

NICE protocol – This protocol is provisional and subject to change.

Review Team

Lead author:	Dr Catherine Meads, Tel 0121-414-6771.	Systematic reviewer.* Email c.a.meads@bham.ac.uk
Senior Lead:	Dr Chris Hyde, Tel 0121-414-7870	Senior lecturer.* Email c.j.hyde@bham.ac.uk

* correspondence to both.

Dr David Moore	Research reviewer and analyst.
Ms Anne Fry-Smith	Information scientist

Department of Public Health and Epidemiology
The University of Birmingham
Edgbaston
Birmingham B15 2TT
Fax: 0121-414-7878

Dr Cristian Salas, Ms Tracy Roberts	Health economists
-------------------------------------	-------------------

Health Economics Facility
Health Services Management Centre
The University of Birmingham
Edgbaston
Birmingham B15 2RT

Title of research question

A rapid and systematic review of the clinical effectiveness and cost utility of photodynamic therapy for age-related macular degeneration

Clarification of research question and scope

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

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

Methods

Clinical effectiveness review

Search strategy

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

The information scientist will design a search strategy, with assistance from the researchers and based on guidance in NHSCR4 (2nd edition), to identify any relevant randomised controlled trials (RCTs) comparing photodynamic therapy to no treatment or to laser photocoagulation for the treatment of neovascular membranes in wet AMD. The information scientist will conduct the search strategy. The researchers will scan all relevant study titles in the databases searched and abstracts will be read if the titles seem potentially relevant.

The following sources will be searched

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

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

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

Inclusion and exclusion criteria

Trials suitable for inclusion will be selected from those identified as potentially relevant by the search strategy, using the criteria listed below.

Study design: RCTs only.

Population: Adults with wet AMD causing any type of neovascular membranes (classic, minimally classic and occult).

Intervention: Photodynamic therapy using any photosensitive drug.

Comparator: Either no treatment (best supportive care) for subfoveal lesions or laser photocoagulation for juxtafoveal and extrafoveal lesions.

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.¹

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

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

Study design: Any study type.

Population: Adults with any AMD.

Intervention: Photodynamic therapy using any photosensitive drug.

Outcomes: Costs, cost consequences, cost utility, cost effectiveness or any generic quality of life.

One reviewer, using explicit predetermined criteria, will make the inclusion and exclusion decisions for the economic evaluation review. This will be checked by a second researcher. Quality of included studies will be assessed using the modified checklist by Drummond et al.²

Economic evaluation

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

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

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

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

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

Company submissions

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

Any 'commercial in confidence' data taken from industry submissions will be underlined in the text of the report.

Project Management

Timetable/milestones

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

Competing interests

(see next page)

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.

Topic-Related Declaration of Specific Competing Interests

Department of Public Health and Epidemiology, The University of Birmingham.

A rapid and systematic review of the clinical effectiveness and cost utility of photodynamic therapy for age-related macular degeneration

Please list below all interests you feel may be relevant to the NICE appraisal process as a whole. For further details of the kind of things that should be declared, please refer to the sheet on DIFFERENT TYPES OF COMPETING INTEREST.

<i>Personal specific</i>	<i>Non-personal specific</i>
	<p>Catherine Meads – Direct contact with the following company stalls at The European Society of Ophthalmology Conference, 3-7 June 2001. Istanbul. Alcon Laboratories Carl Zeiss Coherent Medical Novartis Ophthalmics Pharmacia and Upjohn Corp.</p> <p>David Moore – Direct contact (written, telephone) with the following companies because of a recent systematic review on treatments for acromegaly. Novartis Pharmaceuticals UK Ltd Ipsen Ltd.</p> <p>Christian Salas – Consultancy on competition in the pharmaceutical industry, with data provided by Novartis. September 2000.</p>

Appendices and references

A - Data extraction form

B - Quality assessment scale

C - Background

References

Data Extraction Sheet - NICE PDT for AMD

(Note: Blue for first trial full report, black for subsequent trial report (or use second sheet), red for industry submission)

First author/ Trial acronym:

Date:

Reference manager ID:

Any conflicts of interest:

A. Broad inclusion/exclusion criteria

Is it an RCT?	Y	N	?
Is the population 100% AMD?	Y	N	?
Is the intervention PDT?	Y	N	?
Is the comparator placebo?	Y	N	Other
Is the follow up completed?	Y	N	?

Outcomes (circle)

Visual acuity contrast sensitivity side effects other

Does it include any: economic QALY

B. Trial design

Randomisation method:

Masking Methods:

Unmasking?

PDT substance used (with dose):

Laser used (with dose):

Population

Baseline details (n, %)

	Intervention	Control
Number of patients enrolled		
Number of eyes enrolled		
Age		
Gender		
Baseline mean visual acuity		

Any significant differences:

Follow up

Numbers followed up at each time point (n, %)

Follow up time	Intervention	Control

How are missing values handled:

Numbers of angiographies per patient

Follow up time	Intervention	Control

Numbers of treatments per patient

Follow up time	Intervention	Control

Clinical Outcomes

Primary outcome:

NNT?

Secondary outcomes:

- 1.
- 2.
- 3.
- 4.

Outcome results (include confidence intervals and p values where given)

	Intervention	Control
Primary outcome at follow up time:		

Secondary outcome at fu time

- 1.
- 2.
- 3.
- 4.

Quality assessment – RCTs, NICE PDT for AMD

Trial / date:

A. Randomisation

1. Was the RCT described as randomised?	Y	N	?
2. Was allocation truly random?	Y	N	?

B. Concealment of allocation

Was concealment of treatment allocation truly adequate?	Y	N	?
---	---	---	---

C. Masking

3. Was the trial described as double blind?	Y	N	?
4. Was treatment allocation masked from participants?	Y	N	?
5. Was treatment allocation masked from investigators?	Y	N	?
6. Was treatment allocation masked from outcome assessors?	Y	N	?

D. Completeness of trial

1. Were the number of withdrawals in each group stated?	Y	N	?
2. Was an intention to treat analysis done?	Y	N	?
3. Were the drop out rates similar in both groups?	Y	N	?

Score

Add if A1 YES	+1
Add if C1 YES	+1
Add if D1 YES	+1
Add if A2 YES	+1
Subtract if A1 is YES and A2 is NO or B is NO	-1
Add if C2 is YES and C4 is YES	+1
Subtract if C1 is YES and C2 is NO or C4 is NO	-1
Total score (between 0 and 5)	

Comments:

Quality assessment – Economic Evaluations, NICE PDT for AMD

Trial / date:

	Yes	No	Partially	Unclear	N/A
Was the question well defined?					
Was there a comprehensive description of the alternatives?					
Were all the important and relevant costs and outcomes for each alternative identified?					
Was clinical effectiveness established?					
Were the costs and outcomes measured accurately?					
If the evaluation was derived from a trial, was the costing analysed either concurrently or prospectively?					
Were the costs valued credibly?					
Were the outcomes valued credibly?					
Were the costs adjusted for differential timing?					
Were the outcomes adjusted for differential timing?					
Was incremental analysis of costs and consequences reported?					
Were sensitivity analyses conducted on costs or consequences?					
How far did the study results include all issues of concern to users of the information?					
Were the results generalisable to the setting of interest in the review?					

Comments:

Background - 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.³ Experimental treatments tried include ionising radiation, anti-oxidant vitamin and mineral supplements, antiangiogenic agents including interferon, vascular endothelial growth factor, integrins and thalidomide and surgical interventions including retinal excision and implantation.⁴⁻⁶ No RCTs on these interventions have shown significant benefit to the patient. New treatments currently under evaluation include angiostatic steroids (Anecortave Acetate⁷) and transpupillary thermotherapy (TTT⁸).

For most patients, as with dry AMD, management consists of social support, visual rehabilitation and provision of low vision aids.⁹

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.^{3,4}

If subfoveal lesions are treated with laser photocoagulation, there is an immediate loss of visual acuity from a central dark scotoma but long term follow up has shown some benefit in patients with small new vessel complexes and already poor visual acuity.⁴ 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.³
- ?? Most presenting lesions are subfoveal.¹⁰ The immediate visual acuity loss means that this treatment is not well accepted so is now rarely used.
- ?? There is approximately a 50% chance that leakage will recur during the two years after treatment.³
- ?? There is a small risk (0.5% - 2%) of a RPE tear occurring which will lead to profound loss of vision.^{11,12}

Description of new technology

Photodynamic therapy is the new intervention to be evaluated. It uses photosensitive drugs and a specially developed low-powered laser.

Photosensitive drugs as a group all work in a similar way. An inert substance, usually a benzoporphyrin derivative, is injected into the peripheral bloodstream. After a length of time (minutes or hours) the substance enters or attaches to all cells of the body. It is cleared from healthy cells but preferentially remains with proliferative cells (such as new blood vessels).¹³ 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.¹⁴ The laser is not powerful enough to cause any damage on its own. Photodynamic therapy results in proliferative cells being selectively targeted and destroyed and other cells left alive.

Photosensitive treatments are under investigation for a variety of conditions such as cancers, HIV/AIDS, transplant rejection, bone marrow infection, psoriasis and arthritis.¹⁴ For this report, the two relevant photosensitive substances currently undergoing randomised controlled trials for AMD are verteporfin (trade name Visudyne)¹⁵ and tin ethyl etiopurpurin (SnET2), now called rostoporfin (trade name was Purlytin)¹⁶. Other photosensitive substances being investigated in preliminary trials on humans are motexafin lutetium which is also called lutetium texaphyrin (trade name Lu-Tex)¹⁷ and indocyanine green¹⁸ (which is also used in retinal angiography).

Photodynamic therapy in AMD is intended to stop further leaking from new neovascular membranes and so halt further loss of vision but it is not intended to restore vision already lost. However, results from trials suggest that vision can improve in a small percentage of people¹⁵ but the causal mechanism is unclear. 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.¹⁴ Unlike laser photocoagulation, there is no sudden vision loss (except in a small minority who suffer a choroidal infarction¹⁹). For the remaining patients there may be some slight visual disturbance for a few days after treatment only. Retreatment is needed, sometimes several times before no further growth of new vessels is seen.²⁰ Photodynamic therapy is relatively painless and can be undertaken in the outpatient department. However, there are a number of disadvantages.

- ?? The treatment may only be effective on some patients with wet AMD and not others.¹⁵ It may be tried several times for up to a year before this is known. This could have adverse psychological consequences and visual rehabilitation will be delayed
- ?? The photosensitive drug remains in the body for various durations, depending on the substance (verteporfin 24-48 hours, tin ethyl etiopurpurin 2-4wks, lutetium texaphyrin 1-2wks).²¹ 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.¹⁵
- ?? The long-term effects in humans of photodynamic therapy for wet AMD are unknown.

Licensed indications, contra-indications and warnings

Visudyne® is currently indicated for the treatment of AMD in patients with predominantly classic subfoveal choroidal neovascularisation.²² Following the two year results of the VIP trial, the intention is to treat people with occult subfoveal lesions.²³ It is contra-indicated in patients with porphyria, severe liver impairment or known hypersensitivity to verteporfin or any other component of the infusion. 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. Overdose of drug and/or laser dose can result in permanent irreversible vision loss.²⁴

Reference List

1. Jadad A., Moore R., Carroll D. Assessing the quality of reports of randomised clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;**17**:1-12.
2. Drummond MF, O'Brien B, Stoddart GL, Torrance GW. *Methods for the economic evaluation of health care programmes*. Oxford: Oxford Medical, 1998.
3. Fine SL, Berger JW, Maguire MG, Ho AC. Age related macular degeneration. *New England Journal of Medicine* 2000;**342**:483-492.
4. Chong NH, Bird AC. Alternative therapies in exudative age related macular degeneration. *British Journal of Ophthalmology* 2000;1441-1443.
5. Soubrane G, Bressler NM. Treatment of subfoveal choroidal neovascularisation in age related macular degeneration: focus on clinical application of verteporfin photodynamic therapy. *British Journal of Ophthalmology* 2001;**85**:483-495.
6. National Horizon Scanning Centre. Photodynamic therapy for age-related macular degeneration. 2000. Birmingham UK., The University of Birmingham.
7. D'Amico DJ and Independent Safety Monitoring Committee. Sub-tenons retrobulbar Anecortave Acetate with and without Visudyne PDT in patients with subfoveal age-related macular degeneration (AMD) - Clinical safety profile. 166. 2001. Istanbul - Turkey, XIII Congress of The European Society of Ophthalmology. 3-6-2001.
8. Newsom RS, McAlister JC, Saeed M, McHugh JD. Transpupillary thermotherapy (TTT) for the treatment of choroidal neovascularisation. *British Journal of Ophthalmology* 2001;**85**:173-178.
9. Frith P, Gray R, MacLennan S, Ambler P. *The eye in clinical practice*. Oxford: Blackwell Scientific, 1994.
10. Freund KB, Yannuzzi LA, Sorenson JA. Age related macular degeneration and choroidal neovascularisation. *American Journal of Ophthalmology* 1993;**115**:786-791.
11. Macular Photocoagulation Study Group. Laser photocoagulation of subfoveal recurrent neovascular lesions in age related macular degeneration. Results of a randomised controlled trial. *Archives of Ophthalmology* 1991;**109**:1232-1241.
12. Macular Photocoagulation Study Group. Laser photocoagulation of subfoveal neovascular lesions in age related macular degeneration. Results of a randomised controlled trial. *Archives of Ophthalmology* 1991;**109**:1220-1231.
13. Schmidt-Erfurth U, Miller J, Sickenberg M, et al. Photodynamic therapy of subfoveal choroidal neovascularization: clinical and angiographic examples. *Graefe's Archive of Clinical Experience in Ophthalmology* 1998;**236**:365-374.

14. McCaughan Jr JS. Photodynamic therapy, a review. *Drugs and Aging* 1999;**15**:49-68.
15. Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with Verteporfin. *Archives of Ophthalmology* 1999;**117**:1329-1345.
16. Thomas EL, Murphy RP, Tressler CS, Eriksson M, Rausch AM. Photodynamic therapy with Tin Ethyl Etiopurpurin (SnET2) of subfoveal choroidal neovascularisation (CNV) in age related maculopathy: study design and baseline characteristics. *Investigative Ophthalmology and Visual Science* 2000;**41**:2828
17. Blumenkranz MS, Miller JW, Guyer DR, et al. Preliminary results from a phase II dose response study of photodynamic therapy with Motexafin Lutetium (Lu-Tex) to treat subfoveal CNV. *Investigative Ophthalmology and Visual Science* 2000;**41**:S531-2827.
18. Farah ME, Costa RA, Cardillo JA, and Belfort R. Photodynamic therapy with indocyanine green for occult subfoveal choroidal neovascularisation caused by age related macular degeneration. 389. 2001. Istanbul, European Society of Ophthalmology. 3-6-2001.
19. Bird AC. 2-7-2001. Personal Communication.
20. Schmidt-Erfurth U, Miller J, Sickenberg M, et al. Photodynamic therapy with verteporfin for choroidal neovascularisation caused by age-related macular degeneration. Results of retreatments in a phase 1 and 2 study. *Archives of Ophthalmology* 1999;**117**:1177-1187.
21. Regillo CD. Update on photodynamic therapy. *Current Opinion in Ophthalmology* 2000;**11**:166-170.
22. Committee for proprietary medicinal products. European public assessment report (EPAR). Visudyne. CPMP/1019/00. 2001. London, The European Agency for the Evaluation of Medicinal Products.
23. Anon. Visudyne™. verteporfin product monograph. 2nd Edition. 2001. Bulach, Switzerland, Novartis Ophthalmics AG.
24. Miller J, Schmidt-Erfurth U, Sickenberg M, et al. Photodynamic therapy with Verteporfin for choroidal neovascularisation caused by age-related macular degeneration: Results of a single treatment in a phase 1 and 2 study. *Archives of Ophthalmology* 1999;**117**:1161-1173.