The clinical effectiveness and cost utility of photodynamic therapy for age-related macular degeneration

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Summary

- Age related macular degeneration (AMD) results in a painless loss of central, sharply defined vision used for tasks such as reading. The vast majority of AMD occurs in people over 60 years old and after this age the prevalence rises quickly. The AMD disease category includes a broad spectrum of clinical and pathological findings and is usually classified into dry or wet AMD. In wet AMD new blood vessels called neovascular membranes can grow from the choroid into the retina, leak fluid, bleed and create scars in the macular region, thus disrupting visual acuity.

- Historically, there has been no successful treatment for this condition. Photodynamic therapy has recently emerged for a variety of conditions including wet AMD. It uses photosensitive drugs injected into the blood stream and a specially developed low-powered laser that is targeted towards the neovascular membranes.

- This systematic review examines the clinical effectiveness and cost utility of photodynamic therapy for the neovascular form of wet AMD.

- The Cochrane Library, Medline, Embase, BIDS Pascal, internet sites, national and international HTA sites, NHS EED, DARE and conference abstracts of major ophthalmology conferences were searched for any evidence of clinical or cost effectiveness and to inform the economic evaluation. The findings were one fully reported RCT with twelve months' follow up and two abstracts of RCTs with preliminary data only. Two cost studies only were found.

- The RCT was well conducted with near complete follow up. Photodynamic therapy with verteporfin was given to 402 patients whereas 207 received placebo of 5% dextrose solution. The primary outcome measure results showed less deterioration in visual acuity in the photodynamic therapy group (61.2% vs 46.4% patients lost fewer than 15 letters). The difference in deterioration of visual acuity was both clinically and statistically significant. There was no significant difference in deaths.

- The two cost studies estimated the annual cost per person of photodynamic therapy with verteporfin to be £2,250-£3,000 and £2,400.

- A cost utility analysis was carried out using effectiveness parameters from the RCT. Published studies linking visual acuity to utility values were used to estimate utilities of RCT patients. The results showed an increase in utility for photodynamic therapy over placebo of 0.029 (estimate range 0.022-0.037). The publicly funded costs associated with AMD treatment were in two main categories – photodynamic therapy itself and the costs of rapidly deteriorating vision. The first year cost of photodynamic therapy per person was estimated at £4015.40 (estimate range £3604 to £4491). The incremental cost per QALY was estimated at £137,138. The estimated cost of rapidly deteriorating vision was £3,465 in the first year (estimate range £1,255 - £10,863). When taking the cost of blindness into account the incremental cost per QALY was £120,095 (estimate range £164,579 to £79,247) The total NHS cost impact of photodynamic therapy in the West Midlands lies somewhere between £0.8 million and £5 million.

- More accurate and longer term effectiveness and cost information is required in order to reduce the uncertainty in the above estimates.

Introduction

Photodynamic therapy has recently emerged as a new interventional procedure for a variety of conditions such as cancers, HIV/AIDS, transplant rejection, bone marrow infection, psoriasis and arthritis. It uses photosensitive drugs injected into the blood stream and a specially developed low-powered laser which is targeted towards the lesion. In the ‘wet’ form of age related macular degeneration this treatment is intended to stop further leaking from new neovascular membranes in the central part of the macula at the back of the eye (the subfoveal area) and so halt further loss of visual acuity. Historically, there has not been any successful treatment for this condition although many have been tried. This systematic review examines the clinical effectiveness, costs and cost utility of photodynamic therapy for ‘wet’ age related macular degeneration.

Background

Anatomy of the eye

If the retina at the back of the eye is examined, several structures can be seen. The optic disc is approximately 1.9mm high and 1.8mm wide and this is where the optic nerve and the central retinal artery and vein enter and leave the eye. The retinal arteries and veins spread across all parts of the retina except for the macula which is slightly darker than the rest of the retina, partly due to the accumulation of yellow luteal pigment. The macula is the most important and sensitive area of the retina and is used for central vision. It is approximately 5.5 mm in diameter (i.e. approximately three times the size of the optic disc) and lies within the posterior pole of the eye, approximately 3.5mm lateral and 1mm slightly inferior to the optic disc. At the centre of the macula, the fovea is an area about the same size as the optic disc. It includes the area where light is focused to give sharpest central vision. Clinically, the macula is divided into three areas so that macular lesion positions can be precisely described. Subfoveal is under the centre of the fovea (less than 1µm from the foveal centre)[1], juxtafoveal is the remainder of the foveal region (1-200µm) and extrafoveal is the rest of the macula excluding the fovea.

The retina is a complex structure and contains millions of light sensitive cells (photoreceptors) – 6 million cones responsible for colour vision and 120 million rods for back/white sensation (night vision). The retina is transparent because of its thinness, relative absence of blood vessels (especially in the foveal region) and the regular columnar arrangement of its cells. The retinal distribution of rods and cones varies. The macula has the greatest concentration of cones and it is this that is responsible for the sharply defined colour vision. There are few rods in the fovea but at the edge of the macula there is a high concentration of rods that give high definition night vision. The remainder of the retina has many more rods than cones and the cones are larger than in the fovea. This part of the retina is responsible for peripheral vision and night vision.

From the centre of the eye outwards, underneath the rods and cones are several layers that can be described, firstly the retinal pigment epithelium, then Bruch's membrane, then the choroid and lastly, the sclera. The retinal pigment epithelium (RPE) is a layer of epithelial cells, one of whose many functions is to transport nutrients and waste products between the rods and cones and the choroid. Another function is to recycle metabolites including Vitamin A. The RPE can be considered the outermost layer of the retina. Outside the retina is Bruch's membrane - a semi-permeable barrier under the RPE which may be a support mechanism for the RPE and choroid. The choroid is a darkly pigmented layer which contains numerous blood vessels of various diameters. The narrowest of these flow next to Bruch's membrane in a layer called the choriocapillaris. Outside the choroid is a tough, white membranous coat called the sclera which is the outermost layer of the eyeball.

The back of the eye has two blood supplies – the retinal arteries and veins and the choroidal arteries and veins. These flow either side of all parts of the retina except the centre of the fovea, where the retinal arterioles do not reach. Approximately ten percent of nutrient support for the retina comes from retinal arterioles whereas up to 90% is provided by the choroidal blood supply [2]. The cones in the centre of the fovea are only supplied by the blood vessels in the choroid on the other side of the RPE.

Eye examination

The retina can be examined directly using an ophthalmoscope. If records need to be kept, special cameras are used to document details of the back of the eye (the fundus). These records are usually taken on colour photographic film or using a digital camera and then stored on a computer. Fundus images can be greatly enhanced by the use of angiography. This is where a dye (sodium fluorescein or indocyanine green) is injected into a peripheral vein and travels around the blood steam before being excreted by the kidneys. When the dye passes through the blood circulation in the eye, blue light causes it to fluoresce and emit a green light. Using special filters, this can be used to highlight vascular and anatomical details of the fundus. Angiographic findings are used for diagnosis and classification of retinal disease.

Measurement of vision

Visual function consists of a number of aspects and ways of assessment include visual acuity and visual fields.

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. [3]

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 (log base 10 of 1=0). 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.[3]

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.[3] 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 (see appendix 1). For a scheme conversion table, see appendix 2. 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 is equivalent to a score of 34 letters (four out of five letters correct can be accepted as achieving the level of acuity).

Another way of measuring visual performance is by measuring contrast sensitivity[3-5]. 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.[5] 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.[4]

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.

Age related maculopathy and age related macular degeneration

The early stage of this 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.[6]

The International Age Related Maculopathy (ARM) epidemiological study group has produced a classification of age related maculopathy and age related macular degeneration.[7,8] 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[9,10] 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[7,8] 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.[11]

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 175µm in diameter.[7,8] Dry AMD can progress to wet AMD but the risk factors are largely unknown.[12,13]

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

Wet AMD is associated with a variety of pathological changes in the macula. [7,8]

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.[14] 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 through Bruch's membrane. They 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.[15]

People with wet AMD can have pigment epithelial detachments only and no neovascular membranes.[14] If the term neovascular AMD is used for wet AMD then this can cause some confusion.

Pigment epithelial detachments can be demonstrated on angiography from gradual and uniform staining of the space between the RPE and Bruch's membrane.

Neovascular membranes can be classified as classic or occult according to their appearance on fluorescein angiography.[16] Classic lesions are clearly delineated and leak fluorescein uniformly whereas occult lesions are hard to detect and fluorescein leakage is patchy.[17] Occult lesions can be distinguished from pigment epithelial

detachments angiographically if there are irregular hyperfluorescence areas and spots of intense hyperfluorescence.[16] Comparison of the two types of angiographic media are also used for diagnosis.[18]

Although wet AMD is said to be less common than dry AMD, people with wet AMD have much more visual disturbance or legal blindness.[1]

Description of underlying disease

The vast majority of age related maculopathy 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.[19,20] This section will focus on AMD (late age related maculopathy) causing visual disturbance or legal blindness.

The ICD-10 classification of degeneration of the macula and posterior pole of the eye (H35.3) includes 'angioid streaks, cysts, drusen (degenerative), holes, puckering, Kuhnt-Julius degeneration, senile macular degeneration and toxic maculopathy (drug induced)'.[21] Therefore routine UK health data cannot supply incidence and prevalence of AMD. Published surveys of representative populations have been used instead.

Table 1 shows the incidence of all AMD, dry AMD and wet AMD. 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.[22] 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+. Because the age specific incidence rates rise so quickly, the results of any studies of incidence and prevalence rates will vary depending on the age profile of the population used. Prevalence rates are shown in Table 2. AMD may be more common in women than in men.[23] Age and sex specific prevalence rates are shown in Table 3.[24]

Table 1. Incidence of AMD in either eye

Study	Blue Mountain (AUS)[22]	Beaver Dam (USA)[11]		Melton Mowbray (GB)[25]	
Number in survey	N=2323	N=3497		N=88	
Definition	AMD	Wet	Dry	Wet	Dry
Incidence	1.3% /5yrs	0.6% /5yrs	0.3% /5yrs	1.3% /7yrs	1.3% /7yrs
mean age (range)	(49-90+)	(43-84)		80 (77-90)	

Table 2. Prevalence of AMD

Study	N	Mean age (yrs)(range)	Definition	%
Melbourne (AUS) [23]	4345	60.2	Wet AMD	0.39
			Dry AMD	0.27
			All AMD	0.68
Melton Mowbray (GB)[26]	82	80 (77-90)	Wet AMD	1.9
			Dry AMD	1.9
	82	87 (84-97)	Wet AMD	3.8
			Dry AMD	3.2
Rotterdam (NL)[24]	6251	68.9 (55-98)	Wet AMD	1.1
			Dry AMD	0.6
London (GB)[27]	1547	(65-100)	AMD (where visual acuity<6/12)	8.0 (95%CI 5.8-10.8)

Table 3. Prevalence wet AMD and dry AMD by age[24]

Gender	Age	Sample size	% wet	% dry
Female	55-64	1391	0.1	0
	65-74	1280	0.5	0.2
	75-84	788	2.4	1.4
	85+	253	7.5	4.0
Male	55-64	1033	0.1	0.2
	65-74	977	0.3	0.6
	75-84	456	2.4	1.1
	85+	73	6.8	2.7

Most studies show that the prevalence of wet AMD lower than dry AMD, for example, the NHANES III[19] and Baltimore studies,[20] but a few studies have shown that the prevalence of wet AMD is higher (Rotterdam[24] and Blue Mountains.[28])

If a person has wet AMD in one eye, the risk factors that increase likelihood of wet AMD in the other eye over the following five years include: older age (>60), family history, cigarette smoking, low dietary intake or plasma concentrations of antioxidant vitamins and zinc and white racial background. Possible risk factors include female sex, a light coloured iris, cardiovascular disease and increased exposure to sunlight.[1]

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.[29] The percentages of people registered as blind because of AMD varies between studies (see Table 4). However, not all blind people become registered and the rate of UK registrations varies by cause of blindness so these rates must be regarded as estimates.[30]

Table 4. Percentage of registered blind with AMD

Study	Survey population	Number registered blind	% with AMD	Time span	Age range
Quillen et al[31]	US military veterans	191	37.2%	5 yrs	35-95 (median 74)
Munier et al[32]	Population of Eire	5002	16.2%	6mths	16+
Evans[33]	Population of England and Wales	11,744 (new registrations)	54.5%	1 yr	65+

West Midlands estimates

Estimates of one-year incidence figures for all AMD for the West Midlands are shown in Table 5. These use age and sex specific incidence rates from the Beaver Dam Eye Study[11], age specific incidence rates from the Blue Mountains Eye Study[28] and West Midlands population estimates for 1998[34]). The estimates for wet AMD in Table 5 presume that half the incidence of all AMD will be wet AMD (see Table 1). These estimates suggest that in any one year there may be approximately 2,800 new cases of wet AMD at age 55+.

Table 5. Estimates of numbers of people with AMD in the West Midlands

	Population	1 yr incidence	
		Any AMD	Wet
Beaver Dam[11]	1369332 (55+)	5480	2740
Blue Mountains[28]	1088214 (60+)	5630	2815

The wet AMD category in the Beaver Dam study[11] included pigment epithelial detachments but did not mention the percentage of people with these but no neovascular membranes (There is no mention of this in the Blue Mountains Eye Study report[28]). Other studies have indicated the proportion of AMD patients with pigment epithelial detachments but no neovascular membranes varies from 3.7%[35] to 10%.[36] Also, approximately half of those registered blind have two or more causes of blindness, such as glaucoma, cataract and myopia, in addition to AMD.[33] Taking these two factors into account, the approximate number of uncomplicated new cases of AMD with neovascular membranes would be approximately halved to 1,300.

There are two forms of neovascular membranes – classic and occult (see background). This distinction is important when considering the outcomes of trials for AMD. Although the evidence available is limited, the very approximate ratio of classic to occult is 1:5 (see Table 6). Therefore, there will be roughly 220 new cases of classic neovascular membranes per year in the West Midlands.

Table 6. Estimate of ratio of classic to occult neovascular membranes

Study	Number of classic	Number of occult	Ratio
CNPTRG[37]	1	17	1:17
Epstein[38]	8	38	1:4.75
Sunness[13]	3	9	1:3

Current service provision

Dry AMD

There is no active treatment recommended for dry AMD. There are suggestions that vitamin and mineral supplements may help but this has not been proven.[39] Dry AMD usually progresses only slowly, with no abrupt loss of vision and usually affects each eye differently. Frequently there will be foveal sparing in one eye. Management includes social support and provision of low vision aids. Abrupt visual disturbance or vision loss may indicate wet AMD occurrence.

Wet AMD

Numerous treatments have been tried for wet AMD, many with little success.[1] For most patients, as with dry AMD, management consists of social support and provision of low vision aids.[6] Laser photocoagulation has been used to flatten pigment epithelial detachments but no visual benefit has ensued.[15]

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.[1,40]

If subfoveal lesions are treated with laser photocoagulation then there is an immediate loss of visual acuity from a central dark scotoma but long term follow up has shown some benefit in patients with small new vessel complexes and already poor visual acuity.[40] 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.[1]
- Half of all 'classic' lesions are subfoveal. The immediate visual acuity loss means that this treatment is not well accepted so is now rarely used.
- Recurrence rates in 'classic' lesions of up to 59% within two years have been reported.[41]
- There is a small risk (0.5% - 2%) of a RPE tear occurring which will lead to profound loss of vision.[42,43]

In the West Midlands, laser photocoagulation treatment is available in almost all hospitals which have an eye unit, for example, Hereford, Worcester, Coventry, Shrewsbury, Wolverhampton and Birmingham. An argon laser is usually used.

Other experimental treatments include ionising radiation, anti-oxidant vitamin and mineral supplements, angiogenic agents including interferon, vascular endothelial growth factor, integrins and thalidomide and surgical interventions including retinal excision and implantation.[40,44] No RCTs on these interventions have shown significant

benefit to the patient. Preventive treatments include vitamin and mineral supplements and hormone replacement therapy in women.[44] It is currently unclear as to whether these treatments have any effect.[1]

Description of new intervention

Photodynamic therapy is the new intervention to be evaluated. It uses photosensitive drugs and a specially developed low-powered 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 all cells of the body but is then cleared from healthy cells but preferentially remains in proliferative cells (such as new blood vessels).[45] A low-powered laser calibrated to a specific wavelength of non-thermal red light then activates the photosensitive drug within the cell to form peroxides. The result is cell death by apoptosis, mitochondrial or cell membrane destruction, vascular thrombosis or immune system destruction.[46] The laser is not powerful enough to cause any damage on its own. Photodynamic therapy results in proliferative cells being selectively targeted and destroyed and other cells 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.[46] For this report, the two relevant photosensitive substances currently undergoing randomised controlled trials for AMD are verteporfin (trade name Visudyne)[47] and tin ethyl etiopurpurin (SnET2)(trade name Purlytin)[48]. Another photosensitive substance being investigated in preliminary trials on humans is motexafin lutetium which is also called lutetium texaphyrin (trade name Lu-Tex)[49].

Photodynamic therapy in AMD is intended to stop further leaking from new neovascular membranes and so halt further loss of vision but it is not intended to restore vision already lost. The laser/photosensitive drug combination means that, as long as the dose is correct, no damage occurs to the retinal cells next to the neovascular membranes.[46] This means that subfoveal lesions can be treated. Unlike laser photocoagulation, there is no sudden vision loss (there may be some slight visual disturbance for a few days after treatment). Retreatment is needed, sometimes several times before no further growth of new vessels is seen.[50] 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 ‘classic’ wet AMD and therefore only suitable for about 20% patients with wet AMD.[47]
- 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).[51] 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.[47]
- The long-term effects in humans of photodynamic therapy for wet AMD are unknown.

As mentioned above, long term side effects of verteporfin are not known because of insufficient follow up as yet. It is anticipated that up to 5 year follow up of patients treated with verteporfin will become available. (Mr Yang - personal communication). Other

photodynamic drugs used in different medical specialities may have similar long term side effects to verteporfin. For example, follow up of photodynamic therapy using porfimer sodium for other illnesses, such as cancer, has indicated that the main long term side effects are skin colour changes. With repeated injections, the skin may become yellowish-greenish-brown or dark reddish-brown. With exposure to the sun, patients get a ‘tan’ which lasts for months or indefinitely. Some patients develop periorbital hyperpigmentation. Normal skin areas in the treated field became hyperpigmented or ‘tannish-brown’ or grey-brown from the treatment. No eye symptoms were noted.[46]

Photodynamic therapy for AMD is not currently freely available in the NHS in the West Midlands. It is available in only a few health authorities in England and Wales. Other health authorities are funding this treatment on a named patient basis provided the patients receive treatment in Liverpool. (Mr Yang - personal communication).

Aim of this review

The aim of this review is to establish whether photodynamic therapy is more clinically effective and cost effective than either laser photocoagulation or no treatment in the management of 'wet' AMD.

Methods

Clinical effectiveness review

Search strategy

A scoping search was undertaken, focusing on existing reviews and other key papers, as well as the identification of randomised controlled trials (RCTs) likely to be included. The yield from this was used to develop the protocol for the review, including inclusion and exclusion criteria.

A search was made for RCTs comparing photodynamic therapy to no treatment or to laser photocoagulation for the treatment of wet AMD, using the NHS Centre for Reviews and Dissemination Report 4 search strategy for RCTs. It was widened to include other study types in case insufficient RCT evidence was available. More weight was given to RCT evidence. The search strategy covered the time period 1993 to August 2000, as it was after 1993 that work on photodynamic therapy began. Both index terms and text words were used in the search. All relevant study titles in the databases were scanned and abstracts read if the titles seemed potentially relevant. Key components of the formal search were:

- Searching of electronic databases; The Cochrane Library, Medline, Embase, BIDS Pascal, and internet sites.
- National and international HTA sites were searched for reviews.
- Search of conference abstracts of major ophthalmology conferences in hard copy for the last two years and on the Internet.
- Citations of reviews and RCTs found were checked.

Contacts were made with lead researchers on the published RCT found in order to try to obtain further follow up results and with a local clinical expert to clarify technical details.

For database search strategies on clinical effectiveness, see appendix 3

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 preferred, otherwise, any study type.
Population: Adults with wet AMD.
Intervention: Photodynamic therapy using any photosensitive drug.
Comparator: Either no treatment or laser photocoagulation, depending on the position of the lesion. (see Table 7)
Outcomes: Vision changes or lack of at follow up. Side effects of treatment.
Reporting: Only RCTs and other studies where recruitment had closed and which reported follow up results for all or nearly all recruited patients were included.

Table 7. Choice of treatment for age related macular degeneration

	Subfoveal	Juxtafoveal and Extrafoveal
Classic	Photodynamic therapy or no treatment	Laser photocoagulation or ?photodynamic therapy
Occult	?photodynamic therapy or no treatment	Laser photocoagulation or ?photodynamic therapy

The exclusion criteria were:
1. RCTs and other studies that had not finished recruiting.
2. RCTs that had published only interim results, baseline characteristics or follow up results for only some of the trial participants.
3. Case series, phase 2 trials.
4. 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.

Data extraction and quality assessment strategies

Two reviewers independently assessed the suitability of studies for inclusion and exclusion. One researcher extracted the effectiveness and quality assessment data from all included studies and this was checked by a second researcher. Any discrepancies were resolved by discussion.

Qualitative analysis of results was undertaken. No synthesis of results was appropriate because only one randomised controlled trial was found.

Cost effectiveness review

A systematic review of the literature on costs and health economic impact of photodynamic therapy for AMD was carried out. The clinical effectiveness search strategy was 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 search was then 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.

The economic search strategy included;
- Specific searches on Medline, Embase and BIDS Pascal.
- Searching specialised health economics sources such as NHS EED and DARE.
- Searching for specific information on the Internet to inform the costs of blindness.

Relevant information found during the clinical effectiveness searches was also used.

For cost and cost effectiveness search strategies, see appendix 4.

Inclusion and exclusion criteria, data extraction and quality assessment

One reviewer, using explicit predetermined criteria, made the inclusion and exclusion decisions for the economic evaluation review.

Studies were only included in the cost effectiveness review if they met the following criteria:

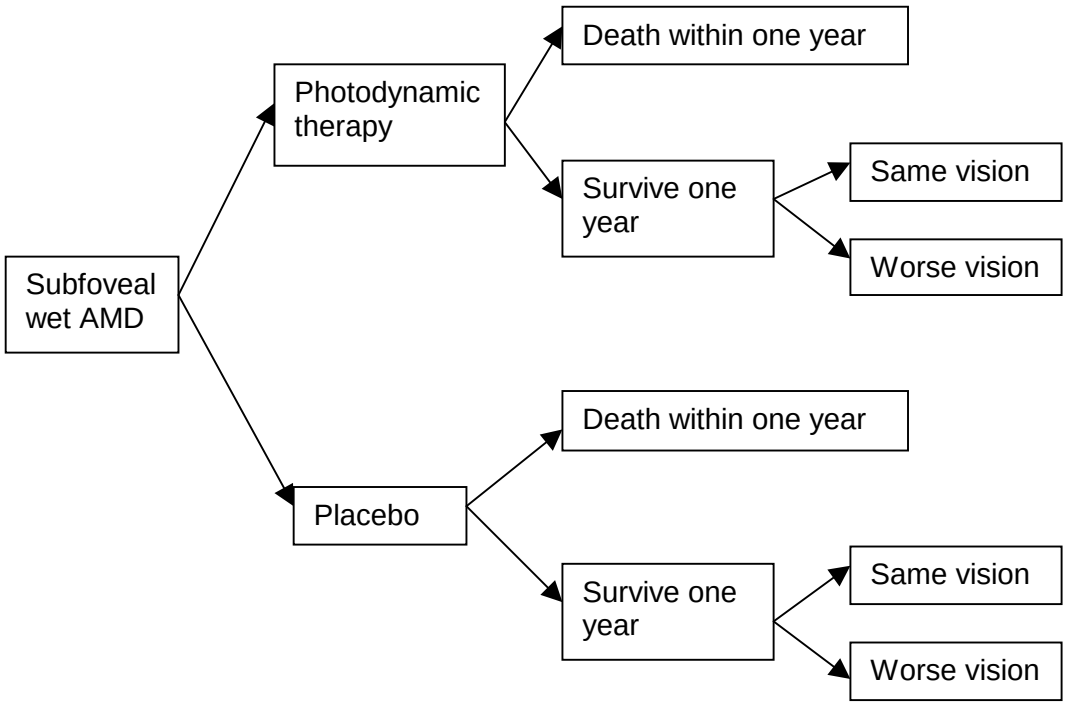
Study design: Any study type.
Population: Adults with any AMD.
Intervention: Photodynamic therapy using any photosensitive drug.
Outcomes: Costs, cost consequences, cost utility, cost effectiveness or any generic quality of life.

One reviewer assessed the suitability of studies for inclusion and this was checked by a second researcher. As no relevant studies were found no quality assessment was necessary.

Economic evaluation

A cost utility analysis was undertaken with the support of a health economist and according to guidance in the West Midlands DES handbook.[52] A simple decision tree was developed (see Figure 1 below), using information from the randomised controlled trial on photodynamic therapy for AMD found during the clinical effectiveness searches[47]. This trial also provided the clinical effectiveness parameters. Published studies linking visual acuity to utility value in the better seeing eye of patients with AMD were used to convert the RCT clinical effectiveness to generic quality of life estimates. The costs of photodynamic therapy were estimated from the current market price of Visudyne and published and local estimates of associated costs. The costs of blindness to the NHS and to other local and central government funded agencies were estimated from a variety of published and unpublished sources. The costs and utility values were entered on the decision tree in order to obtain an incremental cost per QALY value. Extensive sensitivity analysis was carried out.

Figure 1. Decision tree



Results

One randomised controlled trial was found which has been fully reported and includes a one year follow up (TAP Study). [47] Two year follow up has been carried out but is not fully published yet.[53,54]

Abstracts were found for two other RCTs using tin ethyl etiopurpurin [48] and verteporfin[55] where follow up was not yet completed.[56,57]

There were also several phase1/2 or phase 2 trials found using verteporfin[45,58], tin ethyl etiopurpurin[59] and motexafin lutetium.[49]

Full results of clinical effectiveness searches are reported in appendix 3.

Randomised controlled trial

This 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 and for the purposes of this systematic review it will be treated as one trial.

The photosensitive substance used in the TAP trial was verteporfin (6mg per m^2 body surface area) which is a green colour[17] and the placebo was 30ml of uncoloured 5% dextrose in water. The laser used was a diode laser at 689 nanometres wavelength, delivering 50 Joules per cm^2 at an intensity of 600 milliWatts per cm^2 over 83 seconds.[47] The same laser dose schedule was used for all patients (i.e. intervention and placebo).

In the trial 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 the trial. Follow up was at 3 months after each treatment episode for the first year, i.e. at 3, 6, 9, 12 months. A 2 year follow up also appears to have been carried out. Re-treatment with the same treatment only at each follow up visit was permitted.

The patient inclusion criteria were

- Best corrected visual acuity (using a modified LogMAR chart) of 73 to 34 correctly identified letters, corresponding approximately to a visual acuity of 20/40 to 20/200 at a test distance of 2 metres.
- Evidence of neovascular membranes caused by AMD (as demonstrated by fluorescein angiography) where the neovascular membranes extended under the centre of the foveal avascular zone (i.e. subfoveal) of a size no bigger than 5.4mm in the greatest linear dimension.
- The neovascular membranes had to have some element of classic but could include some occult. 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.
- Aged 50 years or more.

The exclusion criteria were

- Tear (rip) of pigment epithelium.
- Any significant eye disease that affected or could affect vision in the study eye which would confound the primary outcome measure.
- Inability to obtain fluorescein angiograms, including because of 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 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.

The method of randomisation was by sealed envelope organised by a central department of the company sponsoring the trial (QLT PhotoTherapeutics Inc.). Randomisation was stratified by participating centre (22 centres) and by baseline visual acuity (categories of 20/40 to 20/80 and 20/100 to 20/200) using separate groups of colour coded envelopes. Randomisation took place after eligibility was confirmed and patient consent was obtained. The randomisation procedure appeared to be successful except that 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. 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. The fundus appearance apparently does not change during infusion of verteporfin so the ophthalmologist administering the laser could not tell group assignment. The intervention and placebo groups appear to have been treated similarly during follow up.

402 patients were assigned to verteporfin and 207 to placebo. The average age for the two groups was approximately 75 years. The baseline characteristics of the two groups were similar except that there were significantly more women and more lesions with blood in the placebo group and more past and current smokers in the intervention group.

Follow up at 12 months was completed for 94% of patients (94.3% in the intervention group and 93.7% in the placebo group).

During the course of the 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.

Patients treated with verteporfin received an average of 3.4 treatments per patient in one year compared to 3.7 treatments per patient with placebo (no significance test given).

This appears to have been a well conducted trial. Random assignment seems to have been carried out effectively and the control and treatment groups comparable at entry. Groups were treated similarly apart from the intervention and outcomes were assessed blind to treatment allocation. Relatively complete follow up achieved. (We have given it a Jadad score of 4). However, there is no mention as to the number of patients eligible to take part in the trial compared to those randomised or of any withdrawals before or after randomisation. Visual acuity data from people who dropped out seem to have been included in the results by using the method of last observation carried forward.

Clinical results

This report concentrates on clinical outcomes rather than fundus appearance, as the former are the most relevant to patient quality of life.

The primary outcome measure was the proportion of eyes that lost fewer than 15 letters (or about 3 lines) on the modified LogMAR chart at one year compared to the baseline examination.

In the verteporfin group 61.2% of eyes lost fewer than 15 letters compared to 46.4% with placebo ($p<0.001$, 95% confidence intervals 56.7% to 66.3% and 39.6% to 53.2%). The number needed to treat to prevent 1 extra person losing 3 or more lines at 12 months, compared to placebo, was 6.7 (95% confidence intervals 4.3 to 14.3)[17]

Secondary outcome measures were

1. The proportion of eyes with fewer than 30 letters lost (about 6 lines) compared with baseline examination.
2. Mean changes in visual acuity
3. Mean changes in contrast threshold
4. Angiographic outcomes of progression of neovascular membranes and size of lesion.

1. In the verteporfin group 85% of eyes lost fewer than 30 letters compared to 76% with placebo (no significance test given).
2. The mean visual acuity at the start of the trial (mean number of letters read) was 52.8 for the intervention group and 52.6 for the placebo group (range for both groups 73-34). The Snellen equivalent for this number of letters is 20/80-2. At twelve months the number of letters read was 42 (Snellen equivalent of 20/160+2) for the intervention group and 35 (Snellen equivalent of 20/200) for the placebo group (range for both groups >73-<33, $p<0.001$). This represents a decrease in the mean numbers of letters read of 10.8 for the intervention group and 17.6 for the control group. (In both groups, there were a few people whose visual acuity had increased by the 12 month follow up.)
3. Over the course of 12 months, the mean number of contrast sensitivity letters lost at each 3 month follow up visit was between 1.1 and 1.4 in the intervention group and

between 2.7 and 4.7 in the placebo group. The trial report does not give the total number of contrast sensitivity letters lost over 12 months.

During the 12 months follow up there were eight deaths in the intervention group and four in the placebo group (not statistically significant), none of which were considered to be related to the trial treatment. An additional seven patients in the intervention group stopped treatment because of adverse reactions that the treating ophthalmologist considered may have been related to the study treatment. These reactions included allergy to fluorescein, subretinal haemorrhage, suprachoroidal haemorrhage with retinal detachment, vitreous haemorrhage, gastrointestinal bleeding and severe back pain. The trial report does not mention the other eight patients in the intervention group and nine patients in the placebo group.

A number of sub group analyses were carried out on the trial results and 12 of these were included in the trial report, where there is no mention that these were planned before the start of the trial. One significant result was that the loss of 15 letters was less likely when lesion areas were composed of more than 50% classic wet AMD. There were no significant differences between the two groups if there was no classic component or if the classic component was less than 50%. This subgroup analysis testing is useful for generating hypotheses but cannot be taken as evidence that photodynamic therapy only works in classic wet AMD. (A second RCT is underway to establish more clearly whether photodynamic therapy is effective in occult wet AMD)[55].

Clinical effectiveness summary

- A single RCT was found matching the review inclusion and exclusion criteria.
- 402 patients received photodynamic therapy and 207 received placebo.
- The trial was reasonably well conducted with near complete follow up.
- There was less deterioration in vision in the photodynamic therapy group (61.2% vs 46.4% patients lost fewer than 15 letters)
- The difference in deterioration of visual acuity was both clinically and statistically significant.
- There was a slight excess in the treatment arm of adverse events considered by the ophthalmologist to be associated with the treatment but no significant difference in deaths.

Economic evidence

Cost effectiveness review

No cost utility or cost effectiveness studies on photodynamic therapy were found. (One cost utility study was found on laser photocoagulation for wet AMD.[60])

The TAP trial did not report any cost information. Two cost studies were found, one by the National Horizon Scanning Centre[44] and one by the Grampian Health Board.[61]

The National Horizon Scanning Centre estimated that the cost of verteporfin would be between £2,250 - £3,000 per patient per year, assuming 3-4 treatments giving a total drug cost in the first year for England of £17 - 23 million, assuming a prevalence of 7,700 patients. The equipment costs would include a laser (£20,000), for angiography (£30,000) and other miscellaneous (£5,000). They also note that there would likely be an increased demand for this treatment and consequently an increased need for specially trained professionals for diagnosis and treatment.

The Grampian Health Board report estimated that the cost per annum in Grampian might be around £120,000, assuming 6000 people in the area with age related macular degeneration, 800 in touch with eye care services and 50 eligible for photodynamic therapy. This gives a cost per person per year of £2,400.

Quality of life measures

No photodynamic therapy quality of life studies were found. The TAP trial did not include any generic measures of quality of life.

Full results of the cost effectiveness searches are reported in appendix 4.

Economic evaluation

As the TAP trial showed that verteporfin to be significantly more effective than placebo in preventing vision loss, a cost utility analysis was undertaken. This uses the published one year clinical effectiveness results for all of the TAP trial participants.

Cost utility analysis - utilities

The clinical effectiveness parameters from the TAP trial used in the cost utility analysis are shown below (Table 8). The ‘average’ column shows that, for the verteporfin group, 16.4% of patients had an increase in visual acuity, 21.6% had no change and 61.9% had a decrease.

Table 8. TAP clinical effectiveness used for cost utility analysis.

	Verteporfin			Placebo		
	n	%	Average	n	%	Average
≥6 line increase	4	1.0	16.4	0	0	7.2
≥3 line to < 6 line increase	20	5.0		5	2.4	
≥1 line to < 3 line increase	42	10.5		10	4.8	
No change	87	21.6	21.6	34	16.4	16.4
≥1 line to < 3 line decrease	93	23.1	61.9	47	22.7	76.3
≥3 line to < 6 line decrease	97	24.1		62	30.0	
≥6 line decrease	59	14.7		49	23.7	
(Total number of patients)	402			207		

At the start of the trial the average visual acuity was 20/80-2 (52.8 letters read) in the verteporfin group and 20/80-2 (52.6 letters read) in the placebo group.

In the TAP trial, by the one year follow up, the average change in visual acuity for the verteporfin group who increased their visual acuity was 15 letters and for those who decreased it was 20 letters. In the placebo group the average increase in number of letters read was 11.5 letters and average decrease was 23 letters. Using the visual acuity conversion table in Appendix 2 to convert from number of letters read to Snellen equivalent, an estimate of the average visual acuity at follow up can be made. (See Table 9).

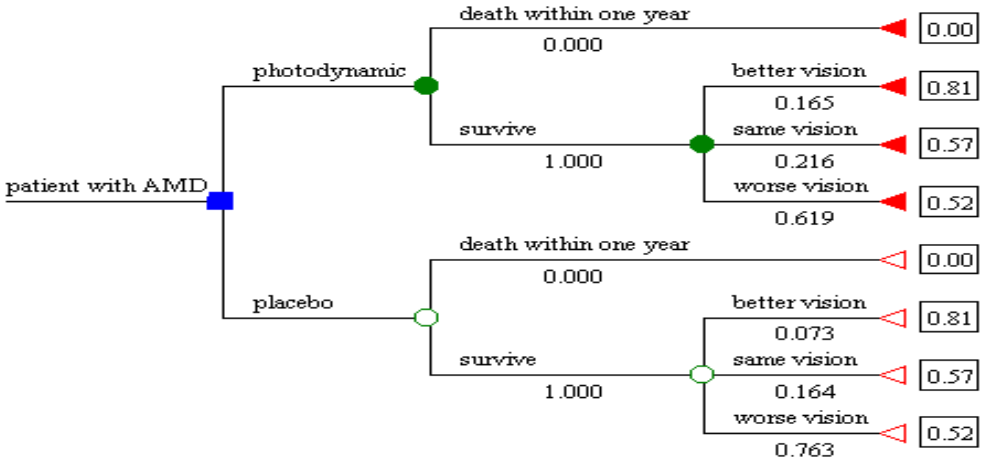
There are published studies which link visual acuity in the better seeing eye to utility value using time trade off and standard gamble techniques.[62-64] In one of these studies[62], 80 patients with age related macular degeneration and a range of visual acuities from 20/20 to light perception only were surveyed. Utility estimates by the time trade off method were given for ranges of visual acuity so that patients with a Snellen score of 20/30 to 20/50 had a mean utility value of 0.81, 20/60 to 20/100 of 0.57 and 20/200 to 20/400 of 0.52. This was used to estimate the utilities of patients in the TAP trial at follow up. (See Table 9).

Table 9. Conversion of letters read to utility value (QALY).

	Verteporfin			Placebo		
	Number of letters	Snellen equivalent	QALY	Number of letters	Snellen equivalent	QALY
Increased visual acuity	67.8	20/40-2	0.81	64.1	20/50	0.81
No change	52.8	20/80-2	0.57	52.6	20/80-2	0.57
Decreased visual acuity	33.2	20/200-2	0.52	29.6	20/250	0.52

The probabilities of an increase in visual acuity, no change or decrease in visual acuity and the estimated utilities of these outcomes were inserted into a decision tree (see Figure 2). The results showed a utility of 0.578 for the photodynamic therapy group, 0.549 for the placebo group and hence an average increase in utility for the photodynamic therapy group over the placebo group of 0.029 per person over 1 year.

Figure 2. Decision tree with probabilities and utility values of outcomes.



Key: Numbers under lines are probabilities of outcomes occurring. Numbers in boxes are the utility associated with that outcome.

Cost utility - costs

The costs associated with treatment of AMD fall into two main categories – the cost of the photodynamic therapy treatment itself and the costs of rapidly deteriorating vision. The former are borne by the NHS whereas the latter are borne by central and local government as well as the NHS.

Cost of photodynamic therapy

The cost of one photodynamic treatment includes
1. an outpatient appointment for angiography to localise the lesion
2. the cost of the angiogram
3. a second outpatient appointment for photodynamic therapy
4. the cost of verteporfin itself, as well as mixing and administration of the drug
5. one laser treatment with a diode laser
6. follow up assessment

The estimates for these costs and their sources are as follows.

1 + 2, Angiography (Fluorescein or Indocyanine) is included in the list of ophthalmic procedures in the National Schedule of Reference Costs 2000.[65] The average cost is £108 with a range for the middle 50% of trusts of £63-£149.
3. Ophthalmology outpatient first attendance (National Schedule of Reference Costs 2000[65]) mean cost is £68 (middle 50% trust range £51-£84). The University Hospital

Birmingham NHS Trust charge £77 for a new outpatient or a pre-assessment appointment.
4. The current NHS price for a single 15mg vial of Visudyne is £850 (advert for Visudyne in British Journal of Ophthalmology 2000 24:11). The cost of mixing and administration is estimated to be approximately £10.
5. Ophthalmology laser treatment of retina attendance (National Schedule of Reference Costs 2000[65]) mean cost is £101 (middle 50% trust range £52-£102). The University Hospital Birmingham NHS Trust charge £151 for an appointment at the laser clinic.
6. Ophthalmology outpatient follow up attendance (National Schedule of Reference Costs 2000[65]) mean cost is £44 (middle 50% trust range £34-£54). The University Hospital Birmingham NHS Trust charge £77 for a follow up outpatient appointment.

This gives a total cost for one photodynamic therapy treatment of £1181. The makers of Visudyne recommend that patients should be re-evaluated every three months (advert for Visudyne in British Journal of Ophthalmology 2000 24:11). In the TAP trial the intervention group received an average of 3.4 treatments per patient. This gives a first year cost per patient of £4015.40. The incremental cost per QALY comparing Visudyne to no treatment is £137,138.00.

The totalcost impact in the West Midlands can be estimated from the annual cost of photodynamic therapy and the annual incidence of uncomplicated wet AMD (assuming each person is only treated for 1 year. This comes to over £5 million. If only classic wet AMD is treated then the cost impact falls to £880,000.

Costs of rapidly deteriorating vision

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. A recent editorial[66] presents a common scenario where an elderly person who lives alone, develops CNV 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. There is significantly more visual impairment between those patients admitted with falls and those admitted with other medical problems.[67] The prevalence of low vision (6/60 or worse in better eye) in residential care homes has been estimated at 32%[68] whereas in the community of a similar age profile, the prevalence has been estimated at 6.6%.[69] The costs of photodynamic therapy may be offset by savings to the NHS and other publicly funded services from fewer people with deteriorating vision.

No studies were found which estimated the cost of blindness in the UK. An Australian study[70] 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 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.

- 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.

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 10. The social security cost is a year's worth of attendance allowance at the lower rate. 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. The tax allowance assumes payment of basic tax rate (22%).

Table 10. Estimate of costs of blindness

Outcome	Estimated cost	Estimate of the proportion with CNV and 20/200 visual acuity who would have this outcome in one year
Low vision aids	£107.43[71]	33%[72,73]
Hip replacement	£3,669 [65]	5%[65,67]
Social security	£1,861.60[74]	67%[75]
Blind registration	£55.85[76] +£36 [77]	50%[33]
Tax allowance	£303.60[78]	35%[75,79]
Community care	£2,719.60[77]	40%[75]
Residential care	£15,184[77]	5%[68]

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 £3,465.40. This does not take into account all of the costs to the individual concerned, both financial and emotional.[80]

The incremental costs for verteporfin over placebo were calculated, using the cost of a year's verteporfin of £4015.40, blindness of £3,465.40 and the outcome probabilities for better, same or worse vision from the TAP trial as shown in the decision tree. This gives an incremental cost for verteporfin of £3,516. The incremental cost per QALY is £120,095. No discounting has been carried out as only one year's clinical effectiveness results are currently available and there is uncertainty as to the long term clinical effectiveness of verteporfin.

The incremental cost effectiveness of £120,095, taking the cost of blindness into account is lower than the original estimate of £137,138.00 comparing Visudyne to no treatment. So there is some reduction in incremental cost effectiveness but not as much as might have been hoped.

The above can be contrasted with the estimated cost per QALY gained of laser photocoagulation for subfoveal choroidal neovascularisation of £9,158 with a sensitivity analysis range of £8,093 to £18,927[60] (using a conversion rate at 3rd January 2000 from US dollars of 1.627). This study assumed approximate survival of seven years following

treatment and presented the cost per QALY gained over no treatment for the whole of that period. The total incremental cost for one course of laser treatment was estimated at £1,703. In the first year following treatment there was a net loss of QALYs of 0.004. Thereafter there was a steady gain in QALYs for the treated group totalling 0.257. Because the benefit of laser photocoagulation is not apparent until after the first year of treatment, no realistic comparison can be made between the cost utility for the first year of photodynamic therapy and the first year of laser photocoagulation. There is insufficient information for a comparison model of the lifetime cost utility of photodynamic therapy.

Sensitivity analysis

In the incremental cost utility calculations there is uncertainty in the effectiveness estimates, the translation of health states into utilities and the costs.

In the utility calculations the assumptions made which are most likely to be inaccurate are the utility values given for various levels of visual acuity in the better seeing eye.[62] The study gave 95% confidence intervals which have been used in the sensitivity analysis.

The assumptions made in the cost calculations which are most likely to be inaccurate are:

1. The costs associated with administration of the new Visudyne treatment. Many of these have been estimated from the National Schedule of Reference Costs which also gives a cost range for 50% of trusts. This has been used for the sensitivity analysis except where the University Hospital Birmingham NHS Trust charge lies outside this range. This results in a range of costs from £3,604 to £4,491.40.
2. The costs associated with blindness. The accuracy of the cost and probability estimates vary and this is reflected in the width of estimate used in the sensitivity analysis. (See Table 11). These result in a range of costs from £1,254.94 to £10,862.95.

Table 11. Blindness cost and probability ranges for sensitivity analysis.

Outcome	Estimated cost	Estimate of the proportion with CNV and 20/200 visual acuity who would have this outcome in one year
Low vision aids	£25 - £419[71,81]	0% - 67%[72,73]
Hip replacement	£1,177 - £3,933[65]	0.5%[65] - 25%[67]
Social security	£1,861.60 - £4,885.40[74,82]	20 - 90%[75]
Blind registration	£37.50-£74.50[76] + £24 - £196[77]	33% - 67%[33,73]
Tax allowance	£0 - £552[78]	20% - 50%[75,79]
Community care	£2,106 - £4,400[77]	20 - 60%[75]
Residential care	£14,508 - £22,516[77]	3 - 10%[25,68]

The variations in QALYs and costs give a range of incremental cost utility estimates. (See Table 12). This shows that the cost utility estimate is more sensitive to change in QALY than change in costs. Also extremes of costs provide a lower cost utility estimate.

Table 12. Range of incremental costs per QALY

	High cost (£)	Medium cost (£)	Low cost (£)
High QALY	134,808	164,579	157,734
Medium QALY	99,817	121,861	116,792
Low QALY	79,247	96,748	92,724

With the lower cost of Visudyne and the higher cost of blindness, keeping the QALYs the same, the incremental cost utility becomes £69,540.

Summary of economic evaluation

- The clinical effectiveness parameters from the TAP trial used in the economic evaluation are shown in Table 8.
- The incremental utility of photodynamic therapy is estimated at 0.029 per person per year (estimate range 0.022-0.037).
- The cost of photodynamic therapy per person in the first year is £4015.40 (estimate range £3604 to £4491).
- The incremental cost per QALY of Visudyne is estimated at £137,138.
- When taking the cost of blindness into account the incremental cost per QALY is £120,095 (estimate range £164,579 to £79,247)
- The cost utility estimate is sensitive to various parameters. More accurate information is required in order to reduce uncertainty.
- The total cost impact in the West Midlands lies somewhere between £0.8 million and £5 million.

Conclusion

The strengths of this systematic review are that there was a clearly defined question, a comprehensive search strategy and extensive economic analysis. The main weakness is the small amount of RCT and economic evaluation evidence available. This means that our conclusions are limited by the availability of data.

The evidence from the single RCT with published results suggests that for people with subfoveal wet AMD, photodynamic therapy with verteporfin is clinically effective. This is particularly encouraging as there is no other successful treatment available for subfoveal AMD. However, the results from the TAP trial suggest that photodynamic therapy is only effective in 'classic' wet AMD, a small proportion of the total number affected by wet AMD. This may be a statistical artefact or a true result.

The trial appears to have been carried out well but the trial report has some discrepancies. For example, '94% of patients completed the 12 month follow up examination'[47] yet 12 month change in visual acuity results are given for 100% of the patients who started the trial. It is uncertain how the last observations carried forward would have affected the clinical effectiveness results and cost utility analysis.

Only one year results have been published. Whether the clinical effectiveness of verteporfin is maintained will be demonstrated when the second year results become available. A recent abstract [53] indicates that vision may deteriorate less quickly in the verteporfin group compared to controls at 12 and 24 months. However, fully published 2 year results would be much more useful. It is also unknown at present whether photodynamic therapy slows progression of wet AMD permanently or whether the disease process will speed up again once photodynamic therapy ceases.

Two more photodynamic drugs are currently being tested in humans and two RCTs are underway. The results from these will be very helpful in determining:

- Whether all photodynamic agents work with similar efficacy or not.
- Whether side effects of photodynamic agents depends on the speed of clearance from the body. If this is so, those with faster clearance such as verteporfin should have fewer side effects than the slower agents such as tin ethyl etiopurpurin.
- Whether photodynamic therapy is effective in both classic and occult AMD.

The current cost of Visudyne is very high. With the extra equipment and staff required to provide photodynamic therapy this cost rises to approximately £4015.40 per patient for the first year. If only classic AMD patients from the West Midlands were treated, the total annual cost could be approximately £880,000. It seems likely, however, that some people with occult AMD will be treated as well. If all these were treated the total annual cost would rise to over £5 million.

The incremental cost utility of Visudyne compared to no treatment is £137,138. When the cost of blindness is taken into account, this only decreases slightly to £120,095.

Sensitivity analysis shows that the incremental cost utility is more sensitive to changes in quality of life than to costs. This may be that the costs are already high so small

variations may not affect the calculations very much. It is unclear as to why extremes of costs provide lower cost utility estimates than the main estimate of costs.

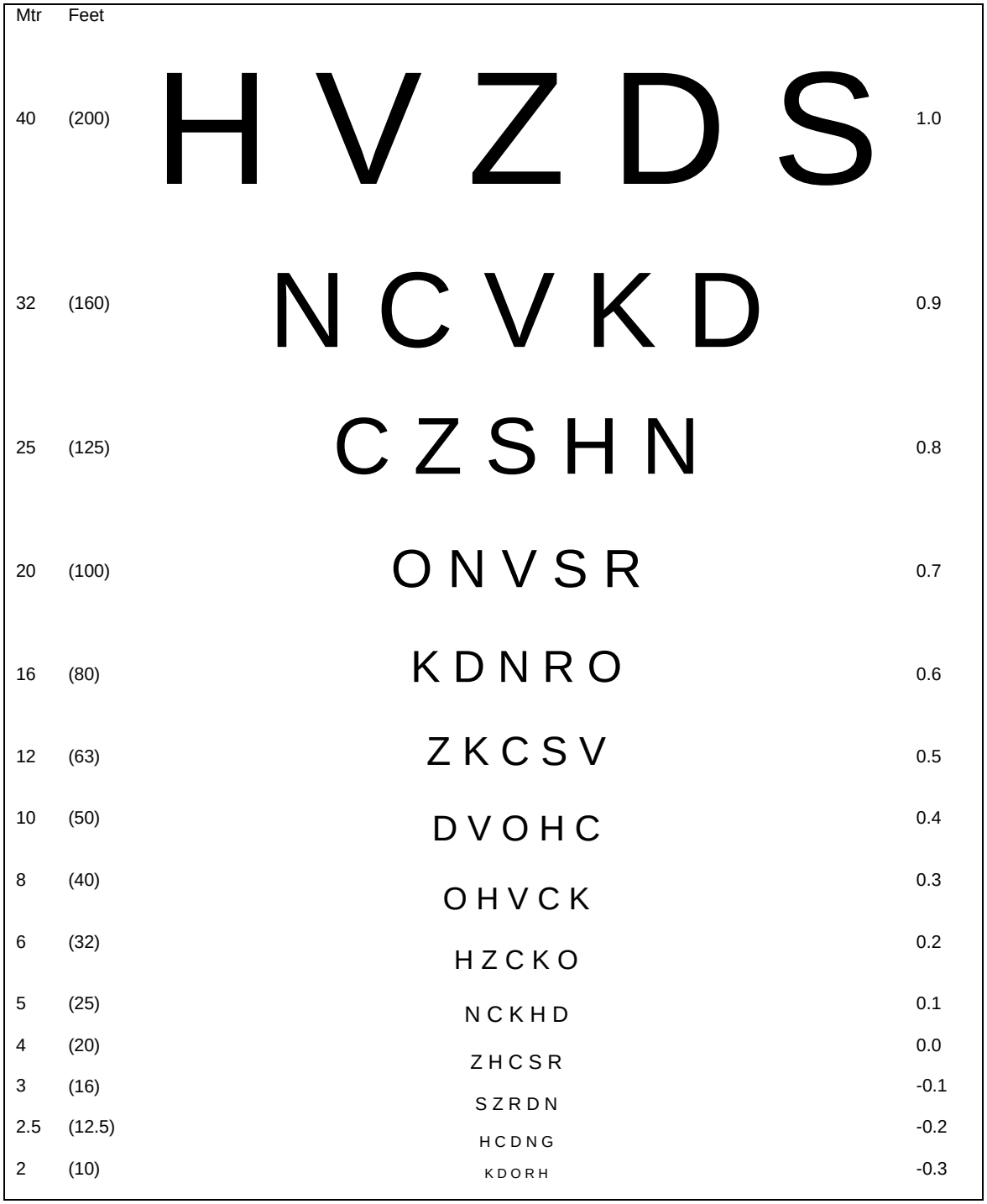
There are no long-term follow up results available for photodynamic therapy in AMD. Initial results showed increased side effects of visual disturbance and injection site adverse events in the verteporfin group. It may be that long-term verteporfin treatment results in similar hyperpigmentation side effects to those seen with porfimer sodium (see section on description of new intervention).

It seems likely that the encouraging results from this trial will accelerate implementation of this new therapy in spite of the large costs. Very careful scrutiny of future clinical effectiveness results will be needed to make sure that this implementation is warranted.

As incremental cost utility is sensitive to quality of life, future trials of photodynamic therapy must include quality of life measures. Further into the future, should photodynamic therapy be accepted as a safe and clinically effective therapy, RCTs of photodynamic therapy compared to laser photocoagulation for juxtafoveal and extrafoveal wet AMD are likely to be undertaken.

Appendices

Appendix 1. Diagram of a LogMAR chart



Appendix 2. Visual acuity conversion table

4m	6m	20ft	Visual angle in minutes	Line	Distance tested	Decimal fraction	LogMAR unit	Number of letters read
		20/800		1	1	0.025	+1.6	5
		20/640	32	2	1	0.031	+1.5	10
		20/500		3	1	0.04	+1.4	15
	3/60	20/400		1	**2**	0.05	+1.3	20
		20/320	16	2	**2**	0.063	+1.2	25
		20/250		3	**2**	0.08	+1.1	30
4/40	6/60	20/200		4	**2**	0.1	+1.0	35
4/32	6/48	20/160	8	5	**2**	0.125	+0.9	40
4/25	6/38	20/125		6	**2**	0.16	+0.8	45
4/20	6/30	20/100		7	**2**	0.2	+0.7	50
4/16	6/24	20/80	4	8	**2**	0.25	+0.6	55
4/12	6/20	20/63		9	**2**	0.32	+0.5	60
4/10	6/15	20/50		10	**2**	0.40	+0.4	65
4/8	6/12	20/40	2	11	**2**	0.50	+0.3	70
4/6.3	6/10	20/32		12	**2**	0.63	+0.2	75
4/5	6/7.5	20/25		13	**2**	0.80	+0.1	80
4/4	6/6	20/20	1	14	**2**	1.00	0.0	85
4/3.2	6/5	20/16		12	4	1.25	-0.1	90
4/2.5	6/3.7	20/12.5		13	4	1.60	-0.2	95
4/2	6/3	20/10		14	4	2.00	-0.3	100

Appendix 3. Clinical effectiveness search strategy

Electronic databases searched

Database	Date	Search strategy	Total number of references	Number of RCTs found
Medline	1993-Aug 2000	See below	88	1
Embase	1980-Aug 2000	See below	78	0
BIDS Pascal	1993-Aug 2000	See below	8	0
Cochrane Library	2000, Issue 3	Age related macular degeneration	110	0
Web of Science (http://wos.mimas.ac.uk/isicgi/CIW.cgi	1981-Aug 2000	Age related macular degeneration and photodynamic therapy	36	0
Healthstar	1993-Aug 2000	Age related macular degeneration (non-medline)	40	0
TRIP	Aug 2000	Macular and degeneration	8	0
mRCT	Aug 2000	Macular degeneration	4	0
National research register (complete + ongoing)	Aug 2000	(Age and (related and (macular and degeneration)))	30	0
References from systematic reviews	Aug 2000	N/A	N/A	0

Medline on Ovid 1993-Aug 2000

	Search history	Number of hits
1	Exp choroid/or exp fluorescein angiography/ or exp macular degeneration/ or exp neovascularization, pathologic/ or exp pigment epithelium of eye/	10375
2	“AGE RELATED MACULAR DEGENERATION”.mp.	939
3	“AGE-RELATED MACULAR DEGENERATION”.mp.	939
4	“ARMD”.mp.	118
5	“AMD”.mp.	472
6	2 or 3 or 4 or 5	1186
7	1 or 6	10695
8	Exp Photochemotherapy/	2655
9	“PHOTODYNAMIC”.mp.	1992
10	“VISUDYNE”.mp.	2
11	“VERTEPORFIN”.mp.	49
12	“TIN ETHYL ETIOPURPURIN”.mp.	15
13	Exp Photosensitizing agents/	3056
14	8 or 9 or 10 or 11 or 12 or 13	4944
15	7 and 14	88
16	Randomized controlled trial.pt.	70788

17	Randomized controlled trials.sh.	11244
18	Random allocation.sh.	10135
19	Double blind method.sh.	26599
20	Single blind method.sh.	4109
21	16 or 17 or 18 or 19 or 20	95821
22	Animal.sh.	862140
23	Human.sh.	2088593
24	22 not (22 and 23)	612345
25	21 not 24	89093
26	15 and 25	3

Embase on Ovid 1980-Aug 2000

	Search history	Number of hits
1	exp neovascularization/ or exp retina macular age related degeneration/ or exp retina macular degeneration/ or exp retina macula senile degeneration/ or exp subretinal neovascularization/	8230
2	“AGE RELATED MACULAR DEGENERATION”.mp.	1170
3	“ARMD”.mp.	117
4	“AMD”.mp.	993
5	1 or 2 or 3 or 4	9044
6	Exp Photodynamics/	10842
7	Exp Photosensitivity/	2413
8	Exp photosensitizing agent/	9251
9	Exp photodynamic therapy/ or exp photofrin/ or “visudyne”.mp.	2863
10	“PURLYTIN”.mp.	1
11	Exp etiopurpurin/ or “tin ethyl etiopurpurin”.mp.	41
12	“VERTEPORFIN”.mp.	49
13	6 or 7 or8 or 9 or 10 or 11 or 12	19416
14	6 and 13	133
15	Limit 14 to human	78
16	Exp randomized controlled trial/ or “randomized controlled trial”.mp.	46633
17	Randomized controlled trial.pt.	0
18	Exp randomization/ or “random allocation.mp.	2896
19	Exp clinical trial/ or exp controlled study/ or exp double blind procedure/ or “double blind”.mp.	1085327
20	16 or 18 or 19	1087465
21	15 and 20	31

BIDS Pascal 1993-Aug 2000

	Search history	Number of hits
1	(photosensitive)@TI,KA	1114
2	(photodynamic)@TI,KA	1500
3	(visudyne)@TI,KA,(verteporfin)@TI,KA,(photosensitive)@TI,KA, (photodynamic)@TI,KA	2903
4	(age related macular degeneration)@TI,KA	55
5	(ARMD)@TI,KA	67
6	(AMD)@TI,KA	450
7	(age related macular degeneration)@TI,KA(ARMD)@TI,KA	554

	(AMD)@TI,KA	
8	((visudyne)@TI,KA,(verteporfin)@TI,KA,(photosensitive)@TI,KA,(photodynamic)@TI,KA) + ((age related macular degeneration)@TI,KA(ARMD)@TI,KA (AMD)@TI,KA)	8

Appendix 4. Cost effectiveness search strategy

Electronic databases searched

Database	Date	Search strategy	Total number of references	Number of studies found
Medline	1993-Aug 2000	See below	11	0
Embase	1980-Aug 2000	See below	43	0
BIDS Pascal	1993-Aug 2000	See below	7	0
Cochrane Library (HTA, NHSEED, DARE)	2000, Issue 3	Age related macular degeneration	5	1
Healthstar	1993-Aug 2000	Age related macular degeneration (non-medline)	40	0
TRIP	Aug 2000	Macular and degeneration	8	0
National research register (complete + ongoing)	Aug 2000	(Age and (related and (macular and degeneration)))	30	0
Citations of reviews and RCTs	N/A	-	-	1

Medline on Ovid 1993-Aug 2000

	Search history	Number of hits
1	Exp choroid/or exp fluorescein angiography/ or exp macular degeneration/ or exp neovascularization, pathologic/ or exp pigment epithelium of eye/ or “age related macular degeneration”.mp.	10579
2	Exp choroidal neovascularization/ or “amd”.mp.	635
3	1 or 2	10788
4	Exp cost-benefit analysis/ or exp health care costs/ or “economic evaluation”.mp.	19473
5	3 and 4	11

Embase on Ovid 1980-Aug 2000

	Search history	Number of hits
1	exp neovascularization/ or exp retina macular age related degeneration/ or exp retina macular degeneration/ or exp retina macula senile degeneration/ or exp subretinal neovascularization/ or“age related macular degeneration”.mp.	8354
2	“AMD”.mp.	993
3	“ARMD”.mp.	117
4	1 or 2 or 3	9044
5	Exp cost benefit analysis/ or exp cost effectiveness analysis/ or exp health economics/ or “ economic evaluation”.mp.	95474
6	4 and 5	43

BIDS Pascal 1993-Aug 2000

	Search history	Number of hits
1	(macular degeneration)@TI,KA	847
2	(economic)@TI,KA	40336
3	(cost*)@TI,KA	113156
4	(economic)@TI,KA,(cost*)@TI,KA	143637
5	(macular degeneration)@TI,KA+(economic)@TI,KA,(cost*)@TI,KA	7

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