On each row of five letters, each letter read has a LogMAR score of 0.02. When a letter is not read, 0.02 is added to the LogMAR score so the final score takes into account every letter read correctly.120

The disadvantages of the Bailey-Lovie type charts and LogMAR scale are that the chart is wider than the Snellen chart and that the scoring is a little more complicated to the uninitiated.120 Also, it is difficult to tell whether the LogMAR score is an ordinal or interval scale but it is commonly treated as an interval scale for research purposes.

For some RCTs a modified testing scheme which can measure lower visual acuity is used with the LogMAR chart. For this and a scheme conversion table, see Table 25 and Table 26. This scheme starts scoring at line 1 (top line) at 1 metre which is equivalent to 20/800. After line three, testing is done at 2 metres with line 1 again which measures 20/400. When using this testing scheme, the number of letters read can be reported rather than the Snellen score. Therefore 20/200 (or 6/60) is equivalent to a score of 34 letters (four out of five letters correct can be accepted as achieving the level of acuity).

Contrast sensitivity
Another way of measuring visual performance is by measuring contrast sensitivity.120-122 One of the easiest ways this can be done is by using a Pelli-Robson chart. This chart has several rows of six letters, all of the same size, arranged in groups of three (two groups per line). The top row has clear black letters which stand out from the background and each subsequent row has decreasing contrast until the bottom row is practically indistinguishable from the background of the chart. The chart is usually viewed from one metre and from top left to as far down as possible. Each correct letter has a contrast threshold value of 0.05 log units.121 This method of measuring visual acuity is said to be a more sensitive indicator of function than Snellen acuity and may provide earlier detection of retinal and optic nerve disease.122

Other vision testing methods
The Amsler Grid is a commonly used test for disturbances in central (macular) vision. It has a simple pattern of 21 horizontal and 21 vertical straight lines in which, when held at 30cm from the eye, each small square subtends one degree of arc. The eye is focused on a central large dot and then the person describes any gaps, kinks or wavy lines seen.
Visual fields
The visual field is defined as that portion of space in which objects are visible at the same moment during steady fixation of the gaze in one direction. There are two main ways of testing the visual field, called static perimetry and kinetic perimetry. In static perimetry each part of the retina is tested for its differential light threshold. Light spots are flashed and their sizes or intensities gradually increased until the patient can see them. In kinetic perimetry the eye is focused on a fixed point in the centre of the visual field and peripheral vision is tested by gradually bringing a test object of different sizes and brightnesses from outside the periphery in towards the centre until the person sees the object. This is repeated for all zones and a map made which is called a perimetry chart.

Definition of blindness
Legal blindness is defined differently by different countries or organisations but a fairly standard definition is visual acuity of 6/60 (or 20/200) or worse in the better eye or a visual field less than or equal to 20 degrees in the better eye.

On the BD8 certificate the legal definition of blindness is ‘so blind as to be unable to perform any work for which eyesight is essential’. The recommendations are 3/60 or worse in the better eye (corrected visual acuity) or 6/60 or worse in the better eye with markedly restricted fields. There is no legal definition of partial sight but the definition on the BD8 form is ‘permanently handicapped by defective vision caused by congenital defect, illness or injury’. The recommendations are 3/60 to 6/60 in better eye with full visual field or 6/24 or worse with moderate constriction of visual field or 6/18 or better with gross visual field defects.
Table 25 Diagrammatic representation of a LogMAR chart

<table>
<thead>
<tr>
<th>Mtr</th>
<th>Feet</th>
<th>Feet</th>
</tr>
</thead>
<tbody>
<tr>
<td>40</td>
<td>(200)</td>
<td></td>
</tr>
<tr>
<td>32</td>
<td>(160)</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>(125)</td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>(100)</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>(80)</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>(63)</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>(50)</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>(40)</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>(32)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>(25)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>(20)</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>(16)</td>
<td></td>
</tr>
<tr>
<td>2.5</td>
<td>(12.5)</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>(10)</td>
<td></td>
</tr>
</tbody>
</table>

| Feet | | Feet |
|------| |------|
|      | |      |
|      | |      |
|      | |      |
|      | |      |
|      | |      |
|      | |      |
|      | |      |
|      | |      |
|      | |      |
|      | |      |

H V Z D S
N C V K D
C Z S H N
O N V S R
K D N R O
Z K C S V
D V O H C
O H V C K
H Z C K O
N C K H D
Z H C S R
S Z R D N
H C D N G
K D O R H

0.1
0.0
-0.1
-0.2
-0.3
Table 26 Visual acuity conversion table.

<table>
<thead>
<tr>
<th>4m</th>
<th>6m</th>
<th>20ft</th>
<th>Visual angle in minutes</th>
<th>Line of chart</th>
<th>Distance tested (metres)</th>
<th>Decimal fraction</th>
<th>LogMAR unit</th>
<th>Number of letters read</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/800</td>
<td>1</td>
<td>1</td>
<td>0.025</td>
<td>+1.6</td>
<td>5</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/640</td>
<td>32</td>
<td>2</td>
<td>1</td>
<td>0.031</td>
<td>+1.5</td>
<td>10</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/500</td>
<td>3</td>
<td>1</td>
<td>0.04</td>
<td>+1.4</td>
<td>15</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/60</td>
<td>20/400</td>
<td>1</td>
<td>2</td>
<td>0.05</td>
<td>+1.3</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/320</td>
<td>16</td>
<td>2</td>
<td>2</td>
<td>0.063</td>
<td>+1.2</td>
<td>25</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20/250</td>
<td>3</td>
<td>2</td>
<td>0.08</td>
<td>+1.1</td>
<td>30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4/40</td>
<td>6/60</td>
<td>20/200</td>
<td>4</td>
<td>2</td>
<td>0.1</td>
<td>+1.0</td>
<td>35</td>
<td></td>
</tr>
<tr>
<td>4/32</td>
<td>6/48</td>
<td>20/160</td>
<td>8</td>
<td>5</td>
<td>0.125</td>
<td>+0.9</td>
<td>40</td>
<td></td>
</tr>
<tr>
<td>4/25</td>
<td>6/38</td>
<td>20/125</td>
<td>6</td>
<td>2</td>
<td>0.16</td>
<td>+0.8</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>4/20</td>
<td>6/30</td>
<td>20/100</td>
<td>7</td>
<td>2</td>
<td>0.2</td>
<td>+0.7</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>4/16</td>
<td>6/24</td>
<td>20/80</td>
<td>8</td>
<td>2</td>
<td>0.25</td>
<td>+0.6</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>4/12</td>
<td>6/20</td>
<td>20/63</td>
<td>9</td>
<td>2</td>
<td>0.32</td>
<td>+0.5</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>4/10</td>
<td>6/15</td>
<td>20/50</td>
<td>10</td>
<td>2</td>
<td>0.4</td>
<td>+0.4</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>4/8</td>
<td>6/12</td>
<td>20/40</td>
<td>2</td>
<td>11</td>
<td>2</td>
<td>0.5</td>
<td>+0.3</td>
<td>70</td>
</tr>
<tr>
<td>4/6.3</td>
<td>6/10</td>
<td>20/32</td>
<td>12</td>
<td>2</td>
<td>0.63</td>
<td>+0.2</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>4/5</td>
<td>6/7.5</td>
<td>20/25</td>
<td>13</td>
<td>2</td>
<td>0.8</td>
<td>+0.1</td>
<td>80</td>
<td></td>
</tr>
<tr>
<td>4/4</td>
<td>6/6</td>
<td>20/20</td>
<td>1</td>
<td>14</td>
<td>2</td>
<td>1.0</td>
<td>0.0</td>
<td>85</td>
</tr>
<tr>
<td>4/3.2</td>
<td>6/5</td>
<td>20/16</td>
<td>12</td>
<td>4</td>
<td>1.25</td>
<td>-0.1</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>4/2.5</td>
<td>6/3.7</td>
<td>20/12.5</td>
<td>13</td>
<td>4</td>
<td>1.6</td>
<td>-0.2</td>
<td>95</td>
<td></td>
</tr>
<tr>
<td>4/2</td>
<td>6/3</td>
<td>20/10</td>
<td>14</td>
<td>4</td>
<td>2.0</td>
<td>-0.3</td>
<td>100</td>
<td></td>
</tr>
</tbody>
</table>

(Personal communication from Mr Y. Yang, Wolverhampton and Midland Counties Eye Infirmary, 1999)

Note: This table is included for the purpose of comparison of Snellen scores and letters read. It is acknowledged that a Snellen score of 6/20 or 6/60 implies that the measurement was carried out holding a chart 6 metres away from the person being tested. A Snellen score of 4/12 or 4/40 implies that the measurement was carried out holding a chart 4 metres away from the person being tested. However, the chart used in the above testing scheme (columns Line of chart and Distance tested (metres)) was probably intended for use at 2 metres rather than 4 or 6 metres and so would have correspondingly smaller text sizes. It is presumed that this is to enable low visual acuities to be measured more accurately in an RCT.
Appendix 3 Protocol

NICE PROTOCOL – THIS PROTOCOL IS PROVISIONAL AND SUBJECT TO CHANGE.

Review Team

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Title of research question

A RAPID AND SYSTEMATIC REVIEW OF THE CLINICAL EFFECTIVENESS AND COST UTILITY OF PHOTODYNAMIC THERAPY FOR AGE-RELATED MACULAR DEGENERATION
Clarification of research question and scope
AMD is a form of central blindness that usually occurs in people over the age of 50 years. There are two forms: wet (neovascular) and dry (non-neovascular) AMD. In wet AMD abnormal new blood vessels (neovascular membranes) can grow beneath the central retina causing leakage and bleeding and disrupting the overlying retina. The aim of photodynamic therapy for people with this condition is to halt the resulting gradual vision loss. A light sensitive dye is given by intravenous infusion and taken up by the vascular endothelium of the new blood vessels. A non-thermal laser is then applied over the lesion to activate the dye in order to destroy the endothelial cells, thus preventing them causing further loss of visual acuity.

Objective: To establish the clinical and cost-effectiveness of photodynamic therapy for the neovascular form of age-related macular degeneration (AMD) relative to current practice and in relation to their licensed indications and in order to produce guidance to the NHS in England and Wales.

METHODS
Clinical effectiveness review
Search strategy
A scoping search has been undertaken, focusing on existing systematic reviews and other background material. The yield from this has been used to develop the protocol for the review, including inclusion and exclusion criteria.

The information scientist will design a search strategy, with assistance from the researchers and based on guidance in NHSCRD4 (2nd edition), to identify any relevant randomised controlled trials (RCTs) comparing photodynamic therapy to no treatment or to laser photocoagulation for the treatment of neovascular membranes in wet AMD. The information scientist will conduct the search strategy. The researchers will scan all relevant study titles in the databases searched and abstracts will be read if the titles seem potentially relevant.

The following sources will be searched
- Bibliographic databases: Cochrane Library Controlled Trials Register, Medline, Embase, Science Citation Index, National Research Register.
- National and international HTA sites.
- Conference abstracts of major ophthalmology conferences in hard copy and on the Internet, covering the last three years.
- Any other relevant internet sites.
- Citations of all relevant articles found.

The search strategy will cover the time period from 1993 to the present as it was after 1993 that work on photodynamic therapy began.

If necessary, contacts with trialists will be made. In addition there will be contacts with clinical experts as and when required.

Inclusion and exclusion criteria
Trials suitable for inclusion will be selected from those identified as potentially relevant by the search strategy, using the criteria listed below.
Study design: RCTs only.
Population: Adults with wet AMD causing any type of neovascular membranes (classic, minimally classic and occult).
Intervention: Photodynamic therapy using any photosensitive drug.
Comparator: Either no treatment (best supportive care) for subfoveal lesions or laser photocoagulation for juxtafoveal and extrafoveal lesions.
Reporting: Only RCTs where recruitment had closed and which report follow up results for all or nearly all recruited patients will be included.

The exclusion criteria will be:
1. RCTs which have not finished recruiting.
2. RCTs publishing only baseline characteristics or follow up results for only some of the trial participants.
3. Case series.
4. Studies carried out on animals.

Although items 1, 2 and 3 above will be excluded from the analysis of clinical effectiveness, their presence will be noted as essential background to the review.

Two reviewers, using explicit predetermined criteria, will make inclusion and exclusion decisions independently. These will be checked for agreement and any differences will be discussed and resolved, if necessary by a third reviewer. Inclusion and exclusion decisions will be made independently of the inspection of trial results.

Data extraction and quality assessment strategies
Two reviewers will independently extract the effectiveness and quality assessment data from all included studies into pre-defined data extraction and quality assessment forms (see Appendices). Any discrepancies will be resolved by discussion and if necessary by a third reviewer arbitrating. The quality of RCTs will be assessed by Jadad score.83

Methods of analysis/synthesis
The tabulated characteristics and results of the included trials will be assessed qualitatively, particularly in relation to possible sources of clinical heterogeneity. If there are sufficient good quality trials with results for the same outcome measures, synthesis of results will be conducted, using both fixed effects and random effects models.

Cost effectiveness review
Search strategy
A systematic review of the literature on costs, health economic impact and quality of life of photodynamic therapy for AMD will be carried out. The clinical effectiveness search strategy will be expanded to look for relevant economic analyses or any studies reporting costs, cost effectiveness, cost utility or generic quality of life outcomes for adults with AMD treated by photodynamic therapy.

The cost effectiveness search strategy will include;
- Bibliographic databases: Medline, Embase, NHSEED and DARE.
- Internet sites of national economics units.
Relevant information found during the clinical effectiveness searches will also be used.

**Inclusion and exclusion criteria, data extraction and quality assessment**

Studies will only be included in the cost effectiveness review if they meet the following criteria:

- **Study design:** Any study type.
- **Population:** Adults with any AMD.
- **Intervention:** Photodynamic therapy using any photosensitive drug.
- **Outcomes:** Costs, cost consequences, cost utility, cost effectiveness or any generic quality of life.

One reviewer, using explicit predetermined criteria, will make the inclusion and exclusion decisions for the economic evaluation review. This will be checked by a second researcher. Quality of included studies will be assessed using the modified checklist by Drummond et al.\(^9^3\)

**Economic evaluation**

Health economists with the support of the researchers will undertake a cost utility analysis. As time and circumstances allow, de novo modelling will be undertaken, incorporating costs and clinical effectiveness and using other ancillary information where necessary and appropriate.

The clinical effectiveness part of the economic evaluation will use information from any RCTs on photodynamic therapy for AMD found during the clinical effectiveness searches or a synthesis of outcome measures if one is carried out. If no quality of life studies in photodynamic therapy are found during the clinical and cost effectiveness searches, published studies linking visual acuity to utility value in the better seeing eye of patients with AMD will be used to convert clinical effectiveness results to generic quality of life estimates.

The costs of photodynamic therapy will be estimated from the current market price of photodynamic drugs and published and local estimates of associated costs and resource use. The cost estimates will take the perspective of costs to the public sector rather than to the NHS alone. It will also include estimates of costs of the clinical effectiveness comparators of no treatment (best supportive care) and/or laser photocoagulation.

The economic model will include the role of examining the eye by angiography to determine eligibility for treatment and retreatment with photodynamic therapy.

Where there is insufficient information for the model, appropriate simplifying assumptions will be made in sensitivity analysis.

**Company submissions**

The company submission(s) will be reviewed for both clinical and cost effectiveness data. We intend that our economic model will be developed before examination of that in the industry submission(s). Our economic model will then be compared to theirs and the differences outlined and discussed.

Any ‘commercial in confidence’ data taken from industry submissions will be underlined in the text of the report.
Project Management

Timetable/milestones

<table>
<thead>
<tr>
<th>Stage</th>
<th>Date (from NICE timetable)</th>
<th>Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Scoping completed</td>
<td>5th July 2001</td>
<td>7</td>
</tr>
<tr>
<td>Draft protocol submission</td>
<td>30th July 2001</td>
<td>10</td>
</tr>
<tr>
<td>Finalised protocol submission</td>
<td>20th Aug 2001</td>
<td>13</td>
</tr>
<tr>
<td>Receipt of industry submissions</td>
<td>26th Oct 2001</td>
<td>23</td>
</tr>
<tr>
<td>Progress report</td>
<td>2nd Nov 2001</td>
<td>24</td>
</tr>
<tr>
<td>Draft final report</td>
<td>24th Jan 2002</td>
<td>34</td>
</tr>
<tr>
<td>Appraisal committee meeting</td>
<td>7th March 2002</td>
<td>40</td>
</tr>
</tbody>
</table>

External reviewers
The rapid review will be subject to external peer review by at least two experts. These reviewers will be chosen according to academic seniority and content expertise and will be agreed with NCCHTA. We recognise that the NICE secretariat and Appraisal Committee will undertake methodological review, but if the rapid review encounters particularly challenging methodological issues we will organise independent methodological reviews. External expert reviewers will see a complete and near final draft of the rapid review and will understand that their role is part of external quality assurance. Where the review contains data that is regarded as ‘commercial in confidence’ we will require peer reviewers to sign a copy of the NICE confidentiality acknowledgement and undertaking. We will return peer reviewers’ signed copies to NCCHTA. Comments from external reviewers and our responses to these will be made available to NCCHTA in strict confidence for editorial review and approval.

Appendices and references

A - Data extraction form*

B - Quality assessment scale*

C – Background*

References*

* Not included in this report
Appendix 4 Search strategies – clinical effectiveness

COCHRANE LIBRARY 2001, ISSUE 3

#1 macular degeneration: ME
#2 retinal degeneration: ME
#3 neovascularization pathologic: ME
#4 (((macula or macular) or retina) or retinal) or choroids) or choroidal) near (degeneration or neovascularization))
#5 maculopathy
#6 1 or 2 or 3 or 4 or 5
#7 photochemotherapy: ME
#8 photosensitizing agents: ME
#9 (((photosensitizing or photosensitizing) or photodynamic) or PDT)
#10 (verteporfin or visudyne)
#11 (tin next (ethyl next etiopurpurin)
#12 (((snet2 or puryltin) or Rostaporfin)
#13 motaxafin next lutetium
#14 ((lutetium next texaphyrin) or lutex)
#15 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
#16 6 and 15

SCIENCE CITATION INDEX (WEB OF SCIENCE) 1993 – SEPT 2001

Because of the long strings included in the strategy, two searches were conducted.

Search 1
(verteporfin OR visudyne OR tin ethyl etiopurpurin OR snet2 OR puryltin OR purlytin OR optrin OR motexafin lutetium OR lutetium texaphyrin OR lutex OR lu tex) AND (macula* degeneration OR retina* degeneration OR choroid* degeneration OR retina* degeneration OR retina* neovasc* OR macul* neovasc* OR choroid* neovasc

Search 2
(photosensitizing agent* OR photosensitising agent* OR porphyrin OR benzoporphyrin OR pdt OR photodynamic) AND (macula* degeneration OR retina* degeneration OR choroid* degeneration OR retina* degeneration OR retina* neovasc* OR macul* neovasc* OR choroid* neovasc*)

MEDLINE (Ovid) 1993 – Aug 2001

1 (verteporfin or visudyne).mp.
2 tin ethyl etiopurpurin.mp.
3 (snet2 or puryltin or optrin or purlytin).mp.
4 (motexafin lutetium or lutetium texaphyrin).mp.
5 (rostaporfin or lu-tex).mp.
6 lutex.mp.
7 photosensitizing agents/
8 photosensiti#ing agent$.ti,ab.
9 (porphyrin or benzoporphyrin or pdt or photodynamic).mp.
10 or/1-9
11 macular degeneration/
12 retinal degeneration/
13 choroidal neovascularization/
14 (((macul$ or retin$ or choroid$) and (degener$ or neovasc$)).mp
15 maculopathy.mp.
16 or/11-15
17 10 and 16
18 randomized controlled trial.pt.
19 controlled clinical trial.pt.
20 randomized controlled trials.sh.
random allocation.sh.
double-blind method.sh.
single-blind method.sh.
or/18-23
(animal not human).sh.
24 not 25
clinical trial.pt.
exp clinical trials/
(clin$ adj25 trial$).ti,ab.
((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.
placebos.sh.
placebo$.ti,ab.
random$.ti,ab.
research design.sh.
or/27-34
35 not 25
36 not 26
comparative study.sh.
exp evaluation studies/
follow up studies.sh.
prospective studies.sh.
(control$ or prospectiv$ or volunteer$).ti,ab.
or/38-42
43 not 25
44 not (26 or 37)
26 or 37 or 45
27 and 46

EMBASE (Ovid) 1993 – Aug 2001
1 retina macula age related degeneration/
2 retina degeneration/
((macul$ or retina$ or choroid$) and (degener$ or neovasc$)).ti,ab.
4 maculopathy.mp.
or/1-4
6 (verteporfin or visudyne).mp.
7 (tin ethyl etiopurpurin or purlytin or purlytin or optrin).mp.
8 snet2.mp.
9 motexafin lutetium.mp.
10 lutetium texaphyrin.mp.
11 lutex.mp.
12 lu-tex.mp.
13 photosensitizing agent/
14 photosensiti#ing agent$).ti,ab.
15 (porphyrin or benzoporphyrin or pdt or photodynamic).mp.
or/6-15
17 5 and 16
Appendix 5 Search strategies – economic evaluation

NHS Economic Evaluation Database (NHS EED) and NHS Database of reviews of Effectiveness (DARE)
See clinical effectiveness search strategy for Cochrane Library (Appendix 4)

Internet sites
Sites of the following health economics units were also searched: University of York Centre for Health Economics, Health Economics Research Unit (University of Aberdeen), Health Economics Research Group (Brunel University).

MEDLINE (Ovid) 1993 – Aug 2001
1 (verteporfin or visudyne).mp.
2 tin ethyl etiopurpurin.mp.
3 (snet2 or puryltin or purlytin).mp.
4 (motexafin lutetium or lutetium texaphyrin).mp.
5 (rostaporfin or lu-tex or optrin).mp.
6 photosensitizing agents/
7 photosensiti#ing agent$.ti,ab.
8 lutex.mp.
9 or/1-8
10 economics/
11 exp "costs and cost analysis"/
12 cost of illness/
13 exp health care costs/
14 economic value of life/
15 economics pharmaceutical/
16 exp "fees and charges"/
17 (cost or costs or costed or costly or costing).tw.
18 (economic$ or pharmacoeconomic$ or price$ or pricing).tw.
19 or/10-18
20 9 and 19
21 from 20 keep 1-2, 4-5, 8-9
22 macular degeneration/
23 retinal degeneration/
24 choroidal neovascularization/
25 ((macul$ or retin$ or choroid$) and (degener$ or neovasc$)).mp.
26 maculopathy.mp.
27 or/22-26
28 19 and 27
29 quality of life/
30 life style/
31 health status/
32 health status indicators/
33 or/29-32
34 19 and 33
35 27 and 33
36 (porphyrin or benzoporphyrin or pdt or photodynamic).mp.
37 9 or 36
38 19 and 37
39 27 and 38
40 21 or 39
Appendix 6 Reasons for disagreements in data extraction

TAP trial.

1. Baseline characteristics. It was described in the text that there were significantly more lesions with blood in the placebo group. In the associated table the p value for ‘lesions included blood’ subgroup was p=0.053. As this was above 0.05 it was agreed that the result in the table not the text be used.
2. The timing of the primary outcome measure was not made explicit in the trial reports. One data extractor considered it to be at 1 year, the other considered that no time was stated. It was agreed that a compromise of both one and two years be adopted.
3. Were the sub group analyses preplanned? One data extractor thought that the correlations to baseline may have been but was unclear about the classic/occult split. The other data extractor thought that it was unclear whether the specific baseline categories had been prespecified, irrespective of whether a sub group analysis had been planned beforehand. Also that there was no indication that the classic/occult split was preplanned. It was agreed that the whole issue of preplanning of subgroups was unclear.

VIP trial.

1. For the number of treatments received by each group at the different follow up times, there was a discrepancy between text and diagram. This was because the diagram gave the percentages to one decimal place whereas the text rounded to whole numbers. It was agreed to use the percentages with one decimal place from the diagram.
2. The primary outcome measure is described differently in the abstract and the text. In the abstract it is described as the loss of at least 15 letters. In the text it is described as the proportion of eyes that had fewer than 15 letters lost. It was agreed that the primary outcome measure probably was fewer than 15 letters, but that this is not how visual acuity loss was reported. What is actually reported is loss of at least 15 letters and, after advice from our medical statistician, this outcome was used in the systematic review.
3. For the treatment discontinued because of adverse event associated with treatment it was unclear whether the one patient who had a non-ocular event as described in the text came from the intervention or the control group. It was decided to reflect this lack of clarity in the systematic review reported side effects results.
Appendix 7 Results of subgroup analyses from the TAP trial at 2 years

Table 27. Eyes with a loss of less than 15 letters at month 24 by treatment group and baseline characteristics* [Shaded cells indicate factors where there is a statistically significant test for interaction (value in final column)]

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Treatment Group</th>
<th>No. of Eyes</th>
<th>Loss &lt;15 Letters, %</th>
<th>Difference, %</th>
<th>P†</th>
<th>P‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>All eyes</td>
<td>V</td>
<td>402</td>
<td>213 (53.0)</td>
<td>15.3</td>
<td>&lt;.003</td>
<td>N/A</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>207</td>
<td>78 (37.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trial</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study A</td>
<td>V</td>
<td>204</td>
<td>104 (51.0)</td>
<td>11.7</td>
<td>.05</td>
<td>.39</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>107</td>
<td>42 (39.3)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study B</td>
<td>V</td>
<td>198</td>
<td>109 (55.1)</td>
<td>19.1</td>
<td>.002</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>100</td>
<td>36 (36.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75</td>
<td>V</td>
<td>194</td>
<td>115 (59.3)</td>
<td>17.9</td>
<td>.005</td>
<td>.53</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>87</td>
<td>36 (41.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥75</td>
<td>V</td>
<td>208</td>
<td>98 (47.1)</td>
<td>12.1</td>
<td>.03</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>120</td>
<td>42 (35.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>V</td>
<td>188</td>
<td>95 (50.5)</td>
<td>16.8</td>
<td>.01</td>
<td>.82</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>77</td>
<td>26 (33.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>V</td>
<td>214</td>
<td>118 (55.1)</td>
<td>15.1</td>
<td>.007</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>130</td>
<td>52 (40.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic hypertension</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Definite§</td>
<td>V</td>
<td>170</td>
<td>90 (52.9)</td>
<td>20.5</td>
<td>.003</td>
<td>.33</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>77</td>
<td>25 (32.5)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>V</td>
<td>232</td>
<td>123 (53.0)</td>
<td>12.2</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>130</td>
<td>53 (40.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>V</td>
<td>135</td>
<td>76 (56.3)</td>
<td>21.5</td>
<td>.002</td>
<td>.51</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>89</td>
<td>31 (34.8)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Past</td>
<td>V</td>
<td>205</td>
<td>104 (50.7)</td>
<td>11.4</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>94</td>
<td>37 (39.4)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>V</td>
<td>62</td>
<td>33 (53.2)</td>
<td>11.6</td>
<td>.34</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>24</td>
<td>10 (41.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial letter score (visual acuity#) in study eye</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>73-54 (20/40-20/80)</td>
<td>V</td>
<td>203</td>
<td>89 (43.8)</td>
<td>9.2</td>
<td>.12</td>
<td>.16</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>101</td>
<td>35 (34.7)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>53-34 (20/100-20/200)</td>
<td>V</td>
<td>199</td>
<td>124 (62.3)</td>
<td>21.7</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>106</td>
<td>43 (40.6)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Greatest linear dimension, diameter of MPS disc area circle</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤3</td>
<td>V</td>
<td>107</td>
<td>66 (61.7)</td>
<td>11.7</td>
<td>.18</td>
<td>.22</td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>46</td>
<td>23 (50.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;3 to ≤6</td>
<td>V</td>
<td>152</td>
<td>84 (55.6)</td>
<td>23.7</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>P</td>
<td>97</td>
<td>31 (32.0)</td>
<td></td>
<td></td>
<td></td>
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</table>
Greatest linear dimension, diameter of MPS disc area circle

<table>
<thead>
<tr>
<th></th>
<th>V</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;6 to ≤9</td>
<td>109</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>(40.4)</td>
<td>(38.5)</td>
</tr>
<tr>
<td>&gt;9</td>
<td>25</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>(44.0)</td>
<td>(25.0)</td>
</tr>
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</table>

Lesion area composed of classic CNV, %

<table>
<thead>
<tr>
<th></th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥50</td>
<td>159</td>
<td>94</td>
</tr>
<tr>
<td></td>
<td>(59.1)</td>
<td>(31.3)</td>
</tr>
<tr>
<td>&gt;0 to &lt;50</td>
<td>202</td>
<td>96</td>
</tr>
<tr>
<td></td>
<td>(47.5)</td>
<td>(44.2)</td>
</tr>
<tr>
<td>0</td>
<td>41</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(56.1)</td>
<td>(30.0)</td>
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</table>

Evidence of occult CNV

<table>
<thead>
<tr>
<th></th>
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<th>P</th>
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</thead>
<tbody>
<tr>
<td>Yes</td>
<td>305</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>(47.7)</td>
<td>(40.8)</td>
</tr>
<tr>
<td>No</td>
<td>93</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>(69.9)</td>
<td>(28.6)</td>
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</table>

Evidence of prior laser photocoagulation

<table>
<thead>
<tr>
<th></th>
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<th>P</th>
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<tbody>
<tr>
<td>Yes</td>
<td>60</td>
<td>28</td>
</tr>
<tr>
<td></td>
<td>(46.7)</td>
<td>(43.5)</td>
</tr>
<tr>
<td>No</td>
<td>340</td>
<td>183</td>
</tr>
<tr>
<td></td>
<td>(53.8)</td>
<td>(37.0)</td>
</tr>
</tbody>
</table>

Area of lesion considered to be fibrosis, %

<table>
<thead>
<tr>
<th></th>
<th>V</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-25</td>
<td>313</td>
<td>161</td>
</tr>
<tr>
<td></td>
<td>(51.4)</td>
<td>(37.3)</td>
</tr>
<tr>
<td>26-50</td>
<td>44</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(52.3)</td>
<td>(37.5)</td>
</tr>
<tr>
<td>&gt;50</td>
<td>39</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>(59.0)</td>
<td>(39.3)</td>
</tr>
</tbody>
</table>

Lesion included blood

<table>
<thead>
<tr>
<th></th>
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<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>133</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>(54.1)</td>
<td>(35.2)</td>
</tr>
<tr>
<td>No</td>
<td>266</td>
<td>139</td>
</tr>
<tr>
<td></td>
<td>(52.3)</td>
<td>(39.5)</td>
</tr>
</tbody>
</table>

NOTES.
V indicates verteporfin-treated group; P, placebo-treated group
* With last observation carried forward
† χ² Test for treatment effect within subgroups
‡ Test of interaction between subgroups
§ Definite hypertension was defined as systolic blood pressure of 160 mm Hg or higher or of 140-159 mm Hg with a history of hypertension or use of antihypertension medications, or diastolic blood pressure of 95 mm Hg or higher or of 90-94 mm Hg with a history of hypertension or use of antihypertension medications.
# Approximate Snellen equivalent.
Appendix 8 Further detail on methods and results for the review of economic and cost studies

Stage 1 - Initial categorisation of studies
Each study was categorised by one of the investigators on the basis of its title and abstract where available. The following initial criteria were used to determine the relevance of each study to the systematic review:

A. The study reports primary research (i.e. original data collected specifically for the study) on the costs or utilisation of care, and includes formal economic evaluation;

B. The study discusses the economic aspects of care, and contains useful primary or secondary (i.e. unoriginal data collected from already published or other sources) cost or utilisation data;

C. The study may have useful information but does not obviously fall into (A) or (B);

D. The study discusses economic aspects of policies for care, but neither (A) nor (B) above;

E. The study does not have any relevance to the economic evaluation of Photodynamic therapy for age related macular degeneration.

Studies in category (A), (B) and (C) were considered relevant to the systematic review. Those in (D) and (E) were not taken any further. Studies were coded as C when there was insufficient information in the title, or abstract to be certain of its relevance to the review.

Stage 2 - Further categorisation of studies
All studies categorised as A, B (or C) were further classified after reading the full paper into the following categories by type of study:

1. Economic evaluation (cost-minimisation analysis, cost effectiveness analysis, cost-utility analysis, cost-benefit analysis);
2. Other cost study;
3. Effectiveness study with some assessment of implications for cost or quantity of resources used;
4. Description of methods used in aspects of PDT;
5. Review of economic aspects of care;
6. Other, such as, survey of resources and facilities, survey of utilisation, estimate of economic burden of disease, discussion of health finance or policy;
7. Not relevant to the economic evaluation of PDT;
8. Foreign language: to be reviewed by relevant linguist.

All studies classified as A1, A2, B1, B2, C1, or C2 were included in the quality assessment section of the review.
Stage 3 – Quality criteria

The quality of the economic evaluations was assessed according to the criteria outlined in Drummond93. The quality of the cost studies was assessed using the following criteria which have been used in a previous published review by one of the same authors91.

- Methods for the estimation of quantities and unit costs are described (or cited);
- Sources of cost data are stated / apparent;
- Indirect costs (if included) are reported separately from direct costs;
- Both currency and price data are recorded;
- Details of currency or price adjustments for inflation or currency conversion are given (if appropriate);
- The discount rate is stated / apparent and justified (if relevant).

If the studies passed all the necessary criteria they were considered for data extraction in Stage IV.

Results of search & inclusion/exclusion

All studies classified as A1, A2, B1, B2, C1, or C2 would be included in the quality assessment section of the review.

Table 28. Economic study inclusion/exclusion results

<table>
<thead>
<tr>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Categorisation based on title and abstract</td>
<td>Categorisation based on full paper</td>
<td>Quality assessment</td>
<td>Data Extraction</td>
</tr>
<tr>
<td>Economic evaluation (n=2)82,123</td>
<td>Confirmed Economic evaluation (n=2)</td>
<td>Pass (n=2)</td>
<td>Yes</td>
</tr>
<tr>
<td>Cost Study (n=4)</td>
<td>Confirmed Cost Study (n=3)12450,125</td>
<td>Failed (n=3)</td>
<td>(sufficient for detailing as excluded study only)</td>
</tr>
<tr>
<td>May be useful (n=4)</td>
<td>Not relevant (n=4)</td>
<td></td>
<td>N/A</td>
</tr>
</tbody>
</table>
Appendix 9 Comments on excluded cost studies

Three cost studies were found from unpublished sources. None of these passed all the predetermined quality criteria for cost studies, the main criticism being that they failed to make explicit the source for the costs that were cited or failed to make explicit the year to which the costs referred. However, we assume that the year is the same as the year in which the report was written. For completeness, we have included the cost details below.

The National Horizon Scanning Centre report - Photodynamic therapy for age-related macular degeneration. January 2000.50
This report assumed an estimated prevalence ceiling of 7,700 patients in order to calculate the total drug cost for patients of £17-23 million in the first year. They also cited the likely equipment and associated costs to each centre providing treatment to be a laser (£20,000), good quality fluorescein angiography (£30,000) and other miscellaneous equipment (£5,000).

Drugs and Therapeutics Bulletin. Can vertporfin help in macular degeneration124
This report presents the cost of one vial of vertporfin (enough for one treatment) as £850. The authors point out that there are several additional costs to consider, including those of outpatient assessments of visual acuity, fluorescein angiography (administration of vertporfin dye, and laser application) although estimates for these are not provided. They cite their own consultants as suggesting that the total costs of a single treatment could be around £1500. As in the previous study they suggest that 3-4 treatments would be needed in the first year and 2-3 in the second.

Grampian Health Board Report - Photodynamic therapy in macular degeneration.125
In the Grampian region the approximate number of patients requiring treatment was estimated to be 50 per year. In addition to the costs presented in Table 29, this report estimated the cost in the Grampian region to be of the order of £120,000 assuming that the threshold for treatment was 100% classic wet AMD. A cost per QALY estimate was given but not a full economic evaluation and since the quality of that study cannot be assessed the result is not presented here.

Table 29. Cost results from excluded cost studies.

<table>
<thead>
<tr>
<th></th>
<th>National Horizon Scanning Centre</th>
<th>DTB</th>
<th>GHB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug cost</td>
<td>750</td>
<td>850</td>
<td>760</td>
</tr>
<tr>
<td>Year</td>
<td>Not stated</td>
<td>Not stated</td>
<td>Not stated</td>
</tr>
<tr>
<td>Vials required per year</td>
<td>3 to 4</td>
<td>3 to 4</td>
<td>3</td>
</tr>
<tr>
<td>Per patient cost</td>
<td>2,250-3000</td>
<td>4500-6000 in first year, 3000-4500 in second year</td>
<td>3</td>
</tr>
<tr>
<td>Laser cost</td>
<td>20,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angiography</td>
<td>30,000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Misc</td>
<td>5000</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local cost</td>
<td></td>
<td>120,000</td>
<td></td>
</tr>
<tr>
<td>Total cost</td>
<td>17-23 million first year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost per QALY</td>
<td></td>
<td>Estimate given but study not a full economic evaluation</td>
<td></td>
</tr>
<tr>
<td>Comment</td>
<td></td>
<td>Based on 50 patients per year</td>
<td></td>
</tr>
</tbody>
</table>
Appendix 10 Notes on sources of uncertainty in calculating costs associated with blindness

**Blind registration:** The high cost is the examination for BD8 in own home plus an hour’s face to face contact with a social worker. The low cost is just the fee for re-examination in consulting room for BD8 certification.

**Low vision aids:** The low cost is from an audit of an ‘in-house’ NHS hospital LVA service. This was not taken as the standard cost as a recent survey has shown that only 32% of LVA services are of this type. For the percentages, the Margrain estimate is the more recent but the RNIB report may be more accurate.

**Low vision rehabilitation:** The high and low costs are the range for 50% of NHS trusts for occupational therapy services.

**Housing Benefit and Council Tax Benefit:** The average housing benefit for disabled people aged under 60 is less than the average housing benefit for all aged under 60. Unfortunately, the data for the over 60’s is not subdivided in this way. However the average weekly rate varies around the country from £35.80 in Scotland to £58.80 in Greater London. This geographical variation is also seen in Council Tax Benefit. There is no information on the number of people who go blind in later life who receive this benefit. The estimate given will include people who were registered blind before and during their working life which may have caused a reduced earning capacity. The percentages also vary depending on whether the household is owned or rented.

**Social Security:** The higher cost estimate is attendance allowance at the higher rate. The lower uptake from the first RNIB survey and higher uptake rate in the second RNIB survey suggests that the drive to increase uptake of attendance allowance has been successful to some extent.

**Tax allowance:** The lower cost estimate assumes payment of tax at the starting rate of 10%. In the first RNIB survey, overall only 5% claimed that they received this allowance, but 18% not in work stated that they claimed it. It is unclear from the report whether this group was of working age or of all ages. No figure was given for people over retirement age or registered blind.

**Depression:** There is very little evidence about the cost of depression in the elderly. The costs quoted are the only UK costs found that were not associated with or comparing the costs of different drug treatments or conditions. Estimates of depression rates vary widely. This may be to do with the method of measurement of depression used in the three studies quoted – GHQ, Geriatric Depression Scale and the Wakefield Self-rating Depression Scale.

**Community care:** The higher cost is for a home care worker for one hour per day whereas lower cost is for two hours per week. The lower estimate of percentage home help has been used in the main estimate as it is from a later source and because there is a trend for home help to be increasingly provided by private agencies, paid for by the individual from their attendance allowance.
Residential care: The high cost is the annual cost for local authority residential care for elderly people. The low cost is for local authority sheltered housing. The estimates of registered blind in the three case studies used are 5%\textsuperscript{95}, 11.8%\textsuperscript{32} and 22%\textsuperscript{111}. From these, using census data for the numbers of elderly in nursing and residential homes and the prevalence of AMD in the elderly\textsuperscript{12}, the approximate proportion of people with low vision caused by AMD who enter residential care can be calculated. This was reduced by 30%, as approximately 30% of residents are self-payers.\textsuperscript{102}
Appendix 11 Notes on HTAG model

Explanation of the cumulative 2 year utility scores
The utility scores in the HTAG model look as if they are for one year only. However, if these scores were multiplied by two, this would assume that the difference in utility started at the beginning of the trial and stayed at the same level throughout the two years. However, a more realistic estimate is that there is no difference in utilities at the start of the trial and that it gradually widens over the two year period. This would give a diagram as shown below:

![Utility Graph](#)

Using the equation for the area of a triangle of \(\frac{1}{2}\) base X height, it can be seen that the area between the two sloping lines equates to the difference in utility score at two years.

Method for varying effectiveness estimates for sensitivity analysis for economic model
The data used in the Base Case of the economic model are the proportions of patients losing a certain number of letters, as follows:

<table>
<thead>
<tr>
<th></th>
<th>Verteporfin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients</td>
<td>402</td>
<td>207</td>
</tr>
<tr>
<td>&gt;=6 line increase</td>
<td>0.7%</td>
<td>0.0%</td>
</tr>
<tr>
<td>&gt;=3 line to &lt;6 line increase</td>
<td>8.2%</td>
<td>3.9%</td>
</tr>
<tr>
<td>&gt;=1 line to &lt;3 line increase</td>
<td>6.5%</td>
<td>6.3%</td>
</tr>
<tr>
<td>No change</td>
<td>14.7%</td>
<td>12.6%</td>
</tr>
<tr>
<td>&gt;=1 line to &lt;3 line decrease</td>
<td>22.9%</td>
<td>15.0%</td>
</tr>
<tr>
<td>&gt;=3 line to &lt;6 line decrease</td>
<td>28.9%</td>
<td>32.4%</td>
</tr>
<tr>
<td>&gt;=6 line decrease</td>
<td>18.2%</td>
<td>30.0%</td>
</tr>
<tr>
<td>Mean VA loss</td>
<td>-2.7</td>
<td>-3.9</td>
</tr>
</tbody>
</table>

The difference in mean loss of VA over 2 years was 1.2 letters. The sensitivity analysis on effectiveness explored the effect of changing this difference. The worst case estimate was to have a difference of 0.6 letters (ie half the effectiveness) and the best case estimate was a difference of 1.8 letters (ie half as much again). In order to do this we kept the mean number of letters for the placebo group the same at -3.9 letters and changed the mean number of letters in the verteporfin group to -3.3 and -2.1 letters respectively.

However, the HTAG economic model is based on the proportions of patients losing a certain number of letters, based on the seven categories in the table above, rather than the mean.
number of letters lost in each group. The reported trial data is approximately normally distributed around the means of 2.7 and 3.9. We estimated the standard deviation from the TAP trial data by dividing the range of the data by 5 (as 99% of values of normally distributed data will fall within +/- 2.5 standard deviations from the mean). This gave an approximate value for the standard deviation of 3.5. Using these approximations, we estimated the proportions falling into the 7 categories for different mean VA letters lost. Data for the placebo group in these scenarios were also estimated in this way to avoid introducing bias.

In order to check that this approach was reasonable, we used the same method to derive the proportions falling into the 7 categories based on the means observed in each group (ie –2.7 for verteporfin and –3.9 for placebo). We then re-ran the Base Case cost-effectiveness analysis using these estimates (fitted data) in order to check that they were consistent with the estimates derived using the trial data directly. Both Base Cases are reported in the cost-effectiveness results.

The proportions in each of the 7 categories for our fitted data and the worst and best case scenarios are shown below (the actual trial data is shown in the table above).

**Table 31. Fitted data for Base Case**

<table>
<thead>
<tr>
<th></th>
<th>Verteporfin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=6 line increase</td>
<td>4.5%</td>
<td>2.2%</td>
</tr>
<tr>
<td>&gt;=3 line to &lt;6 line increase</td>
<td>9.4%</td>
<td>5.6%</td>
</tr>
<tr>
<td>&gt;=1 line to &lt;3 line increase</td>
<td>7.5%</td>
<td>5.2%</td>
</tr>
<tr>
<td>No change</td>
<td>9.3%</td>
<td>7.1%</td>
</tr>
<tr>
<td>&gt;=1 line to &lt;3 line decrease</td>
<td>22.1%</td>
<td>19.5%</td>
</tr>
<tr>
<td>&gt;=3 line to &lt;6 line decrease</td>
<td>29.3%</td>
<td>32.7%</td>
</tr>
<tr>
<td>&gt;=6 line decrease</td>
<td>17.3%</td>
<td>27.4%</td>
</tr>
<tr>
<td>mean</td>
<td>-2.7</td>
<td>-3.9</td>
</tr>
</tbody>
</table>

**Table 32. Best and Worst Case scenario data**

<table>
<thead>
<tr>
<th></th>
<th>Verteporfin (worst)</th>
<th>Verteporfin (best)</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;=6 line increase</td>
<td>3.2%</td>
<td>6.2%</td>
<td>2.2%</td>
</tr>
<tr>
<td>&gt;=3 line to &lt;6 line increase</td>
<td>7.4%</td>
<td>11.5%</td>
<td>5.6%</td>
</tr>
<tr>
<td>&gt;=1 line to &lt;3 line increase</td>
<td>6.3%</td>
<td>8.6%</td>
<td>5.2%</td>
</tr>
<tr>
<td>No change</td>
<td>8.3%</td>
<td>10.2%</td>
<td>7.1%</td>
</tr>
<tr>
<td>&gt;=1 line to &lt;3 line decrease</td>
<td>21.0%</td>
<td>22.5%</td>
<td>19.5%</td>
</tr>
<tr>
<td>&gt;=3 line to &lt;6 line decrease</td>
<td>31.4%</td>
<td>26.6%</td>
<td>32.7%</td>
</tr>
<tr>
<td>&gt;=6 line decrease</td>
<td>22.0%</td>
<td>13.3%</td>
<td>27.4%</td>
</tr>
<tr>
<td>Mean</td>
<td>-3.3</td>
<td>-2.1</td>
<td>-3.9</td>
</tr>
</tbody>
</table>
10. REFERENCES


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