

NORCOM

North Derbyshire, South Yorkshire and Bassetlaw Commissioning Consortium

REVISED POLICY ON PHOTODYNAMIC THERAPY FOR MACULAR DEGENERATION (AGE AND NON-AGE RELATED)

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ABBREVIATIONS

AMD	Age-related macular degeneration
CNV	Choroidal neovascularization
NICE	National Institute for Clinical Excellence
PDT	Photodynamic therapy
RCT	Randomised controlled trial
TAP	Treatment of AMD with PDT
VA	Visual acuity
VIP	Verteporfin in PDT

DEFINITIONS

AMD: Degeneration of the macula (the central area of the retina) in people aged over 50 years with no other apparent cause for the degeneration. The VA may vary from normal to severe impairment.

Age related maculopathy: Early stage of AMD.

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

Classic CNV: Characterised by an area of choroidal hyperfluorescence with well-demarcated boundaries that can be discerned in the early phase of the fluorescein angiogram. In the later phases of the angiogram, progressive pooling of dye leakage occurs in the overlying subsensory retinal space and usually obscures the boundaries of the CNV.

CNV leakage (choroidal neovascular leakage): This means that the choroidal vessels have penetrated the retinal pigment epithelial barrier and are leaking or have bled into the sub-retinal space. It is as a result of this leakage the term *wet* AMD is derived.

Drusen: Yellow subretinal amorphous deposits.

Fluorescein angiogram: A procedure for viewing and photographing the inner eye, involving injection of a dye into the bloodstream.

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

Macula: Small area of the retina used for central vision.

Neovascularization: The formation of new blood vessels.

Occult CNV: There are two types: (i) is leakage of undetermined origin on fluorescein angiography; and (ii) is pigment epithelial detachment on stereoscopic fluorescein angiography.

Pigment epithelial 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.

Predominantly classic CNV: CNV in which more than 50% of lesion area consists of classic CNV on fluorescein angiography.

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

Verteporfin: A photosensitive dye used in PDT.

1. AIM OF PAPER

1.0 This paper presents the revised NORCOM Commissioning Policy on photodynamic therapy (PDT) for age and non-age related macular degeneration. It supersedes the previous policy dated 1 June 2003.

This policy primarily focuses on age-related macular degeneration (AMD), which is the main cause of macular degeneration in this country.

2. BACKGROUND

2.1 The National Institute for Clinical Excellence (NICE) published its final guidance on the use of PDT as a treatment for AMD in September 2003.ⁱ

2.1 This paper is based on NICE's final guidance and the 2001 Royal College of Ophthalmologists Guidelines for PDT in the management of subfoveal choroidal neovascularisation (CNV) secondary to AMD.ⁱⁱ CNV is the development of new blood vessels beneath the retina.

3. AGE-RELATED MACULAR DEGENERATION

3.01 AMD is defined as degeneration of the macula (the central area of the retina) in people aged over 50 years with no other apparent cause for the degeneration.

3.02 It is the commonest cause of loss of vision as people age. It accounts for about 50% of registered blindness in England and Wales.ⁱⁱⁱ

3.03 AMD causes painless loss of central vision. The impairment can have a disabling impact on individuals. They may for example be unable to read, recognise faces or drive.

3.04 The cause is unknown. Ocular risk factors include the development of drusen (yellowish subretinal spots), and other retinal changes collectively known as age-related maculopathy. Systemic risk factors include hypertension, smoking and a positive family history.^{iv} AMD may be more common in women than in men.^v

3.05 Incidence rises with age: 0.7–1.4% per annum of people aged 65–75 years and 11–19% per annum of people aged over 85 years.^{vi} Prevalence rises with age: Around 10% of people aged 65–75 years and approximately a third of people aged over 75 years.

3.06 Because age is the primary risk factor for AMD, crude incidence and prevalence of the condition is expected to increase as the population ages. Estimates suggest that there will be nearly three times the number of new cases of AMD in the population in the NORCOM area by 2016.

3.07 There are two forms of AMD, *dry* (non-neovascular) and *wet* (neovascular) as shown in [Appendix A](#). Dry AMD is characterised by drusen, retinal pigment epithelial changes, hyperplasia and atrophy, and secondary retinal changes. Wet AMD is characterised by CNV accompanied by exudates, haemorrhage and neurosensory retinal detachment. Both forms can co-exist in the same eye.

3.08 Dry AMD accounts for 90% of cases.

3.09 In *dry* AMD vision loss is gradual (over years) and does not respond to PDT. In *wet* AMD vision loss is usually more rapid (within weeks) and a proportion of cases (with greater than 50% CNV) may respond to PDT.

3.10 *Wet* and *dry* AMD can be differentiated in some circumstances on fundoscopy. General practitioners or optometrists are not easily able to differentiate between the two forms.

1.11 CNV can be subdivided into *classic* and *occult* forms according to their appearance on fluorescein angiography. CNV lesions may exhibit different proportions of classic and occult leakage.

1.12

4. PHOTODYNAMIC THERAPY

4.1 PDT is a newly developed treatment for AMD. No other treatments exist for the condition, except social support, visual rehabilitation and provision of low vision aids.

4.2 PDT aims to stop leaking blood vessels in the back of the eye and prevents further loss of vision. The treatment does not restore vision already lost.

4.3 The procedure is done in the outpatient clinic and takes around 30 minutes.

4.4 Before treatment, patients are assessed using stereoscopic fluorescein angiography for suitability. This is usually repeated every three months in patients receiving treatment. If CNV leakage is present they are retreated. It is likely that an average patient will require six treatments over a 3 year period.

4.5 The treatment consists of a short intravenous infusion of a light sensitive dye (Verteporfin) that sticks to the inner lining of the new blood vessels. A laser activates the dye which damages the vessels causing closure.

4.6 Common adverse effects of treatment include transient visual disturbance, injection site reactions, infusion related back pain and photosensitivity.

4.7 PDT should be considered to be a course of treatment. Medical, social or other factors should not ordinarily prevent the patient in following the treatment programme.

5. EVIDENCE BASE

5.1 NICE has reviewed the evidence available on the effectiveness of PDT for AMD. It found two large randomised controlled trials (RCTs) which demonstrated, through post hoc sub-group analysis, that PDT is probably effective in AMD with greater than 50% CNV.

5.2 Cost per QALY estimates ranged from £61,000 to £182,000 at two years. They were lower with better VA at baseline in the better-seeing eye. These estimates of cost-effectiveness are at the margins of what is considered to be an efficient use of health care resources within the NHS. More favourable estimates have been obtained in models extrapolating beyond two years.

5.3 Additional details of evidence base are in [Appendix B](#).

5.4 Once wet AMD has developed in one eye, the risk of developing it in the other eye is about 42% by five years.^{vii} When a patient presents with one affected eye, it is not known whether or not that eye will ultimately turn out to be the better of the two. As there is a limited time period in which PDT will be effective, and that the second eye may develop a lesion that is not treatable, NICE considers it appropriate to treat classic with no occult lesions regardless of whether they occur in the first or second eye that develops the condition.

5.5 In 2001, The Royal College of Ophthalmologists Guidelines expressed concern about the widespread use of PDT. Reasons for this included uncertainty over optimal treatment regime, lack of quality of life data, incidence of early visual loss following treatment, and uncertainty over number of patients likely to need treatment.

6. THE NEW SHEFFIELD SERVICE

6.1 A 'hub and spoke' model for the PDT service across the NORCOM area is being developed. The 'hub' will be the Sheffield Ophthalmology Unit at the Royal Hallamshire Hospital. Sheffield has been the designated provider of PDT treatment for the eligible NORCOM population since 1 April 2003. The 'spokes' will be all the District General Hospitals (DGHs) in the NORCOM area.

6.2 The Sheffield Ophthalmology Unit will be the treatment centre for all the eligible NORCOM population and undertake the initial assessment of patients with macular degeneration for suitability for PDT treatment for the local, mainly Sheffield, population.

The DGH's in the NORCOM area will undertake the initial assessment of patients in their local population and refer patients suitable for treatment on to the Sheffield service. The Sheffield ophthalmology unit will only accept tertiary referrals from the ophthalmologists in the NORCOM DGH's. Patients that are unsuitable for treatment should be appropriately managed by the DGHs. If a GP or optometrist suspects treatable wet AMD, they should initially refer the patient to their local hospital's ophthalmic department.

6.3 NICE estimates applied to the population covered by NORCOM suggest that 170-260 patients will present with

predominantly classic wet AMD each year. Of these, approximately 60%¹ will have classic lesions with no occult component. This means that around 100-160 new patients are eligible for PDT every year in the NORCOM area.

6.4 The cost per treatment in Sheffield is approximately £1,663 (2003/04 prices). Assuming that an average patient will have two treatments per year, the estimated 3 year cost for a cohort of patients is shown in the table below. The Year 4 figures show the likely ongoing annual cost of the service once it is fully implemented.

Estimated annual cost of PDT service				
Number of new patients receiving PDT per year	Year 1	Year 2	Year 3	Year 4
100	£332,600	£665,200	£997,800	£997,800
160	£532,160	£1,064,320	£1,596,480	£1,596,480

6.5 As wet AMD can progress rapidly, the Sheffield service will ensure that individuals with early wet AMD and without serious visual loss are fast-tracked through the referral and waiting list processes in order to receive treatment before further loss of vision occurs.

6.6 Sheffield, in accordance with NICE and the Royal College of Ophthalmologists, is able to provide the required quality of service. This includes:

- Medical retina specialisation
- Standardised vision assessment
- Stereoscopic fluorescein angiography
- Rehabilitation service

6.7 Details of the agreed service standards for the PDT service in Sheffield are set out in [Appendix C](#). The service standards are based on national guidance.^{viii}

¹ Estimate based on the patient characteristics in the TAP studies and on data from the PDT user group SERNIP surveillance programme

7. TREATMENT CRITERIA

7.1 The revised treatment criteria for PDT for AMD are in Box 1.

Box 1: PDT CRITERIA FOR AMD

General

- (i) **Patient must be able to complete a course of treatment.**

Treat if:

- (i) **Wet AMD; and**
- (ii) ***Classic with no occult* subfoveal CNV; and**
- (iii) **Best corrected vision of 6/60 or better.**

PDT is not recommended for the treatment of predominantly classic subfoveal CNV associated with wet AMD, except as part of ongoing or new clinical studies that are designed to generate robust and relevant outcome data (Note: Entry into the national PDT Cohort Study meets these requirements).

7.2 PDT may also be considered for patients with the following non-age related conditions who may have similar pathology:

- Pathological myopia (high degree myopia/severe short-sightedness)
- Single gene disorders
- Secondary to trauma/injury

7.3 Individual PCTs will deal with requests for PDT for non-age related macular degeneration conditions on a named patient service agreement basis with prior approval. It is expected that the number of such cases will be small.

7.4 All patients that undergo PDT should be entered into the Verteporfin PDT Cohort Study. This is a condition for receiving NHS funded treatment. Primary objectives of this UK-wide study include determining the long-term benefit of PDT and optimum treatment regimen.

8. POLICY STATEMENT

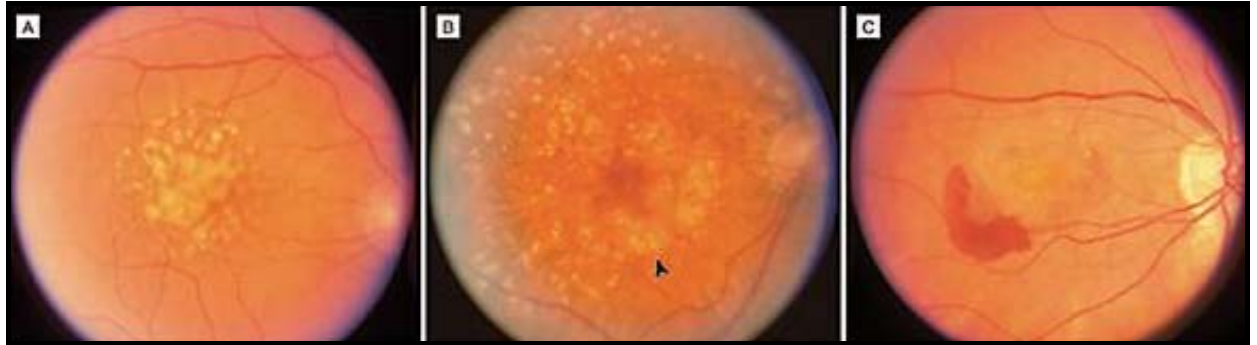
8.1 The following statement sets out the position of NORCOM in respect of future referrals and funding requests for PDT for macular degeneration.

- ***The Sheffield Ophthalmology Unit is the designated treatment centre for PDT in the NORCOM area.***
- ***All referrals for PDT treatment should be made to Sheffield after having been assessed for suitability for treatment at the District General Hospital level.***
- ***The quality of the Sheffield PDT service should meet the agreed standards.***
- ***Revised patient criteria for PDT for age-related macular degeneration are in Box 1.***
- ***Individual PCTs will deal with requests for PDT for non-age related macular degeneration conditions on a named patient service agreement basis with prior approval.***

8.2 This policy will be reviewed when further significant information becomes available, either from clinical trials or NICE.

APPENDIX A

Figure: Fundus photographs of AMD



A: Dry AMD with many soft drusen clustered within the central macula.

B: Late dry AMD.

C: Wet AMD with blood beneath the retina in the temporal macula.

APPENDIX B

10.01 Details of evidence base

10.02 There are two published RCTs of Verteporfin PDT:

- Treatment of age-related macular degeneration with photodynamic therapy (TAP) study
- Verteporfin in photodynamic therapy (VIP) study.

10.03 Both trials are of high quality. The TAP study randomised 609 patients (402 Verteporfin; 207 placebo PDT) and the VIP study randomised 339 (225 Verteporfin; 114 placebo PDT). Both trials were double-blinded and placebo-controlled with an intention to treat analysis. Most participants were either North American or European.

10.04 Patients received follow-up every 3 months for two years. Patients required 3-5 treatments during the follow-up period.

10.05 The TAP study included patients with AMD and subfoveal CNV with some evidence of classic CNV, and VA between 6/12 (mild visual impairment) and 6/60 (severely impaired vision). The VIP study included patients with AMD. Most of these patients had occult CNV and 6% had predominantly classic CNV.

10.06 In both studies the main outcome was change in VA (as the proportion of eyes with fewer than 15 letters lost or about 3 lines) in the randomised eye up to two years post-treatment.

10.07 Both studies found less deterioration in VA in the intervention group compared with the placebo-treated group. In the TAP trial at 2 years 47% of eyes treated with PDT had lost 15 or more letters of VA compared with 62% of placebo treated eyes. For the VIP study in AMD, the corresponding figures were 54% and 67%. The loss of 15 letters of VA corresponds to being able to read 3 fewer lines on an eye-test chart. Findings in both studies were clinically and statistically significant.

10.08 A subgroup analysis of 243 patients (159 Verteporfin; 84 placebo PDT) in the TAP trial found that the treatment effect was larger in patients whose lesions were at least 50% classic CNV. In this subgroup at 2 years 41% of eyes treated had lost 15 or more letters of VA compared with 69% of placebo treated eyes. There was no benefit noted for patients with minimal classic lesions (<50% of the total lesion burden), even though angiographic findings improved. This may reflect a lack of power for subgroup analysis, or may reflect difficulties in correctly classifying lesions.

10.09 Three economic evaluations have been based on the TAP study. The Assessment Group used whole trial data whilst the manufacturers and a North American publication focused on the classical subfoveal CNV subgroup. These evaluations expressed the benefits of treatment in terms of QALYs, which were related to change in VA alone.

10.10 Cost per QALY estimates ranged from £61,000 to £182,000 at two years. This is at the margins of what is considered to be an efficient use of health care resources within the NHS. NICE noted that all estimates of cost-effectiveness contained an inherent (optimistic) assumption that it was the patient's better seeing eye that was being treated. More favourable estimates of cost-utility have been obtained in models extrapolating beyond 2 years, the limit of RCT data.

APPENDIX C

11.1 Service standards

11.2 Organisational aspects of the service

- a) The service should be led by a retinal specialist.
- b) Retinal specialists undertaking PDT should have attended the Royal College of Ophthalmologists accredited workshop on stereo recognition of angiographic subtypes of CNV.
- c) Acuity examiners carrying out initial assessment of patients should have undergone appropriate training.
- d) Medical photographers undertaking angiography should be accredited by a Reading Centre.
- e) The service should be able to fast-track referrals from GPs, optometrists or ophthalmologists suspecting treatable wet AMD.
- f) Systems and support for data collection for the Verteporfin PDT Cohort Study should be in place.
- g) Electronic links to Reading Centres should be in place.
- h) The Macular Degeneration Society should be offered a presence in outpatient clinics and their roles and remit should be formally agreed.
- i) Appropriate low vision support should be made available to patients with bilateral visual impairment.

11.3 The patient pathway

- j) 100% of patients in whom there is a high degree of suspicion that the presenting eye harbours a recent onset classic or predominantly classic subfoveal CNV should be referred from the point of first contact to a retinal specialist at a PDT centre for assessment and initiation of management. (NB. *In the NORCOM area the initial*

assessment will be undertaken by the local ophthalmology service in the DGH).

- k) The initial visit should include relevant clinical history to identify duration of visual symptoms in the eye to be treated, the fellow eye and if available VA at initiation of referral. Best corrected VA following refraction must be recorded at the baseline visit and may be undertaken by a nurse who has received appropriate training or by an optometrist. Testing must be performed using an appropriate eye test chart to a standardised protocol. Diagnosis of CNV must be made on the basis of stereo colour fundus photography and angiography with frames captured for up to 10 minutes preferably on a digital capture system. These investigations must be completed prior to undertaking PDT.
- l) PDT should be initiated by a retinal specialist trained in stereo recognition of the angiographic characteristics of classic or predominantly classic CNV.
- m) The retinal specialist should submit clinical and angiographic data within 1 week of the patient visit/treatment to the national co-ordinating centre.
- n) Patients should undergo repeat best corrected VA, clinical examination and fluorescein angiography 3 months after PDT treatment. Re-treatment should be based upon VA and fluorescein angiography findings. (NB. *The review visits will take place at the treatment centre to ensure prompt access to retreatment*).
- o) Appropriate low vision support should be available to patients requiring it.
- p) All patients should be made aware of the voluntary organisations available to support them at the time of diagnosis.

11.4 Service outcomes

- q) 100% of eligible patients with subfoveal classic with no occult CNV or predominantly classic with occult CNV with VA equal to or better than 6/60 should be treated with PDT within 2 weeks of presentation to the service.
- r) 100% of eligible patients should have VA in the eye to be treated measured prior to PDT and fluorescein angiography performed within 1 week of treatment at first and at all subsequent treatments.
- s) Data is collected on all patients treated with PDT and submitted for analysis to the national co-ordinating body for the national cohort study.
- t) There is improvement in the diagnosis of eligibility for PDT using angiographic definitions and in reduced variation in practice.

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