NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of epiretinal brachytherapy for wet age-related macular degeneration

Treating abnormal blood vessel growth in wet age-related macular degeneration using localised radiotherapy

Age-related macular degeneration (AMD) is an eye disorder affecting the macula, which is the area at the centre of the retina (the back of the eye) responsible for central vision (seeing things straight in front of you). Wet AMD happens because fluid leaks out of abnormally formed arteries and veins into the area under the macula (the choroid layer), causing distorted vision and scarring. Loss of vision is progressive and often rapid.

Radiotherapy has sometimes been used in conjunction with pharmaceutical injections in people with wet AMD to treat the abnormal blood vessels growing under the macula. A probe is carefully inserted into the eye through a small incision and radiation therapy is used to destroy the vessels. The aim of this procedure is to slow down the growth of the blood vessels or stabilise the patient's vision, and to reduce the number of pharmaceutical injections required.

Introduction

The National Institute for Health and Clinical Excellence (NICE) has prepared this overview to help members of the Interventional Procedures Advisory Committee (IPAC) make recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in April 2011 and updated in October 2011.

Procedure name

- Epiretinal brachytherapy for wet age-related macular degeneration

Specialty societies

- Royal College of Ophthalmologists
- British Society of Interventional Radiology
- Royal College of Radiologists.

Description

Indications and current treatment

The macula is the part of the retina responsible for central vision and the appreciation of fine detail and colour. Damage to the macula impairs vision, and in the UK, AMD is a common cause of blindness. There are two main types of AMD: 'dry' (or atrophic), which is the most common, and 'wet' (or neovascular). This is characterised by the abnormal growth of new blood vessels in the choroidal layer underneath the macular retina (also called choroidal neovascularisation or CNV). In patients with wet AMD, blood and fluid leaks from these abnormal (neovascular) vessels, which can cause retinal scarring and impair vision. Both eyes are usually affected, sometimes sequentially.

The visual prognosis of patients with wet AMD without treatment is poor. Some patients are diagnosed at an advanced stage and therefore the treatments are less effective and may not be indicated.

Treatment depends on lesion size, location and disease stage. Treatment options for wet AMD include laser photocoagulation, photodynamic therapy or intravitreal injections of anti-vascular endothelial growth factor agents. Patients with advanced AMD may benefit from optical aids such as magnifying glasses, eccentric viewing training and implantation of miniature lens systems.

What the procedure involves

This procedure aims to slow down the growth of blood vessels that causes wet AMD. This is done by administering beta radiation therapy (a form of radiation that is relatively less toxic compared with other forms) targeted at the abnormal, leaking vessels.

The procedure is usually performed with the patient under local anaesthesia, and is normally used in combination with an anti-vascular endothelial growth factor (VEGF) agent. A vitrectomy is performed, and an intraocular epiretinal probe is placed in the vitreous cavity, over the fovea, before beta radiation is delivered. The radiation dose received by the patient is less than the dose received during a typical chest X-ray. The sclera is closed with an absorbable suture. Prophylactic antibiotics and steroids are usually administered, and the eye patched.

A number of devices are available for this procedure.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to epiretinal brachytherapy for wet age-related macular degeneration. Searches were conducted of the following databases, covering the period from their commencement to 25 July 2011: MEDLINE, PREMEDLINE, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches (see appendix C for details of search strategy). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial, or a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with wet age-related macular degeneration
Intervention/test	Epiretinal brachytherapy
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on approximately 68 patients from 2 case series, 1 of which has been described in 2 studies[1–3].

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (table 2) have been listed in appendix A.

Table 2 Summary of key efficacy and safety findings on epiretinal brachytherapy for wet age-related macular degeneration

Abbreviations used: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; Gy, Grays; VEGF, anti vascular endothelial growth factor

Study details	Key efficacy findings	Key safety findings	Comments
Avila MP (2009)[1] **Case series** International Recruitment period: 2005 to 2006 Study population: patients with Subfoveal CNV secondary to AMD. Mean BCVA 37.7. **n = 34 (34 eyes)** Age: 73 years (mean) Sex: 62% male Patient selection criteria: patients with BCVA 20/70 to 20/400, loss of two lines of visual acuity in past 2 months, or new-onset blood / lipid leakage in the macular region. Lesions composed of > 50% CNV. Technique: strontium-90 beta radiation brachytherapy with a delivery device directed over the area of CNV via pars plana vitrectomy. 15 Gy (n = 8) or 24 Gy (n = 26) of radiation delivered over 3 to 5 minutes. **Follow-up: 12 months minimum** Conflict of interest/source of funding: two authors have a proprietary interest in the device	Number of patients analysed: **n = 34** **Visual acuity** Among the patients who received 15 Gy of radiation, the mean change in visual acuity was a loss of 1.0 letters. In patients receiving 24 Gy, the mean change was a gain of 4.4 letters. Percentage of patients achieving outcome at 12 months Outcome / 15 Gy brachytherapy / 24 Gy brachytherapy Lost < 15 letters: 100% / 83% Gained > 1 letter: 50% / 63% Gained > 15 letters: 0% / 21%	**Complications** There were no reports of radiation-induced toxicity or adverse events that could be attributed to radiation exposure at 12-month follow-up. Outcome / Rate Retinal tear: 5.9% (2/34)* Cataract in phakic eye (none visible postoperatively): 42%** Loss of > 3 lines visual acuity: 14.7% (5/34) Intraretinal blood: 2.9% (1/34) Pigment on the lens: 2.9% (1/34) Submacular haemorrhage: 2.9% (1/34) Cotton wool spots: 2.9% (1/34)*** *1 prior to introduction of device, 1 following contact with retina treat by laser coagulation **Absolute numbers not reported *** Observed at 1-month and disappeared at 2-month follow-up.	**Follow-up issues**: Prospective follow-up to 3 years is planned. All patients analysed on an intention-to-treat basis; 1 patient was lost to follow-up. A per-protocol analysis with missing data analysed by last observation carry forward was also undertaken. **Study design issues**: 4 participating sites Concomitant medication/treatment not described. **Study population issues**: Patient inclusion criteria/selection by an independent central centre. **Other issues**: Authors note that radiation toxicity may only become evident several years after treatment. It is not stated that anti-VEGF medication was used concomitantly in this study or not.

Abbreviations used: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; Gy, Grays; VEGF, anti vascular endothelial growth factor

<table>
<tr><th>Study details</th><th>Key efficacy findings</th><th>Key safety findings</th><th>Comments</th></tr>
<tr>
<td>Avila MP (2009)[2]

Case series
International
Recruitment period: 2006 to 2007
Study population: patients with Subfoveal CNV secondary to AMD. Mean BCVA 40.65.
n = 34 (34 eyes)
Age: 72 years (mean)
Sex: 35 % male

Patient selection criteria: patients with BCVA 20/40 to 20/320, Lesions composed of > 50% CNV.

Technique: strontium-90 beta radiation brachytherapy with a delivery device directed over the area of CNV via par plana vitrectomy. 24 Gy of radiation delivered over 3 to 5 minutes. Plus 2 doses of intravitreal bevacizumab.

Follow-up: 12 months (median)

Conflict of interest/source of funding: two authors have a proprietary interest in the device</td>
<td>Number of patients analysed: n = 34

Visual acuity
The mean change in BCVA observed at 12 months was a gain of 8.9 letters.

<table>
<tr><td>Outcome</td><td>24Gy brachytherapy plus VEGF</td></tr>
<tr><td>Lost < 3 lines</td><td>91.2% (31/34)</td></tr>
<tr><td>No difference / Gained > 1 letter</td><td>67.6% (23/34)</td></tr>
<tr><td>Gained ≥ 3 lines(clinically significant improvement)</td><td>38.2% (13/34)</td></tr>
</table>
</td>
<td>Complications
No radiation-associated adverse events were observed at 12-month follow-up.

<table>
<tr><td>Outcome</td><td>Rate</td></tr>
<tr><td>Retinal tear (sequelae not reported)</td><td>2.9% (1/34)</td></tr>
<tr><td>Subretinal haemorrhage</td><td>2.9% (1/34)</td></tr>
<tr><td>Subretinal fibrosis</td><td>5.9% (2/34)</td></tr>
<tr><td>CNV leakage (not otherwise described)</td><td>20.6% (7/34)</td></tr>
<tr><td>Cataract</td><td>25.0% (6/24)</td></tr>
<tr><td>Increased intraocular pressure</td><td>5.9% (2/34)</td></tr>
<tr><td>Epiretinal membrane</td><td>2.9% (1/34)</td></tr>
<tr><td>Conjunctivitis</td><td>2.9% (1/34)</td></tr>
<tr><td>Tubercular uveitis</td><td>2.9% (1/34)</td></tr>
<tr><td>Preretinal blood</td><td>2.9% (1/34)</td></tr>
<tr><td>Cystoid macular oedema</td><td>2.9% (1/34)</td></tr>
<tr><td>Vitreous haemorrhage</td><td>2.9% (1/34)</td></tr>
</table>
</td>
<td>Different study to previous Avilla (2009) study, patient demographics are different and patients received concomitant VEGF treatment
Follow-up issues:
Prospective follow-up. All patients analysed on an intention-to-treat basis (10 of 34 patients treated did not meet the inclusion criteria but were included in the analysis).
3-year follow-up planned.
Study design issues:
Multicentre study (3 sites).
Study population issues:
None.
Other issues:
Timing and overall duration (and number of doses) of concomitant intravitreal VEGF injection treatment was not standardised across all patients.</td>
</tr>
</table>

Abbreviations used: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; Gy, Grays; VEGF, anti vascular endothelial growth factor

Study details	Key efficacy findings	Key safety findings	Comments
Avila MP (2011)[3] Case series International Recruitment period: 2006 to 2007 Study population: patients with Subfoveal CNV secondary to AMD. Mean BCVA 40.65. n = 34 (34 eyes) Age: 72 years (mean) Sex: 35 % male Patient selection criteria: patients with BCVA 20/40 to 20/320, Lesions composed of > 50% CNV. Technique: strontium-90 beta radiation brachytherapy with a delivery device directed over the area of CNV via par plana vitrectomy. 24 Gy of radiation delivered over 3 to 5 minutes. Plus 2 doses of intravitreal bevacizumab. Follow-up: all patients were followed up for 24 months and a smaller cohort (n = 19) were followed up for a minimum of 36 months. Conflict of interest/source of funding: two authors have a proprietary interest in the device.	Number of patients analysed: n = 34 Visual acuity at 24-month follow-up: • Lost ≤ 15 letters from baseline = 64.7% (22/34) of eyes • Gained ≥ 1 letter = 35.3% (12/34) of eyes • Gained ≥ 15 letters = 14.7% (5/34) of eyes The mean change in visual acuity at 2 years4 months was –5.6 Early Treatment Diabetic Retinopathy Study letters. The authors noted that the reduction in visual acuity was likely attributable to cataract development. Visual acuity at 36-month follow-up: • Lost ≤ 15 letters from baseline = 89.5% (17/19) of eyes • Gained ≥ 1 letter = 52.6% (10/19) of eyes • Gained ≥ 15 letters = 21.1% (4/19) of eyes The mean change in visual acuity at 36 months was +3.9 Early Treatment Diabetic Retinopathy Study letters. **Retreatment** • Year 1 (n = 34): 4 additional injections of bevacizumab were administered to 3 eyes • Year 2 (n = 34): 10 injections were administered to 7 eyes • Year 3 (n = 19): 4 injections were administered to 4 eyes	**Complications** **Device-related adverse events (relationship determined by principal investigator):** • Retinal tear = 2.9% (1/34) • Subretinal haemorrhage = 2.9% (1/34) • Subretinal fibrosis = 2.9% (1/34) • Non-proliferative radiation retinopathy = 2.9% (1/34) (observed at 36-month follow-up; there was no adverse effect on visual acuity and the changes were stable at 43-month follow-up) **Delivery/injection procedure-related adverse events (relationship determined by principal investigator):** • Cataract in – patient cohort followed up to 24 months = 50% (12/24) (percentage of patients who were phakic at baseline; 4 patients had intraocular lens implantation by 24 months) – patient cohort followed up to 36 months = 54% (7/13) among phakic eye patients; 4 patients had phacoemulsification and intraocular lens implantation by 36 months. • Retinal fibrosis = 5.9% (2/34) • Epiretinal membrane = 2.9% (1/34) • Trace anterior chamber cells = 2.9% (1/34) • Faint anterior chamber flare in immediate postoperative period = 8.8% (3/34) In the cohort of patients evaluated up to 36 months, 54% (7/13) of phakic patients had developed cataracts; 4 had phacoemulsification and intraocular lens implantation by 36 months.	Same study as previous Avilla (2009) study but with longer follow-up. **Follow-up issues:** Prospective follow-up. All patients analysed on an intention-to-treat basis (10 of 34 patients treated did not meet the inclusion criteria but were included in the analysis). One site that enrolled 19 patients agreed to re-consent and follow up of patients for 3 years. **Study design issues:** Multicentre study (3 sites). **Study population issues:** Baseline characteristics were similar in the 2 cohorts, with a slightly larger proportion of predominantly classic lesions in the cohort followed up for 3 years. **Other issues:** Timing and overall duration (and number of doses) of concomitant intravitreal VEGF injection treatment was not standardised across all patients. There are some discrepancies between the results reported in the abstract and the main body of the text; for the purposes of this overview, the results have been taken from the main body of text. The authors stated that the

Abbreviations used: AMD, age-related macular degeneration; BCVA, best-corrected visual acuity; CNV, choroidal neovascularisation; Gy, Grays; VEGF, anti vascular endothelial growth factor			
Study details	**Key efficacy findings**	**Key safety findings**	**Comments**
			decrease in visual acuity at 24 months was probably caused by the development of cataracts, some of which were treated by 36 months.

Efficacy

Visual acuity

A case series of 34 patients treated by epiretinal brachytherapy (concomitant treatment not described), reported that 63% and 50% of patients receiving 24 Gy and 15 Gy of radiation respectively gained 1 or more letters of visual acuity at 12-month follow-up[1]. In the same study, 21% and 0% of patients respectively improved visual acuity by > 15 letters.

A case series of 34 patients treated by epiretinal brachytherapy plus anti-VEGF injections reported that a mean change in best-corrected visual acuity was a gain of 8.9 letters at 12-month follow-up; 38% (13/34) of patients demonstrated a clinically significant improvement of 3 lines or more[2]. At 36-month follow-up, the mean change in visual acuity was a gain of 3.9 letters (n = 19); 21% (4/19) of patients had gained 15 letters or more[3].

Safety

Radiation-induced toxicity

A case series of 34 patients treated by epiretinal brachytherapy alone reported that there were no radiation-induced toxicity adverse events at 12-month follow up[1]. A case series of 34 patients treated by epiretinal brachytherapy plus intravitreal VEGF therapy reported that 1 patient had non-proliferative radiation retinopathy, observed at the 36-month follow-up[3]. The finding was not considered to have an adverse effect on visual acuity and the changes remained stable at 43-month follow-up.

Retinal tear

Retinal tear was reported in 6% (2/34) and 3% (1/34) of patients respectively in the case series of 34 patients treated by epiretinal brachytherapy alone and the case series of 34 patients treated by epiretinal brachytherapy plus anti-VEGF injections[1,2].

Visual loss

The case series of 34 patients treated by epiretinal brachytherapy alone reported a loss of 3 or more lines of visual acuity in 15% (5/34) of patients[1].

Intraocular pressure

The case series of 34 patients treated by epiretinal brachytherapy plus anti-VEGF injections reported raised intraocular pressure in 6% (2/34) of patients (length of follow-up not reported)[2].

Cataract formation

The case series of 34 patients treated by epiretinal brachytherapy plus anti-VEGF injections reported that 25% (6/24), 50% (12/24) and 54% (7/13) of phakic eye patients developed cataracts at follow-up periods of 12, 24 and 36 months[2,3].

Validity and generalisability of the studies

- Few long-term outcomes are reported for a procedure with potential radiation toxicity.
- Radiation dose delivered varies both within and between studies.
- Concomitant anti-VEGF therapy may make evaluation of outcomes difficult.
- Most studies have small patient numbers, with a number of sites involved, therefore operator experience may be limited.
- Few efficacy outcomes are reported.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B gives details of the recommendations made in each piece of guidance listed.

Interventional procedures

- Radiotherapy for age-related macular degeneration. NICE interventional procedures guidance 049 (2004). Available from www.nice.org.uk/guidance/IPG49

- Transpupillary thermotherapy for age-related macular degeneration. NICE interventional procedures guidance 058 (2004). Available from www.nice.org.uk/guidance/IPG58

- Implantation of miniature lens systems for advanced age-related macular degeneration. NICE interventional procedures guidance 272 (2008). Available from www.nice.org.uk/guidance/IPG272

Technology appraisals

- Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal 155 (2008). Available from www.nice.org.uk/guidance/TA155

Specialist Advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and does not represent the view of the society.

Mr I Pearce, Mr T Jackson, Mr S Prasad, Mr Y Yang (Royal College of Ophthalmologists).

- The Specialist Advisers were divided in their opinion as to the current status of the procedure, categorising it as either definitely novel and of uncertain safety and efficacy, or as the first in a new class of procedures.
- The key efficacy outcomes for this procedure are retention of visual acuity, number of anti-VEGF injections required, and time to recurrence of AMD.
- The main comparator treatment would be monotherapy anti-VEGF injections.
- Adverse events known from experience or reported in the literature include cataract formation, retinal haemorrhage, retinal tears/detachment, infective endophthalmitis, and radiation retinopathy.
- Additional theoretical adverse events may include radiation optical neuropathy, and malignancy.
- Vitreoretinal-trained ophthalmic surgeons should be able to perform the procedure with minimal input.
- There is a significant burden to the patient and the NHS with repeated intravitreal injections.
- The procedure may be particularly relevant to patients with AMD that is resistant to anti-VEGF injections.

- To provide the procedure requires having the device and suitable storage for the radiation source.

Patient Commentators' opinions

NICE's Patient and Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

- The two studies by Avila are discrete trials (one uses concomitant anti-VEGF medication).
- A different retinal brachytherapy procedure is also being developed and evaluated currently, using implantable brachytherapy seed (plaques) inserted into the eye.

References

1 Avila MP, Farah ME, Santos A et al. (2009) Twelve-month safety and visual acuity results from a feasibility study of intraocular, epiretinal radiation therapy for the treatment of subfoveal CNV secondary to AMD. Retina 29: 157–169.

2 Avila MP, Farah ME, Santos A et al. (2009) Twelve-month short-term safety and visual-acuity results from a multicentre prospective study of epiretinal strontium-90 brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularisation secondary to age-related macular degeneration. British Journal of Ophthalmology 93: 305–309.

3 Avila MP, Farah ME, Santos A et al. (2011) Three-year safety and visual acuity results of epimacular ^{90}strontium/^{90}yttrium brachytherapy with bevacizumab for the treatment of subfoveal choroidal neovascularization secondary to age-related macular degeneration. Retina in press.

Appendix A: Additional papers on epiretinal brachytherapy for wet age-related macular degeneration

There were no additional papers identified.

Appendix B: Related NICE guidance for epiretinal brachytherapy for wet age-related macular degeneration

Guidance	Recommendations
Interventional procedures	**Radiotherapy for age-related macular degeneration. NICE interventional procedures guidance 049 (2004).** 1.1 Current evidence shows radiotherapy for age-related macular degeneration to have little efficacy. There are also concerns about its safety. It is suitable for use only within good quality research studies approved by a research ethics committee, specifying the dose of radiation used and with explicit patient consent. Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute is not undertaking further investigation at present **Transpupillary thermotherapy for age-related macular degeneration. NICE interventional procedures guidance 058 (2004)** 1.1 Current evidence on the safety and efficacy of transpupillary thermotherapy for age related macular degeneration does not appear adequate for this procedure to be used without special arrangements for consent and for audit or research 1.2 Clinicians wishing to undertake transpupillary thermotherapy for age-related macular degeneration should take the following action. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the uncertainty about the procedure's safety and efficacy and provide them with clear written information. Use of the Institute's Information for the Public is recommended. • Audit and review clinical outcomes of all patients having transpupillary thermotherapy for age-related macular degeneration. 1.3 Publication of safety and efficacy outcomes will be useful in reducing the current uncertainty. The Institute may review the procedure upon publication of further evidence. **Implantation of miniature lens systems for advanced age-related macular degeneration. NICE interventional procedures guidance 272 (2008)** 1.1 Evidence on the efficacy of implantation of miniature lens systems for advanced age-related macular degeneration (AMD) shows that the procedure can improve both vision and quality of life in the short term. Short-term safety data are available for limited numbers of patients. There is currently insufficient long-term evidence on both efficacy and safety. Therefore this procedure should only be used with special arrangements for clinical governance, consent and audit or research 1.2 Clinicians wishing to undertake implantation of miniature lens systems for advanced AMD should take the following actions. • Inform the clinical governance leads in their Trusts. • Ensure that patients understand the need to adapt to having a lens

	system implanted into one eye, the risk of early complications and the uncertainties about long-term efficacy and safety. They should provide clear information. In addition, the use of the Institute's information for patients ('Understanding NICE guidance') is recommended (available from www.nice.org.uk/IPG272publicinfo). • Audit and review clinical outcomes of all patients having implantation of miniature lens systems for advanced AMD (see section 3.1). 1.3 Patient selection is crucial and should include detailed assessment to predict the patient's ability to process visual stimuli following the operation. 1.4 Further publication of safety and efficacy outcomes would be useful, specifically with regard to longer term follow-up. The Institute may review the procedure upon publication of further evidence.
Technology appraisals	**Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal 155 (2008).** 1.1 Ranibizumab, within its marketing authorisation, is recommended as an option for the treatment of wet age-related macular degeneration if: • all of the following circumstances apply in the eye to be treated: • the best-corrected visual acuity is between 6/12 and 6/96 • there is no permanent structural damage to the central fovea • the lesion size is less than or equal to 12 disc areas in greatest linear dimension • there is evidence of recent presumed disease progression (blood vessel growth, as indicated by fluorescein angiography, or recent visual acuity changes) **and** • the cost of ranibizumab beyond 14 injections in the treated eye is met by the manufacturer 1.2 It is recommended that treatment with ranibizumab should be continued only in people who maintain adequate response to therapy. Criteria for discontinuation should include persistent deterioration in visual acuity and identification of anatomical changes in the retina that indicate inadequate response to therapy. It is recommended that a national protocol specifying criteria for discontinuation is developed 1.3 Pegaptanib is not recommended for the treatment of wet age-related macular degeneration 1.4 People who are currently receiving pegaptanib for any lesion type should have the option to continue therapy until they and their clinicians consider it appropriate to stop

Appendix C: Literature search for epiretinal brachytherapy for wet age-related macular degeneration

Database	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	25/07/2011	Issue 7 of 12, Jul 2011
Database of Abstracts of Reviews of Effects – DARE (CRD website)	25/07/2011	n/a
HTA database (CRD website)	25/07/2011	n/a
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	25/07/2011	Issue 3 of 4, Jul 2011
MEDLINE (Ovid)	25/07/2011	1948 to July Week 2 2011
MEDLINE In-Process (Ovid)	25/07/2011	July 22, 2011
EMBASE (Ovid)	25/07/2011	1980 to 2011 Week 29
CINAHL (NLH Search 2.0/EBSCOhost)	25/07/2011	n/a
Zetoc (for update searches only)	25/07/2011	n/a

The following search strategy was used to identify papers in MEDLINE. A similar strategy was used to identify papers in other databases.

1	Macular Degeneration/
2	Wet Macular Degeneration/
3	(macul* adj3 degenerat*).tw.
4	(age adj3 relat* adj3 macul*).tw.
5	(age-relat* adj3 macul*).tw.
6	AMD.tw.
7	ARMD.tw.
8	or/1-7
9	Brachytherapy/
10	brachytherap*.tw.

11	epiretinal.tw.
12	epiretinal.tw.
13	(internal radiotherap* or internal radiation therap*).tw.
14	or/9-13
15	8 and 14
16	Animals/ not Humans/
17	15 not 16