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Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Age-related macular degeneration (AMD) 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 years. There are two main types: wet AMD and dry AMD (see below).

Age-related maculopathy (ARM) Early stage of AMD.

Amsler grid A hand-held chart with black horizontal and vertical lines on a white background, used to test for central visual field defects.

Blindness Various definitions but usual standard is a visual acuity of 6/60 (20/200) or worse in the better eye or a visual field of < 20° in the better eye.

Choroid Layer of the eye containing the blood supply to the outer retina.

Classic neovascular membranes/lesions Neovascular membranes that are clearly delineated on fluorescein angiography and leak fluorescein uniformly.

Drusen Subretinal amorphous deposits, often age related.

Dry AMD More benign of the two forms of AMD in which neovascular membranes do not occur.

Extrafoveal area The area of the macula excluding the fovea.

Fovea Small area of the retina, lying within the macula, where light is focused to give sharpest central vision.

Juxtafoveal area The remainder of the foveal area, excluding the subfovea.

Laser photocoagulation Technique whereby new neovascular membranes are removed by laser 'burns', which concurrently damage overlying retina.

Macula Small area of the retina used for central vision, divided into three sections – subfoveal, juxtafoveal and extrafoveal.

Neovascularisation The formation of new blood vessels, often fragile and inappropriate to location, underneath or in the retina.

Neovascular AMD Alternative name for wet AMD. Avoided wherever possible throughout this report because it gives the impression that wet AMD is always associated with neovascular membranes, which is false.

Neovascular membranes New blood vessels formed by the process of neovascularisation.

Occult neovascular membranes/lesions Neovascular membranes that are hard to detect on fluorescein angiography and where fluorescein leakage is patchy.

Photodynamic therapy (PDT) Injection of photosensitive dye then application of laser, intended to treat neovascular membranes.

Pigment epithelial detachment (PED) or RPE detachment 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.

Retinal pigment epithelium (RPE) A layer of epithelial cells lying between the photoreceptors of the retina and the choroidal blood supply.

continued

Glossary *contd*

Photoreceptors The rods and cones in the retina that are sensitive to light.

Scotoma An area of partial or complete vision loss surrounded by an area of normal vision.

Subfoveal area Area of the macula less than 1 μm from the foveal centre.

Tin ethyl etiopurpurin (SnET2) One of the two main types of dyes used in PDT for wet AMD.

Verteporfin One of the two main types of dyes used in PDT.

Visudyne® (Novartis Ophthalmics AG; Switzerland) 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.

Visual acuity The clearness of vision, which depends on the sharpness of the retinal image, the finest of details that an eye can distinguish.

Visual field The area or extent of space visible to an eye in a given position of gaze.

Wet AMD 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.

Wet AMD – classic type Wet AMD with classic neovascular membranes/lesions (see appendix 1).

Wet AMD – occult type Wet AMD with occult neovascular membranes/lesions (see appendix 1).

Abbreviations

AMD	age-related macular degeneration
ARM	age-related maculopathy
ARVO	Association for Research in Vision and Ophthalmology
BNF	*British National Formulary*
BSC	best supportive care
CI	confidence interval
CNV	choroidal neovascularisation (also known as CRN, CRNV, SRN, SRNV)
DARE	Database of Abstracts of Reviews of Effectiveness
df	degrees of freedom
DSS	Department of Social Security
ICER	incremental cost-effectiveness ratio
LogMAR	logarithm of the minimum angle of resolution
MPS	Macular Photocoagulation Study
N/A	not available
NHS EED	NHS Economic Evaluation Database
NICE	National Institute for Clinical Excellence
NNT	number needed to treat
NR	not reported
PDT	photodynamic therapy
PED	pigment epithelial detachments
QALY	quality-adjusted life-year
RCT	randomised controlled trial
RNIB	Royal National Institute for the Blind
RPE	retinal pigment epithelium
ScHARR	School of Health and Related Research
SnET2	tin ethyl etiopurpurin
SOE	European Society of Ophthalmology
TAP	Treatment of Age-related Macular Degeneration with Photodynamic Therapy (trial)
TTO	time trade off
TTT	transpupillary thermotherapy
VF-25	25-item vision function (questionnaire)
VIM	Visudyne® in minimally classic CNV (trial)
VIO	Visudyne® in occult CNV (trial)
VIP	Verteporfin in photodynamic therapy (trial)
WMHTAC	West Midlands Health Technology Assessment Collaboration

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices in which case the abbreviation is defined in the figure legend or at the end of the table.

Executive summary

Background

Age-related macular degeneration (AMD) is a major cause of blindness affecting the central portion of the retina (the macula). Wet AMD is one form of the condition and involves the formation of neovascular membranes. It is through the leakage and bleeding of these blood vessels that vision loss, which is usually irreversible, occurs. Wet AMD can be further subdivided into classic and occult and it is the classic form that is more threatening to sight. The prevalence of wet AMD has been estimated at 3 per 1000 at age 60–64 years and 117 per 1000 at 90 years and over. There are approximately 50 new cases of classic neovascular membranes per year in a typical health authority of population 500,000.

Photodynamic therapy (PDT) is a new intervention that uses photosensitive drugs (e.g. verteporfin) and a specially developed low-powered laser, and is intended to treat patients with new neovascular membranes in wet AMD who still retain some visual acuity. Its aim is to stop further loss of vision rather than restore vision already lost.

Objective

- To establish the clinical and cost-effectiveness of PDT for the neovascular form of wet AMD relative to current practice and in relation to current licensed indications.

Methods

A systematic review of randomised controlled trials (RCTs) and economic evaluations addressing the clinical effectiveness and cost–utility of PDT in AMD was undertaken. Searches in electronic databases, health technology assessment Internet sites, reference lists from publications, conference abstracts and the Novartis Industry Submission to the National Institute for Clinical Excellence for completed and ongoing RCTs and for economic evaluations, were carried out up to August/September 2001. Decisions on the inclusion or exclusion of RCTs and economic evaluations were made by one reviewer, independently of results, and checked by another. Duplicate data extraction and quality assessment were carried out using predefined criteria. Synthesis was mainly qualitative for both clinical effectiveness and cost–utility. Forest plots were carried out for the RCT primary outcome measure of clinical effectiveness. A health economist, taking a public finance perspective and using a simple decision model, carried out a cost–utility analysis for this report. PDT with best supportive care was compared with best supportive care only, using clinical effectiveness data from one RCT, published utility and treatment cost studies and blindness cost estimates.

Results

Number and quality of studies, and direction of evidence

In the Treatment of Age-related Macular Degeneration with Photodynamic Therapy (TAP) trial there was consistent evidence at both 1 and 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 (three lines) or more at 2 years was 0.75 (95% confidence interval (CI), 0.65 to 0.88). This effect is both statistically significant and clinically important. The Verteporfin in Photodynamic Therapy (VIP) trial showed a similar result. There is an increase in adverse events associated with verteporfin PDT. Most are minor, but sudden visual loss occurs in 1.0–4.4% 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 invites re-examination of 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 subgroup 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.

Economic analysis

Costs

The cost of one vial of verteporfin 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 between £16.4 million and £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/quality-adjusted life-year

There is uncertainty about the cost–utility of verteporfin PDT. Cost-effectiveness studies reviewed estimated that the cost per quality-adjusted life-year at 2 years ranged from £60,000 to £122,000. The economic model developed as part of this report obtained a base-case estimate of between £151,000 and £182,000. The sensitivity analyses ranged from the best scenario of £47,000 to a worst scenario of £342,000. 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. More favourable estimates of cost–utility have only been obtained in models extrapolating beyond 2 years, the limit of RCT data.

Conclusions

Need for further research

There is a need to conduct a large, multicentre, publicly funded pragmatic double-blind RCT with parallel health economic evaluation to assess not just the impact of PDT 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.

Chapter 1
Aim and background

Aim of the review

To establish the clinical and cost-effectiveness of photodynamic therapy (PDT) for the neovascular form of age-related macular degeneration (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.

Background

Description of underlying health problem

Nature of AMD

AMD is the most common cause of blindness in people registered blind over the age of 65 years.[1,2] 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. 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. Wet AMD is associated with several pathological features – pigment epithelial detachments (PED), neovascular membranes, retinal scarring, haemorrhages and exudates.[3] 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).[4] 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 further explanation of visual function and how it is measured 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.[5] 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.[4] Classic neovascular membranes are associated with faster progression to legal blindness than occult neovascular membranes.[6] Annually, classic neovascular membranes develop in up to 50% of occult lesions.[7]

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 eye (up to 42% within 5 years).[8]

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.[4] It is unlikely that primary prevention of wet AMD will be possible in the near future.

Epidemiology

The vast majority of AMD occurs in people over 60 years of age. However, pathological changes (presence of drusen, retinal pigment epithelium (RPE) depigmentation, increased retinal pigment) without visual defects can be seen at an earlier age.[9,10] This section will focus on AMD causing visual disturbance or legal blindness.

The International Classification of Disease (tenth revision) 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)'.[11] 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 (CIs)) according to visual impairment and type of AMD,[12] (see *Table 1*). Women and men probably have similar prevalence rates.[12] There is no evidence to suggest that the prevalence varies by geographical region.

AMD as a cause of blindness appears to have increased by about 30–40% per age-adjusted head of population over the past 40 years.[1]

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 and wet). 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 5-year incidence of AMD was 0.9% at 60–69 years, 2.6% at 70–79 years and 6.8% at 80 plus years.[13] In the Beaver Dam Eye Study, the 5-year incidence rates for wet AMD were 0% under the age of 55 years and 3.2% in those aged 75 years plus.

Prevalence and/or incidence in an average health authority

From *Table 1* the prevalence of wet AMD in an average health authority of population 500,000 would be approximately 1946 people.

Estimates of 1-year incidence figures for all AMD and wet AMD for a typical health authority are shown in *Table 3*. These estimates use age- and sex-specific incidence rates from the Beaver Dam Eye Study,[15] age-specific incidence rates from the Blue Mountains Eye Study[13,19] and Rotterdam Study[18] and census population estimates for England.[20]

The wet AMD category in the Beaver Dam study[15] included PEDs 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 PEDs 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 with 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.

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]

TABLE 1 *Prevalence of partial sight, blindness and wet AMD per 1000 population*

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

* *Partially sighted – best visual acuity of 6/60 to 3/60*
† *Blind – best visual acuity of < 3/60 to no perception of light*

TABLE 2 *Incidence of AMD in either eye*

Study	No. in survey followed-up	Definition	Incidence	Mean age in years (range)
Avon (UK)[14]	942,000	Registered blind from AMD	0.06%/2 years	(All ages)
Blue Mountain (Australia)[13]	2323	AMD	1.3%/5 years	(49–90+)
Beaver Dam (USA)[15]	3684	Wet Dry	0.6%/5 years 0.3%/5 years	(43–84)
Melton Mowbray (UK)[16]	88	Wet Dry	1.3%/7 years 1.3%/7 years	80 (77–90)
Denmark[17]	Population of Denmark as at 1/1/1994	Registered blind from AMD	0.1%/5 years	(60–99)
Rotterdam (The Netherlands)[18]	5095	AMD	0.24%/2 years	(55–85+)

TABLE 3 *Estimates of annual incidence of AMD and wet AMD in a typical health authority (~ 500,000 population)*

	1-year incidence	
	Any AMD	Wet AMD
Beaver Dam[15]	529	158
Blue Mountains[13]	537	
Rotterdam[18]	186	103

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 5000 new cases in England and Wales.

It is acknowledged that this is only a rough estimate and is likely to be an underestimate. There is little information available regarding the proportion of people with AMD who would be eligible for treatment with PDT. Also people who have glaucoma or cataract in addition to wet AMD may well be considered eligible.

This figure agrees well with a recent UK estimate of 5000 people with classic AMD requiring treatment in England and Wales per year.[26] From a different case study of 1000 patients with any AMD attending a US retinal practice, 171 were found to be indicated for PDT, using the predominantly classic criteria.[23] If this rate is applied to a typical health authority of population ~ 500,000 there would be 90 new cases, and 9000 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 the total number of individuals who might become blind (all causes) in any one year in an average health authority is approximately 135, with 180 registering as partially sighted.[27]

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[28] presents a common scenario where an

TABLE 4 *Estimate of ratio of classic to occult neovascular membranes*

Study	No. of classic	No. of occult	Ratio
Choroidal Neovascular Prevention Trial Research Group, 1998[24]	1 (classic only)	17 (whole or part occult)	1:17
Margherio *et al.*, 2000[23]	256 (classic with occult)	136 (occult only)	1:0.53
Sunness *et al.*, 1999[25]	4 (classic + classic with occult	8 (occult only)	1:2

elderly person who lives alone, develops wet AMD in her better eye. At 6 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,[29,30] and there is significantly more visual impairment between those patients admitted to hospital with falls and those admitted with other medical problems.[31] The prevalence of low vision (6/60 (20/200) or worse in the better eye) in residential care homes has been estimated at 19.6%[32] and 32%[33] whereas in the community of a similar age profile, the prevalence has been estimated at 6.6%.[34] People with rapidly deteriorating vision also tend to suffer more depression and anxiety due to their loss of vision and reduction in independence.[35–39]

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

Although vision loss can be severely disabling to an elderly person, visual acuity may not correlate well with functional ability.[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.[44] The two main aspects of rehabilitation for people with visual acuity loss caused by AMD are activities for daily living and reading skills. There are many modified appliances that can help around the home such as liquid level indicators, talking clocks and scales, and special marking clips. Vision rehabilitation includes training in their use, so that people can continue to cook meals and tell the time. AMD causes central vision loss so people need to be taught eccentric fixation techniques, where the eye is focused away from the fovea.[28,44] Together with appropriate magnification, reading standard sized newsprint is possible for up to 90% of those referred to a specialist low-vision clinic.[45,46] 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.[47] Unfortunately, the provision of low-vision rehabilitation around the country is patchy.[47]

Beyond adaptation to vision loss, a further issue which makes the relationship between vision and functionality more complex is the fact that 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.

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.[4] Experimental treatments include ionising radiation, antiangiogenic agents (including interferon, vascular endothelial growth factor, integrins and thalidomide) and surgical interventions (including retinal excision and implantation).[48–50] No RCTs on these interventions have shown significant benefit to the patient.

A recent RCT of antioxidant vitamin and mineral supplements (vitamins C and E, beta carotene and zinc) has indicated that this combination may delay progression of AMD.[51]

For most patients, as with dry AMD, management consists of social support, visual rehabilitation and provision of low-vision aids.[52]

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.[4,48]

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.[48] 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[4]
- most presenting lesions are subfoveal[53]

- the immediate visual acuity loss means that this treatment is rarely used; this immediate visual loss is purported to be not well accepted, in spite of some research evidence to the contrary[54]
- there is approximately a 50% chance that leakage will recur during the 2 years after treatment[4]
- there is a small risk (0.5–2%) of an RPE tear occurring that will lead to profound loss of vision.[55,56]

Description of new intervention

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/PED). Diagnosis of AMD and its wet form is not straightforward. General practitioners and ophthalmologists who are not retinal specialists may err on the side of caution and as a result it is likely that more people will be referred for assessment.

Neovascular membranes can be classified as classic or occult according to their appearance on fluorescein angiography.[57] Classic lesions are clearly delineated and leak fluorescein uniformly whereas occult lesions are hard to detect and fluorescein leakage is patchy.[58] Occult lesions can be distinguished from PEDs angiographically if there are irregular hyperfluorescence areas and spots of intense hyperfluorescence.[57] Comparison of the two types of angiographic media are also used for diagnosis.[59,60] There is no information available on the sensitivity and specificity of these tests.

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.[61,62] The causal mechanism for this is unclear.

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).[63] 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.[64] 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.[64] For this report, the two relevant photosensitive substances currently undergoing RCTs for AMD are verteporfin (Visudyne® (Novartis Ophthalmics AG, Switzerland))[61] and tin ethyl etiopurpurin (SnET2), now called rostaporfin (trade name was Purlytin® (Pharmacia and Upjohn, USA and Sweden; Miravant Medical Technologies, USA).[65] 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))[66] and indocyanine green[67] (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.[64] Unlike laser photocoagulation, there is no sudden vision loss (except in a small minority who suffer a choroidal infarction (Bird A, Moorfields Eye Hospital, London: personal communication, 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.[68] PDT is relatively painless and can be

undertaken in the outpatient department. However, there are a number of disadvantages.

- The treatment may be effective only in some patients with wet AMD but not others.[61] 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, SnET2 2–4 weeks, lutetium texaphyrin 1–2 weeks).[69] 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.[61]
- The long-term effects in humans of PDT for wet AMD are unknown.
- The treatment does not influence the underlying pathological process that 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.[70]
- If used on patients with PEDs, it is liable to cause severe loss of vision.[71]

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 (CNV). 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.[72] However, following the 2-year results of the Verteporfin in Photodynamic Therapy (VIP) trial, there is an intention to seek to extend the licence to treat people with occult subfoveal lesions.[73] Application has been made to the Canadian and European licensing authorities for this extension.[74,75]

(Note: 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 two names are synonymous with respect to PDT for wet AMD, as Visudyne is the only commercially available formulation of verteporfin.)

Verteporfin is contraindicated in patients with porphyria, severe liver impairment or known hypersensitivity to verteporfin or any other component of the infusion, including egg proteins.[72] It is produced from porcine hemin as a starting material[72] 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 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."[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 where possible.[73] Bearing in mind that the average age of recipients is 75 years old, extravasation is fairly common, happening in approximately 3% of cases.[61,62]

The entry for verteporfin in the *British National Formulary* (*BNF*)[76] is shown in *Box 1.*

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).[77]

The equipment and supplies needed are:

- angiographic photography system
- syringe or infusion pump, needles for injection
- 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.[77]

PDT with verteporfin can be carried out in a standard outpatient clinic.[77]

Requirements for PDT with other photosensitive agents particularly SnET2, cannot be stated with

BOX 1 Details from the *BNF* entry for verteporfin.[76] Reproduced with permission from the British Medical Association/Royal Pharmaceutical Society of Great Britain

Subfoveal choroidal neovascularisation
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.

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, pruritus, hypercholesterolaemia, hypertension, chest pain, syncope, fever; rarely lacrimation disorder, subretinal or vitreous haemorrhage; injection site reactions including pain, oedema, inflammation, haemorrhage, discoloration.

Dose: by intravenous infusion over 10 minutes, 6 mg/m^2

Visudyne® (Novartis Ophthalmics)

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

Method of preparation: reconstitute each 15 mg with 7 ml water for injections to produce a 2 mg/ml solution then dilute requisite dose with infusion fluid (5% dextrose) to a final volume of 30 ml 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*
The BNF *is published twice a year in March and September. Please refer to the most recent issue for the most up-to-date information on verteporfin*

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.

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 30 ml water for injection and given to the patient intravenously over 10 minutes, using an infusion pump. Fifteen minutes after the start of the infusion, the patient is seated 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 nm wavelength and the dose is 50 J/cm^2 at an intensity of 600 mW/cm^2 using a spot size with a diameter 1 mm larger than the greatest linear dimension of the lesion.[61] 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[78] or for 2 days[76] 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.[77] As the treatment does not affect the underlying pathological process, long-term follow-up may be required.

Degree of diffusion

PDT 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 Ophthalmics separate from their industry submission suggest that there is equipment to perform PDT at 75 NHS eye units, 23 private hospitals and two private rooms (definition of private room not stated). There is some verteporfin use at 28 NHS eye units, 12 private hospitals and one private room. There is regular verteporfin use at 12 NHS eye units, seven private hospitals and one private room. (Please note that NHS eye units all have private wings). (Novartis Ophthalmics AG, Bulach, Switzerland. Visudyne outlets. Unpublished presentation: personal communication.) Of the 20 units regularly treating with PDT, only 12 are NHS eye units (Novartis Industry Submission to the National Institute for Clinical Excellence (NICE), page 15).[79] Novartis estimate that the number of new patients currently receiving PDT at NHS expense each year is 500 (Submission, page 44).[79]

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 6 mg/m^2)[76]
- specially made diode laser system – purchase cost £14,750, servicing and warranty £500 per year (Novartis spreadsheet).[79]

However, the true cost of PDT for wet AMD needs 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.

Other new approaches to the treatment of wet AMD

Research into the 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 these are angiostatic steroids (anecortave acetate[80]) and transpupillary thermotherapy (TTT).[81] TTT is a laser therapy in which 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 (Wormald R, Moorfields Eye Hospital, London: personal Communication, 2002).

Summary

Condition

- AMD is a major cause of blindness, affecting the central portion of the retina (the macula).
- There are several types of AMD, 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 subcategorisation 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 and these suggest that for an average health authority of 500,000 persons:
  - there are approximately 150 new cases of wet AMD
  - the number of new cases of wet AMD not co-existing with other sight-impairing conditions like cataracts and glaucoma (uncomplicated wet AMD) is 75
  - the number of new cases of uncomplicated wet AMD with some classic neovascular membranes is 50, in most of which the lesions would be would subfoveal in location
  - the number of new cases of uncomplicated wet AMD with just occult neovascular membranes is 25, in most of which the lesions would be would subfoveal in location
- Putting this in context, an average health authority would expect to have 135 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. 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.
- Rehabilitation can be successful.

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 suboptimal.
- For wet AMD where neovascular membranes are located outside the fovea (extrafoveal and juxtafoveal) laser photocoagulation may halt the progression of the disease. However, laser photocoagulation has important limitations, not least of which is that most neovascular lesions are subfoveal.

Proposed treatment – PDT
- PDT has two components – injection of a photosensitive agent followed by directing a low-energy laser onto the affected areas of the retina. 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 to date. The current licence is for the treatment of AMD in patients with predominantly classic subfoveal CNV. An extension of this licence to occult subfoveal CNV 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.

Chapter 2

Effectiveness

Methods for reviewing effectiveness

Search strategy

As the authors had completed a previous systematic review on the same subject in 2001,[82] no formal scoping search was undertaken. The previous systematic review was used as the basis for the protocol for this technology assessment. This was undertaken in accordance with the pre-defined protocol (see appendix 3) and there were no major departures.

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 Medical Research Council current controlled trials register – September 2001
- national and international health technology assessment sites (July 2001):
  - International Association for Health Technology Assessment (INAHTA)
  - National Horizon Scanning centre (NHSC)
  - Canadian Coordinating Office for Health Technology Assessment (CCOHTA)
  - Danish Institute for Health Technology Assessment (DIHTA)
  - Norwegian Centre for Health Technology Assessment (SMM)
- conference abstracts
  - The Association for Research in Vision and Ophthalmology (ARVO) 1999, 2000, 2001
  - The European Society of Ophthalmology (SOE) 2001
- Internet sites (Novartis, Visudyne® (Novartis Ophthalmics, Switzerland))
- citations of all relevant articles found and the data outline sent to us by Novartis separate from their industry submission.

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

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**: RCTs
- **Population**: adults with wet AMD
- **Intervention**: PDT using any photosensitive drug
- **Comparator**: either no treatment (best supportive care (BSC)) for subfoveal lesions or laser photocoagulation for juxtafoveal or extrafoveal lesions
- **Outcomes**: any of visual acuity, contrast sensitivity, quality of life, side-effects of treatment
- **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:

- RCTs that had not finished recruiting (a separate list of ongoing RCTs found during the searches was made, see *Number of studies identified* below)
- RCTs that had published only baseline characteristics or follow-up results for a small proportion of the trial participants
- studies carried out on animals.

Although the above studies 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.

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]

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.

Results

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.

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 with placebo – six RCTs (two completed, four ongoing)
   A1. Verteporfin versus placebo – five RCTs (two completed, three ongoing)
   A2. SnET2 versus placebo – one RCT (ongoing)
B. PDT compared with laser photocoagulation – no RCTs
C. PDT plus usual visual rehabilitation compared with optimised visual rehabilitation – no RCTs
D. PDT compared with new approaches (e.g. TTT) – no RCTs
E. one type of PDT compared with another – no RCTs.

For the comparison of PDT with placebo (categories A1 plus A2) the possible comparisons are either:

a) single treatment – one ongoing RCT
b) multiple treatment – two completed RCTs and three ongoing RCTs.

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.

Comparison b) above gives 12 possible combinations (*Table 5*), 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 a proportion of wet AMD have no neovascular lesions.

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 (i.e. reviews, case series or animal studies). This left 28 references that required further consideration. Ten studies were excluded on scrutiny of the full text (six because the trial design was not RCT, three because they were not RCTs of PDT but of anecortave acetate and one because it was a review) and 13 because they were duplicate reports of the five 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 five RCTs, seven were from the Treatments of Age-related Macular Degeneration with Photodynamic Therapy (TAP) RCT, four from the VIP RCT and two from Thomas and co-workers[65] (see below).

TABLE 5 *Multiple treatment RCTs of PDT in wet AMD found (ongoing RCTs in brackets)*

	Subfoveal	Juxtafoveal	Extrafoveal
No neovascular lesions	None found	None found	None found
Classic neovascular lesions only	TAP, (SnET2), VIP if visual acuity > 70 letters	None found	None found
Combined classic and occult	TAP, VIP, (VIM)	None found	None found
Occult neovascular lesions only	VIP, (VIO)	None found	None found

Of the six ongoing or completed RCTs of PDT in wet AMD identified, the four ongoing studies were excluded from the analysis of current evidence on effectiveness, because the data were incomplete. These four ongoing studies are detailed below.

***Gierek-Lapinska and co-workers, 2001*[84,85]**
This is a single treatment RCT using verteporfin. It may also be the only trial found that is independent of drug company sponsorship. Details of this RCT are from one poster[84] and one abstract.[85] 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 and co-workers, 2000*[65]**
This is a multiple treatment RCT sponsored by Miravant Medical Technologies, USA. It was started in 1999 and compares SnET2 in two doses with placebo and uses a different laser setting to the TAP trials.[65] Recruitment finished in approximately June 2000, and 933 patients were randomised. The 2-year follow-up has been completed on approximately one-third of these (as of June 2001). Follow-up should be complete on the remainder in early 2002. A total of 86% of patients had wet AMD with some classic neovascularisation; the remainder had occult neovascular lesions. (Glitter KA. Presentation at the SOE conference: 3–7 June 2001; Istanbul, Turkey.)

Visudyne® in Minimally Classic CNV (VIM) trial
The VIM trial (sponsored by Novartis Ophthalmics AG, Switzerland), is another multiple treatment RCT but has only recently started and is still in the recruitment phase. It compares a standard dose of verteporfin (6 mg/m^2) with placebo, with standard or reduced laser settings. To date (as of June 2001), approximately 270 patients have been randomised (Stur M. Presentation at the SOE conference: 3–7 June 2001; Istanbul, Turkey.). We have no information on the target number of patients.

Visudyne® in Occult CNV (VIO) trial
The final ongoing multiple treatment RCT is the VIO trial, also sponsored by Novartis Ophthalmics AG, Switzerland. Again it has only recently started and is in the recruitment phase. It compares verteporfin with placebo with standard laser settings in patients with occult only wet AMD.[86] We have no information on the target number of patients.

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 were 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 5.

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 has been 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[58]) given at 6 mg/m^2 body surface area diluted to 30 ml, and the placebo was 30 ml 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 nm wavelength, delivering 50 J/cm^2 at an intensity of 600 mW/cm^2 over 83 seconds, using a spot size 1 mm greater than the largest dimension of the lesion.[61] 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 2 years (i.e. at 3, 6, 9, 12, 15 18, 21 and 24 months). Retreatment 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 6*.

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 non-foveal 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 choose 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 PDT 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 (e.g. pathological myopia) associated with CNV 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 7*. 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.

The outcomes measured in the two trials were:

- visual acuity
  - number of people who lost 15 or more letters compared with baseline
  - number of people who lost 30 or more letters compared with baseline

TABLE 6 *Included RCT inclusion criteria*

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

TABLE 7 *Included RCT participant characteristics and follow-up*

	TAP		VIP	
	Intervention	**Control**	**Intervention**	**Control**
N	402	207	225	114
Mean age (years)	74.9	76.0	75	74
Women (%)	53.2	62.8	58	62
White (%)	98.5	98.1	99	98
Mean visual acuity in treated eye	52.8 letters	52.6 letters	66 letters	65 letters
Mean visual acuity in fellow eye	48.9 letters	51.8 letters	44 letters	48 letters
Proportion with visual acuity > 73 letters in fellow eye (%)	36.3	38.2	27	29
Lesion area subfoveal (%)	89.1	90.3	85	81
Some classic component (%)	89.8	90.4	24	19
Some occult component (%)	75.9	75.8	93	96
Follow-up at 12 months (%)	94.3	93.7	93.3	91.2
Follow-up at 24 months (%)	87.3	86.0	85.8	86.8
Mean no. treatments per patient (1st year)	3.4	3.7	3.14	3.55
Mean no. treatments per patient (2nd year)	2.2	2.8	1.81	2.36
Mean no. angiographies per patient	Not given	Not given	Not given	Not given

  - 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 visual acuity of less than 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 visual acuity.

Neither of the RCTs reported the impact of treatment on function (such as Nottingham Health Profile) on generic quality of life (such as the European Quality of Life measure) or vision-specific quality of life (such as the National Eye Institute 25-item vision function questionnaire (VF-25)).

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.

Blinding 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

coordinator 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 blinding of the ophthalmologists, patients, vision examiners and the people reading the fundus photographs. Although the two infusions were different colours (green versus 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, blinding 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 unblinded to treatment allocation. This was because of leaking infusions, angiographic fundus appearance after 1 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 with 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. 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.

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

(The majority of participants had some classic neovascular lesions.) The main results are summarised in *Table 8*.

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% CIs 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 2-year follow-up. In the placebo group the equivalents were 52.6 and 32.9 (with respect to the corresponding figures in *Table 8*. Note that five letters is approximately equivalent to one 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 2-year follow-up but not the 1-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 *Adverse events in included studies*, below).

VIP trial

(Minority of participants had some classic neovascular lesions.) The main results are summarised in *Table 9*.

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.

TABLE 8 *TAP – clinical and angiographic results at 1 and 2 years*

	TAP – 1 year			TAP – 2 years		
	Verteporfin PDT	**Placebo PDT**	**Relative risk (95% CI)***	**Verteporfin PDT**	**Placebo PDT**	**Relative risk (95% CI)***
Total no. of patients	402	207		402	207	
Lost 15 or more letters	156 (38.8%)	111 (53.6%)	0.72 (0.61 to 0.86)	189 (47.0%)	129 (62.3%)	0.75 (0.65 to 0.88)
Lost 30 or more letters	59 (14.7%)	49 (23.7%)	0.62 (0.44 to 0.87)	73 (18.2%)	62 (30.0%)	0.61 (0.45 to 0.81)
Mean visual acuity (no letters)	42	35	N/A	39.4	32.9	N/A
Mean change in visual acuity (lines)	–2.2	–3.5	N/A	–2.7	–3.9	N/A
Mean no. contrast sensitivity letters lost	–1.3	–4.5	N/A	–1.3	–5.2	N/A
Proportion with visual acuity of < 34 letters (< 20/200)	140 (34.8%)	99 (47.8%)	0.73 (0.60 to 0.89)	165 (41.0%)	114 (55.1%)	0.75 (0.63 to 0.88)
Progression of classic CNV†‡	177 (44.4%)	142 (68.9%)	0.64 (0.56 to 0.74)	NR (unclear)	NR (unclear)	N/A
Mean size of lesion§	NR	NR	N/A	NR	NR	N/A

* *Calculated using Review Manager software version 4.1*
† N = *399 and 206 for the verteporfin and placebo groups, respectively*
‡ *Unclear whether 2-year progression results are for all trial patients or a subgroup only*
§ *Lesion sizes reported in TAP trial as a histogram of size distribution*

TABLE 9 *VIP – clinical and angiographic results at 1 and 2 years*

	TAP – 1 year			TAP – 2 years		
	Verteporfin PDT	**Placebo PDT**	**Relative risk (95% CI)***	**Verteporfin PDT**	**Placebo PDT**	**Relative risk (95% CI)***
Total no. of patients	225	114		225	114	
Lost 15 or more letters	114 (51%)	62 (54%)	0.93 (0.75 to 1.15)	121 (54%)	76 (67%)	0.81 (0.68 to 0.96)
Lost 30 or more letters	NR	NR	N/A	67 (30%)	54 (47%)	0.63 (0.48 to 0.83)
Mean visual acuity (no letters)	NR	NR	N/A	NR	NR	N/A
Mean change in visual acuity (lines)	NR	NR	N/A	NR	NR	N/A
Mean no. contrast sensitivity letters lost	NR	NR	N/A	NR	NR	N/A
Proportion with visual acuity of < 34 letters (< 20/200)†	NR	NR	N/A	NR	NR	N/A
Progression of classic CNV	NR	NR	N/A	NR	NR	N/A
Mean size of lesion‡	NR	NR	N/A	NR	NR	N/A

* *Calculated using Review Manager software version 4.1*
† *Not reported despite being mentioned as an outcome of interest in the methods section of paper*
‡ *Outcome is mentioned but not reported*

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 visual acuity 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 *Adverse events in included studies*, below).

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.*

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[87] 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.

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 ten 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 6. These results relate to the outcome loss of less than 15 letters of visual acuity in the randomised eyes, and are hence the inverse of the results presented in *Table 8* (i.e. loss of 15 or more letters). Twelve 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; percentage 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 subgroup analysis, and the no occult component in the second subgroup analysis. By comparison, the effect size in the whole trial was relative risk 0.75 (95% CI, 0.65 to 0.88).

This subgroup analysis by percentage 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,[87] 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

* See addendum for further discussion of subgroup analyses

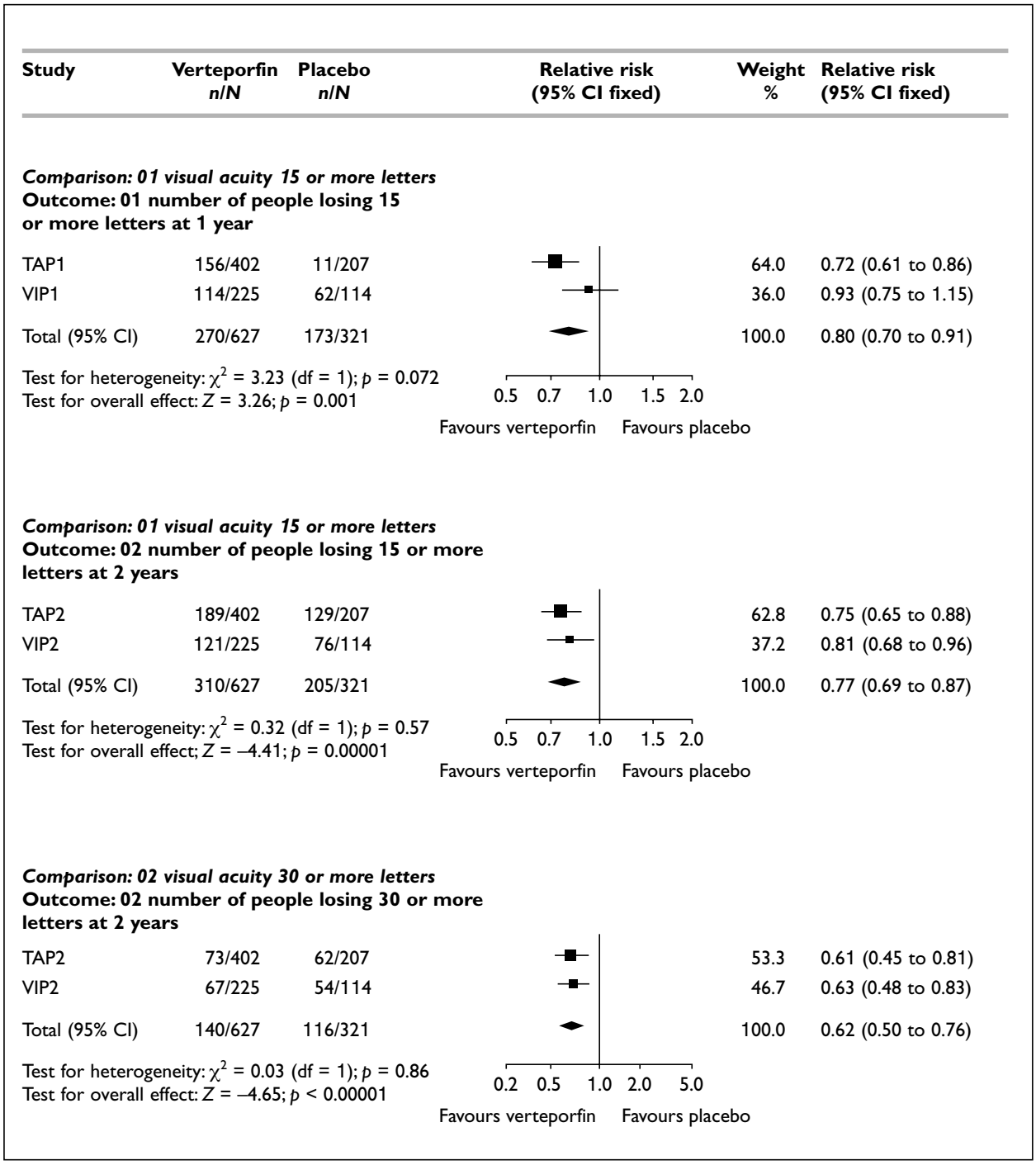

FIGURE 1 *Heterogeneity between TAP and VIP trials*

because the presence of occult disease and the percentage lesion composed of classic disease will tend to group patients in similar ways.

A corollary of the frailty of the subgroup results presented is that the results of the VIP trial do not lend any support to the subgroup findings from TAP. Of patients in the VIP trial, 94% had evidence of occult disease, with 76% having occult disease with no classic disease at all. A total of 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.

Study	Verteporfin n/N	Placebo n/N	Relative risk (95% CI fixed)	Weight %	Relative risk (95% CI fixed)
Comparison: 06 subgroup					
Outcome: 01 predominantly classic					
01 predominantly classic					
TAP2	65/159	57/83		0.0	0.60 (0.47 to 0.75)
02 minimally classic					
TAP2	106/202	58/104		0.0	0.94 (0.76 to 1.17)
03 occult only					
TAP2	18/41	14/20		0.0	0.63 (0.40 to 0.98)
			0.1 0.2 1.0 5.0 10.0		
			Favours verteporfin Favours placebo		
Comparison: 06 subgroup					
Outcome: 02 any occult					
01 yes occult					
TAP2	159/305	93/157		0.0	0.88 (0.74 to 1.04)
02 no occult					
TAP2	28/93	35/49		0.0	0.42 (0.30 to 0.60)
			0.1 0.2 1.0 5.0 10.0		
			Favours verteporfin Favours placebo		

FIGURE 2 *Claimed subgroup effects in TAP*

There is therefore no strong evidence that there are subgroups of patients who benefit more or less from verteporfin PDT. The subgroup 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.

Adverse events in included studies

The first year and cumulative 2-year safety and adverse event data are shown in *Tables 10* and *11*.

In general there seem to be increases in all adverse events anticipated and reported in the treatment arm compared with placebo in both trials, with the exception of allergic reactions. Of concern are the statistically significant increases in adverse events associated with treatment (TAP and VIP) and visual disturbance (VIP). One adverse event of particular concern is severe visual acuity loss within 1 week (loss of 20 letters). Although this is relatively rare (0.7–4.4%) 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.

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.

TABLE 10 *First-year safety and adverse events for TAP and VIP trials*

	TAP		VIP	
	Verteporfin	**Placebo**	**Verteporfin**	**Placebo**
Total no. of patients	402	207	225	114
Mortality	8	4	NR	NR
Severe visual acuity loss within 1 week (loss of 20 letters)	NR	NR	NR	NR
Visual disturbance	71 (17.7%)	24 (11.6%)	NR	NR
Adverse event associated with treatment	185 (46.0%)	74 (35.7%)	NR	NR
Stopped treatment from adverse event	7 (1.7%)	0	NR	NR
Injection site adverse events	54 (13.4%)	7 (3.4%)	NR	NR
Allergic reactions	5 (1.2%)	7 (3.4%)	NR	NR
Photosensitivity reactions	12 (3.0%)	0	NR	NR

TABLE 11 *Cumulative 2-year safety and adverse events for TAP and VIP trial*

	Verteporfin	**Placebo**	**Relative risk* (95% CI)**	**Verteporfin**	**Placebo**	**Relative risk* (95% CI)**
Total no. of patients	402	207	0.84	225	114	0.68
Mortality	13 (3.2%)	8 (3.9%)	(0.35 to 1.99)	4 (1.8%)	3 (2.6%)	(0.15 to 2.97)
Severe visual acuity loss within 1 week (loss of 20 letters)	3 (0.7%)†	?0†	3.61 (0.19 to 69.62)	10 (4.4%)	0	10.69 (0.63 to 108.75)
Visual disturbance	89 (22.1%)	32 (15.5%)	1.43 (0.99 to 2.07)	94 (41.8%)	26 (22.8%)	1.83 (1.26 to 2.66)
Adverse event associated with treatment	192 (47.8%)	70 (33.8%)	1.41 (1.14 to 1.75)	96 (42.7%)	21 (18.4%)	2.32 (1.53 to 3.51)
Stopped treatment from adverse event	7 (1.7%)	0	7.74 (0.44 to 134.90)	8 or 9† (3.6% or 4.0%)	0 or 1‡ (0.6% or 0.9%)	9.67 (0.57 to 164.65)
Injection site adverse events	64 (15.9%)	12 (5.8%)	2.75 (1.52 to 4.97)	18 (8.0%)	6 (5.3%)	1.52 (0.62 to 3.72)
Allergic reactions	8 (2.0%)	8 (3.9%)	1.37 (0.37 to 5.12)	3 (1.3%)	3 (2.6%)	0.51 (0.10 to 2.47)
Photosensitivity reactions	14 (3.5%)	0	14.97 (0.90 to 249.68)	1 (0.5%)	1 (0.9%)	0.51 (0.03 to 8.03)

* *Calculated using Review Manager software version 4.1*
† *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*

In this respect, unfortunately, the included RCTs provide no direct information, such as might be obtained from instruments measuring quality of life such as the Short Form – 36-item or EuroQol – 5 dimensions, or vision-specific quality of life instruments, such as VF-25.

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 in the TAP trial (who mostly had classic 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 relative risk was 0.75 (95% CI, 0.65 to 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 a number needed to treat (NNT) to avoid one person losing 15 letters (three 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 to 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 of this risk.

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 quality of life 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 chapter 3.

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 quality of life 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 (i.e. pure occult neovascular lesions) and on the effects of SnET2 PDT. It is also apparent that there are many areas of potential importance where no research appears to be planned.

Another issue is that we believe that the subgroup 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 (see addendum for further discussion of subgroup analyses). Estimates of effect should be based on whole trial results, not estimates arising from subgroup analyses. Using subgroup 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% (i.e. 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 chapter 3. The absence of any believable subgroup effect also has implications for rational targeting of 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 in some respects but not others. There were four other completed systematic reviews found on PDT. One[58] reviewed the 1- and 2-year TAP trial results and the remaining three reviewed the 1-year results of the TAP trial only.[61] Two were very positive about PDT[88,89] 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[58] did mention impact on quality of life and the impact of the second eye. It also echoed our concerns regarding 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[90] stated that: "It is not known whether this benefit (of PDT) leads to a real improvement in daily life activities". It also mentions that the retrospective subgroup analyses provide only weak evidence and that further trials are needed.

Summary

Studies identified

- A total of 417 potentially relevant citations were initially identified from the searches.
- A total of 28 required detailed scrutiny to include/exclude.
- A total of 23 were excluded; the main reasons for which were not RCTs ($n = 7$), not RCTs of PDT ($n = 3$) and duplicate reports of RCTs found ($n = 13$).
- Six RCTs were identified (five from the searches, one from a conference), but four of these were ongoing 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 ongoing 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 ongoing 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 plus 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 large minority 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 2 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 reasonable to combine their results.

Results

- In TAP (majority have classic neovascular lesions) there was consistent evidence at both 1 and 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 (three lines) or more at 2 years was 0.75 (95% CI, 0.65 to 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 insufficient grounds for using a summary estimate of effect obtained by combining the results of TAP and VIP.
- Extensive subgroup 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 0.7–4.4% 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.

Chapter 3
Economic analysis

Methods for economic analysis

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[91] and has subsequently been established in other reviews.[92]

Search

The following sources were searched for information on costs, cost-effectiveness and quality of life:

- bibliographic databases: MEDLINE (Ovid) 1993 – August 2001; NHS EED and DARE (Cochrane library, 2001, issue 3)
- Internet sites of national economics units.

Details of the search terms used are given in appendix 4. 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. Inclusion and exclusion decisions were made independent of any study authors. Studies were only included if they met the following criteria.

- **Study design**: any study type
- **Population**: adults with any AMD
- **Intervention**: PDT using any photosensitive drug
- **Outcomes**: costs, cost consequences, cost–utility, cost-effectiveness or any generic quality of life measure.

One researcher extracted data from the included studies and a second researcher checked this. Data extraction was performed independently of any study authors.

There were three stages used for the review of cost and economic studies. In Stage 1 each study was categorised 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 that have been used in a previous published review by one of the current authors.[92]

Analysis

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

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

* See addendum for further discussion on economic evaluation.

effectiveness searches. BSC only 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 plus 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 1- and 2-year results. The VIP trial was not considered, both because it deals with an indication for verteporfin PDT that is not currently licensed and because the finding 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.

Results

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 7. In brief the search identified 64 articles (plus seven duplicates) 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 three reached Stage 3 of the review and none of them passed the quality assessment stage. Details of these three excluded studies are given in appendix 8.

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

Meads C and Moore D. The clinical effectiveness and cost utility of photodynamic therapy for age related macular degeneration. Report No. 24, November 2001. WMHTAC, Department of Public Health and Epidemiology, University of Birmingham

Description: The evaluation took the form of a cost–utility analysis that 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[40,41,94] were used to link the visual acuity estimates of patients in the TAP trial at follow-up to utility values using the TTO technique. The costs of PDT were disaggregated into the costs of one typical treatment. The cost of the drug was £850 at 2000 prices. The cost data were taken from one main published source (National Schedule for Reference Costs[95]) 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 quality-adjusted life-year (QALY) of treatment compared with 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 focused on the two main areas of uncertainty namely the translation of health states into utilities and costs of both 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.

***Sharma S, Brown G, Brown M, Hollands H, Shah G. The cost effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularisation secondary to age-related macular degeneration.* Ophthamology *2001; 108:2051–9.*[96]**

Description: The evaluation took the form of a cost–utility analysis. It assessed PDT for the

treatment of subfoveal CNV in patients with disciform degeneration in one eye (i.e. end-stage wet AMD causing blindness) and whose second better-seeing eye develops visual loss secondary to predominantly classic subfoveal CNV. 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 with placebo for 2 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 were taken from the TAP trial. The authors have a track record of published studies that derive patient-based utilities linked to visual acuity, which have also provided the source of the utility estimates[40,41,94] 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 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 and co-workers[97] and the recommendation that healthcare technologies are considered cost-effective if they cost less than US$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 with 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 cost /QALY for PDT treatment was US$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 neovascular membranes who received PDT was 0.8816. This compares with 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 cost/QALY for PDT treatment was US$173,984.

The authors conclude that within the recommendations of Laupacis and co-workers,[97] 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 US$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, equivalent UK values (2000) for those presented in the paper by Sharma and co-workers are provided in *Table 12*.

Novartis submission to NICE, October 2001. Section 1.4: Economic Burden of AMD (and Novartis Appendix 2, Care pathways).[79]

Description: This section of our discussion of the Novartis 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 (ScHARR), sponsored by the pharmaceutical company.

In Novartis Appendix 2, a flow diagram is presented that makes explicit the diagnosis and treatment decisions, and which leads to a typical

TABLE 12 *Sharma* et al. *costs associated with PDT in US$ for 2000 and converted into £sterling*[96]

Cost per visit	US$	£sterling
Visit	162	114
Fluorescein	380	267
Angiography photography	75	53
Verteporfin cost	1453	1021
Laser fee	544	382
Total	2702	1899
Incremental cost of treatment	1822	1281
Cost per QALY for PDT (Initial visual acuity = 20/40)		
2-year model	86,721	60,954
11-year model	43,547	30,608
Cost per QALY for PDT (Initial visual acuity = 20/200)		
2-year model	173,984	122,288
11-year model	87,197	61,288

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 general practitioner 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 trusts was £63–149). 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,[79] 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[79]) 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 are 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 less than 6/24. For PDT, using evidence based on the TAP studies, after the first verteporfin treatment a patient will see the consultant ophthalmologist every 3 months making a total of 12 visits over 3 years. Fluorescein angiography is conducted at each visit and, if there is any new leakage, the patient is given repeat PDT with verteporfin. 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 13*. The average annual cost of PDT with verteporfin is shown to be £2435. 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]

In Section 5 of Appendix 2, BSC is discussed in terms of visual rehabilitation, the provision of low-vision aids and the strategies that are

TABLE 13 *Cost of 3-year verteporfin PDT treatment course (from Novartis Industry Submission Appendix 2)*[79]

Resource	Cost estimate (£)	Units consumed	Total cost (£)
Fluorescein angiography (digital)	63	12	756
Verteporfin	850	7	5950
Consultant ophthalmologist	54.50	7	381.5
Staff nurse (day ward) (40 minutes)	20.67	7	144.69
Laser	5.96	7	41.72
Total over 3 years			**7304**
Average annual cost of PDT with verteporfin			**2435**

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 (DSS, now the Department for Work and Pensions) in terms of The Disability Living Allowance and Attendance Allowance 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 DSS 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 (Novartis Appendix 2, page 14[79]) which present a breakdown of the relevant costs to the DSS. 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 but the calculations 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 of 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).[79]

Description: An economic model was used to assess the cost-effectiveness of verteporfin PDT compared with placebo. The model took a Markov approach and was based on the data from the TAP trial. In the model the proportion of patients in each of 18 possible visual acuity states is calculated for each 3-monthly period, which was the time between measurements in the TAP trial. For the first 2 years of the model the transition matrices are based directly on the TAP trial data and the proportions following through each transition reflect closely those found from the trial data. Beyond the 2 years of the TAP trial, assumptions had to be made as to the further progression of patients in both cohorts.

Utility values were attributed to each of the visual acuity states, allowing QALYs as well as vision years to be used as outcome measures. The authors note that the TAP trials showed that verteporfin also had significant benefit in reducing loss of contrast sensitivity, but that no utility estimates linked to contrast sensitivity were available in the literature. Only studies linking visual acuity to utilities were available in the literature. Consequently the effect on contrast sensitivity is not considered in the model. This is likely to lead to an underestimate of the difference in QALYs gained between the verteporfin PDT and placebo-treated patient in the model and overstate the relative cost-effectiveness ratio.

In Novartis Appendix 7, the visual acuity measures are presented. It is not specifically stated, but it appears that the main outcome measure used is the change in visual acuity in terms of a change of 0.1 in the logMAR scale. The use of TAP data in the model and their application to clinical practice is also described. In order to demonstrate how verteporfin PDT is used in practice the patients were divided into responders and non-responders at 6 months. It is assumed that 26% of patients would be classified into non-responders who would receive no more than two treatments, although it is not clear that the estimate of 26% is justified.

The calculation of the transition matrices are presented and the approach appears to be logical and sound. The authors model outcomes

of visual acuity beyond those recorded in the TAP trial and attempt to establish that the rate of decline in visual acuity of the two cohorts has stabilised. They argue that: "Using the last 3 months of data reflect an aberrant kink in the curve and ignores the evidence of the rest of that year that on average the patients eyesight is relatively stable" (page 8[79]). They suggest that the patients' eyesight is changing at a fairly constant rate in the second year, and therefore it is reasonable to assume that transition matrices based on the 2-year data will give realistic projections beyond the trial data. However, there is no firm evidence to support the assumption behind this projection. The authors argue that to ignore their (implied) evidence would severely underestimate the cost-effectiveness of the treatment. Sensitivity analyses are presented on the basis of projection.

Other data used in the model include mortality data, utility values and costs. The utility values, which link quality of life to visual acuity, were taken from the studies by Brown and co-workers[40] (see *Review of research on quality of life in AMD* and *Table 15* below). The work of these authors is well established in the AMD literature. Sensitivity analysis is presented around these values.

There are three main categories of costs that have been considered in the model; the cost of verteporfin treatment, the transition costs of becoming blind and the ongoing costs of being visually disabled. As the authors state the costs and their sources were described in the care pathways of Novartis Appendix 2. The direct costs of the treatment presented were directly taken from the sources cited in that section and are unproblematic. However, the final tables of costs which presented the costs of developing partial sight and the costs of going blind did not follow from the logical breakdown and explanation that preceded them. So there is uncertainty about much of the cost data, which provide the basis for *Table 3.5.3: One off costs associated with declining vision*,[79] in this section of the submission.

In the cost scenarios, the authors state that costs are discounted by 6% and benefits by 1.5% annually. This is the recommendation of NICE. But NICE also recommends carrying out sensitivity analyses around setting the discount rates for costs and benefits to 6% and this does not appear to have been done.

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 five different time horizons: 2 years, 5 years, 7 years, 10 years and lifetime. Similar results are presented for outcomes for the same five periods, both in terms of vision years and QALYs. These are reproduced in *Table 14*.

Comment: The model presented in Section 3 of the Novartis Industry Submission was clearly presented and appears to be basically sound and it satisfied our predetermined quality criteria for economic evaluations with the exception of one. The outcome measure used in the economic model was not explicitly stated although it was implied. In terms of the predetermined quality criteria for cost studies it was questionable on three of the points.

First, although the methods for the estimation of unit costs are described in Novartis Appendix 2 these were confusing as already mentioned. Second, price and currency data are not made explicit anywhere. It is apparent that much of the cost data are taken from sources published in 2000 (e.g. Netten and Curtis[113]), but it would have been helpful if an explicit statement had been made about which year the price data refer. Finally some of the costs came from different sources published at different points in time so an explicit statement explaining inflationary adjustments for example, would also have been helpful.

Appropriate sensitivity analyses were carried out for some of the important assumptions presented in the analysis. Sensitivity analysis was carried out on the assumption that 26% of patients would be classified into non-responders, and all patients were assumed to continue treatment. This does have a significant impact on the cost-effectiveness ratios.

Sensitivity analysis was also carried out on the projections beyond the end of the TAP trial.

TABLE 14 *The cost-effectiveness ratios for verteporfin versus placebo as presented in Novartis Industry Submission to NICE*[79]

	2 year	5 year	7 year	10 year	Lifetime
Marginal cost per vision year (£)	13,096	6,044	4,547	4,174	2,996
Marginal cost per QALY (£)	70,492	33,137	24,986	19,516	14,754

The most important point here is that the model assumes that visual acuity will be stable over time and that the second-year results can be used to extrapolate to the future. But there is no evidence underlying this assumption as the TAP trial provides evidence for only 2 years. Furthermore, the model does not take into account the fact that the recurrence rate for wet AMD in the second eye is approximately 42% at 5 years.

The sensitivity analysis on the utility values is appropriate as is that carried out on costs, but there is doubt over the cost figures presented because of the confusion in Novartis Appendix 2.

The results of sensitivity analyses on the discount rates used for costs and benefits would have been interesting. If benefits had been discounted at the same rate as costs at 6% then the cost-effectiveness ratios for the 5-year and beyond scenarios would have been higher.

Furthermore, threshold analysis assessing the impact of different visual acuity starting levels and their response to treatment would have been beneficial. There is some suggestion from the TAP trial subgroup analysis to show that the effectiveness of treatment depends on the visual acuity level before treatment,[99] suggesting that the clinical effectiveness of PDT treatment is less if patients start with better visual acuity.

There are a number of concerns about the validity of the modelling exercise. First, the sample sizes used to estimate the transition matrices for the Markov models were exceedingly small. The transition matrices are of dimension 18 × 18, meaning that 324 transition probabilities needed to be estimated for each one. It is somewhat doubtful that this could have been adequately achieved with the small sample sizes of patients in the verteporfin and placebo arms (115 responders, 83 placebo). Conventionally in contingency table analysis, the prescription is that the sample size should be at least 5 for each probability estimated. Thus, the sample sizes may have been too small to enable accurate estimation of the transition matrices required to implement the Markov approach chosen by Novartis.

Related to this, there are also concerns about the way that losses from the sample due to death or other causes were dealt with in estimating their transition matrices. Basically, these transition matrices do not allow death or losses from the sample to occur: there is no absorbing state in the model. Instead, when a patient is lost from the sample between successive periods, they attempt to impute what their subsequent behaviour would have been by looking at the transitions made by surviving patients who were in the same state as the person who was lost. The justification for doing this is unclear and it may have distorted the results. Another way of doing this would be to simply ignore the drop-outs when estimating transition probabilities for subsequent periods, rather than try to impute their transitions. Either way, the assumption is being made that the reason for the drop-out was not connected to the treatment, so it should (theoretically) make no difference to the probability estimates if these people are ignored when they drop out. It may be that it was deemed necessary to try to impute their behaviour because the small sample sizes were creating problems for the modelling. If this were the case, then we would question this modelling approach.

Another point of concern is the assumption in the model that patients could be categorised into two groups – responders who could continue to receive treatments at 3-monthly intervals throughout the modelling period and non-responders who Novartis assumed could never receive more than two treatments. As Novartis themselves admit in their report, this assumption is at odds with the procedures adopted in the TAP trial where all patients in the verteporfin arm continued to receive treatment if there was evidence of leakage, even if continuing decreasing visual acuity suggested that the patient was not benefiting from treatment. They argue that the TAP trial approach is unrealistic because, in practice, ophthalmologists would not continue treatment if a patient's visual acuity score declined instead of improving after 6 months. As shown by sensitivity analyses presented later in their report, the effect of this assumption is to significantly reduce the incremental cost-effectiveness ratio (ICER) for PDT relative to BSC, making it appear more cost-effective. The validity of this assumption therefore needs to questioned.

The model attempts to project beyond the 2-year period covered by the TAP trial. The longer they extend the models beyond the end of the TAP trial, the more dramatic the decline seems to be in the ICER of PDT relative to no treatment, making PDT appear to be more and more cost-effective. Novartis argue that this is because most or all of the costs of treatment are incurred in the first few years of treatment, whereas the benefits continue to accrue beyond this time frame. This however, is an **assumption** not a **result** of their model, and one

that is not supported by any empirical evidence. To project beyond the end of the trial, they used transition matrices that they estimated using the second-year data from the TAP trial, arguing that the eyesight of patients is changing at a constant rate by the second year so it is reasonable to treat the transition matrices as being constant from then on. There is no reliable empirical evidence at all for this assumption, and therefore no justification for extending the models beyond the 2-year period of the trial in this way.

Another aspect of the Novartis Industry Submission modelling exercise that needs to be questioned is the choice of the subsample of 115 predominantly classic responders, on which they based their analysis. This differs from the sample used in the TAP trial (402 patients in the treatment arm, 207 patients in the placebo arm), and there is no clear justification given for this. It is necessary to ensure that the choice of subsample was justified on the basis of valid *a priori* considerations, and that it was not chosen after 'data dredging' to try to identify the subsample that yielded the most favourable results in terms of the cost-effectiveness of PDT.

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 may not be comparable. 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 2-year model, for an initial visual acuity of 20/200, of £122,288 in the study by Sharma and co-workers. But the study by Meads and Moore did not specify the initial visual acuity score.

In their 2-year model with an initial visual acuity of 20/40, the Sharma study estimated the cost per QALY to be approximately £60,954. This is similar to the estimate of the Novartis Industry Submission of £70,492 per QALY although an initial visual acuity is not specified in the Novartis 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 has been converted to UK currency. But international comparisons may not be appropriate, as many resource components, such as staff costs, can be valued differently in different countries.

Both the Sharma study and the Novartis Industry Submission model outcomes beyond the end points of the 2-year TAP trials. For the projections beyond 2 years the discounting of the costs and benefits will have an impact. In the Sharma study both costs and benefits have been discounted at the same rate of 3% as recommended by the Washington Panel[100] for the USA. The Novartis Industry Submission has followed the NICE recommendations and discounted costs by 6% and benefits by 1.5%. This inconsistency in the discounting approach will favour the cost per QALY results for the Novartis Industry Submission because the discounted costs will be relatively lower and their discounted benefits will be relatively higher than the costs and benefits presented in the Sharma study.

For a comparison of the cost–utility studies see page 40.

Review of research on quality of life in AMD

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

However, there are good-quality studies that measure utility in AMD using TTO 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 TTO technique.[40] The utility values are shown in *Table 15*. (These same utility values are used in the Novartis Industry Submission and the two other cost–utility analyses reviewed in this report.)

TABLE 15 *Utilities for given levels of visual acuity for the better-seeing eye in AMD (inputs to WMHTAC model)*

Visual acuity	Utility (TTO)	95% CI
20/20–20/25	0.89	0.82 to 0.96
20/30–20/50	0.81	0.73 to 0.89
20/60–20/100	0.57	0.47 to 0.67
20/200–20/400	0.52	0.38 to 0.66
Count fingers to light perception	0.40	0.29 to 0.50

Note that a decrease in visual acuity in the worse-seeing eye does not appear to cause a drop in utility (see chapter 1, *Significance in terms of ill-health (burden of disease)*).[42]

Review of cost data, and estimation of costs

No published studies were identified that had detailed investigations of costs for PDT compared with placebo. No cost data were 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.[76] We estimate that the disposable materials used 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 1 week before PDT in order to localise the lesion. The patients then return a week later in order to undergo the procedure if required. Whether the procedure is required or not, an assessment is still made following the angiogram and a follow-up appointment carried out. The costs for each of these elements are shown in *Table 16*. 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 16 *Costs for verteporfin PDT treatment (inputs to WMHTAC model)*

Item	Cost (£)
Verteporfin and disposables[76]	860
Laser[95]	101
Angiography[95]	108
First outpatient appointment for PDT[95]	68
Follow-up outpatient appointment[95]	44

In the TAP trial each patient received a PDT treatment at time 0 and then had an angiography session every 3 months until 21 months and was then followed-up at 24 months. 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 appointment 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 17*.

TABLE 17 *Costs and probability of PDT by number of treatments (inputs to WMHTAC model)*

No. of treatments	Probability	Undiscounted costs (£)
1	0.045	2245
2	0.072	3206
3	0.102	4167
4	0.085	5128
5	0.144	6089
6	0.127	7050
7	0.137	8011
8	0.288	8972

From the figures in *Table 17,* costs were calculated corresponding to each possible number of treatments. For example, the mean costs for a patient who had two treatments (and therefore six 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 all eight treatments. Therefore if more than one and less than eight 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

Sensitivity analysis was undertaken to incorporate the observed uncertainty around high and low combined costs of laser, angiography, assessment and outpatient appointment for PDT.[95] The high and low estimates are the minimum and maximum ranges for 50% of NHS trusts and are presented in *Table 18*.

TABLE 18 *Sensitivity analysis on costs of verteporfin PDT treatment (inputs to WMHTAC model)*

Item	Cost (£)	High estimate (£)	Low estimate (£)
Verteporfin and disposables	860	–	–
Laser	101	102	52
Angiography	108	149	63
Assessment	44	54	34
Outpatient appointment for PDT	68	84	51

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.

One study was found that estimated the cost of blindness in the UK (Scotland in 1981–82).[101] Their estimate of the cost per blind adult was £3575 and included staffing costs of the Blind Welfare Service and from state benefits. Using the Retail Price Index (to December 2000) this equates to £7433.

An Australian study[102] estimated that the direct financial costs to the government and community of blindness of a pensioner (male over 65 years, female over 62 years) was Aus$14,686 (range, $9749–22,507). Using average 1999/00 exchange rates this converts to £5795 (range, £3847–8881). 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 Retail Price Index. 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 19*. 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[12] and the number of registered blind and partially sighted people. Frequently, the Royal National Institute for the Blind (RNIB) survey has been quoted, suggesting that only 50% of those eligible are actually registered.[29] However, the prevalence estimate for vision impairment in this RNIB survey is well outside the 95% CIs of the recent review (500,000 versus 312,000), which suggests that the earlier study is less accurate. A second RNIB survey, focusing on older visually impaired people, gives a 93% registration rate.[30]

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 years. 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

TABLE 19 *Estimate of costs of blindness (inputs to WMHTAC model)*

Outcome	Estimated cost (£)	Estimate of the proportion with CNV and 20/200 visual acuity who would have this outcome in 1 year (%)
Blind registration	59.70[103] + 37.71[98]	94.5[12]
Low-vision aids	136.33[104]	33[45,46]
Low vision rehabilitation	205.30[98]	11[29]
Housing benefit and council tax benefit	2714.40[105]	45[29]
Social security	1924[106]	63[30]
Tax allowance	319[107]	5[29]
Depression	391.97[108]	38.6[38]
Hip replacement	3669[95]	5[31,33,95,109]
Community care	2848.63[98]	6[30]
Residential care	15,904.41[98] (–30%)	30[12,20,32]

psychiatric hospital in the UK. The sample was small (n = 28) with an 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.[110]

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 £6455. In the second and subsequent years of blindness this figure falls to £6295 per annum.

This does not take into account all of the costs to the individual concerned, both financial and emotional.[111]

Sensitivity analysis around cost of rapidly deteriorating vision

There is uncertainty about particular components of these costs. The issues are detailed in appendix 9 and summarised in *Table 20.*

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 £1375–17,100. In the second and subsequent years of blindness this range falls to £1325–16,800 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.

TABLE 20 *Sensitivity analysis on costs of blindness (inputs to WMHTAC model)*

Outcome	High cost (£)	Low cost (£)	High probability (%)	Low probability (%)
Blind registration	169.73[98,103]	40.10[103]	94.5[12]	50[29]
Low-vision aids	136.33[104]	56.41[104]	74[29]	33[46]
Low vision rehabilitation	309[95]	125[95]	11[29]	11[29]
Housing benefit and council tax benefit	3588[105]	2412.80[105]	73[29]	21[29]
Social security	2875.60[106]	0	63[30]	17[29]
Tax allowance	319[107]	145[107]	18[29]	5[29]
Depression	391.97[108]	391.97[108]	50[39]	6[37]
Hip replacement	3933[95]	1177[95]	24.7[27,31,95]	0.5[20,95]
Community care	4,758.80[98]	1138.36[98]	40[29]	6[30]
Residential care	23,584.28[98]	7,843.27[98]	56[112]	13[33]

WMHTAC Economic model of cost–utility

*WMHTAC 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™ 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 eight branches representing the possible number of treatments over the 2-year follow-up. At the end of each of the eight branches is a further chance node with seven branches representing the seven possible utility outcomes. At the end of the BSC arm there is a chance node with seven branches representing the seven 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*.

There are three 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 were unable to obtain data that would have enabled us to distinguish utility outcomes for different numbers of PDT treatments.
- The utilities reported are cumulative utilities over the 2-year period. This uses the assumption that the difference in utilities for the two groups at start is zero. Over the 2-year period the utility declines at a steady rate in both groups, but declines less in the PDT group than the placebo group. At 2 years the difference in utility between the two groups is the same as the cumulative difference over the 2-year period (see appendix 10; NB. this should be read in conjunction with the addendum).
- 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. The 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 WMHTAC model

The effectiveness data are based on the whole trial results of TAP, not the subgroup analyses. The WMHTAC 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:

- ≥ 6-line increase
- ≥ 3- to < 6-line increase
- ≥ 1- to < 3-line increase
- no change
- ≥ 1 to < 3-line decrease
- ≥ 3- to < 6-line decrease, and
- ≥ 6-line decrease.

The number of lines was then converted to the number of letters by multiplying by 5 (there are five letters to a line in the Early Treatment Diabetic Retinopathy Study 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 15*.

The result is shown in *Table 21*. This table also shows the probabilities of being in each of the seven categories for PDT and placebo groups.

Cost data for WMHTAC model

Cost data were taken from our estimates of costs reported above (see *Review of cost data and estimation of costs*).

Sensitivity analyses used in WMHTAC model

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

- effectiveness – this incorporates uncertainty due to both small sample size and using results from only one trial. The sensitivity analyses were around estimates of effectiveness for

* See addendum for further discussion of the West Midlands Health Technology Assessment Collaboration (WMHTAC) model.

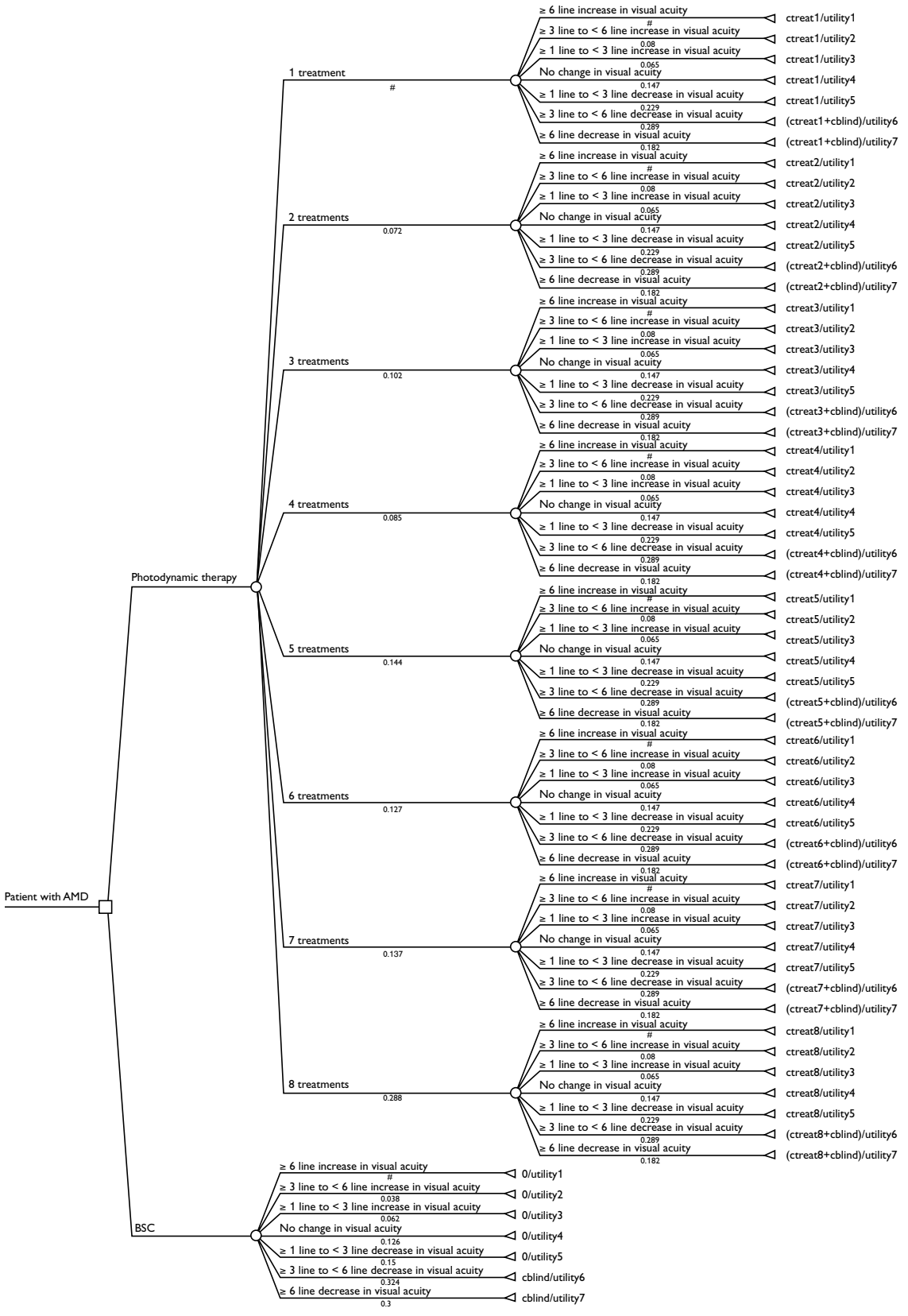

FIGURE 3 *Decision tree for WMHTAC economic model*

TABLE 21 *Utilities and probabilities for visual acuity at 24 months for PDT and BSC (inputs to WMHTAC model)*

Change in visual acuity (lines)	Mean utility score	PDT probability	BSC probability
≥ 6-line increase	0.89	0.008	0
≥ 3-line to < 6-line increase	0.81	0.080	0.038
≥ 1- line to < 3-line increase	0.81	0.065	0.062
No change	0.57	0.147	0.126
≥ 1-line to < 3-line decrease	0.52	0.229	0.150
≥ 3-line to < 6-line decrease	0.52	0.289	0.324
≥ 6-line decrease	0.40	0.182	0.300

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 10.
- utilities – the high and low utility scores from the published paper linking visual acuity to utility score were incorporated (see *Table 15*).
- costs of verteporfin PDT (see *Table 18*)
- using discounting at 6% or undiscounted costs of verteporfin PDT
- costs averted by avoidance of blindness (see *Table 20*).

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 this to be 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 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,[40,41,94] 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.

*WMHTAC model results – base case**

The base-case results are shown in *Table 22*. 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 22 *WMHTAC model base-case results*

	1 year of blindness	2 years of blindness
Incremental cost of PDT	£5,658	£4,695
QALYs gained	0.0311	0.0311
ICER	£182,188	£151,179

The results indicate that PDT is associated with a cost–utility of between £151,000 and £182,000 over 2 years.

*WMHTAC model results – sensitivity analysis**

All of the sensitivity analyses were carried out using the costs of blindness for 1 year only (except for varying the costs of blindness) so vary around the cost–utility estimate of £182,188. For results see *Table 23*.

Before varying the estimate by best- and worst-case effectiveness scenarios (see appendix 10), the fitted data for the base-case model were compared with the trial effectiveness data. This effectiveness distribution reduced the cost–utility estimate to £137,000. The fitted

* This should be read in conjunction with the addendum.

TABLE 23 *Results of sensitivity analysis, WMHTAC cost–utility model*

		Base case (£)	Upper variable (£)	Lower variable (£)
Effectiveness	Trial data	182,000		
	Fitted data	137,000	304,000	83,000
Utility		182,000	179,000	179,000
Cost of PDT		182,000	196,000	158,000
Cost of blindness		182,000	129,000	207,000
			Worst case	**Best case**
All variables		182,000	342,000	47,000

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 1 year only increased the cost–utility to £207,000. Using the highest cost of blindness over 2 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 with 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.

Limitations of the cost–utility analysis (WMHTAC model) and comments[*]

The WMHTAC 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 2 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 details of the model at the beginning of this section. If the data that were 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. However, in addition to the model presented, we did investigate model structures that did not require as many assumptions. These made no difference to the estimates of cost–utility, and are hence not presented, but details are available from the review team on request.

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 2 years of follow-up.

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

[*] This should be read in conjunction with the addendum.

Comparison of cost–utility studies

A comparison was made of the three cost–utility studies found in the review of past cost, cost-effectiveness and cost–utility studies section and the cost–utility model developed for this report. The results are shown in *Tables 24*, *25* and *26*.

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 1 year, 7500 will have uncomplicated wet AMD and 5000 will develop classic AMD. The numbers of treatments as per the TAP trial were 3.4 in the first year, 2.2 in the second and 1.4 in the third years. Our estimate of the cost of PDT is £1181, with low and high estimates of £1060–1249. This means that the first year's cohort of classic AMD would cost £20.1 million. As there will be a new cohort of 5000 each year, by the third year the cost will rise to £41.3 million (£37.1–43.7 million) per year. If the licensed indication for PDT is extended to occult (applications already in place in Europe and Canada[74,75]) then the costs will

TABLE 24 *Review of economic studies: economic evaluation and costs*

Criterion	Meads & Moore[82]	Sharma *et al.*[96]	Novartis/ScHARR[79]	WMHTAC
Comparators	PDT (verteporfin) and placebo	PDT (verteporfin) and placebo	PDT (verteporfin) and placebo	PDT (verteporfin) and placebo
Perspective	Health Sector and Society	For-profit third-party insurer	Health Sector and Society	Health Sector and Society
Type of economic evaluation	Cost–utility (incremental cost per QALY gained)	Cost–utility (incremental cost per QALY gained)	Cost–utility (incremental cost per QALY gained) plus cost-effectiveness (incremental cost per vision year)	Cost–utility (incremental cost per QALY gained)
Source for effectiveness data	TAP trial	TAP trial	TAP trial	TAP trial
Cost of PDT	£4015.40 (first year only)	US$2702 (£1899) (total cost)	£2435 (average annual total cost)	£2245–8972 per annum depending on no. of treatments
Incremental cost	Not given	US$1822 (£1281)	£4447 (at 2 years); £5181 ('lifetime')	£5658 (including 1 year of blindness) £4695 (including 2 years of blindness)
Base-case ICER for 1–2-year model	£137,000 per QALY to NHS £120,000 per QALY when taking cost of blindness into account	US$86,721 per QALY (£60,954) with initial visual acuity of 20/40 US$173,984 per QALY (£122,288) with initial visual acuity of 20/200	£70,492 per QALY £13,096 per vision year	£182,188 (including 1 year of blindness) £151,179 (including 2 years of blindness)
Base-case ICER for extended model	N/A	11 years: US$43,547 per QALY with initial visual acuity of 20/40 US$87,197 per QALY with initial visual acuity of 20/200	10 years: £19,516 per QALY Lifetime: £14,754 per QALY (average life expectancy 7 years)	N/A
Funding	WM R&D	CNIB and research funds	Novartis	NCCHTA

TABLE 25 *Review of economic studies: data sources and analysis*

Criterion	Meads & Moore[82]	Sharma *et al.*[96]	Novartis/ScHARR[79]	WMHTAC
Effectiveness RCT	TAP trial 1st year	TAP trial 2 years plus projection	TAP trial 2 years plus TAP extension to 3 years plus projection	TAP trial 2 years
Effectiveness sample	Whole intervention versus whole placebo	Whole intervention versus whole placebo	Responder subgroup in predominantly classic subgroup versus placebo in predominantly classic subgroup	Whole intervention versus whole placebo
Address two-eye problem	Not mentioned	In discussion	Not mentioned	In discussion
Quality of life data	Published studies by Brown and Sharma[40,41] linking visual acuity to utility using TTO technique	Same published studies	Same published studies plus using linear regression	Same published studies
Resource use data for cost of PDT	Cost of PDT includes: cost of angiogram, first and follow-up outpatient appointment, verteporfin, laser treatment	Cost of PDT includes: cost of angiogram, first outpatient appointment, verteporfin, laser treatment	Cost of PDT includes: consultant time, nurse time, verteporfin and laser treatment, capital costs of laser	Cost of PDT includes: cost of angiogram, first and follow-up outpatient appointment, verteporfin, laser treatment
Sources for cost of PDT data	Visudyne advert, national schedule of reference costs, University Hospital Birmingham NHS Trust	1999 Medicare reimbursement tables	National schedule of reference costs, *BNF*, personal communication, patient flow research conducted by Novartis	National schedule of reference costs, *BNF*
Cost of blindness	1st year £3465	Not included	Transition costs to blind £152.79, to partially sighted £109.77 Ongoing costs per person £169.95 or £63.19 (social security) + ~£246 (residential care)	1st year £6455; subsequently £6295
Sources for cost of blindness	National schedule of reference costs, DSS, RNIB, NHS executive, unit costs of health and social care, Inland Revenue, various published studies	N/A	Primary research by Novartis and ScHARR on pathway provision of services, unit costs of health and social care, RNIB, national schedule of reference costs, DSS, various published studies	National schedule of reference costs, DSS, RNIB, NHS executive, unit costs of health and social care, Inland Revenue, various published studies
Analysis	Decision model	Markov model	Markov model	Decision model
Price year	2000	1999 in paper	2000	2001
Discounting	No	3% for costs and benefits	6% for costs 1.5% for benefits	No

TABLE 26 *Review of economic studies: sensitivity analysis*

Criterion	Meads & Moore[82]	Sharma *et al.*[96]	Novartis/ScHARR[79]	WMHTAC
Approach	One way and best and worst scenario	One way (and two way)	?One way only	One way and best and worst scenario
Parameters	Translation of health states into utilities, costs of PDT and costs of blindness	Estimates of efficacy from the TAP trial, translation of health states into utilities and number of PDT treatments for the 11-year model, (and utilities and efficacy together)	Using whole of predominantly classic subgroup rather than responders only, how much of the 2-year TAP trial data to be used to calculate transition matrices for projection up to 10 years, translation of health states into utilities, cost of PDT and blindness	Effectiveness estimates, translation of health states into utilities, costs of PDT, discounted versus undiscounted costs of PDT and costs of blindness
Result (most sensitive first)	QALY, costs of PDT and blindness	Cost of PDT treatment, initial visual acuity, utilities, efficacy	Utilities, all patients continuing treatment, forecast basis, costs of PDT and blindness	Effectiveness estimates, cost of blindness, cost of PDT, utilities

rise to £30.1 million (£27.0–31.8 million) in the first year and £62.0 million (£55.6–65.6 million) per annum by the third year. If all people who present with wet AMD are treated with PDT it will cost £63.4 million (£56.9–67.1 million) in the first year and £130.6 million (£117.2–138.1 million) per annum by the third year.

Novartis estimate that the cost of verteporfin per person over 3 years would be £7304 and the average annual cost would be £2435. They estimate that 5000–7500 new cases could benefit from treatment and 4000 would be treated each year. They estimate that the incremental expenditure would be £7.95 million in the first year, rising to £16.64 million per year by the third year, remaining at that level thereafter (Novartis Industry Submission, page 44[79]). This assumes that if 4000 people were treated, in the first year the cost per person would be £1987.50, 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 two treatments in the first year and none thereafter is 26%
4. any training needs are ignored.

If the Novartis data are used, they estimate that there will be 21,000 new cases of wet AMD in the UK per annum and that 7500 will have predominantly classic AMD eligible for treatment under the current licensed indication. They estimate that the cost of PDT is £931 (but this does not include the cost of angiography of £108.00). Using the same numbers of treatments as per the TAP trial, the cost of treating predominantly classic AMD would be £23.7 million (£22.4–23.9 million) in the first year. By the third year it would rise to £48.9 million (£46.1–49.2 million). If all people with new wet AMD were treated the first year costs would be £66.5 million (£62.8–67.0 million) rising to £136.9 million (£129.2–137.9 million) 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 chapter 4.

By way of comparison, the National Service Framework for Older People has set aside a budget of £150 million in 2000/01 rising to £405 million in 2003/04 to pay for intermediate care intended, among 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 £5.4 million (£2.9–7.0 million). Using the Novartis estimate the cost in the UK would be £7.2 million (£3.8–9.4 million).

Discussion and conclusions*

Our estimate of cost–utility at 2 years was between £151,000–182,000 whereas the Novartis Industry Submission model estimate at 2 years was £70,000. 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.

- The nature of the models. The Novartis Industry model employed a more sophisticated Markov approach, although it is debatable whether there were sufficient data to operate such a model.
- The Novartis model used a subgroup of a subgroup of the TAP trial to determine the clinical effectiveness parameters (i.e. they used the responders only in the predominantly classic subgroup, whereas the WMHTAC model used whole trial data from the TAP trial).
- The Novartis model assumed that non-responders in the treatment arm received two treatments only whereas in the WMHTAC model all patients received between one and eight treatments, irrespective of whether they responded or not.
- The estimates of cost of PDT treatment are lower in the Novartis model because they did not include the cost of angiography for retreatment, disposables used during the procedure or the cost of follow-up appointments, whereas the WMHTAC model included all these.
- The laser costs in the Novartis model are much less per treatment than in the WMHTAC model.
- The Novartis model mean annual cost of PDT was incorrectly added up from data supplied in their report. Their totals for 5-year costs appear to be less than their 3-year costs.
- The Novartis model estimate for mean cost of low-vision aid is much lower than that used in the WMHTAC model, as is the cost for blindness registration by a consultant ophthalmologist.
- The percentages of patients who develop blindness and partial sight in the Novartis model are lower than in the WMHTAC model and appear to be based on misleadingly reported study results.
- In the Novartis model, the costs of developing blindness and partial sight appear to have been wrongly calculated from the tables presented, resulting in lower costs for these parameters.
- The Novartis model seems to be quite sensitive to the transition probabilities of entering residential care, and the additional risk per 0.1 LogMAR decrease used is not clear. It appears that their stated best estimate for this parameter is used in the sensitivity analysis, not as the base case. In the WMHTAC model the risk of entering residential care is a major component of the costs of blindness and is subject to sensitivity analysis.

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 that are somewhat questionable. For example, we had to assume that the probabilities of each of the seven 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 thus 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.

The Novartis model was a more sophisticated Markov approach but made a number of questionable departures from the TAP trial data, for example by assuming that patients could be categorised as responders and non-responders, by using only a subsample of predominantly classic patients from the original TAP trial sample, and by trying to project for a number of years beyond the end of the trial. All of these departures may reasonably be suspected of leading to a downward bias in the estimated ICER of PDT relative to BSC, making PDT appear to be more cost-effective than it actually is. It is not, therefore, too surprising that the ICERs estimated by Novartis tend to be considerably lower than those we estimated. It is interesting to note that when these assumptions are stripped away from their models as much as possible, their estimated ICERs rise to levels that approach those we estimated. For example, in Table 3.6.4 on

* This should be read in conjunction with the addendum.

page 19 of Appendix 7 in the Novartis Industry Submission,[79] the ICER for the 2-year model, assuming that all patients continue treatment (as in the TAP trial), is £85,157. This is quite a high ICER by conventional standards.

Further investigation of the source of the different estimates of cost–utility at 2 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 subgroup effectiveness data. We have already argued this to be invalid, and thus believe that 2-year cost–utility estimates are likely to be well above £100,000/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 2 years are universally unfavourable. More acceptable values only occur in models that extrapolate beyond 2 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 co-morbidity are highly likely, extrapolating in the absence of empirical data is highly dangerous and potentially misleading. To illustrate this the Novartis model essentially assumes that the difference between PDT plus BSC and BSC alone remains constant during the period of extrapolation, and generates optimistic cost–utilities. In contrast the study by Sharma and co-workers, although also extrapolating beyond 2 years, incorporates a reduction in size of effect of 10% per annum beyond 2 years. Cost–utilities are much less optimistic. 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 BSC lies above accepted thresholds denoting efficient use of healthcare 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 (Wormald R, Moorfields Eye Hospital, London; and Murray P, Birmingham and Midland Eye Centre: personal communication, 2002).

Summary

- Three assessments of health economic impact, including the Novartis Industry Submission to NICE, were identified in the review. Although none were perfect, all were sufficiently robust to deserve serious consideration. All essentially compare verteporfin PDT plus BSC with BSC alone.
- The perspective of three studies were either NHS and government costs (Meads and Moore, Novartis Industry Submission) or third-party insurer (Sharma and co-workers).
- All examine the benefits and costs of verteporfin PDT where wet AMD affects the better-seeing eye, the scenario where halting the deterioration in visual acuity is likely to have most impact on patient function. Only the study by Sharma and co-workers does this explicitly. However, implicitly it is also true for the other assessments as all analyses use the same utility data, which are attached to visual acuity in the better-seeing eye.
- All the ICERs referred to in the economic evaluation thus assume verteporfin PDT being given to the better-seeing eye, whereas the RCTs examined in the effectiveness section clearly indicate that a substantial proportion of patients could receive verteporfin PDT where wet AMD occurs in the worse-seeing eye.
- 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.
- All the included economic evaluations base their estimates of effectiveness on the TAP RCT. However, both the Novartis Industry Submission and the study by Sharma and co-workers use the effectiveness data from the subgroup analyses. As stated in the effectiveness

section we believe this is inappropriate and will overestimate the efficiency of verteporfin PDT.
- The submission from Novartis models the benefits and costs beyond the 2 years of follow-up in the TAP RCT by assuming that visual acuity and function remains stable after that time. We believe this is unreasonable given that there are no empirical data to support this observation and there are strong grounds to challenge the assumption, not least because of the relatively advanced age of the majority of patients who are affected. There is a strong likelihood of co-morbidity, both general and specific to vision.
- The costs averted by avoidance of blindness are highly uncertain. They are different in the different economic evaluations and this parameter is likely to be very influential in any assessment of the efficiency of verteporfin PDT.
- These observed differences go some way to explaining the variation in estimates of cost–utility.
- At 2 years the values for cost per QALY were:
  – £70,000 (Novartis Industry Submission)
  – £61,000 (where initial visual acuity is 20/40) or £122,000 (where visual acuity is 20/200) (Sharma and co-workers)
  – £120,000 (Meads and Moore).
- However, all these estimates are at best at the margins of what is generally considered to be an efficient use of healthcare resources.
- More optimistic assessments of cost–utility only occur when models are extended beyond the 2 years, the limit of the RCT data. In this, the effects are assumed to remain constant, the cost of verteporfin PDT is spread over a longer period (as it is thought unlikely in these models that further treatment or monitoring will occur after the third year – this, however, is debatable and monitoring may continue long term) and the costs averted through avoidance of blindness magnified.
- 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 for 2 years only and included effectiveness, utilities, costs of treatment (undiscounted and discounted at 6%) and costs of blindness in the sensitivity analyses (see also addendum).
- The estimate of cost–utility was £151,000–182,000. The estimate was mostly sensitive to estimates of effectiveness, then the costs of blindness, costs of treatment and least to utilities and discounting.
- There are several reasons for the discrepancies in cost–utility estimate between the Novartis model and our own, not least the different estimates of effectiveness used.
- 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 healthcare resources. To emphasise, this statement does not consider the scenario in which 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, particularly falls and institutionalisation, do have substantial associated mortality. There are, 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 million and £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.

Chapter 4

Discussion and conclusions

Implications for other parties

There are important implications for 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 healthcare 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 that 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 that has been presented in this report and that has been used to draw our conclusions.

Factors relevant to the NHS

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." (Novartis Industry Submission, page 44)[79]

> "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." (Novartis Industry Submission, page 45)[79]

> "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. Registrars are already giving the treatment at some centres." (Novartis Industry Submission, appendix 7, page 13)[70]

However, others are of a different opinion. The National Horizon Scanning Centre[50] 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[58] 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[26] 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:

- an ophthalmologist with expertise in case selection and management of AMD (e.g. completed a medical retina fellowship or hold dedicated medical retina or macula clinics regularly as laid down by higher specialist training guidelines of the Royal College of Ophthalmology)
- facilities for standardised vision assessment by a suitably trained optometrist or technician
- facilities for stereoscopic fluorescein angiography by a suitably trained photographer or technician.

Currently there are approximately 790 consultant ophthalmologists of whom approximately 150–200 are medical retina specialists or consultants who do some medical retina work in the UK (Miss Hallendorf, Royal College of Ophthalmology: personal communication, 2001). Therefore to cover 2800–4650 sessions per year (as estimated by Novartis) 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.[113])

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 eight per session then 2625 sessions will be required for this alone. This may result in each of the 150–200 medical retinal specialists devoting one day per week to PDT.

National targets

Care of older persons is a defined national target area.[114] 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 National Service Framework.

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.

Discussion

Main results

- 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 more than 15 letters (three 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 £1181 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 2 years range from £60,000 to £122,000. The economic model developed as part of this report obtained a base-case estimate of between £151,000–182,000. The sensitivity analyses ranged from £342,000 to £47,000 (see also addendum).
- Favourable estimates of cost–utility have been obtained in past economic evaluations, but only by modelling the cost–utility beyond 2 years (the length of follow-up in the two included RCTs) and by basing the results of effectiveness on subgroup 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 £50,000, and that verteporfin PDT is consequently an inefficient use of healthcare 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

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 below.

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 subgroup 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.

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 persons' 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.

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 Novartis Industry Submission suggests that they would be minimal.

Estimation of efficiency and cost–utility

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

- use of subgroup analyses to provide estimates of effect
- variation in the magnitude of costs averted
- extending the modelling beyond the 2-year follow-up of the RCTs, raising uncertainty about whether the visual acuity state at 2 years is stable.

Need for further research

Each of the above sources of uncertainty should ideally be reduced by further research.

- **Subgroup 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 subgroup effect exists

will be greatly enhanced if an individual patient data meta-analysis was conducted. A new RCT focusing on just 100% 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 subgroup 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 2 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 periods beyond those 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 and co-workers 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 plus BSC versus placebo PDT plus BSC (the nature of BSC being made explicit so that its equal availability 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 5 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 any 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 a relevant bid may have been recently submitted (Wormald R, Moorfields Eye Hospital, London: personal Communication, 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, the report also notes the importance of supporting research in related areas. In particular:

- 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 (i.e. BSC 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 (i.e. TTT) may be required too.

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 licensed for those forms where classic neovascular lesions predominate.

Whether this is an efficient use of healthcare 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. Principal among these is a large publicly funded pragmatic RCT with parallel health economic evaluation. Treatment of wet AMD with verteporfin, with other types of PDT, and with other new technologies are areas under very active investigation, so this technology should be kept under close review.

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Contributions of the authors

Catherine Meads (Research Officer) was the main project worker, developed the protocol and carried out the systematic review of effectiveness.

Christian Salas (Statistical Analyst) performed the modelling of cost–utility and advised on the cost-effectiveness review.

Tracy Roberts (Health Economist) wrote the cost-effectiveness review.

David Moore (Research Analyst) extracted the data, and undertook quality assessment and proof-reading. He also assisted with information technology.

Anne Fry-Smith (Information Specialist) performed the literature searches and proof-read the report.

Chris Hyde (Senior Lecturer) was the main editor of the report and wrote the conclusions. He also gave advice on the systematic review of effectiveness.

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Appendix 1

Classification of ARM and AMD

The early stage of disease of the macula is termed early age-related maculopathy (ARM, also maculopathy or occasionally macular dystrophy). The late stages of ARM are called late ARM 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.[115]

The International ARM Epidemiological Study Group has produced a classification of ARM and AMD.[3,116] 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[117,118] and there are several alternative terms for a number of the pathological features seen in ARM. This systematic review uses the international classification terminology and alternative terms are included in parentheses where appropriate.

Early ARM

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 ARM is that the pigment of the RPE may be disturbed, giving areas of hyper- and/or hypopigmentation.

The international classification[3,116] defines early ARM in people aged over 50 years as having the following signs (in the absence of other diseases that may be causing these lesions)

- soft drusen > 63 µm 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 ARM 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 ARM can progress to AMD, resulting in gradually deteriorating sight. Approximately 10% of people with early ARM in both eyes will go on to develop AMD within 5 years.[15]

AMD

The result of AMD (late ARM) 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 AMD)**. 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 µm in diameter.[3,116] Dry AMD can progress to wet AMD but the risk factors are largely unknown.[8,25]

2. **Wet AMD (disciform, exudative or neovascular AMD)**. Wet AMD is associated with a variety of pathological changes in the macula.[3,116]
   a. PED or RPE detachment. In this a lipid/protein filled space can develop between the retinal pigment epithelium and Bruch's membrane.[119] This can be associated with neurosensory retinal detachment.
   b. Subretinal or sub-RPE neovascular membranes (subretinal neovascularization, CNV, 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 chorio-capillaris and then spread under the RPE or grow through it into the area between the RPE and the photoreceptor cells of the retina (the subretinal 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.[5]

People with wet AMD can have PEDs only and no neovascular membranes.[119] 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[57] and are the more aggressive form of the condition, usually causing rapid blindness.[7] Occult lesions have poorly demarcated boundaries and are associated with less vision loss.[7] However, classic lesions can develop in occult lesions to give a mixed picture.[7] This conversion from occult to classic can happen after TTT.[120]

AMD can be subdivided as shown in *Figure 4*.

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 *Figure 5*.

Since the TAP trial[61] a further subdivision has been created 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 *Figure 6*).

All the above types, particularly those involving neovascular membrane formation may be further subclassified according to where the lesions occur in relation to the fovea:

- subfoveal – lesions located behind the middle of the fovea
- juxtafoveal – lesions locate behind fovea, but not the middle of it
- extrafoveal – lesions located outside the fovea.

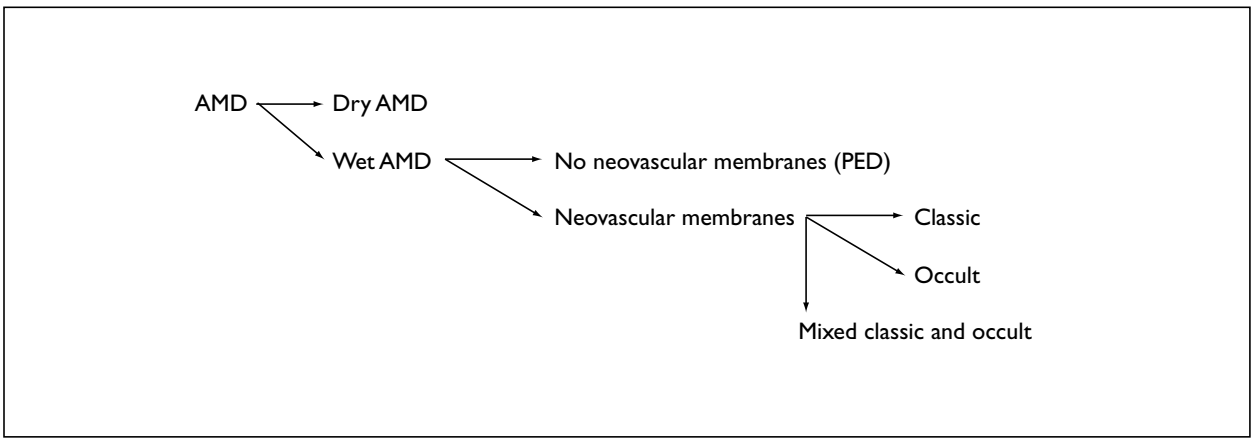

FIGURE 4 *Subdivisions of AMD classification*

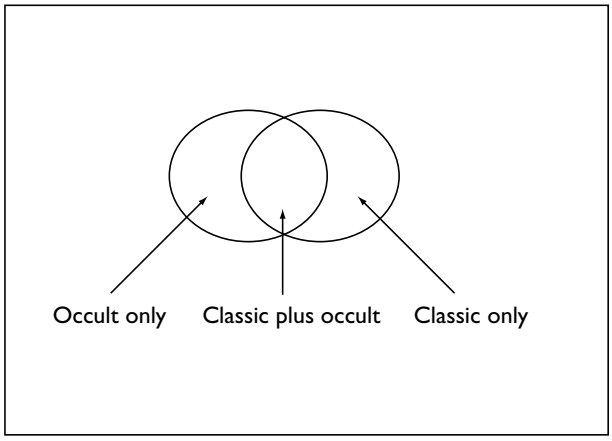

FIGURE 5 *Venn diagram of wet AMD classification 1*

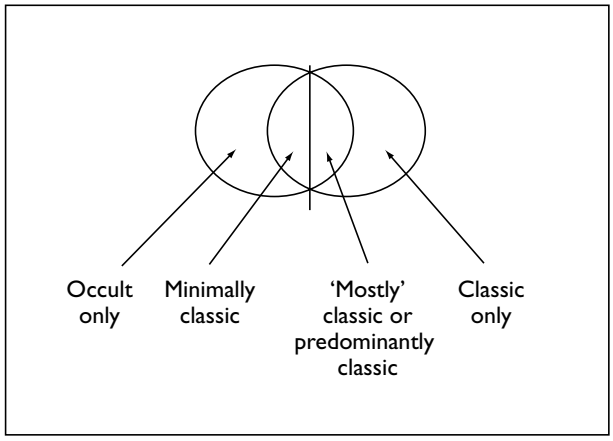

FIGURE 6 *Venn diagram of wet AMD classification 2*

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 1/60th 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 m and for the smallest it is 4 m. When a person's visual acuity is tested, they are placed at 6 m 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 m, 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 m then they are gradually brought closer to the Snellen chart, to a minimum distance of 1 m. 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 ft 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 that 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 three lines and there are no agreed standards for the exact notation in these situations.[121]

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 the LogMAR chart see *Figure 7*.

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, (five 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.[121]

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.[121] 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 *Figure 7* and *Table 27*. This scheme starts scoring at line 1 (top line) at 1 m which is equivalent to 20/800. After line three, testing is done at 2 m 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.[121–123] 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.[122] 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.[123]

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 30 cm 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.

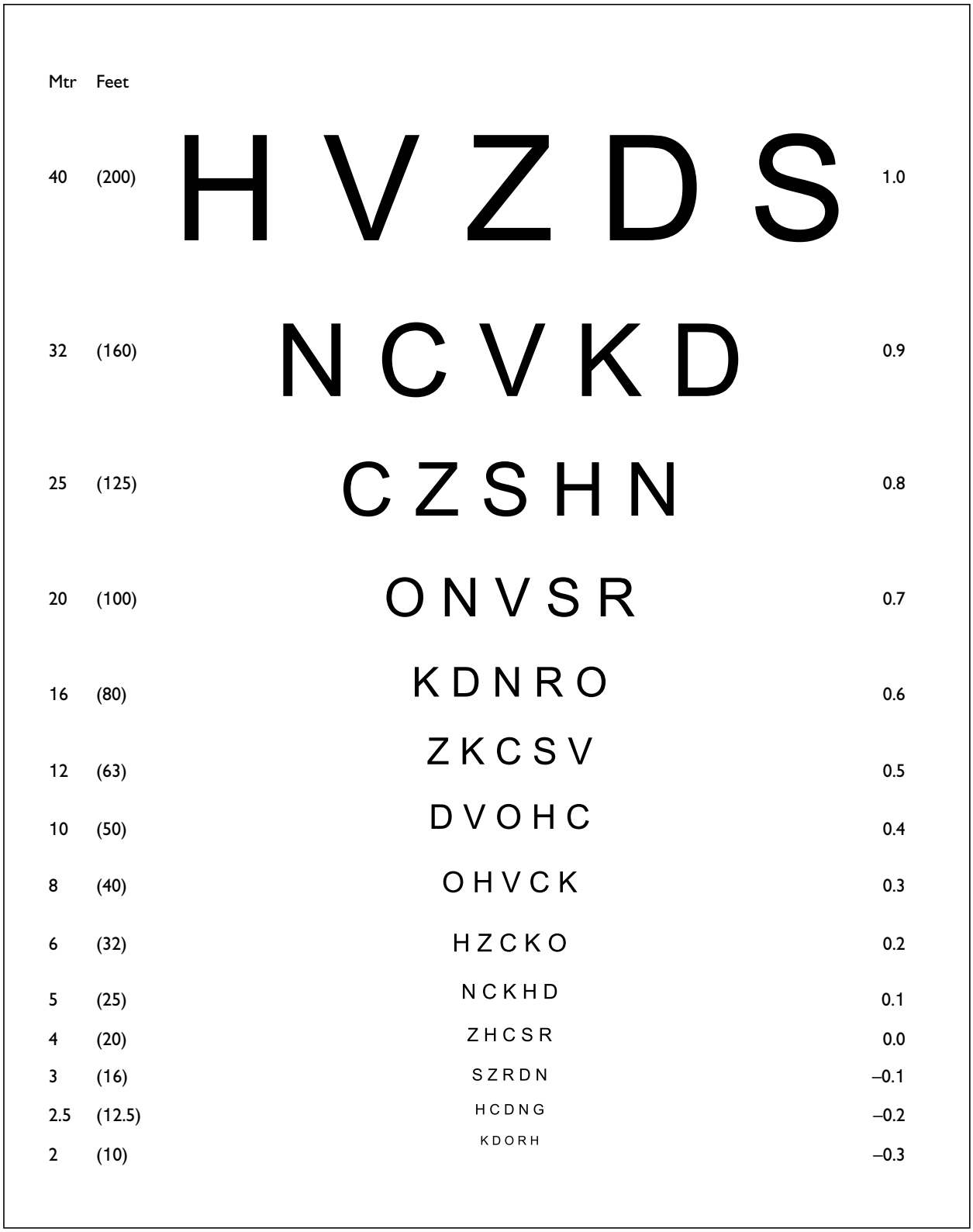

FIGURE 7 *Diagrammatic representation of a LogMAR chart*

TABLE 27 *Visual acuity conversion table*

4 m	6 m	20 ft	Visual angle in minutes	Line of chart	Distance tested (m)	Decimal fraction	LogMAR unit	No. 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

(Y Yang, Wolverhampton and Midland Counties Eye Infirmary: personal communication; 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 m 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 m away from the person being tested. However, the chart used in the above testing scheme (columns Line of chart and Distance tested (m)) was probably intended for use at 2 m rather than 4 or 6 m 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

Age-related macular degeneration (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 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 3 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 subfovial lesions or laser photocoagulation for juxtafoveal and extrafoveal lesions.
Outcomes:	Visual acuity, contrast sensitivity, quality of life, side-effects of treatment.
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, NHS EED 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 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.*[93]

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

TABLE 28 *Timetable/milestones*

Stage	Date (from NICE timetable)	Week
Scoping completed	5 July 2001	7
Draft protocol submission	30 July 2001	10
Finalised protocol submission	20 August 2001	13
Receipt of industry submissions	26 October 2001	23
Progress report	2 November 2001	24
Draft final report	2 January 2002	34
Appraisal committee meeting	7 March 2002	40

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$)).mp
15. maculopathy.mp.
16. or/11-15
17. 10 and 16
18. randomized controlled trial.pt.
19. controlled clinical trial.pt.
20. randomized controlled trials.sh.
21. random allocation.sh.
22. double-blind method.sh.
23. single-blind method.sh.
24. or/18-23
25. (animal not human).sh.
26. 24 not 25
27. clinical trial.pt.
28. exp clinical trials/
29. (clin$ adj25 trial$).ti,ab.
30. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.
31. placebos.sh.
32. placebo$.ti,ab.
33. random$.ti,ab.
34. research design.sh.
35. or/27-34
36. 35 not 25
37. 36 not 26
38. comparative study.sh.
39. exp evaluation studies/
40. follow up studies.sh.
41. prospective studies.sh.
42. (control$ or prospectiv$ or volunteer$).ti,ab.
43. or/38-42
44. 43 not 25
45. 44 not (26 or 37)
46. 26 or 37 or 45
47. 17 and 46

EMBASE (Ovid) 1993 – Aug 2001

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

Economic evaluation

NHS EED and DARE

See clinical effectiveness search strategy for Cochrane Library (above)

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 5

Reasons for disagreements in data extraction

TAP trial

- 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.
- 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 1 and 2 years be adopted.
- Were the subgroup 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 subgroup 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

- 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.
- 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.
- 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 6

Results of subgroup analyses from the TAP trial at 2 years

TABLE 29 *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))*

Characteristic	Treatment group	No. of eyes	Loss of < 15 letters (%)	Difference (%)	*P*[†]	*P*[‡]
All eyes	V	402	213 (53.0)	15.3	< 0.003	N/A
	P	207	78 (37.7)			
Trial						
Study A	V	204	104 (51.0)	11.7	0.05	0.39
	P	107	42 (39.3)			
Study B	V	198	109 (55.1)	19.1	0.002	
	P	100	36 (36.0)			
Age (years)						
< 75	V	194	115 (59.3)	17.9	0.005	0.53
	P	87	36 (41.4)			
≥ 75	V	208	98 (47.1)	12.1	0.03	
	P	120	42 (35.0)			
Gender						
Men	V	188	95 (50.5)	16.8	0.01	0.82
	P	77	26 (33.8)			
Women	V	214	118 (55.1)	15.1	0.007	
	P	130	52 (40.0)			
Systemic hypertension						
Definite[§]	V	170	90 (52.9)	20.5	0.003	0.33
	P	77	25 (32.5)			
Others	V	232	123 (53.0)	12.2	0.02	
	P	130	53 (40.8)			
Smoking history						
Never	V	135	76 (56.3)	21.5	0.002	0.51
	P	89	31 (34.8)			
Past	V	205	104 (50.7)	11.4	0.07	
	P	94	37 (39.4)			
Current	V	62	33 (53.2)	11.6	0.34	
	P	24	10 (41.7)			
Initial letter score (visual acuity[¶]) in study eye						
73–54 (20/40–20/80)	V	203	89 (43.8)	9.2	0.12	0.16
	P	101	35 (34.7)			
53–34 (20/100–20/200)	V	199	124 (62.3)	21.7	< 0.001	
	P	106	43 (40.6)			
Greatest linear dimension, diameter of MPS disc area circle						
≤ 3	V	107	66 (61.7)	11.7	0.18	0.22
	P	46	23 (50.0)			
> 3 to ≤ 6	V	152	84 (55.6)	23.7	< 0.001	
	P	97	31 (32.0)			

continued

***TABLE 29* contd** *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))*

Characteristic	Treatment group	No. of eyes	Loss of < 15 letters (%)	Difference (%)	P[†]	P[‡]
Greatest linear dimension, diameter of MPS disc area circle						
> 6 to ≤ 9	V	109	44 (40.4)	1.9	0.82	
	P	52	20 (38.5)			
> 9	V	25	11 (44.0)	19.0	0.34	
	P	8	2 (25.0)			
Lesion area composed of classic CNV (%)						
≥ 50	V	159	94 (59.1)	27.8	< 0.001	0.02
	P	83	26 (31.3)			
> 0 to < 50	V	202	96 (47.5)	3.3	0.58	
	P	104	46 (44.2)			
0	V	41	23 (56.1)	26.1	0.06	
	P	20	6 (30.0)			
Evidence of occult CNV						
Yes	V	305	146 (47.7)	6.9	0.16	< 0.001
	P	157	64 (40.8)			
No	V	93	65 (69.9)	41.3	< 0.001	
	P	49	14 (28.6)			
Evidence of prior laser photocoagulation						
Yes	V	60	28 (46.7)	3.2	0.79	0.29
	P	23	10 (43.5)			
No	V	340	183 (53.8)	16.9	< 0.001	
	P	184	68 (37.0)			
Area of lesion considered to be fibrosis (%)						
0–25	V	313	161 (51.4)	14.2	0.004	0.92
	P	153	57 (37.3)			
26–50	V	44	23 (52.3)	14.8	0.24	
	P	24	9 (37.5)			
> 50	V	39	23 (59.0)	19.7	0.11	
	P	28	11 (39.3)			
Lesion included blood						
Yes	V	133	72 (54.1)	18.9	0.006	0.48
	P	88	31 (35.2)			
No	V	266	139 (52.3)	12.8	0.2	
	P	119	47 (39.5)			

MPS, Macular Photocoagulation Study; P, placebo-treated group; V, verteporfin-treated group

[*] *With last observation carried forward*

[†] χ^2 *test for treatment effect within subgroups*

[‡] *Test of interaction between subgroups*

[§] *Definite hypertension was defined as systolic blood pressure of 160 mmHg or higher or of 140–159 mmHg with a history of hypertension or use of antihypertension medications, or diastolic blood pressure of 95 mmHg or higher or of 90–94 mmHg with a history of hypertension or use of antihypertension medications*

[¶] *Approximate Snellen equivalent*

Appendix 7

Further details 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 AMD.

Studies in categories 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 Drummond.[93] 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 authors.[91]

- 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 4 (data extraction).

Results of search and inclusion/exclusion

All studies classified as A1, A2, B1, B2, C1, or C2 would be included in the quality assessment section of the review (*Figure 8*).

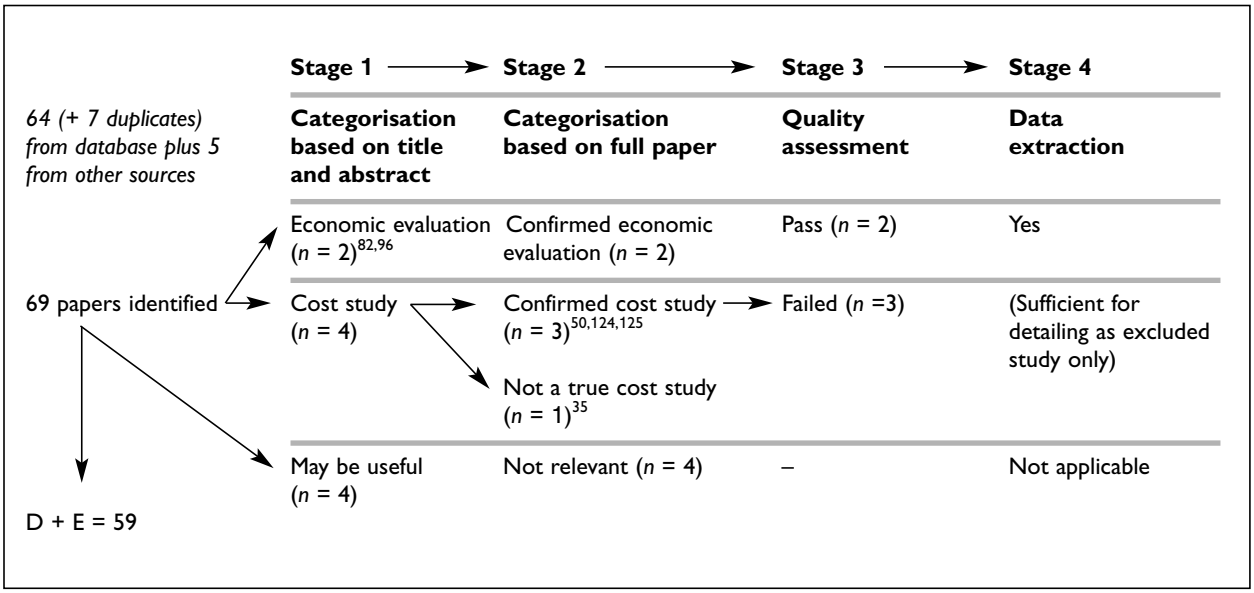

FIGURE 8 *Economic study inclusion/exclusion results*

Appendix 8

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. University of Birmingham, January 2000[50]
This report assumed an estimated prevalence ceiling of 7700 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 (£5000).

***Drugs and Therapeutics Bulletin.* Can vertporfin help in macular degeneration? 2001**[124]
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. 1999[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 30*, 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 as the quality of that study cannot be assessed the result is not presented here.

TABLE 30 *Cost results from excluded cost studies*

	National Horizon Scanning Centre	*Drugs and Therapeutics Bulletin*	Grampian Health Board
Drug cost (£)	750	850	760
Year	Not stated	Not stated	Not stated
Vials required per year	3–4	3–4	3
Cost per patient (£)	2250–3000	4500–6000 in first year, 3000–4500 in second year	
Laser cost (£)	20,000		
Angiography (£)	30,000		
Miscellaneous (£)	5000		
Local cost (£)			120,000
Total cost (£)	17–23 million in first year		
Cost per QALY			Estimate given but study not a full economic evaluation
Comment			Based on 50 patients per year

Appendix 9

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 low-vision aids service. This was not taken as the standard cost as a recent survey has shown that only 32% of low-vision aids services are of this type.[47] 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 years is less than the average housing benefit for all aged under 60. Unfortunately, the data for the over 60s are 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.[126] 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 – general Health Questionnaire (GHQ),[39] Geriatric Depression Scale[38] and the Wakefield Self-rating Depression Scale.[37]

Community care The higher cost is for a home care worker for one hour per day whereas lower cost is for 2 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%,[95] 11.8%[32] and 22%.[112] From these, using census data for the numbers of elderly in nursing and residential homes and the prevalence of AMD in the elderly,[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.[110]

Appendix 10

Notes on the WMHTAC model

Explanation of the cumulative 2-year utility scores

The utility scores in the WMHTAC model look as if they are for 1 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 2 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 2-year period. This would give a diagram as shown in *Figure 9*.

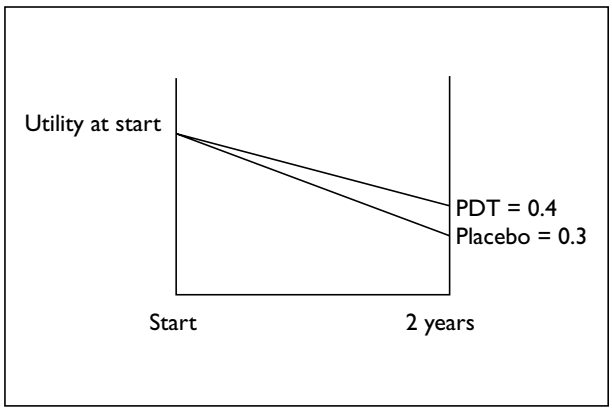

FIGURE 9 *Change in utilities over the 2-year treatment period*

Using the equation for the area of a triangle of half base × height, it can be seen that the area between the two sloping lines equates to the difference in utility score at 2 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 shown on *Table 31*.

The difference in mean loss of visual acuity 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 (i.e. half the effectiveness) and the best-case estimate was a difference of 1.8 letters (i.e. 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 WMHTAC economic model is based on the proportions of patients losing a certain number of letters, based on the seven categories in *Table 31*, rather than the mean number of letters lost in each group. The reported trial data are 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 seven categories for different mean visual acuity 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 seven categories based on the means observed in each group (i.e. –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 seven categories for our fitted data and the worst- and best-case scenarios are shown in *Tables 32* and *33* below (the actual trial data are shown in *Table 31*).

TABLE 31 *TAP trial base-case results*

	Verteporfin	Placebo
No. of patients	402	207
≥ 6-line increase	0.7%	0.0%
≥ 3-line to < 6-line increase	8.2%	3.9%
≥ 1-line to < 3-line increase	6.5%	6.3%
No change	14.7%	12.6%
≥ 1-line to < 3-line decrease	22.9%	15.0%
≥ 3-line to < 6-line decrease	28.9%	32.4%
≥ 6-line decrease	18.2%	30.0%
Mean visual acuity loss	–2.7	–3.9

TABLE 32 *Fitted data for base case*

	Verteporfin	Placebo
≥ 6-line increase	4.5%	2.2%
≥ 3-line to < 6-line increase	9.4%	5.6%
≥ 1-line to < 3-line increase	7.5%	5.2%
No change	9.3%	7.1%
≥ 1-line to < 3-line decrease	22.1%	19.5%
≥ 3-line to < 6-line decrease	29.3%	32.7%
≥ 6-line decrease	17.3%	27.4%
Mean	–2.7	–3.9

TABLE 33 *Best- and worst-case scenario data*

	Verteporfin (worst)	Verteporfin (best)	Placebo
≥ 6-line increase	3.2%	6.2%	2.2%
≥ 3-line to < 6-line increase	7.4%	11.5%	5.6%
≥ 1-line to < 3-line increase	6.3%	8.6%	5.2%
No change	8.3%	10.2%	7.1%
≥ 1-line to < 3-line decrease	21.0%	22.5%	19.5%
≥ 3-line to < 6-line decrease	31.4%	26.6%	32.7%
≥ 6-line decrease	22.0%	13.3%	27.4%
Mean	–3.3	–2.1	–3.9

Addendum

Clinical effectiveness and cost–utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation

Introduction

The purpose of this addendum is to discuss issues raised following submission of the technology appraisal report (TAR) to NICE. It responds to the most important scientific criticisms raised during the NICE consultation process. It does not include any issues raised by external peer reviewers, amendments for which were incorporated into the TAR before it was submitted to NICE. The TAR has not been changed in response to the issues raised, so that it remains a fair record of what was originally submitted. It does, however, now include cross-references indicating parts of the report where further comments made in this addendum are particularly pertinent.

The three issues discussed are:

- whether the subgroup analysis results of the TAP trial are the most accurate representation of the effect size likely to be achieved by verteporfin PDT in people with predominantly classic wet AMD (the licensed indication in the UK when the TAR was compiled)
- when the benefits associated with verteporfin PDT should be counted from in the cost–utility model
- whether benefits should be considered beyond 2 years (the end of the TAP trial) in modelling cost–utility and if so, how long extrapolation should extend.

Issue 1 – subgroup analysis

Critiques of the TAR maintain that the TAP subgroup analysis of those patients with predominantly classic wet AMD must necessarily be the correct estimate to indicate the effect of verteporfin PDT in the main population group it currently has a licence for (i.e. people with predominantly classic wet AMD). The TAR argues that the most valid clinical effectiveness estimate of verteporfin PDT in patients with predominantly classic wet AMD is the whole trial data from the TAP study, because the estimate from the TAP study subgroup analysis is probably a statistical fluke. If there is doubt about whether the result for a subgroup is truly different from the whole trial, then however counter-intuitive it may appear, the result most likely to indicate the effect of treatment in any particular sub-population (including patients with predominantly classic wet AMD) is the whole trial result. The problem is well recognised in the statistical literature which support the TAR's interpretation (1–4).

Which estimate is used makes an important difference to the size of effect attributed to verteporfin PDT in people with predominantly classic wet AMD. This is illustrated in *Table 34* for the outcome "loss of 15 or more letters" at 2 years.

It is clear that verteporfin PDT has a clinical effect that is unlikely to be accounted for by chance alone, irrespective of whether the whole trial result or the subgroup result is used. The size of the effect however is very different, and which estimate is used is likely to have a major impact on the relationship between net benefit and cost. In using the whole trial estimate of effectiveness, the TAR is argued to have made cost–utility much less favourable. It is thus important to carefully consider whether the TAR critics' arguments as to why using the whole trial estimate is inappropriate have any foundation. This is the purpose of the following paragraphs, in which the arguments presented by critics of the TAR are given in italics.

Whole trial data contains individuals who do not have predominantly classic wet AMD, the group for whom verteporfin PDT has been licensed

This appears to be the biggest barrier to understanding why the whole trial data provide the most appropriate basis to assess the effect of verteporfin

TABLE 34 *Size of effect attributable to verteporfin PDT in people with predominantly classic wet AMD depending on whether the whole trial or subgroup analysis estimate of the TAP trial is used*

Measure of effect on loss of 15 letters or more of visual acuity at 2 years	**TAP whole-trial result** (PDT – 402 participants, 189 events; placebo – 207 participants, 129 events)	**TAP predominantly classic wet AMD subgroup result** (PDT – 159 participants, 65 events; placebo – 83 participants, 57 events)
Odds ratio*	0.54 (95% CI, 0.38 to 0.76)	0.32 (95% CI, 0.18 to 0.55)
Relative risk*	0.75 (95% CI, 0.65 to 0.88)	0.60 (95% CI, 0.47 to 0.75)
Absolute risk reduction†	15% (95% CI, 24 to 7)	28% (95% CI, 40 to 15)
NNT‡	7 (95% CI, 4 to 14)	4 (95% CI, 2 to 7)

* *Values less than 1.0 indicate PDT better than placebo; the nearer to zero the greater the advantage*
† *Positive values indicate PDT better than placebo; the larger the value the greater the advantage*
‡ *Positive values indicate PDT better than placebo; the smaller the value the greater the advantage*

PDT. It is so intuitive that the group in the trial that most closely matches the population to whom we wish to apply the results, should be the one whose results are used. However, the TAP trial was primarily designed and executed to test the effect of verteporfin PDT in a wide range of individuals. People with predominantly classic wet AMD make up a minority of the participants. In TAP, as in most trials, there was interest in seeing whether the effect was different in many different subgroups of the whole trial population. However, the more subgroups that are investigated, the more likely it is that one of those subgroups will appear to be statistically significantly different from the whole group. If a significance level of 5% ($p = 0.05$) is used, one statistically significant subgroup difference will emerge for every 20 subgroups examined.* Fourteen were planned in the TAP trial, 12 were reported and two inter-dependent factors were statistically significant ($p = 0.02$ (% of lesion area composed of classic CNV) and $p < 0.001$ (evidence of occult CNV)). This is sufficiently close to the number of statistically significant results that might be expected by chance alone to suggest that the subgroup phenomenon was not real, or would be better treated as a hypothesis requiring further data to support it. Without such confirmatory data, the immediate conclusion must be that there is no difference between the subgroup and the whole population. The inevitable consequence of this in turn is that the whole trial estimate is the best measure of effect of any subgroup.

Concerns regarding subgroup analyses are not consistent with conclusions drawn by regulatory authorities, SERNIP, other systematic reviews and the Royal College of Ophthalmologists

It is difficult to comment on the interpretation of evidence by other bodies when we neither know what evidence was provided to them nor the nature and timing of the decision that they were trying to make. With respect to the regulatory authorities, where the pre-eminent concern is to ensure that verteporfin PDT is effective and safe, it is possible that the degree of scrutiny afforded any subgroup analysis will be less where both whole trial and subgroup estimate indicate a statistically significant beneficial clinical effect. In contrast, where measuring cost-effectiveness is of interest, the validity of any subgroup analysis will come under very close scrutiny, particularly when it magnifies the size of effect to the degree observed in the TAP trial.

Concerning conclusions in other systematic reviews, it is untrue that others have not drawn attention to the problem associated with the use of subgroup analyses. The most up-to-date version of the Cochrane Review (5) mirrors our concern, stating: "any conclusions (from the subgroup analyses) can only be tentative" and "the effects observed in the subgroups could be a statistical artefact".

Comments on behalf of the Royal College of Ophthalmologists, received as part of the NICE

* "A crude analogy might be trying to cut a cake in half while blindfolded. If you were placed in front of the cake, the chance of dividing it roughly equally may be reasonable. However, the more times the exercise was repeated the more likely it would be that the cake would be divided extremely unequally. Given twenty attempts it is quite feasible that one might miss the cake completely!"

consultation process, suggest that their views about the validity of the subgroup analyses are changing. The Royal College of Ophthalmologists guidelines actually mention the concern of the authors of the Cochrane Review about the estimate of effect of PDT in predominantly classic AMD being based on a subgroup analysis.

Concerns regarding subgroup analyses are not consistent with NICE's Guidance to Manufacturers and Sponsors
NICE guidance (6) (in section 2.8.4) does indeed advocate subgroup analyses, "which help to target interventions on those patients likely to benefit most". However, there are some important provisos:

> "Subgroup analysis is justified where there is a sound biological a priori rationale for doing so (e.g. high risk patients) and where there is evidence that clinical effectiveness or cost effectiveness may vary between such groups"

and

> "The credibility of subgroup analysis is improved if confined to the primary outcome and to a few predefined subgroups on the basis of biologically plausible hypotheses."

and

> "Statistical tests of interaction, assessing whether a treatment effect differs between subgroups, are required rather than inspection of subgroup *p*-values, which may encourage inappropriate subgroup claims. The analysis should make corrections for multiple comparisons."

In our opinion, key provisos are not adhered to in the TAP trial, particularly restricting subgroup analyses to a **few** predefined subgroups and correcting for multiple comparisons.

Subgroup analyses were pre-planned and specified a priori – *documentation supporting this claim provided*
The TAP trial documentation does indeed support the fact that subgroup analyses were planned. The protocol (page 27) states:

> "Subgroup analyses based on gender, race and number of treatments required will also be performed. Additional subgroup analyses will be made to evaluate any effect on outcome of CNV lesion size, lesion components and recurrent versus new lesions"

Further, the TAP trial statistical plan (section 6.3) pre-specifies 14 subgroup analyses, including percentage classic CNV at baseline and presence of occult CNV. It also makes clear that the objective for these analyses is part of routine exploration of the robustness of the trial data, stating:

"Subgroup analyses will be performed on the responder rates for visual acuity to determine if the response to treatment is consistent across the subgroup levels." This may explain the large number of subgroup analyses planned and the absence of any clear associated statement of the biological rationale for PDT being more effective in predominantly classic wet AMD, or indeed any of the other subgroups put forward. The statistical plan gives no details of how adjustment would be made for multiple comparisons.

In short the documentation provided, although supporting the fact that the predominantly classic subgroup analysis was strictly speaking pre-specified, albeit among many other subgroups, clarifies that it was not a focused subgroup analysis, the type indicated as being particularly useful in the *NICE Guidance to Manufacturers and Sponsors*.

Strong biological plausibility of PDT being more effective in predominantly classic wet AMD
It is certainly true that classic wet AMD is more sight threatening than occult wet AMD, and it is plausible that the effect of PDT could be more pronounced in eyes with predominantly classic lesions. However, it would also suggest that the effect would progressively decrease as one considered subgroups with less and less classic component (predominantly classic then minimally classic then occult only). This is not observed. The full subgroup analysis presented in the original paper (see also Figure 2 of the TAR) actually shows that the effect is statistically significantly greater in both predominantly classic **and the occult only** categories, relative to the minimally classic subgroup. This undermines the support to the validity of the subgroup analysis potentially provided by biologically plausibility, a point also noted by the consultee replying on behalf of the Royal College of Ophthalmologists.

Issue 2 – timing of onset of any benefits associated with verteporfin PDT

In the TAR cost–utility model, assumptions had to be made concerning when the outcomes measured at 2 years actually occurred. For example, the TAP results were that after 24 months 47.1% and 62.4% had lost three or more lines of visual acuity in the PDT and placebo groups respectively. However, did these losses occur uniformly throughout the 2-year period, or did the losses in vision occur predominantly in the earlier stages of the study, say during the first 12 months? Further, were

there any differences in the rates at which the losses occurred in the PDT and placebo groups? How one answers these questions could make an important difference to the size of benefit assessed. This is illustrated in the *Figure 10*.

The dashed and solid lines below and above triangle A represent progressive accumulation of patients with a loss of three or more lines of visual acuity at a constant rate over the 24 months from the start of the trial in the PDT group and the placebo group. The area of triangle A gives the amount of additional benefit attributable to PDT. In contrast, the lines around B represent the situation if all patients identified as losing three or more lines of visual acuity at 24 months, sustain this loss very soon after the beginning of the study. The area of the polygon B gives the benefit attributable to PDT. The area of B is larger than A, indicating that the benefit attributable to PDT is greater if the outcomes develop early in the course of the trial. This is intuitively what would be expected because avoidance of a damaging loss of sight by PDT is being achieved by more patients for a longer period in situation B. If the losses of visual acuity in the PDT and placebo group occur instantaneously with the beginning of the study, the polygon B becomes a rectangle, whose area is twice that of triangle A. Thus, making two different assumptions about how the outcomes accumulate during the course of the study (loss of visual acuity occurs at a constant rate throughout the study or loss occurs in all patients very close to the onset of the study) could potentially change the estimate of the amount of benefit attributable to PDT by a factor of 2.

The assumption made in the internally produced model of cost–utility in the TAR is that changes in visual acuity occurred at constant rates in both PDT and placebo arms (i.e. situation A). This assumption has been challenged on the basis that there is evidence that the majority of the patients who were measured as having changes in visual acuity at a specified level at 24 months entered these states early in the course of the TAP trial. The particular example used to validate this challenge is the profile of mean visual acuity in the subgroup of patients with predominantly classic wet AMD. The mean change in visual acuity at 24 months was an 11.7-letter reduction for PDT and 22.6-letter reduction for placebo; at 12 months the equivalent figures were approximately a 10-letter and a 21-letter reduction, respectively. This is used to develop an argument that the benefit attributed to PDT in the TAR report has been greatly underestimated and that the number of QALYs gained with PDT over 2 years is 0.056 as opposed to 0.031.

We examined this argument using whole trial data on the outcome percentage of patients with a three-line (15 letter) loss of visual acuity. In *Figure 11* the actual data at 3 and 12 months are shown superimposed on *Figure 10* in bold lines.

This shows that assuming visual acuity states accumulate at a constant rate between the start

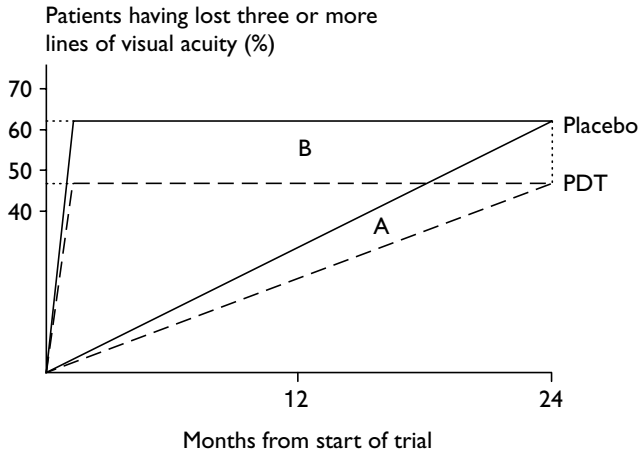

FIGURE 10 *Illustration of the impact of different assumptions about when patients in the TAP trial develop the outcome, loss of three lines or more of visual acuity*

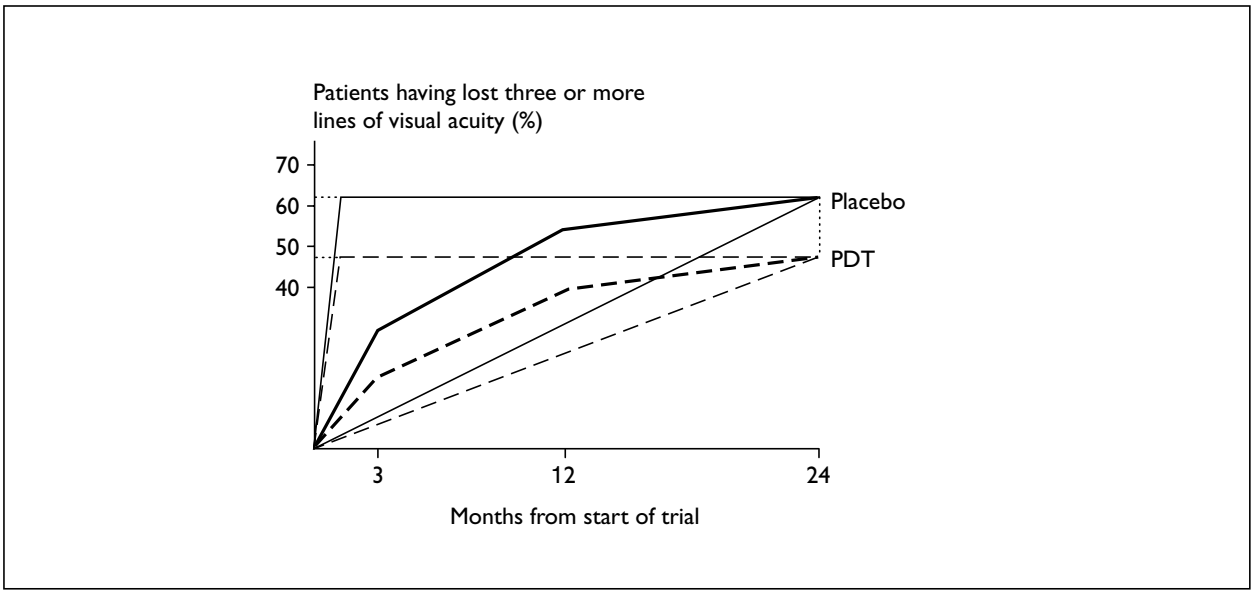

FIGURE 11 *Illustration of the impact of different assumptions about when patients in the TAP trial develop the outcome, loss of three lines or more of visual acuity; actual TAP trial data superimposed*

of TAP and its conclusion at 24 months, has indeed led to an underestimation of benefit in the TAR cost–utility model. The exact size of the factor is difficult to confirm. However, the suggested underestimation of the average number of QALYs attributable to PDT treatment over 2 years being 0.056 as opposed to 0.031 is reasonable. This in turn suggests that the base-case cost–utilities offered in the TAR report should be £84,000–101,000 per QALY, rather than £151,000–182,000. However, even with this correction, the original interpretation that the estimates of cost–utility at 2 years are at the margins of what would generally be considered an efficient use of healthcare resources still holds.

We can confirm that the NICE Appraisal Committee took the adjustment of the TAR report's 2-year cost–utility figures into account in drawing up their guidance.

Issue 3 – extrapolating benefits in models of cost–utility

In the TAR, we have argued that the duration of modelling should be restricted to the duration of the TAP trial (i.e. 2 years). Consequently our model did not extrapolate beyond 2 years, a decision that has been criticised. The bases of the criticism appear to be:

- *NICE Guidance for Manufacturers and Sponsors* supports extrapolation (6)
- failure to extrapolate implies that any benefits occurring up to 2 years cease immediately after 2 years, which is implausible and thus a model incorporating this assumption is invalid
- evidence is available to support extrapolation.

Two cost–utility models (Sharma and co-workers and ScHARR) have extrapolated beyond 2 years, both making assumptions about changes in visual acuity in PDT and placebo groups up to 11 years and 10 years, respectively, after wet AMD first develops. The estimates of cost–utility fall progressively the longer the time horizon, and in one model they approach levels of cost–utility that would generally be considered cost-effective after 5 years.

The following discussion considers the criticisms levelled at our assessment of cost–utility and whether they have foundation. This is extended into a wider consideration of the potential value of extrapolation in estimating the cost–utility of verteporfin PDT.

NICE Guidance for Manufacturers and Sponsors supports extrapolation

The guidance (section 2.4.4) states:

> "The time span of the analysis should cover the period over which the main health effects and health care resource use are expected to be experienced. This may require extrapolation beyond the period for which data from controlled trials are available."

This support for extrapolation is tempered by the statement: "In the choice of time horizon there

may be a trade-off between the economically relevant period and the period for which reliable clinical and economic data are available." It also makes clear that where extrapolation is undertaken: "The nature of the modelling used in the extrapolation should be fully explained and the sensitivity of the results to the method of extrapolation and the choice of time horizon should be thoroughly tested."

The NICE guidance is thus not a blanket statement advocating use of extrapolation in all situations where it might possibly be relevant. It makes clear that there is a trade-off between desirability and reliability. There may be situations where data on effectiveness and cost, although not perfect, are sufficiently robust to allow some speculation about the differences between treatment and control at a time beyond that which the differences have been measured directly. Equally, there may be situations where the frailty or complete absence of clinical and economic data mean that extrapolation should not be undertaken even though there may be potentially relevant benefits, disbenefits and costs occurring in the extrapolated period. A particular concern is where extrapolation of benefits is possible, but extrapolation of disbenefit and cost more difficult and possibly ignored as a result. In this situation an important role of the TAR should be to point out inadequacies in the extrapolated data and the method of extrapolation which they believe make the extrapolations themselves potentially misleading. Finding such inadequacies, as was the case here, means that it is illogical to proceed to extrapolation oneself. Failure to extrapolate should thus not be interpreted as a shortcoming motivated by deliberate attempts to inflate estimates of cost–utility, unless the concerns about the quality of the data used in the extrapolation can be shown to be unfounded. In general it seems reasonable that if a sponsor's case for cost-effectiveness relies on extrapolation of data, the onus should be on them to ensure that the quality of the data is adequate. Suggesting that evaluators should proceed with extrapolation regardless of major concerns about data reliability does not seem reasonable.

Failure to extrapolate implies that any benefits occurring up to 2 years cease immediately after 2 years, which is implausible and thus a model incorporating this assumption is invalid

As indicated above, not extrapolating beyond the end of the available RCT data does not necessarily imply that it is believed that benefits cease immediately at the end of the trial. We acknowledge that benefit in outcome may extend beyond 2 years. However, extrapolating cost–utility depends not just on an estimate of benefit in those receiving PDT, but extrapolating outcome in those not receiving treatment, extrapolating utility in all patients, extrapolating cost of treatment and extrapolating costs averted. Our grounds for not extrapolating and criticising extrapolation are the uncertainties around **all** parameters, leading to an unacceptably high level of uncertainty overall. To us this suggests that the extrapolated estimates of cost–utility are likely to be highly misleading. The problem is amplified by the length of the periods of extrapolation, both models offering estimates of cost–utility at 10 years, five times the duration of the TAP trial data and 2.5 times the duration the TAP trial plus open-label extension data. The problem is further compounded by the fact that the cost–utility models for verteporfin PDT which do extrapolate, fail to demonstrate the sensitivity of their results to the method of extrapolation chosen. They do not reflect the true impact of uncertainty in the key data, often using implausibly narrow ranges in sensitivity analyses.

One critique of the TAR's cost–utility model notes:

> "Modelling in the absence of data from randomised controlled trials has become accepted practice to derive estimates of cost effectiveness. Provided the assumptions on which the models are based are reasonable and explicit, modelling is an invaluable tool to aid the decision-making process."

We agree with this and would point out to extrapolate or not is a key assumption or decision in any model. We have been explicit about not extrapolating and believe that the assumption is reasonable, again being explicit about why. We would thus challenge any assertion that a model which does not extrapolate is invalid and has no value in the decision-making process. In this technology, particularly where other models of cost–utility do extrapolate, it makes clear just how big an effect on cost–utility extrapolation makes, indicating that whether it is undertaken and how it is undertaken is a key issue for decision-makers to scrutinise.

Evidence is available to support extrapolation

There is some data on visual acuity in those treated with verteporfin PDT in the TAP trial in the period 24 to 48 months. This open-label extension to the TAP trial has been used to support the assertion that the effect of PDT on visual acuity, as demonstrated by unchanged mean visual acuity (loss of 9.5 letters at 24 months; loss of 10.1 letters at 36 months), is maintained

between 24 months and 48 months. This in turn is used to justify extrapolation of the same size of effect in the ScHARR model of cost–utility from 2 years onwards. Unfortunately these data are limited in a number of important ways.

- It is uncontrolled and unblinded, so detection bias is highly likely to be operating.
- The quoted results are for the predominantly classic subgroup, so if one accepts that the results in this subgroup of the TAP trial are a statistical fluke, this applies equally to the 3-year data.
- The quoted results are only for the PDT-treated arm; the open-label extension provides no data about the untreated arm.
- Of the 159 patients with predominantly classic wet AMD followed to 24 months in the TAP trial, only 124 were enrolled in the extension.
- Of the 124 enrolled in the extension, only 105 were assessed at 36 months and included in the results.
- Hence, there is considerable loss to follow-up (54/159, 34%).
- Further, as *Table 35* shows there is evidence that the 66% of patients reported are a highly selected group, with a marked bias towards those with better outcomes at 24 months.

From Table A2, it is clear that the groups being followed-up in the open-label extension of the TAP trial, are not typical of the groups for whom the cost–utility of PDT is being sought, particularly all those receiving PDT in the TAP trial. They are not even typical of the TAP trial participants with predominantly classic PDT, although we continue to challenge whether restricting analysis of cost–utility to this subgroup is appropriate. It is thus debatable whether 'stability' in visual acuity from 24 months onwards has been demonstrated at all by the additional data. The recognised tendency for participants with poorer outcomes to be preferentially lost from follow-up suggests that deterioration in mean visual acuity from 24 months onwards would be the more likely finding if results for the complete cohorts could be obtained. The possibility of deterioration in mean visual acuity in those treated with PDT beyond 24 months certainly seems sufficiently high that it should be considered among the sensitivity analyses of models of cost–utility. The model by ScHARR, which generates the most optimistic picture of improvements in cost–utility the longer the period of extrapolation, does not do so.

Considering all the concerns about data from the open-label extensions of the TAP trial, not just the problems illustrated in *Table 35,* it is clear that although there is some information on which to base extrapolation of benefit, it is appropriate to question whether its reliability is adequate to make meaningful estimates of cost–utility beyond 2 years. This is particularly so if the impact of plausible variation has not been investigated in any sensitivity analyses. If other parameters also have a weak evidential basis, the credibility of extrapolated cost–utility will be further undermined.

Availability and quality of information on other parameters required for extrapolation of cost–utility
Information is required on the outcome in untreated patients beyond the 2 years of the trial in addition to information on the impact of verteporfin PDT on those receiving treatment. Those using extrapolation in PDT cost–utility models suggest that visual acuity is unlikely to improve and will remain constant in untreated people with established wet AMD. Support for this comes from the Macular Photocoagulation Study Group trial (7) that we do not challenge. However, although the control groups' mean visual acuity might remain stable over 2 or 3 years, it is improbable that it will remain constant over the 10-year period of extrapolation employed. In older people the incidence of other events that might threaten sight is high, occurrence of wet AMD in the second eye being a particularly important consideration. Fortunately for models of cost–utility the impact of this uncertainty on the difference in effect between PDT and no PDT is likely to be minimal as each group will probably be equally affected.

Beyond changes in visual acuity measures, cost–utility also requires good information on the changes in the 'utility' or impact on quality of life arising from given changes in visual acuity with and without treatment.

There were no direct measures of utility or quality of life in the TAP trial. All cost–utility models, irrespective of whether they have extrapolated beyond the 2-year trial data, have relied on the high quality observational studies reporting quality of life in patients with wet AMD. All the models equate a given level of visual acuity to a specific utility, for example 20/20, 6/6 or 85 letters to a measured utility of 0.89. However, certain assumptions are being made in using the data in this way.

- The 80 patients on which the estimates are based are typical of those in which PDT will be applied.

TABLE 35 *TAP trial: comparing characteristics in terms of visual acuity change from 0 to 24 months of cohorts in which further visual acuity change from 24 to 48 months was measured, relative to those of most relevance in the models of cost–utility*

Visual acuity change from 0 to 24 months	PDT – all (%)	PDT – predominantly classic subgroup (%)	PDT – predominantly classic enrolled in open-label extension (%)	PDT – predominantly classic in extension followed-up at 36 months (%)	PDT – predominantly classic in extension followed-up at 48 months (%)
N	402	159	124	104	93
≥ 6-line increase	3 (0.8)	N/A	N/A	2 (1.9)	N/A
≥ 3-line increase to < 6-line increase	33 (8.2)	N/A	N/A	9 (8.7)	N/A
≥ 3-line increase to < 1-line increase	26 (6.5)	N/A	N/A	7 (6.7)	N/A
No change	59 (14.7)	N/A	N/A	21 (20.2)	N/A
≥ 1-line decrease to < 3-line decrease	92 (22.9)	N/A	N/A	26 (25.0)	N/A
All above	213 (53.0)	94 (59.1)	N/A	65 (62.5)	60 (64.5)
≥ 3-line decrease to < 6-line decrease	116 (28.9)	41 (25.8)	N/A	25 (24.0)	33 (35.5)
≥ 6-line decrease	73 (18.2)	24 (15.1)	N/A	14 (13.5)	
Mean lines (letters) lost 0–24 months	2.7 (13.4)	2.4 (11.7)	2.0 (10.1)	1.9 (9.5)	1.7 (8.7)
Mean lines (letters) lost 0–36 months	N/A	N/A	N/A	2.0 (10.1)	2.0 (9.9)
Mean lines (letters) lost 0–48 months	N/A	N/A	N/A	N/A	2.1 (10.4)

- The utilities are measured outside the context of a trial and may be open to detection bias as a result.
- The visual acuity is that in the best-seeing eye; it is unclear whether the utility would be the same if the visual acuity was based on binocular vision. It is further unclear how the relationship between the visual acuity and utility in the best-seeing eye is modified by visual acuity in the other eye.
- It assumes that the utility associated with visual acuity in the best-seeing eye is constant over time – this is probably incorrect as research has suggested that utility improves with longer duration of vision loss.

The last of these is a particularly important source of uncertainty in the context of extrapolation because it challenges the fixed relationship between visual acuity and utility employed in the extrapolation in the ScHARR model in particular. Even if one accepts the questionable assumption that visual acuity remains constant beyond 2 years, with no further deterioration, the disutility associated with the loss of visual acuity is unlikely to remain constant. Adaptation will reduce the impact of a given loss of visual acuity on quality of life in the third and subsequent years of loss, relative to the first and second years. This means that in terms of utility, any advantage of PDT over placebo will diminish with time, although by how much is difficult to quantify.

Finally, there are important uncertainties about costs, particularly costs of blindness avoided and particularly costs beyond 2 years. Even apparently straightforward treatment costs are open to some doubt. Although it is tempting to suggest that additional costs associated with treatment decrease to virtually zero during any period beyond 2 years, evidence from the open-label extensions to the TAP trial indicate that treatment continued in some patients for up to 4 years. The mean number of treatments in each year was: 3.7, 2.2, 1.5 and 0.5. Thus, although costs associated with treatment clearly decrease beyond 2 years, they do not descend to zero.

Uncertainty associated with costs potentially offset by avoiding blindness and partial sight is much

more obvious, and already indicated section 4.2.3 of the TAR. Particularly important is the sensitivity analysis reported in Table 21 of the TAR suggesting that the mean annual cost of blindness might plausibly vary by over an order of magnitude from £1300 to £17,000. What the true cost is will clearly have a major impact on the cost–utility. The greater the cost associated with blindness, the more favourable the cost–utility of PDT will be, all other parameters (particularly effect and cost of treatment) being equal. However, the impact of this uncertainty on cost–utility will be greatly magnified the longer the period of extrapolation. Over 10 years the cumulative difference between low and high estimates will be £150,000 rather than the £15,000 over 1 year.

Methods of extrapolation employed in other models of cost–utility identified by TAR report

As indicated in the Guidance for Manufacturers and Sponsors, as important as the decision to extrapolate is indicating the sensitivity of the results to the method of extrapolation. Appropriate analysis can to some extent overcome, or at least make explicit, uncertainty arising from inadequacies in the data, which inevitably grow the longer the period over which one tries to model cost–utility. A detailed analysis of how models extrapolating beyond the 2 years of the TAP trial data achieved this is thus important, and is provided in *Table 36*.

Table 36 illustrates clearly that neither of the models extrapolating beyond the extent of the TAP trial deals satisfactorily with the high levels of uncertainty in many of the parameters beyond 2 years. They either fail to test the effect of a particular source of uncertainty on cost–utility or underplay the amount of variation likely in a particular parameter. Consequently the models do not give a true indication of the sensitivity of cost–utility to method of extrapolation and the choice of assumptions. However, an important difference in the reporting of the results is that the model by Sharma and co-workers acknowledges that the results of its extrapolation to 11 years is speculative and needs to developed further and populated with more accurate data. In contrast, the model by ScHARR presents the cost–utilities emanating from extrapolation as though there was no such uncertainty, which is inappropriate.

Summary and conclusion

The TAR preceding this addendum was undertaken to inform guidance by NICE on use of verteporfin PDT in the NHS in people with predominantly classic wet AMD. Three components of the TAR attracted well-argued criticism during the NICE consultation process. This addendum aimed to make explicit what the stated arguments under-pinning the criticisms were and consider whether these had any scientific foundation.

Concerning the use of subgroup analyses we believe that we have reinforced the arguments made in the TAR and clearly refuted any specific criticisms. We remain convinced that the whole trial TAP estimate of effect is the most appropriate effect size to use in estimating cost–utility of verteporfin PDT in people with predominantly classic wet AMD. We suggest that models of cost–utility not considering the likelihood that the larger effect size obtained in the predominantly classic subgroup analysis of the TAP trial is an artefact are offering estimates of cost–utility considerably more optimistic than is likely to be the truth.

Concerning extrapolation, we believe we have presented strong counter-arguments to the criticisms levelled against the decision not to extrapolate in this particular technology. In turn we show why the high level of uncertainty surrounding most parameters in the period beyond 2 years, particularly taken together, suggests extreme caution is required in taking any extrapolated estimates of cost–utility offered at face value. Failure to consider and present the impact of likely variation in all key parameters, further challenges the validity of the two models of cost–utility offering estimates beyond 2 years. Concern about the truthfulness of extrapolated estimates of cost–utility is important because the most favourable estimates of cost–utility only arise when projecting net benefit and cost considerably beyond the extent of rigorous effectiveness data.

Finally, we have also carefully examined the arguments made concerning timing of benefits and found that arguments made do have foundation. The suggestion that cost–utility has been overstated in the TAR through this route is accepted and that revision of our base-case cost–utilities from £151,000–182,000, to £84,000–101,000 per QALY is appropriate. Even with this, it should be emphasised that the acceptance does not make any material difference to the overall conclusions of the original report. These were that although effective, there is a great deal of uncertainty about whether verteporfin PDT for predominantly classic wet AMD is an efficient use of healthcare resources and that on balance we believe that it is inefficient.

TABLE 36 *Methods used in models estimating cost–utility beyond 2 years; the extent of the TAP RCT data*

Feature	Novartis/ScHARR	Sharma S *et al.*
Model description	18-state Markov, 3-month cycle, using predominantly classic subgroup data from TAP trial	Two-state Markov, 1-year cycle, using predominantly classic subgroup data from TAP trial
Extrapolation period	2 years onwards	2–11 years
How impact on visual acuity with PDT assessed	**Method** The 324 transition probabilities for last 12 months of TAP trial are carried forward indefinitely. Suggests visual acuity likely to remain constant, but extrapolation using other bases (i.e. last 3 months data) suggests marked continuing deterioration **Issues** 324 individual probabilities are based on small numbers (~159 patients) so chance variation needs to be incorporated into the model. Constancy of visual acuity apparently supported by actual data from TAP open-label extensions. However, selection bias in these studies is highly likely suggesting that continuing deterioration in mean visual acuity is actually more likely than constancy **Sensitivity of cost–utility to variation in approach tested?** No attempt to incorporate effect of small numbers used to calculate the many individual transition probabilities. Sensitivity to use of different periods to calculate future transition probabilities tested done. Little effect on cost–utilities, but using last 3–months data which suggested marked continuing deterioration in mean visual acuity not included in sensitivity analysis	**Method** Treatment effect assumed to reduce by 10% per annum during period of extrapolation, with proportions in untreated arms at 2 years remaining constant **Issues** Unclear what the basis for this assumption is. The speculative nature of the assumptions and the need for long-term effectiveness data is however clearly acknowledged **Sensitivity of cost–utility to variation in approach tested?** No attempt to assess the sensitivity of cost–utilities to alternative assumptions about how effectiveness data could be extrapolated
How impact on visual acuity with no treatment assessed	**Method** The 324 transition probabilities for last 12 months of TAP trial are carried forward indefinitely. Suggests visual acuity most likely to remain constant **Issues** Individual probabilities are based on even smaller numbers (~ 84 patients) so it is essential that chance variation is incorporated into the model. Constancy of visual acuity supported by data from another trial on effects of laser photocoagulation in extrafoveal AMD, but only from 3 to 5 years. No directly relevant data to corroborate extrapolation **Sensitivity of cost–utility to variation in approach tested?** No attempt to incorporate effect of very small numbers used to calculate the many individual transition probabilities Sensitivity to use of different periods to calculate future transition probabilities tested done. However assumption about base of future transition probabilities in control linked to that in PDT arm (i.e. if transition probability assumed to be constant for PDT), same assumption automatically applied to control. Not able to assess the possibility of a different assumption in the control group. Not able to assess the possibility that difference in mean visual might narrow over long time periods such as 10 years or more	**Method** See box above **Issues** See box above **Sensitivity of cost–utility to variation in approach tested?** See box above

continued

***TABLE 36* contd** *Methods used in models estimating cost–utility beyond 2 years; the extent of the TAP RCT data*

Feature	Novartis/ScHARR	Sharma S *et al.*
How change in visual acuities converted into utilities	**Method** Utilities derived from a variety of published sources allotted to each of the 18 visual acuity states. QALYs calculated by summing one-quarter utility value for each 3-month period	**Method** Utilities derived from authors' own published work and allocated to two alternative states (3-line loss of visual acuity or no 3-line loss), assuming two starting visual acuities (20/40 or 20/200)
	Issues These utilities assume visual acuity is in better eye. Utilities associated with given visual acuity state assumed to remain constant (i.e. utility for 6/60 or 20/200 vision is the same irrespective of whether a person has been in that state for 3 months, 1 year or 5 years)	**Issues** These utilities assume visual acuity is in better eye. Utilities associated with given visual acuity state assumed to remain constant
	Sensitivity of cost–utility to variation in approach tested? Yes, but only to alternative methods of allocating utility to visual acuity state not measured in original study. No testing of assumption key to validity of extrapolation, that utility associated with visual acuity state remains constant over time	**Sensitivity of cost–utility to variation in approach tested?** No testing of assumption key to validity of extrapolation, that utility associated with visual acuity state remains constant over time
How costs of treatment assessed	**Method** Data taken directly from TAP trial, bar 26% 'non-responders' assumed to have only two treatments. No PDT treatment said to occur in TAP trial after 42 months, so no treatment costs included beyond 4 years	**Method** Different treatment costs calculated for one to eight treatments
	Issues Data from open-label extension indicates mean number of treatments per patient followed-up from 36 to 48 months was 0.5. Suggests that treatment costs beyond 4 years may occur	**Issues** Assumes mean cumulative number of treatments does not exceed 8. However this is probably reasonable
	Sensitivity of cost–utility to variation in approach tested? No. Probably should have examined possible impact of some treatment costs continuing beyond 4 years	**Sensitivity of cost–utility to variation in approach tested?** Yes. Considered sensitivity of cost–utilities to varying cost of treatment from mean of 1 to 8 treatments per patient
How costs of blindness averted assessed	**Method** Annual costs associated with blindness and partial sight are accumulated in direct proportion to the number of years over which the model is run and the number of persons in each of these states during the period considered	**Method** Perspective of analysis is as a for-profit third-party insurer. Costs potentially averted from reduced social care not considered
	Issues Great uncertainty about the true levels of costs potentially averted. The level of discounting becomes critical the longer the period of extrapolation and the effect of different levels should be examined	**Issues** While accepting that perspective is legitimate, debatable how useful such a focused analysis is, particularly in the context of the NHS
	Sensitivity of cost–utility to variation in approach tested? Sensitivity to variation in costs was assessed and apparently shown to have little effect on cost–utility. Arguably this is because the difference between high and low estimates does not reflect the true level of uncertainty. Sensitivity analysis to different levels is limited to discounting at suggested rates, or not discounting at all which is probably not sufficient	**Sensitivity of cost–utility to variation in approach tested?** No. Should have considered the potential difference to extrapolated cost–utility of including costs potentially averted

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