THE VERTEPORFIN PHOTODYNAMIC THERAPY COHORT STUDY FOR THE UNITED KINGDOM

Manual of Operations

Version 2.1

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Principal Investigators: Professor Usha Chakravarthy, Queen's University Belfast

Mr Simon Harding, St Paul's Eye Unit, Liverpool

Dr Barnaby Reeves, London School of Hygiene and Tropical Medicine

On behalf of the Royal College of Ophthalmologists, London

LIST OF ABBREVIATIONS

AMD	Age-related macular degeneration
CARF	Central Angiographic Resource Facility (Belfast)
CNV	Choroidal neo-vascularisation
CS	Contrast sensitivity
DP	Designated provider
BDVA	Binocular distance visual acuity
ETDRS	Early Treatment for Diabetic Retinopathy Study
FAD	Final appraisal determination
GLD	Greatest lesion diameter
GP	General practitioner
logMAR	Log minimum angle of resolution
LREC	Local research ethics committee
LSCG	Local specialist commissioning group
MDVA	Monocular distance visual acuity
MREC	Multi-centre research ethics committee
NEIVFQ	National Eye Institute Visual Functioning Questionnaire
NICE	National Institute for Clinical Excellence
NCCHTA	National Coordinating Centre for Health Technology Assessment
PCT	Primary care trust
PDT	Photodynamic therapy
QoL	Quality of life
RCOphth	Royal College of Ophthalmologists
SD	Standard deviation
SF-36	Short-Form 36 item questionnaire
SFRADS	Sub-Foveal RADiotheraphy Study
SRVF	Self-reported visual function
TAP study	'Treatment of Age-related macular degeneration by photodynamic Therapy' study
VIP study	'Visudyne In Photodynamic therapy' study

1. Overview of Manual of Operations for the VPDT Cohort Study

1.1 Content of the Manual of Operations

This **manual of operations** has been written as a handbook for designated providers (DPs) registered with the VPDT Cohort Study. It should be read in conjunction with the user guide for the data transfer software and, if appropriate, the data entry forms. It includes protocols / instructions for:

- standardised methods for undertaking visual assessments,
- undertaking fundus photography and angiography,
- angiographic definitions,
- angiogram submission,
- eligibility criteria for treatment based on NICE guidance,
- guidelines for assessments at follow-up and re-treatment decision-making,
- treatment delivery.

We expect that it will be necessary to clarify some aspects of this manual as the study proceeds, because of the difficulty of anticipating all eventualities at the outset. Modifications of the manual will be circulated to all contacts at registered DPs. The most up-to-date version of the manual will also be available through the website for the study:

http://www.lshtm.ac.uk/hsru/vpdt

1.2 Changes made in this revision

1. The Overview section has been revised to include this sub-section, itemising the revisions changes since the last version, and a quick reference sub-section.
2. The term “treating centre” has been changed to “designated provider” (DP) throughout, to highlight that centres providing PDT have been designated by Local Specialist Commissioners.
3. Section 4.1: revised to clarify (a) that patients should be consented immediately when they attend the PDT clinic, i.e. irrespective of whether subsequently found to be eligible or not, (b) that data for patients ineligible for PDT should be entered

into the database and submitted to the Data Management Centre (DMC) and (c) the distinction between partial and full consent.

4. Section 5.5: revised to provide more explicit guidance on data collection.
5. Section 6: revised to clarify that, in DPs collecting the extended dataset, patients should complete/have administered quality of life and resource use questionnaires at the first visit (except for questions 1 and 2 of the resource use questionnaire).
6. Section 7: revised to include a reminder that the DMC provides duplicate forms for collecting raw monocular distance visual acuity data and that, for every patient every 3 months, one copy of this form should be returned to the DMC.
7. Section 12: revised to include a description of data transmission for DPs who use the revised LSHTM clinical database.
8. Appendix 3: revised registration form (contact details)
9. Appendix 4: revised patient information sheet
10. Appendix 5: inclusion of details about measuring binocular VA; details of suppliers of ETDRS and Pelli-Robson charts have been added.
11. Appendix 8: revised contact details for the Central Angiographic Resource Facility
12. Appendix 10: revised instructions for the resource use questionnaire.
13. Appendix 11: recommended paper datasheet and notes on data collection.

1.3 Quick reference guide

This section aims to summarise what designated providers are required to do.

At first 'screening' visit:

Collect the following data on ***all screened*** patients that give full or partial consent, irrespective of whether they are treated or not:

(a) Informed consent (p. 19)
(b) Clinical history (p.21)
(c) Binocular presenting distance visual acuity (BDVA, p.21)
(d) Refraction (p. 21)
(e) Monocular distance visual acuity (MDVA, p.21)
(f) Ophthalmic examination (p.20)
(g) Stereo colour photography and angiography (p.22)

And, if also collecting the extended dataset:

(h) Contrast sensitivity (p.25)

(i) Quality of Life (p.26, p.29)

(j) Resource use questionnaire (p. 27, p.30)

At the first and subsequent visits, collect the following data for ***all treated*** patients:

(k) Refractive error, based on a protocol refraction, at least every 12mths (p. 23)

(l) Monocular LogMar VA collected at least every 3mths (p.21 and Table 1)

(m) Binocular LogMar VA collected every 3mths (p. 21 and Table 1)

(n) Stereo colour photography and angiography every 3mths, if treated at the previous visit, otherwise six monthly (p. 22)

(o) Treatment details on all visits when treatment is given (p.26)

(p) Adverse events or reactions (p.28)

And, if also collecting the extended dataset:

(q) Contrast sensitivity every 6 months (p.22)

(r) Quality of life every 6 months (p. 22)

(s) Resource use questionnaire every 6 months (p. 22)

(t) Adverse reactions and events (p28)

Raw MDVA data should be collected on to the duplicate forms provided by the DMC. The 'flimsy' copies of these forms must be collected and returned periodically to the DMC.

The data collected should be entered into the database provided. Ideally, the database will be installed on the hospital's local area network, allowing different staff to access the database simultaneously and to enter data as a patient progresses through his or her visit. Otherwise, DPs can use, or adapt, the data collection sheet (Appendix11) and enter data at a later time.

The DMC will provide a data report to DPs, summarising the data submitted and listing items of missing or suspect data. DPs must respond to these queries:

1. providing data for missing items, if they are available, or confirming that missing data are not recoverable, and
2. correcting suspect data or confirming the original data are correct.

2. Introduction

2.1 Verteporfin photodynamic therapy (PDT) for the treatment of choroidal neovascularisation (CNV) of the eye

Choroidal neovascularisation (CNV) is the hallmark of the condition known as exudative age-related macular degeneration (AMD) of the eye. The untreated natural history of CNV is one of relentless vision loss culminating in central visual impairment of varying severity. This loss interferes with daily tasks such as reading, driving, watching television and recognising peoples' faces and frequently results in loss of independent living.

When CNV is subfoveal (that is, when CNV is under the centre of the fovea, the part of the retina that allows people to see fine detail), it is not amenable to thermal laser photocoagulation, a form of therapy that has been the mainstay of management for many years. None of the treatments tested in recent years have been shown to improve vision once it is lost, nor have there been treatments that consistently prevent additional decline in vision from the time of their application.

Because the visual impairment caused by vision loss from exudative AMD is so severe, it is now accepted that treatments which are only partly effective may nevertheless yield important visual, quality of life and economic benefits. Recently a treatment called **verteporfin photodynamic therapy (PDT)** has been shown to result in a better outcome when compared with the natural history of CNV patients who did not receive PDT. In the randomised controlled clinical trial the "Treatment of Age-related macular degeneration by Photodynamic therapy (TAP) study", eyes with CNV exposed to laser irradiation following systemic infusion of the drug verteporfin were more likely to have maintained visual function when compared with patients with similar CNV who received placebo followed by similar irradiation **[1]**. The treatment works because the drug verteporfin is internalised by the vascular endothelium. Light activation of the drug results in the release of free radicals that damage endothelium and adjacent tissues and cells. By targeting a low energy laser into the region of the CNV, the endothelium of the aberrant blood vessels may be selectively irradiated, causing focal damage to the vessel wall and closure of the vessels comprising the CNV.

2.2 NICE Guidance on Verteporfin PDT

Verteporfin PDT was referred in 2000 for appraisal by the National Institute of Clinical Excellence (NICE) **[2]**, which reviewed available evidence. In the TAP trial, 15%

more patients in the verteporfin treatment arm than the placebo arm had lost fewer than 15 letters on the letter chart 24 months after treatment (53% vs 38%; $p < 0.001$). In a pre-specified subgroup analysis, the TAP trial demonstrated that eyes with certain subtypes of CNV experienced a greater benefit. Specifically, lesions with classic and no occult CNV (all of the lesion is classic CNV) or predominantly classic CNV (>50% of the lesion is classic CNV) had a better outcome relative to placebo (59% vs 31% losing fewer than 15 letters; $p<0.001$). In addition, benefit was also shown in the subgroup of eyes with occult with no classic but surprisingly no benefit was detected in the subgroup of eyes with minimally classic CNV.

A second randomised controlled trial known as VIP investigated PDT in the subgroup of patients with occult and no classic CNV. VIP found no statistically significant difference between treatment and placebo group in the proportion of patients losing 15 letters at 12 months (51% vs 55% respectively ; $p>0.05$). However, the difference increased by 24 months and was just statistically significant (55% vs 68% respectively ; $p=0.03$). NICE reviewed the sub-group comparisons and recommended (a) that patients with lesions with classic and no occult CNV should be offered PDT treatment in the NHS and (b) that patients with predominantly classic lesions should be treated as part of new clinical studies, such as the VPDT study. After consideration of the evidence, the NICE appraisal team also decided that although the existing trials were supportive of clinical effectiveness in subgroups of patients with CNV, benefit in terms of patient-centred outcomes or cost-effectiveness was lacking. Therefore guidance from NICE has limited the use of PDT to be undertaken within the NHS under specific and defined conditions while additional evidence on its role and value in the treatment of CNV are acquired **[2]**.

The guidance from the 2nd Final Appraisal Determination (FAD) dated September 2003 has been posted on the NICE website and is reproduced in **Box 1** below.

2.3 Impact of NICE guidance on clinical practice

The guidance from NICE proposes selection of patients for PDT treatment using acuity criteria, thus demanding that the clinical assessments are undertaken to specified standards. It is accepted that routine NHS clinics do not operate to these standards and visual function tests that are routinely performed may be unreliable.

Box 1: NICE Guidance on Verteporfin Photodynamic Therapy, 2nd Final Appraisal Determination (FAD), September 2003 [2]

1.1 Photodynamic therapy (PDT) is recommended for the treatment of wet age-related macular degeneration for individuals who have a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularisation (CNV), and best-corrected visual acuity of 6/60 or better. Only retinal specialists should carry out PDT with expertise in the use of this technology.

1.2 PDT is not recommended for the treatment of people with predominantly classic subfoveal CNV (that is, 50% or more of the entire area of the lesion is classic CNV but some occult CNV is present) associated with wet age-related macular degeneration, except as part of ongoing or new clinical studies that are designed to generate robust and relevant outcome data, including data on optimum treatment regimens, long-term outcomes, quality of life and costs.

1.3 The use of PDT in occult CNV associated with wet age-related macular degeneration was not considered because the photosensitising agent (verteporfin) was not licensed for this indication when this appraisal began. No recommendation is made with regard to the use of this technology in people with this form of the condition.

1.4 Patients currently receiving treatment with PDT could experience loss of well-being if their treatment is discontinued at a time they did not anticipate. Because of this, all NHS patients who have begun a course of treatment with PDT at the date of publication of this guidance should have the option of continuing to receive treatment until their clinical condition indicates that it is appropriate to stop.

NICE guidance also specifically requires angiographic classification of the CNV for the purposes of ascertaining eligibility for PDT treatment and for assessing outcomes by CNV subtype. The classification and grading of CNV requires a systematic approach and it is not always possible for treating clinicians to make subtle distinctions on CNV subtypes with certainty. Post treatment patient review and criteria for re-treatment are also likely to vary. In the absence of standardised assessment and data collection, these variations would interfere with the systematic analysis of outcomes which NICE wish to see at their planned review.

2.4 Limitations of the evidence about PDT

Early in the NICE appraisal process it became evident that unrestricted access to verteporfin photodynamic therapy (PDT) was unlikely to be made available within the NHS for several reasons:

(a) The PDT trials used sub group analysis which was predefined as part of the protocol.

(b) There was heterogeneity of outcomes between the multiple trials.

(c) No information was collected on visual functioning.

(d) There was no formal attempt to collect cost of illness data concurrent with the studies.

(e) The size of the benefit was modest and the average effect was one of continuing decline of VA even in subjects enrolled in the treatment arm.

The Royal College of Ophthalmologists (RCOphth) who represent the ophthalmic profession in the UK convened an expert professional panel which concurred with many of the findings of the NICE appraisal panel.

Members of this expert professional panel constructed a proposal for a cohort study to address the uncertainties identified by the NICE appraisal and to allay the concerns of the appraisal team in that the proposed study was designed to obtain robust long term information on outcomes following PDT. This proposal was submitted to NHS R and D, Department of Health and was also made available to the NICE appraisal team. Following an evaluation of the scientific merits of the study, funding was agreed for a nationwide VPDT cohort study.

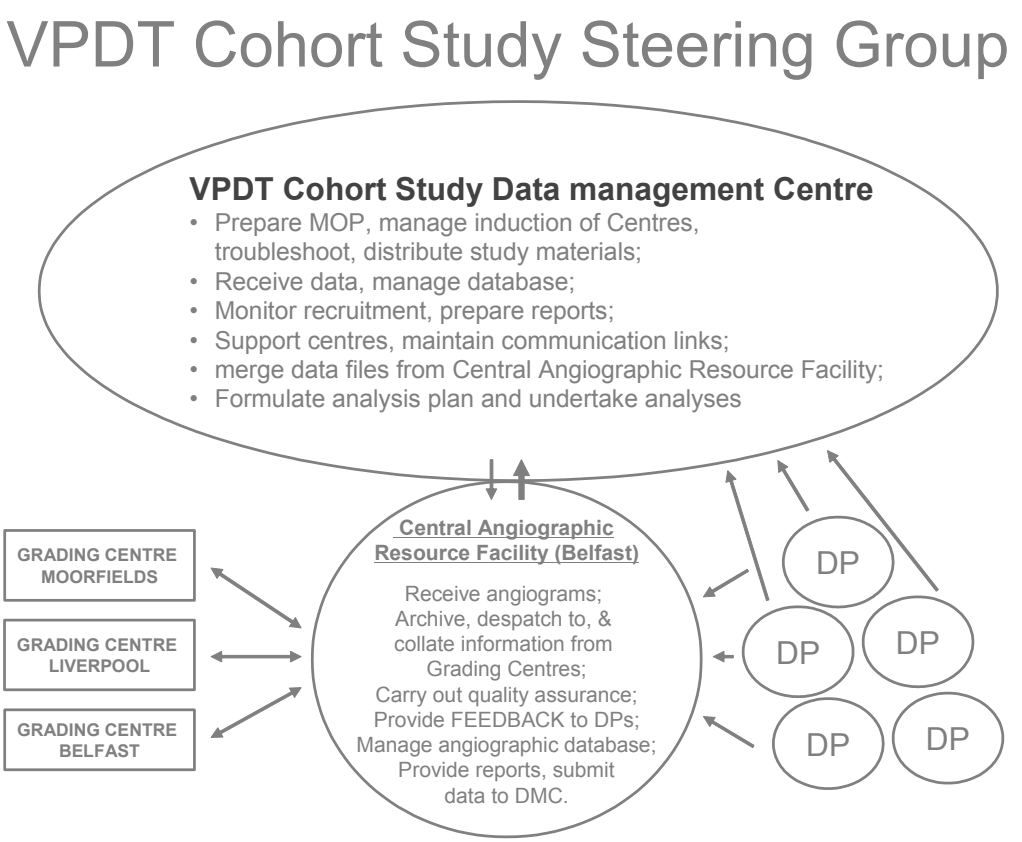
In order to meet these limitations in the evidence as identified by NICE, and to address variations in VA collection and angiogram interpretation, standard data collection protocols have been developed and a reading centre infrastructure established.

3. Features of the VPDT Cohort Study

3.1 Aim of VPDT Study

The overarching aim of the VPDT cohort study is to broaden the understanding of the pathogenesis of CNV and its management through a longitudinal analysis of outcomes in patients undergoing PDT for CNV secondary to AMD. **Figure 1** gives an overview of the VPDT cohort study. Key advantages are described in **Box 2**.

Figure 1 **Overview of the VPDT cohort study**



MOP – manual of procedures; DP – designated provider of PDT; DMC – Data Management Centre

Members of the Steering Group are listed in **section 13.1**.

Contact details for the Data Management Centre, the Angiographic Resource Facility and the Chief Investigator three main study entities are listed in **section 13.4**.

Box 2 Key advantages of the VPDT cohort study

- ***The study provides a pioneering framework within which the introduction of a new technology is managed and evaluated.***
- ***The study will address the gaps in knowledge about cost-effectiveness and optimal treatment regimens for patients with predominantly classic CNV with occult (NICE paragraph 1.2) and patients with classic CNV without occult (NICE paragraph 1.1).***
- ***We will learn more about the effectiveness of PDT for the treatment of CNV resulting from non-AMD causes of CNV***
- ***The VPDT cohort study also provides a means to quality assure clinical practice through standardised training and feedback.***

3.2 Objectives of the VPDT cohort study

1. To estimate the prevalence and incidence of patients with CNV being referred for PDT and who meet the eligibility criteria for treatment.
2. To describe the clinical management of patients with CNV being referred for PDT and who meet eligibility criteria for treatment.
3. To characterise changes over time in clinical outcomes, self-reported visual functioning (SRVF), generic quality of life (QoL) and the societal costs of illness in patients receiving PDT and who meet eligibility criteria for treatment.
4. To describe the relationship between clinical outcomes, SRVF and health-related QoL.
5. To estimate incremental cost-effectiveness, cost-utility and cost impact on the NHS (using data estimated for objectives 1-4) of implementing PDT in the NHS for patients who meet eligibility criteria for treatment.

3.3 General Study Design

The VPDT study is a cohort study of the outcomes of treatment with PDT. It will collect standardised and robust clinical information on patients undergoing verteporfin photodynamic therapy within the UK. The diagram showing the overview of the study is shown in **Figure 1**. Brief and relevant medical and lifestyle history will be recorded. Tests will include measures of vision, fundus photography and angiography and

patients will be asked to complete a set of questionnaires at specified clinic visits. Entering all patients treated with PDT in to the study is crucial to the success of the Cohort Study.

Direct comparisons of outcome will be made within the cohort, e.g. between sub-groups of patients with different lesion characteristics or aetiologies. However, it is also important to estimate the effectiveness and cost-effectiveness of treatment with PDT, in everyday practice, compared with no treatment. The cohort study does not include untreated patients (other than documenting ineligible patients at baseline). Therefore, these overall effects of treatment will be estimated indirectly (see **10.4**).

3.4 Study duration

The study will last a minimum of 3 years and data will be collected longitudinally for all subjects recruited into the study during this period. The period of data collection may be extended if recommended by NICE and/or Department of Health.

4. Study population

4.1 Inclusion criteria for the reference population

- All patients referred for assessment at a PDT clinic in a DP, whether eligible or not, will form the reference population; there are no exclusion criteria for people in the reference population. DPs should submit a full set of data at the screening visit for all ineligible patients seen in person at the PDT clinic; the angiogram used for decision making should be submitted, whether the angiogram was carried out by the DP or by a referring centre.
- Patients with subfoveal CNV due to AMD or any other disorder are eligible for inclusion in the VPDT study.
- As part of the assessment the ophthalmologist in charge of the patient will make a decision on eligibility for treatment (see below). The decision to proceed to treatment will be made in conjunction with the patient.
- Patients may be of any ethnicity or either gender.

4.2 Criteria for treatment eligibility

- CNV must be wholly or predominantly classic (that is 50% or more of the entire lesion must be comprised of classic CNV)
- Best corrected visual acuity in the eye being considered for treatment must be equal to or better than Snellen 6/60, approximately equivalent to seeing any letter on the line corresponding to logMAR 1.0, or >30 letters

Appendix 1 provides an algorithm to help the clinician to classify CNV lesions, in order to determine eligibility for treatment.

4.3 Exclusion criteria for treatment

- Patients with minimally classic or occult CNV
- History of liver disease or severe photosensitivity due to any cause
- Previous history of adverse reaction to either fluorescein or verteporfin
- Patients who are unable to attend for treatment and follow-up.

4.4 Follow-up and re-treatment

Patients will undergo 3 monthly ophthalmological and angiographic examinations to determine whether repeat therapy is needed. The decision to re-treat will be based on

a range of clinical and angiographic evidence. **Appendix 2** includes examples of flow charts used for making re-treatment decisions. Re-treatment criteria were also considered by the Verteporfin Round Table [3].

5. Recruitment to the cohort study

5.1 Multicentre Research Ethics Committee approval

An application for ethical approval was submitted to the London Metropolitan Multicentre Research Ethics Committee (MREC), which was considered in Nov 2003. The MREC Committee approved the study in principle on 28 Nov 2003 but required (a) clarification of some details and (b) modifications to the patient information sheet and consent form. Responses to these queries were submitted in Dec 2003, but further modifications to the patient information sheet were requested. These were submitted in Jan 2004 and the MREC Chair gave final approval in Feb 2004. The reference number for the study is MREC/03/11/103. Copies of the MREC letter of approval and other documents are distributed to DPs when they register for the study.

5.2 Recruitment of centres nominated as 'designated providers'

Local Specialist Commissioning Groups (LSCGs) and Primary Care Trusts (PCTs) are responsible for identifying their local 'designated provider' (DP), with whom contracts to provide PDT will be placed. The identities of the DPs are communicated to the study investigators and the Data Management Centre, and the Data Management Centre sends invitations to the DPs to register with the study. (During the early stages of implementation, in order to avoid delays, some invitations were also sent to centres that were considered very likely to be DPs, e.g. because they were already providing PDT, but which had not yet been confirmed as designated providers by LSCGs/PCTs.) Registration requires the lead clinician at a DP to send back a short questionnaire to the Data Management Centre (see **Appendix 3**).

5.3 Local Research Ethics Committee approval

The 'local principal investigator' in each DP must obtain ethical approval from the Local Research Ethics Committee (LREC). This approval is in addition to the MREC approval. LRECs may require minor revisions to the patient information and consent forms, or request modifications owing to special local circumstances, but may not over-rule the approval already given by the MREC.

The local principal investigator in each DP must also register the study with the Research Office / R and D Office of the local Trust.

The Data Management Centre will prepare as much of the paperwork as possible for a DP to submit for LREC and local R&D approval. Much of the information requested in the registration questionnaire is used for this purpose.

5.4 Consent

Participation in the cohort study is not optional for patients in the reference population being assessed for treatment on the NHS. The minimum dataset and angiograms must be submitted to the Data Management Centre and to the Central Angiographic Resource Facility (CARF) at Belfast for all such patients.

Some DPs will be nominated by their local commissioners to collect the extended dataset, which requires patients to complete quality of life and resource use questionnaires. Patients may withhold consent from taking part in the extended data collection but still consent to submission of their clinical data.

The consent form for the study that has been approved by the MREC therefore has two levels of consent. Consenting at the first level ("partial consent") indicates that a patient consents to information required for the minimum dataset to be forwarded to the Data Management Centre and for angiograms to be sent to the CARF. The minimum dataset only includes information required for treating and managing a patient; patients consenting at this first level are not required to undergo any additional tests or provide any biological samples other than those that may be required for their treatment. Consenting at the second level ("full level") indicates that a patient consents to completing the quality of life and resource use questionnaires and for this information also to be forwarded to the Data Management Centre.

The MREC approved patient information sheet and consent form are included in **Appendix 4**. DPs will need to reproduce these documents on local headed paper and obtain local LREC approval before use.

5.5 Overview of data collection

The cohort study requires different kinds of information to be collected, i.e. demographic, clinical, angiographic, quality of life and resource use data (see Figure 1). The demographic data, most clinical data and the angiograms constitute the *minimum dataset*. The minimum dataset, contrast sensitivity, the quality of life and resource use data constitute the *extended dataset*. All DPs must collect all of the items that make up the minimum dataset; *it is not sufficient to assume that the information required will be documented in the medical notes*. A representative sample of DPs, nominated by the commissioners, will collect the extended dataset; their contracts will include extra funding to cover additional resources required to collect the additional data. The schedule of visits and the information to be collected on each visit are shown in **Table 1**.

6. Background data collection on the first, 'screening' visit

All background / baseline data form part of the minimum dataset. The precise way in which patients are screened for PDT treatment will vary in different DPs; **Figure 2** shows schematically the path that we expect patients to follow and illustrates varied referral routes. Our intention is to capture these background data for all patients *considered for PDT treatment*, i.e. including patients who have been referred for PDT but who, on subsequent examination in the PDT clinic, are found to be ineligible. In some DPs, the visit on which eligibility for treatment is determined may be the same visit on which the first PDT treatment is given. The data include the patient's:

- Administrative and demographic information; the patient's name, date of birth, address and postcode, consultant, hospital number.
- Referral pathway; source and date when referred from primary care, consultation with any ophthalmologist en route to the DP, and any delays in referral. (Referral pathways involving the private sector may be complicated. After an initial private consultation, patients may be referred from the private sector to an NHS DP, or to a private centre, for PDT treatment; patients may also transfer from private to NHS DPs as the latter become established. The study aims to collect the minimum dataset in the private sector as well as the NHS, but establishing data collection in the NHS is being prioritised.) *Note that these details may not be documented routinely in the medical notes or correspondence accompanying a referral; the ophthalmologist responsible for a patient will usually need to ask the patient for this information.*
- Symptom history, ocular comorbidity, visual acuity and diagnosis at the time of referral, any previous treatments and details of important confounding factors, i.e. smoking history, family history of AMD, cardiovascular comorbidity, use of statins.
- In DPs collecting the extended dataset, contrast sensitivity should be documented and the quality of life and resource use questionnaires should be completed by / administered to patients at the screening visit whether subsequently treated, observed or ineligible. (NB. Questions 1 and 2 of the resource use questionnaire should not be asked at the screening visit, see **Appendix 10**.)

For additional details about background data collection, please see the database user guide and the database itself. Information about how to complete the database fields required for the minimum dataset will be provided during on-site training.

7. Clinical data collection on the first and subsequent visits

The following clinical data must be collected for all patients on all visits:

- The patient's presenting *binocular* visual acuity (BDVA) must be recorded first, prior to carrying out a refraction or testing the monocular distance visual acuity (MDVA) in each eye separately. The patient's BDVA should be recorded using chart R (see **Appendix 5, section 7**) with the patient wearing the distance spectacles that they usually wear. The number of letters read should be recorded in the relevant box on the duplicate form provided for recording BDVA (and in the database). Recording of BDVA is very important for interpreting the QoL data.
- Monocular distance visual acuity (MDVA); MDVA must be assessed using ETDRS logMAR visual acuity charts (see **Appendix 5, section 1**), with precise details of the letters seen/not seen on each line being recorded on the duplicate paper form supplied by the Data Management Centre. The top copy of the form should be retained and be placed in the patient's notes. The duplicate copy should be sent to the Data Management Centre. The protocol for MDVA assessment is described in **Appendix 5**. Note that it is essential to record the date of assessment and the patient's hospital number on the form. Details of the supplier of ETDRS charts can be found in **Appendix 5.**
- A full refraction protocol is encouraged at every clinic visit, but must be done at the screening visit, the visit when a patient is first treated (0 months), and yearly (12, 24 and 36 months). On other visits, it is acceptable to record MDVA using the trial lenses of the prescription most recently used for vision testing.
- The DMC provides duplicate (no-carbon-required) paper forms for recording the number of letters read on each line when testing MDVA. The second, 'flimsy' copies of the completed forms must be forwarded periodically to the DMC.

Table 1: Schedule of visits and tests for the VPDT cohort study

Activity	Screening Visit	Month 0	Month 3	Month 6	Month 9	Month 12	Month 15	Month 18	Month 21	Month 24	Month 36
Minimum dataset:											
Informed consent	X										
Clinical history	X										
Refraction [a]	X	X				X				X	X
BDVA & MDVA measurement [b]	X	X	X	X	X*	X	X*	X	X*	X	X
Ophthalmic Exam	X										
Stereo colour photography and angiography [cd]	X	X	X	X	X*	X*	X*	X*	X*	X*	X*
Extended data set:											
Contrast sensitivity test (Pelli-Robson)	X			X		X		X		X	X
Quality of life & resource use questionnaires		X		X		X		X		X	X

Notes for Table 1

The screening / baseline visit and 'month 0' may be the *same visit* if a patient is treated at the screening visit. Three monthly clinical visits, with distance visual acuity (BDVA and MDVA) checks, are mandatory up to 6 months *after the first PDT treatment* in all treated patients. Three monthly visits are also required in all patients *continuing to receive treatment*. In patients who do not continue to receive treatment, we require 6 monthly assessments, e.g. at months 12, 18, 24 if no treatment is given after month 6. After two years, we would like a follow-up visit at 3 years, if this falls within the duration of the study. Given that the scheduling of visits after 6 months depends on whether or not a patient is treated, some later visits (with asterisks) cannot be specified definitively.

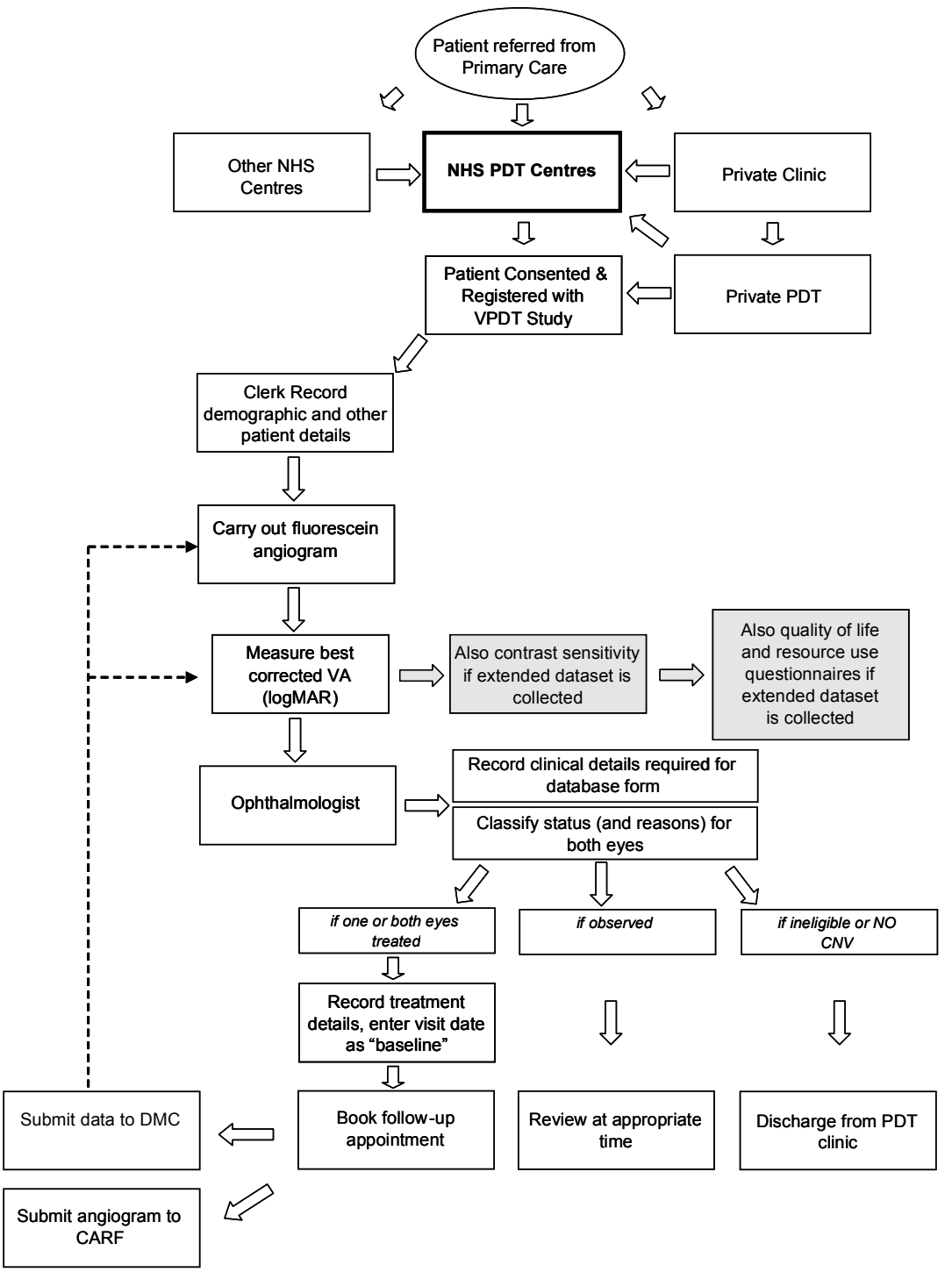
[a] Protocol refraction is encouraged at every visit, but must be carried out at the screening visit, the first treatment visit (month 0) and yearly (see **Appendix 5, section 6**).

[b] Presenting BDVA and best corrected MDVA measurements must be recorded at every clinic visit (see **Appendix 5, section 7**); MDVA must be recorded using the forms supplied by the DMC (or a similar form showing the number of letters read on each line) and duplicate copies returned to the DMC.

[c] Stereo colour photography and angiography to be performed at month 0 and at every visit until the treated eye has been shown to be free of leakage on two occasions or until treatment has been stopped for clinical reasons. Photography and angiography are mandatory at treatment-related visits.

[d] In years 2 and 3, stereo colour photography and angiography is required on at least one visit, but timing is not critical if the angiography is not treatment-related.

Figure 2 :Flow diagram showing patients' pathways in the VPDT cohort study; dotted line indicates that patients re-enter the pathway at different points, depending on schedule of visits (see Table 1)



- Contrast sensitivity (CS); CS need only be collected by DPs who have been nominated to collect the extended dataset. CS must be assessed using Pelli Robson CS charts, with precise details of the letters seen/not seen on each line being recorded on the paper form supplied by the Data Management Centre. The form should be retained and be placed in the patient's notes. The protocol for CS assessment is described in **Appendix 6**. Note that it is essential to record the date of assessment and the patient's hospital number on the form. Details of the supplier of Pelli-Robson CS charts can be found in **Appendix 5.**

- Fluorescein angiography: details of the date and type of angiogram carried out must be entered in the database. (As details are entered for one eye the database automatically fills in same details for other eye.) The protocol for undertaking fluorescein angiography and colour photography is described in **Appendix 7**. Details of how to submit angiograms to the Angiographic Resource Facility in Belfast are described in **Appendix 8**.

- Eye status: at the first visit (and subsequent visits if an eye is not treated), the ophthalmologist examining the patients must select one of four options: (a) no CNV, (b) ineligible, (c) observed, (d) treatment this visit. Additional information is requested, depending on the eye status selected, e.g. reasons for ineligibility or observation, lesion characteristics if treated. It is assumed that when the patient is undergoing the clinical examination that a fundus fluorescein angiogram, carried out in accordance with the protocol (see **Appendix 7**) will be available to help the clinician reach a decision on whether the lesion is eligible . To make the decision about eligibility, the clinician will need to be familiar with the classification of CNV (see **Appendix 1** for an algorithm for classifying CNV lesions).

- After an eye has been treated, on subsequent visits the eye status options for that eye are restricted to (a) treated or (b) not treated. Note that eye status should be chosen independently for right and left eyes so that, for example, a fellow eye can become a treated eye at any time. Note also that the 'clock' describing months since baseline does not start 'ticking' until an eye is first treated. For treated eyes, the ophthalmologist must enter 'months since baseline' to indicate which the current visit is considered to be. For example, a follow-up visit may take place 4 months (rather than exactly 3 months) after initial treatment; the ophthalmologist should indicate that this represents the '3 month visit' using the months since baseline data field.

- Additional clinical features: for treated patients, the database includes fields to record additional details about the lesion.
- Treatment details: the treating ophthalmologist must record the greatest lesion diameter (GLD), any deviation from the standard protocol for treatment (as defined in the TAP reports), and any adverse reaction during or just after treatment (see below).
- Next scheduled visit: this should be recorded as one of the categories provided in the drop-down list in the database (i.e. record as the category nearest to the actual time to the next visit).
- 'Signing off' the data for a visit: the ophthalmologist responsible for the treatment decision on the visit must sign off the data entry, thereby taking responsibility for the data for that visit for that patient.

For additional details about background data collection, please see the database user guide and the database itself, the recommended paper data collection sheet and notes on data collection (see **Appendix 11**). Information about how to complete the database fields required for the minimum dataset will be provided during on-site training. **Appendix 9** gives a description of site implementation and training.

Quality of life (QoL) questionnaires (NEIVFQ, SF-36, Visual Independent Living Questionnaire; see also section 9.4 and 9.5):

Completion of these questionnaires at the screening visit and every 6 months forms part of extended dataset. It is envisaged that patients will complete these questionnaires on paper during their visits, e.g. while waiting for tests or treatment. The lead clinician at a DP collecting the extended dataset must nominate an individual or individuals who have (joint) responsibility for ensuring the questionnaires are completed, and for providing help in doing so if required. Funding to cover the time spent helping patients to complete these questionnaires is included in the contracts for DPs collecting the extended dataset. Details of the instructions to patients on how to complete these questionnaires are described in **Appendix 10**.

The main clinical database includes forms for entering responses. Alternatively, DPs can copy the completed questionnaires and send them by secure means to the Data Management Centre.

Resource use questionnaire:

Completion of this questionnaire at the screening visit and every 6 months also forms part of the extended dataset. The questionnaire must be *administered* and the lead clinician at a DP collecting the extended dataset must nominate an individual or individuals who have responsibility for doing this. (As in the case of the QoL questionnaires, funding to cover the cost of administration is included in the contracts of DPs collecting the extended dataset.)

Details of the instructions to patients on how to complete this questionnaire are described in **Appendix 10**. Note that questions 1 and 2 should not be completed at the first administration. The database supplied to DPs includes data entry screens, linked to the main clinical database, for these questionnaires. Alternatively, DPs can copy the completed questionnaires and send them by secure means to the Data Management Centre.

8. Recording adverse reactions and events

All adverse reactions (during or just after treatment) or events (between treatment visits) must be recorded in the database. Any adverse reaction or event considered to be *serious* and *possibly, probably* or *definitely* associated with treatment must be reported to the Data Management Centre within 24 hours in accordance with Good Clinical Practice in research (see contact details, **section 13.4**).

Adverse reactions may occur during or just after treatment, and adverse events at some time during the interval between visits. The database records adverse reactions and events in different ways:

- Adverse reaction during or just after treatment; the database contains a mandatory, yes/no, field which must be completed on any visit on which treatment is given. If the treating ophthalmologist enters 'yes', additional details must be completed. Finally, the treating ophthalmologist must make a judgement about the likelihood of the event being attributable to the treatment; this field is mandatory.
- Adverse event since last visit; the database contains a mandatory, yes/no, field which must be completed on any visit following a visit on which a treatment is given. If the treating ophthalmologist enters 'yes', additional details must be completed. Appropriate details should be completed for as many of these fields as necessary, including the (approximate) dates of onset and resolution of the event. Finally, the treating ophthalmologist must make a judgement about the likelihood of the event being attributable to the treatment; this field is mandatory. A reduction in the number of letters read in a treated of ≥ 20 letters should always be considered an adverse event.

9. Study outcomes

9.1 Primary and secondary outcomes

MDVA, measured on a logMAR scale (see **Appendix 5**), is the primary outcome. Statistical analyses will consider both the mean change in MDVA at set time points, and the duration of follow-up until a study eye loses 15 letters (0.3 logMAR), using survival techniques. .Secondary outcomes include: safety, CS, QoL, resource use, and morphological changes in treated lesions.

9.2 Clinical measures of vision

MDVA is measured on both eyes at each visit using the ETDRS logMAR charts. CS is measured on both eyes at each visit using the Pelli-Robson chart in DPs collecting the extended dataset. Protocols for measuring BDVA, MDVA and CS are given in **Appendices 5** and **6**.

9.3 Safety Outcomes

Data characterising adverse reactions, events and complications are essential to quantify and describe possible harms of PDT treatment. Relevant data characterising events during or just after treatment will be collected on all visits when treatment is given (back pain, acute ocular events). Data characterising adverse events arising between visits will be collected at all visits following a visit on which treatment was given. Data will be collected systematically on transient and severe visual loss, photosensitivity, delayed clinical and angiographic ocular events. DPs will also be encouraged to report any other events that are suspected to be attributable to treatment. Frequencies of adverse outcomes will be reported as incidence rates for the whole cohort and by DP.

9.4 Self reported visual functioning and quality of life

Clinical measures of vision, e.g. MDVA, quantify some dimensions of visual functioning but do not adequately capture other aspects of vision such as metamorphopsia, changes in contrast function, colour vision and stereo perception. Questionnaires that ask about visual symptoms and the ability to carry out a range of common tasks dependent on vision (SRVF) take into account a patient's broader experience and complement clinical measures. Responses to such questionnaires usually correlate with levels of vision estimated by clinical measures in the better eye of an individual but also assess contributions to vision from the worse-seeing eye. Therefore, information obtained from such instruments describes better the overall

level of benefit from treatment. The proposed study will measure both SRVF (NEIVFQ **[4]**) and generic QoL (SF-36 **[5]**). Defining the relationships between changes in clinical measures of vision and SRVF/QoL is a specified secondary objective of the study, allowing the average reduction in QoL experienced by AMD patients per unit of MDVA or CS lost to be estimated. Questionnaires will be administered 6 monthly.

9.5 Resource use

As described above, a questionnaire will be administered to patients every 6 months (as part of the extended dataset) to ask patients about the costs and consequences to them of having the treatment and about their use of resources in other agencies (e.g. GP, district nurse) relating to the intervention. Treatment resources used will be identified from the number of treatments given (documented in the database) and from observation of the resources used in providing treatment in a number of DPs. When measuring the total costs of the intervention, the resources used in providing the intervention will be recorded separately from the unit costs. The review performed for the NICE appraisal found that cost-utility estimates for PDT could be influenced by the number of treatments and that the same benefits as found in the existing trials of PDT might be achieved at lower costs. In particular, the frequency of re-treatment in routine practice, which may be a key component of costs, may differ from a clinical trials setting. The review also suggested additional resources might be needed to implement the intervention at each DP which have been ignored in previous cost utility analyses. The resources used in setting up the service will be recorded by site-visits to several of the DPs, chosen to reflect differences in clinical practice. In addition to the costs of providing the intervention to the health service, the resources used by patients and their carers in accessing the service will be recorded and compared indirectly with the resource use for untreated patients (see **10.4**).

9.6 Morphological changes in lesions

These secondary outcomes will be estimated from angiographic evidence of change in total lesion size, total CNV leakage, classic leakage and fibrosis. Note, these parameters will be used for analysis and should not be confused with the lesion features that determine eligibility and re-treatment (see **section 4**).

10. Statistical issues

10.1 Sample size considerations

The study population size is the number of patients recruited during the study period. Uncertainties, e.g. about the proportion of ineligible patients identified, the proportions of eligible patients categorised as having different CNV sub-types, and the precise ways in which control data will be modelled, make it difficult to provide a clear sample size calculation. However, for illustrative purposes, we have considered a simple comparison of a continuously scaled outcome, i.e. MDVA, between two subgroups of patients with different types of CNV lesions **[6]**. The following assumptions have been made for this illustration: (a) equal sample sizes for the two groups, (b) analysis adjusted for baseline MDVA, (c) SD of changes in MDVA = 0.1 logMAR, (d) 2-tailed significance level of 0.01, (e) power = 0.95. Such a comparison would require only about 50 subjects in each group to detect a difference of 0.1 logMAR in the mean change between groups. Other outcomes may have a larger SD, and groups may not have equal sample sizes. A comparison for a continuously scaled outcome with SD=0.3, and two groups with sample sizes as unequal as 4:1, would require a total of about 1200 (960:240). These simple illustrations do not take into account the added strength from the longitudinal nature of the data, but also do not consider dependencies between patients treated by the same retinal teams.

10.2 Descriptive statistical analyses

Monthly reports will be generated for the Steering Committee for monitoring purposes. Similar information, tabulated by DP providing PDT, will be produced for commissioners and DPs. Each DP will receive patient specific information for its own service.

Details of the information that will be provided in reports has not been finalised, and additional information may be added as the study progresses. However, the following items are illustrative of the information that will be distributed:

- number of subjects for whom data have been submitted and recruitment rates over time;
- number of subjects considered for PDT and treated, by CNV category;
- demographic and baseline data;
- details of treatments provided;

- comparison of numbers of subjects in different CNV categories, as classified by treating ophthalmologists and angiogram reading centres;
- reports of adverse events and protocol violations.

10.3 Main analyses

Objectives 1 and 2 are descriptive and will be addressed by summaries of the dataset, calculating appropriate standard errors to take into account the hierarchical nature of the data structure (see below).

The dataset for patients in the cohort will have a complex structure. Data will be recorded for varying numbers of visits/duration of follow-up within patients, up to about 8 visits and 3 years of follow-up. Patients will also be 'nested' within groups of retinal specialists and DPs. Therefore, the dataset will be analysed by multi-level modelling, an extension of conventional regression methods to take into account statistical dependency between observations that are 'clustered' in the data structure, e.g. observations within patients or patients within retinal teams.

Follow-up of patients throughout the study period will allow changes in outcomes over time to be described in detail. The main outcomes are continuously scaled and can be analysed by multi-level modelling. Multi-level models will also be used to quantify associations between clinical outcomes, SRVF and QoL (objective 4). Outcomes may also be analysed in different ways in order to provide the best information to satisfy the objectives. For example, change in MDVA may be dichotomised as a deterioration of greater than or equal to 3 logMAR lines or not (a deterioration expected to occur in about 50% of participants) and survival analysis may be used to describe the cumulative probability of a deterioration of this degree with increasing duration of follow-up. The effect of the number and timing of treatments (and other co-variates) can be estimated with such models.

The composition of the cohort will influence the nature of the analysis. Therefore, a detailed plan of analyses will be written after carrying out preliminary descriptive analyses of the baseline clinical and treatment characteristics of patients recruited to the cohort but before carrying out any comparative analyses. A number of baseline factors are expected to influence outcomes independently following photodynamic therapy, including MDVA at presentation, CNV composition, fellow eye status and co-morbidities, and analyses will need to take all of these factors into account.

10.4 Methods for establishing 'control' data for indirect estimation of effectiveness, cost-effectiveness and cost-utility

Objectives 3 and 5 require comparisons to be made with untreated patients and the lack of a concurrent control group is a limitation of the study. A number of strategies are possible for estimating outcomes for untreated patients. We propose to use the following three methods and to investigate the impact of using different methods on estimates of effectiveness, cost-effectiveness and cost-utility:

(a) Extrapolation from trial data: Existing trials of PDT provide estimates of effectiveness. Longitudinal data for MDVA, PRCS, SRVF and QoL outcomes also exist from a previously conducted UK based clinical trial of CNV of AMD in which the intervention was not effective at the specified outcome points. Self-reported use of resources in relation to AMD were also collected in this study. These data, together with the characteristics of participants, can be used to model indirect comparisons between treated and untreated patients.

(b) Extrapolate use of health and personal resources: Use of health and personal resources can be extrapolated from associations between use of resources and visual function and other outcomes in the groups documented in the study. For example, if there is a relationship between use of resources and amount of deterioration over time, the use of resources could be extrapolated to the level of deterioration in acuity expected without treatment.

(c) Estimate use of health and personal resources from the cohort: This method assumes that resource use for an untreated control group would be similar to patients observed in the cohort who receive PDT but who show no benefit (i.e. whose VA and PRCS outcomes deteriorate in similar way to patients in the control groups in trials). This method requires estimates to be adjusted for any difference in clinical characteristics between patients who show no benefit in the cohort study and patients in the control groups of trials.

10.5 Analyses of safety

DPs must report any serious adverse events to the Data Management Centre immediately. Other adverse events are collected as part of the minimum dataset. Descriptive summaries of adverse events will be provided for review by the Steering Committee on a regular basis, and will be tabulated in detail in the final report.

10.6 Sub-group analyses

The effectiveness and cost-effectiveness will be compared between different CNV sub-types, with sub-types defined as in Appendix 1, using data from the assessments carried out by the angiogram reading DPs. Variations in effectiveness will also be investigated for sub-types defined by the ophthalmologist at the time of treatment, and for the individual lesion components on which the definitions are based. Other sub-group analyses have not yet been formulated. The Steering Committee is committed to approving a detailed analysis plan, in advance of carrying out any treatment-related analyses, to ensure that sub-group analyses can be clearly distinguished as *a priori* or *post-hoc*.

10.7 Interim analyses

Serious adverse effects of PDT are not anticipated, since none have been identified in trials of PDT that have been carried out to-date. Given the circumstances in which it has been commissioned, the VPDT cohort study is also very unlikely to halt recruitment early. Therefore, no interim analyses are planned. Other aspects of data and safety monitoring are discussed below (see **13.2**).

11. Documentation and use of study findings

11.1 Documentation

Regular descriptive summaries of the progress of the project will provide on-going documentation (see **10.2**). All minutes of the Steering Committee, updates to this protocol, and progress reports to the NCCHTA, will be carefully archived.

Details of arrangements for final reporting of the study findings have not yet been finalised, but will need to take into account the need for NICE to be able to review the findings in time for its review of PDT. Whatever arrangements are agreed for final reporting, it is envisaged that the study findings will be presented at appropriate conferences and written up for publication in peer-reviewed journals (see **11.2**).

11.2 Publication / dissemination policy

Investigators and lead contacts from all DPs will form the "Verteporfin Photodynamic Therapy Cohort Study" group. Publications will be authored by a "writing committee" on behalf of this group. All group members will be listed and acknowledged on the RCOphth website and in all publications or journal websites, subject to the conditions for publishing in specific journals.

12. Data issues

12.1 Data protection

The Data Management Centre has registered the study with the Data Protection Officer at the London School of Hygiene and Tropical Medicine.

12.2 Data confidentiality

All data will be treated as confidential. Information to identify patients is required in order to link study participants with the National NHS Register. Making this link is required to identify promptly patients who have died, or who have moved. Identifying patients who move into residential accommodation is of particular importance because of the societal costs of these changes in circumstances.

12.3 Data security

DPs are responsible for holding their own database securely. However, it should be noted that DPs are not holding any more information than they would hold anyway, for the purposes of managing and treating their patients efficiently.

The Steering Committee are extremely aware of the sensitivity about transmitting identifiable patient data outside the NHS. Two methods of data transmission are being used.

First, submission of data from the Strategen database generates two password protected and encrypted files. One contains clinical and treatment data and an arbitrary identifying code, generated by the database. A second file contains patients' names and addresses, genders, dates of birth, hospital numbers, arbitrary consultant and DP codes, but no clinical data. The first file is transmitted to Strategen, the company that administers the clinical database, so that the company can troubleshoot any problems with the database that DPs experience. These data are subsequently transmitted to the Data Management Centre. The second file is transmitted directly to the Data Management Centre. The Data Management Centre will transmit sufficient identifying information about patients, but no clinical data, to the Office of National Statistics to allow the patients to be identified on the National NHS Register.

Second, a revised 'LSHTM' database is being implemented which allows submission of data using SSL, the gold standard method for secure transmission which is approved by the NHS Information Authority. From this database, all data are

submitted directly to the Data Management Centre, avoiding the need for data to be routed via a third party.

Data reports from the Data Management Centre to DPs are usually sent by email as password protected electronic documents. DPs can request paper copies if required.

All data held by the Data Management Centre will be stored on a secure institutional network, in accordance with the policy on data security of the London School of Hygiene and Tropical Medicine.

12.4 Data ownership

The entire cohort study dataset will be under the guardianship of the Steering Committee. For the duration of the study, the dataset will be held and maintained at the Data Management Centre, London School of Hygiene and Tropical Medicine.

All data for a particular DP can be made available to the originating DP (formatted and cleaned) at the end of the study. Summaries of data will be fed back to DPs regularly (see 10.2) during the study, for local review. Requests for additional statistics in regular reports, and secondary analyses of the whole dataset, will be considered by the Steering Committee. Requests for all data for a DP *during the study* will also be considered by the Steering Committee, but will need to justify the special circumstances that make this necessary because of the potentially time-consuming nature of satisfying such one-off requests.

The dataset will be archived securely at the end of the study and any requests for access or further analysis will be considered by the Steering Committee, or by a skeleton committee after the disbandment of the existing Steering Committee to consist of one of the investigators, a separate representative of the Royal College of Ophthalmologists, and one other member of the original Steering Committee who has no day-to-day involvement with the study.

13. Organisation

13.1 Steering Committee and other key personnel

The Steering Committee consists of the individuals listed in **Table 2**.

Table 2: Members of the Steering Committee

Chair	Mr N Astbury
Deputy Chair, and representative of the RCOphth Scientific Committee	Mr D Wong
Retina specialists	Professor A Bird, Professor U Chakravarthy, Mr S Harding, Mr B Dhillon, Mr Y Yang
Editor, Cochrane Eyes and Vision Collaborative Review Group	Mr R Wormald
Public Health Consultant	Dr D Austin
Independent Scientific Advisor	Professor A Fletcher
Data Management Centre representative	Dr B Reeves
NCCHTA representative	Professor K Woods (until 31/10/03), Dr P Davidson (from 01/11/03)
Consumer representative	Mr T Bremridge
Department of Health representative	Mr D Busby
Novartis representative	Mr N Gwatkin (until 29/02/04), Ms J Potts (from 01/03/04)
Representative for Local Specialist Commissioners	Mr Peter Graham

13.2 Data safety and monitoring

The Steering Committee has taken responsibility for data and safety monitoring. The Data Management Centre has responsibility for regular submission of a core set of summary descriptive data for review by the Committee. The details of these summary statistics have not yet been finalised, but will include all reports of adverse events, recruitment rates overall and by DP, and details of treatments given by CNV category.

13.3 Central Angiographic Resource Facility

Professor U Chakravarthy has responsibility for the Central Angiographic Resource Facility (CARF) at Queen's University, Belfast. All angiograms from DPs must be submitted to the CARF, which will then digitise angiograms submitted on film and distribute digital images between the three Angiogram Reading Centres (Belfast, Moorfields and Liverpool) in accordance with their capacity and current workloads. The submission, distribution and assessment of angiograms will be supported by software designed for the study by Digital Health Care, Cambridge.

13.4 Contact details

Data Management Centre:

Dr Barney Reeves	barney.reeves@lshtm.ac.uk
Ms Sonia Dhiman	parminder.dhiman@lshtm.ac.uk
Miss Julia Langham	Julia.langham@lshtm.ac.uk
Ms Annette Croucher	annette.croucher@lshtm.ac.uk
LSHTM, Keppel Street, London WC1E 7HT	
E-mail address for data	VPDT@lshtm.ac.uk

Central Angiographic Resource Facility (CARF):

Alison Murphy; Nicola Duff; Liam Patterson Ophthalmic Research Centre, Queen's University of Belfast, Royal Victoria Hospital, Belfast BT12 6BJ	CARF@qub.ac.uk

Database support:

Mr John Fullarton Strategen	johnrfullarton@aol.com
Mr Ian Keary	ian.keary@strategen.co.uk

Chief Investigator:

Professor U Chakravarthy Dept Ophthalmology, Queen's University of Belfast, Royal Victoria Hospital, Belfast BT12 6BJ	u.chakravarthy@qub.ac.uk	See above for CARF

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15. Appendices

Appendix 1: Classifying choroidal neovascularisation in the macular

Appendix 2: Examples of flow charts for making re-treatment decisions

Appendix 3: Invitation to register questionnaire

Appendix 4: Patient information sheet and consent form

Appendix 5: Protocol for logMAR visual acuity assessment and refraction

Appendix 6: Protocol for Pelli-Robson contrast sensitivity assessment

Appendix 7: Protocol for fluorescein angiography and colour photography

Appendix 8: Submission of angiograms to the Angiographic Resource Facility (CARF)

Appendix 9: Site implementation and training

Appendix 10: Instructions for completing and administering quality of life and resource use questionnaires

Appendix 11: Recommended paper data collection forms and notes about data collection

Appendix 1: Classifying choroidal neovascularisation in the macula

The table below describes a standardised method for determining the category of choroidal neo-vascularisation from stereoscopic fundus fluorescein angiograms. It is designed to help in the assessment of suitability of cases for treatment within the NICE recommendations issued in 2003 but will be useful to all those involved in grading and assessing CNV. The decision tree includes recently developed terminology from grading centres involved in TAP, VIP and SFRADS. (Yit Chiun Yang, Usha Chakravarthy, Simon Harding – April 2004)

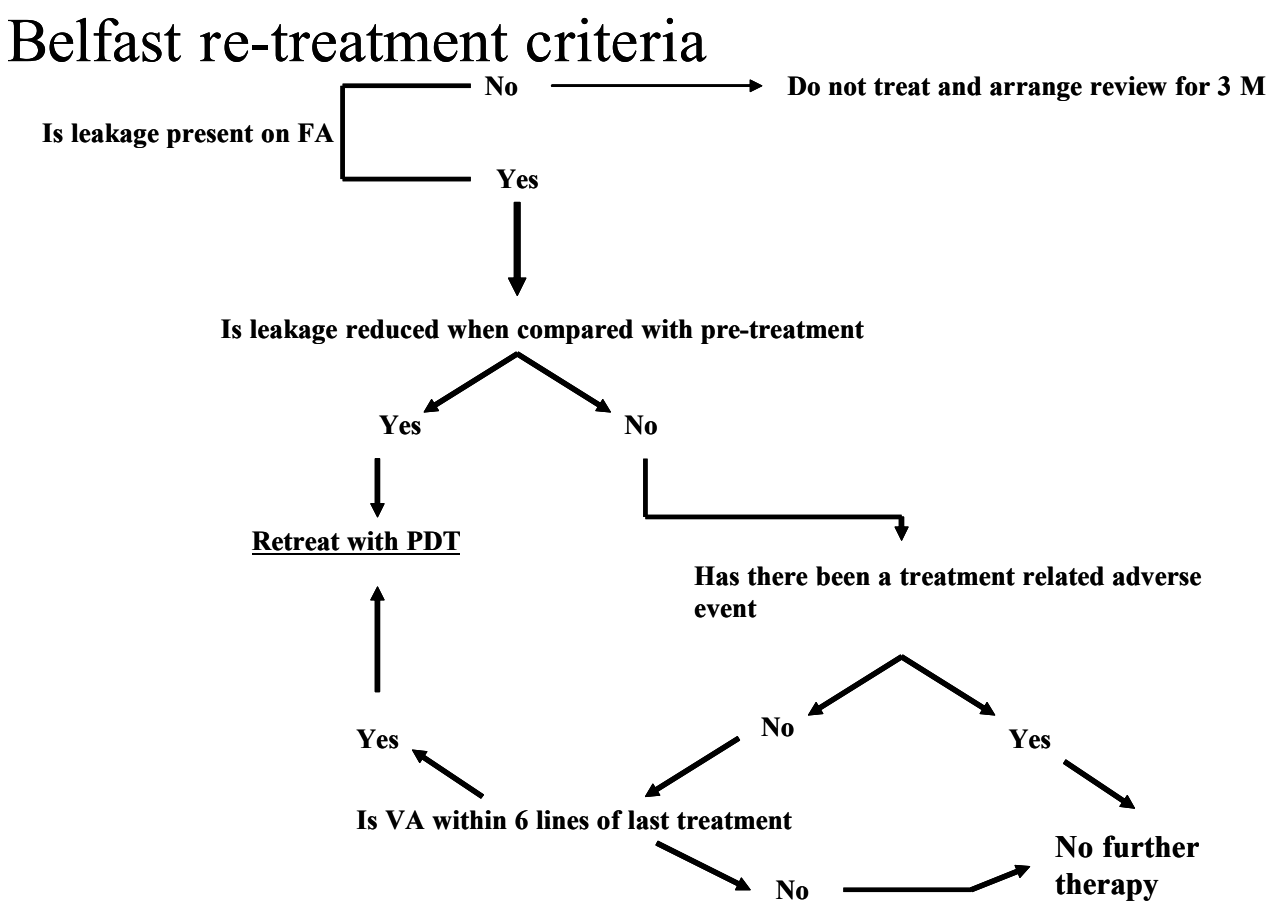
<table>
<tr>
<th>A. Identify morphological features
Use stereos of colour and angiographic frames to assist in recognition of the following lesion components</th>
<th>B. Assess total lesion size</th>
<th>C. Categorise lesion subtype</th>
</tr>
<tr>
<td rowspan="3"><u>1. CNV Lesion Components</u>
<u>Fluorescein leakage associated with CNV</u>
Classic CNV
Occult CNV: fibrovascular PED; late leakage of undetermined origin
<u>Features contiguous to CNV which prevent determination of extent of leakage and which therefore constitute part of the lesion</u>
Blood
Elevated Blocked Fluorescence (EBF) not due to blood
- may be due to RPE hyperplasia, thick exudate, fibrous tissue
Serous PED</td>
<td rowspan="3">1. Define the boundaries of the lesion

2. Define the boundaries of the area of classic leakage

3. Estimate proportion of classic relative to total lesion size

4. Ineligible for PDT if less than 50% of lesion is CNV</td>
<td rowspan="3"><u>1. Classic with no occult (NICE FAD 1.1)</u>
1A. Classic leakage accounts for 100% of lesion
1B. Classic leakage accounts for 50-99% but lesion has <u>no</u> occult component
<u>2. Predominantly classic with occult (NICE FAD 1.2)</u>
Classic leakage accounts for 50-99% of lesion <u>with</u> some occult
<u>3. Minimally classic</u>
Classic leakage accounts for less than 50% of the lesion
<u>4. Occult with no classic</u>
Classic is 0%. Any CNV leakage is of the occult variety</td>
</tr>
<tr>
<td><u>2. Other features associated with CNV which are NOT used to define the boundaries of the lesion</u>
Atrophy: geographic atrophy (GA) and non GA
Flat blocked fluorescence
Fibrosis not contiguous to CNV boundary
Thick exudate not contiguous to CNV boundary</td>
</tr>
<tr>
<td><u>3. Other features which help with categorisation of CNV or which may modify natural history</u>
Retinal angiomatous proliferation
Chorio-retinal anastamoses
Idiopathic polypoidal choroidopathy</td>
</tr>
</table>

Appendix 2: Examples of flow charts for making re-treatment decisions.



If acute vision loss noted after treatment do not retreat

Liverpool re-treatment criteria

	Retreat	Don't retreat
FFA	**leakage**	**no leakage**
		no leakage at centre
VA	**dropping**	**stable**
		< 20 letters
SRF	**persistent**	**cleared**
Haem/ex	**new**	**cleared**
CNV	**extension**	**inactive**
		CRA
Fibrosis		**> 75%**
Visit	**3 months**	**9 + months**

Appendix 3: Invitation to register questionnaire

VPDT Cohort Study

Site Specification and Invitation to Participate

Dear Colleague

The VPDT Study is ready for implementation. Unfortunately there has been a delay in the formal notification to the Study Team of the designated providers for each Strategic Health Authority. However we are keen to get started and, since your unit has been actively treating for some years and has been contributing to the existing surveillance programme, we would like to invite you to register now.

Please could you provide details about yourself and your retinal team so that we can help you to get set up to provide the data for the cohort study.

Lead Clinician Details

Full name .....

Qualifications .....

NHS Organisation .....

Address .....

Email .....

Telephone .....

Fax .....

Have you attended a workshop on FFA Interpretation of CNV Yes / No

Main Contact Details

Please give contact details of the local administrator who will act as main contact for the study

Full name .....

Address .....

Email .....

Telephone .....

Fax .....

Service Structure

Please provide the following details of your PDT service

1. Who do you take referrals from? GPs □ optometrists □ ophthalmologists □

2. Currently, what is the average time between receiving a referral and the first assessment in your clinic? ……. (weeks)

3. Please indicate on which days your PDT treatment clinic runs:

   Monday □ Tuesday □ Wednesday □ Thursday □ Friday □

4. Please indicate if you will provide the following:

   Best corrected VA based on the full refraction protocol □
   Contrast sensitivity □
   OCT □

5. Please indicate who will be undertaking VA measurements

   Optometrist □ Nurse □ Other (specify) □

6. Would you like your VA examiner to undergo training Yes / No

7. What is your preferred mode of data capture

   Paper forms □ Electronic Forms □

   If electronic please answer the next section:

IT infrastructure

Please describe your local IT structure so that our IT team can consider the most appropriate implementation for your centre

1. Please indicate your preferred electronic capture method for clinical data:

   Installation on a free standing computer workstation or laptop, e.g. held by local administrator or medical secretary ☐

   Installation on hospital network, so that more than one member of staff can access the database at multiple computer workstations in your clinics ☐

2. Do you have a reliable local ophthalmology network? Yes / No
3. Is your server connected to:

   NHS net ☐ academic (ac.uk) ☐
   Other ☐ None ☐

IT Contact Details

Please give contact details of the local IT administrator who will act as lead for the study:

Full name .....

Address .....

Email .....

Telephone .....

Fax .....

Angiography

Is your FFA system digital or film based:

Digital ☐

Film ☐

Model and make of camera .....

Image acquisition software (if digital) .....

For digital camera-users, we will provide software to import images from existing systems and to enable effective database management and smooth transfer of the electronic information. We only have one licence per site. Are you likely to be using more than one capture location and thus more than one acquisition system?

Yes/No

Has your photographer (s) been certified by any one of the ongoing studies for angiographic stereo-capture protocols? Yes / No

If “yes”, please list studies: If “no”, would you wish your photographer to be trained?

Although the final decision rests with the commissioners please state if you are willing to collect the extended dataset (measurement of contrast sensitivity and completion of quality of life questionnaires). Yes / No

If known please identify the PCT’s your contract covers:

Please return these details to:

Sonia Dhiman
Health Services Research Unit
Department of Public Health and Policy
London School of Hygiene and Tropical Medicine
Keppel Street
London WC1E 7HT
Email parminder.dhiman@lshtm.ac.uk

Upon receipt of this questionnaire Strategen will contact you to arrange a database installation date and we will send you details of the LREC application process, database training and implementation, reading centre processes and data collection protocols.

Please feel free to contact any of the members of the study team at the email addresses given below

We look forward to working with you on this exciting study.

With best wishes

Barney Reeves: barney.reeves@lshtm.ac.uk
Usha Chakravarthy: u.chakravarthy@qub.ac.uk
Simon Harding: simonpharding@aol.com

Circulation list:
John Fullarton, Strategen
Rob Stitchbury, Digital Healthcare

Appendix 4: Patient information sheet and consent form

Please note: A revised (shorter) patient information sheet has recently been submitted to the MREC for approval. The patient information sheet and consent form shown below have been approved by the MREC and should be used until the revised version is approved and distributed to DPs.

Hospital /Institution Headed paper

VERTEPORFIN PHOTO DYNAMIC THERAPY IN SUBFOVEAL CHOROIDAL NEOVASCULARISATION: THE UK COHORT STUDY

Lay title: A study to monitor the effect of photodynamic therapy in choroidal neovascularisation

PATIENT INFORMATION LEAFLET AND ANSWERS TO FREQUENTLY ASKED QUESTIONS

You are being invited to take part in a study which aims to collect information on the impact of eyesight deterioration on ability to function and the results of other tests which are undertaken as part of the treatment you are receiving for your eye condition. If you wish to have this document read to you please ask one of the clinical staff involved in your care. We are also happy to answer any questions which you may have.

WHY HAVE I BEEN ASKED TO TAKE PART IN THIS STUDY?

The recent changes that you have noticed in your eyesight are due to the development of new abnormal blood vessels in the eye, behind the retina. These abnormal blood vessels are leaking fluid and blood into the central area of the retina called the macula causing it to malfunction. These abnormal blood vessels form a lesion called a choroidal neovascular membrane, or CNV for short. Without treatment, most people with this problem will lose central vision over a period of weeks or months. The development of CNV is a feature of wet Age-related Macular Degeneration (called AMD for short) and, less often, some other eye conditions.

There are many different types of CNV. Two of the types of CNV, namely classic or predominantly classic CNV, cause extremely rapid and severe sight loss. Results from a clinical trial carried out in 22 different countries suggest that a treatment called photodynamic therapy may slow down or stop the sight loss in classic or predominantly classic CNV.

This treatment, called PDT for short, has been made available on the NHS for those people who have been diagnosed as having classic or predominantly classic CNV. Your retina specialist will tell you if you fall into these categories

WHAT IS THE STUDY I AM BEING ASKED TO TAKE PART IN?

The study is called the verteporfin photodynamic therapy cohort study, or VPDT cohort study for short. Although PDT has been approved for use in the NHS, the NHS needs to know the condition of patients' eyes before treatment and the results of the treatment. The cohort study is designed to do this.

The cohort study is not a trial of a new treatment. All persons found to have subfoveal classic and predominantly classic CNV are being offered treatment on the NHS. For the purposes of the study we simply wish to have access to the information on your eye condition in order to assess the value of PDT treatment over time. In addition, if you agree, we may ask you to complete questionnaires which help us to assess the impact of sight loss on your ability to carry out usual, day-to-day activities and the costs you incur, or the costs incurred by relative or friends, for example when you come to hospital apppointments. The data will be entered into a secure computer and will include information on your eyesight, details of the clinical and photographic examination and relevant medical history. Information will be collected at every visit. Your personal details are confidential and only designated people such as the doctors and nurses involved in your care will have access to this. If you experience any side effects from the treatment, we are obliged to inform the company and/or the Health Authorities. This will be done without giving them any details that might enable them to

know your name. We will inform your GP that you are taking part in the cohort study as long as you have no objections to us letting your GP know.

WHAT IS PHOTODYNAMIC THERAPY AND HOW IS IT PERFORMED ?

The treatment uses a special drug called verteporfin (marketed under the name of visudyne), which sensitises the blood vessels so that they can be destroyed using a low energy laser. Visudyne is injected into the bloodstream and when there is enough visudyne in the body, a specially designed laser is focused on the retina through a contact lens placed on the eye. The whole process should cause little or no discomfort. Because the drug is mainly concentrated in the abnormal blood vessels these are preferentially destroyed and further leakage and bleeding is reduced. The surrounding normal blood vessels are also damaged but the damage is minimal and they recover very rapidly. The retina itself does not take up the drug and so does not become damaged although it is exposed to the laser. The treatment is performed by ophthalmologists who have specialised in treating retinal disorders.

The abnormal damaged vessels may recover and this is why the treatment may have to be repeated several times. You will need to come back every 3 months to have further photographs taken of the back of your eye, and whenever the abnormal blood vessels leak again, you will need another treatment. This may happen up to 4 times per year. Many patients have already been on treatment for up to 2 years. Although initially you will be asked to return every 3 months to see your eye specialist, he or she may reduce the frequency of these visits if your eye condition stabilises. We expect this to happen around 1 year after treatment is started.

WHY IS THE VPDT COHORT STUDY BEING DONE?

PDT is a treatment which has been available for use since 2000 but which has only recently been approved for use in the NHS. The clinical trials which tested this treatment showed that patients who received the active treatment lost less vision (measured by

testing on vision test charts) than patients who received a dummy treatment. However, many of the treated patients also continued to lose eyesight. The treatment is extremely expensive and may not be of benefit to some patients. It is important that the results are monitored for several reasons. These include, knowing how many people actually benefit from the treatment, how long the treatment should continue, the optimum way it should be undertaken, how sight loss impacts on the person's quality of life and whether PDT treatment makes a difference to this and how much the treatment actually costs. In the VPDT cohort study we are hoping to answer these questions.

WILL BEING IN THE STUDY INVOLVE HAVING TO UNDERGO ANY ADDITIONAL TESTS?

Almost all the information required for the study is collected as part of the normal examinations and tests that you will have to undergo before you can receive PDT treatment. These tests including having your sight tested in detail, and having drops inserted into your eyes to dilate the pupil so that the retina can be examined thoroughly. After these tests are completed your retina specialist will order a fluorescein angiogram, which involves using a special camera to photograph the eye. The photographs are taken through the dilated pupil. A nurse or doctor will place a needle in a suitable vein in your forearm or the back of the hand and inject a yellow dye called fluorescein. This dye enters the circulation and photographs of the blood vessels of the eye are taken. The entire procedure for the fluorescein angiogram will take about 20 minutes. If these tests show that you have classic or predominantly classic CNV, you will then be offered PDT. You may be asked to provide some additional information about the impact of your eye condition on your ability to function and the economic consequences of having sight loss. This involves asking you to answer some questionnaires. However you do not have to agree to answer these questionnaires. Your refusal to fill out the questionnaires will not jeopardise your treatment with PDT if you need it. Even if you initially give consent to filling out the questionnaires, you can change your mind at any time.

WILL I SUFFER ANY SIDE EFFECTS?

Visudyne will make your skin extremely light sensitive in the first 24 - 48 hours after injection. If you stay in bright light for too long, your can suffer a reaction which is like having a bad sunburn. Therefore you will be asked to take precautions which will include the wearing of dark glasses to protect your eyes, keeping the skin of your arms and legs covered and preferably staying indoors for about 48 hours.

In some people the eye sight in the treated eye may be even more blurred than it was before treatment and this may last a few days. If the drug leaks out of the blood vessel during the injection, you are likely to experience some pain where the injection is given. In this case, there may be a rash and the skin covering the leak will need to be covered for several days to protect it from light.

A small number of patients have had back pain and have felt sick during the injection. These feelings went away once the injection was stopped. In a few people, severe worsening of eyesight after visudyne treatment has been noticed. This is because some of the normal blood vessels in the retina are also accidentally shut down during treatment. Very occasionally, bleeding may occur inside the eye, eyesight may become abnormal or eye pain and redness may be experienced. Some of these symptoms may also be due to the AMD itself. Some patients have had one or more of the following other side effects, namely headaches, dizziness or a drop in blood pressure.

Approximately 1 in a 100 people develop severe sight loss immediately following PDT which may never recover. The exact reason why this happens is unclear but it may be due to haemorrhage from damaged blood vessels or damage to the normal blood vessels of the retina. However people with CNV who have not had any treatment whatsoever can also develop sudden severe sight loss owing to haemorrhage from the CNV. Therefore it is very difficult to tell if the treatment itself had

something to do with the sight loss. On balance, however, the chances of the treatment itself causing sight loss is very small (about 1 in a 100) and, comparatively speaking, the chances of having some benefit are very high (about 1 in 3).

WHAT IF SOMETHING GOES WRONG?

Overall, PDT has been shown to be extremely safe. Many thousands of patients have received this treatment worldwide and the side effects are few. This treatment is now being made available to you on the NHS and therefore you will be entitled to compensation if you suffer an injury due to medical negligence. If you suffer an adverse reaction from the drug or other aspect of the treatment which is not due to negligence then compensation will not be available.

WHO IS FUNDING THE STUDY

The study is being funded by the Department of Health and the regional commissioners of specialised health services (these are the people who provide funding to hospitals in the UK to provide treatment to people living in their region).

ARE THERE ANY ALTERNATIVE TREATMENTS THAT I CAN HAVE?

At present there are no other treatments which have been shown to help patients when CNV is present under the centre of the retina. However, you do not have to agree to have this treatment and, if you wish, we will continue to monitor your eyesight and offer you other supportive care. You can also change your mind at any time if you wish to be reconsidered for treatment.

WHAT IF NEW INFORMATION OR TREATMENTS BECOME AVAILABLE?

A number of new treatments for CNV are being studied but these are still being evaluated. Being in the cohort study is unlikely to impact on your management, if a new treatment is found to be better. Your specialist will keep you informed about

any new developments and take this into consideration while planning your treatments.

ARE THERE ANY BENEFITS FROM TAKING PART IN THIS STUDY?

The various eyesight tests and the other tests which are done to assess your suitability for treatment will be performed to high standards which mean that the effects of treatment can be understood better. Also the results of the fluorescein angiogram will be examined by experts who will provide information to your own specialist which may assist with your care. We also believe that collecting information for the study will allow us to fine tune this treatment and help provide the best care to others who may develop this disorder.

WHEN WILL THE STUDY STOP AND WHAT WILL HAPPEN TO ME AFTER THAT?

We are planning to collect information for up to 3 years. From past experience we know that people receiving PDT are usually kept under review for a period of 3 to 5 years. Your specialist will decide whether you need any additional follow up even after this study finishes.

WHAT WILL HAPPEN TO THE INFORMATION COLLECTED?

The data which are collected will be analysed and published in medical and other journals to inform the scientific and lay public. It will also be made available to government bodies and health authorities.

WHAT SAFEGUARDS ARE IN PLACE TO ENSURE THAT INFORMATION COLLECTED FROM ME WILL BE KEPT CONFIDENTIAL?

The details of the study have been examined carefully by the London Metropolitan Multicentre Research Ethics Committee, one of 13 national research ethics committees. This Committee has approved the study, which means they are satisfied that information will be kept confidential. In addition, the Royal

College of Ophthalmologists, which represents eye specialists, has set up a body of people to monitor the study while it is being carried out. This body includes eye specialists, public health specialists and a representative from the Macular Disease Society, an organisation which represents the interests of patients with macular degeneration. This body will ensure that patient confidentiality and health are not jeopardised in any way.

If you have any other questions about the cohort study please feel free to speak with a member of the clinical team looking after you. A contact name and number is provided below

Named contact: ----------Telephone:----------

Hospital /Institution Headed paper

CONSENT

I have read or have had read to me the above concerning the treatment of Age Related Macular Degeneration using Visudyne in the UK PDT cohort study. All my questions have been answered and I am willing to allow information on my eyesight and clinical condition to be made available to the researchers undertaking this work.

I am / am not willing to complete the questionnaires in the cohort study.

I agree / do not agree to my GP being informed about my participation in this study.

_____	_____	_____
Date	Name of Patient	Signature

_____	_____	_____
Date	Name of Doctor	Signature

Appendix 5: Protocol for logMAR visual acuity assessment and refraction

Standardising visual acuity testing is the key to obtaining repeatable and reliable measurements. The procedure described below has been developed and refined from a number of previously conducted clinical trials including the MPS studies, SFRADS and TAP/VIP.

- Acuity testing should preferably be undertaken in dedicated facilities using charts with standardised and uniform lighting.
- The testing distances should be accurately marked out and the procedure followed should be identical from one patient to the next and when the patient returns for subsequent visits.
- While equipment and light bulbs may be replaced as required every attempt must be made to keep conditions as unchanged and as standardised as possible.

1 ETDRS LogMAR Visual Acuity Charts

- There are a number of ETDRS charts. For the purposes of the cohort study only Charts 1 and 2 and Chart R are needed.
- Chart R is used for refraction, and for recording presenting BDVA (see **7** below).
- After refraction is complete Charts 1 and 2 are used for testing the right and left eye respectively.
- Each line has 5 uniformly sized and spaced letters which decrease progressively in size from the top most line.

LogMAR charts were developed and popularised by Bailey and Lovie and hence they are sometimes referred to as Bailey Lovie Charts. The visual angle is largest with the largest letters. The advantage of these charts is that there is a geometric progression of the visual angle with a doubling or a halving with every 3 line change. Therefore calculation of the visual angle is very simple and allowances are made for the testing distance.

- The charts may be standardised for testing at any distance, provided the appropriate conversions are clearly understood.
- Changing the testing distance simply extends the range of acuity the chart can test.
- Thus, for example, when used at a distance of 4M the acuity range is -0.3 logMAR to 1.0.
- By moving the chart to 2M, the range becomes 0.0 logMAR to 1.3.
- When testing is undertaken at 1M, acuities as poor as 1.6 can be assessed.
- Although standardised for the 4M distance, the chart can be easily used at 2M or 1M.
- In order to obtain an acuity, when the chart has been used at 2M or 1M the examiner simply adds 15 letters or 0 letters (for 2M and 1M respectively) to the number of letters read at the testing distance. (DPs already familiar with recording logMAR acuities in logMAR units may use this format instead of letters, but must inform the Data Management Centre that they wish to do so.)
- Details of how the results of the tests should be recorded and scored are provided below (see **7** and **8**). Duplicate forms for recording logMAR acuities will be supplied to DPs.

2 Retroilluminated Visual Acuity Box

- The illuminated box can be mounted on a wall or be used free standing.
- The box should be placed so that the top of the third row of letters (0.8 logMAR at 4 Metres testing distance) is 49 ± 2 inches (124.5 ± 5.1cm) from the floor.

3 Ambient lighting

- The room lights should preferably be turned off during the monocular visual acuity test.
- Retro-illumination within the box itself provides the appropriate level of illumination to undertake the test and should also allow the examiner to record the test results without any additional lighting.

4 Visual Acuity Lanes

- A distance of 2 meters (78.7 inches) is required between the patient's eyes and the visual acuity chart for the 2 metre test, and a distance of exactly 1 meter (39.37 inches) is required for the 1 metre test.
- Wall-mounted box: In addition to the 4 meter lane, 17.78 cm (7 inches) must be allowed for the depth of the box plus space for the patient. If space is insufficient, the test may be undertaken at any specified distance as long as this is taken into account during the recording of information.
- Stand-mounted box: In addition to the 4 meter lane, 33.02cm (13 inches) must be allowed for the stand's casters plus space for the patient.

5 Marking the distance

- The distances are measured from the lateral canthus of the eye of the patient, seated comfortably in a chair with his or her back firmly placed against the chair back, to the centre of the second (left eye) or fourth letter (right eye) of the third line of the chart. The horizontal distance must be measured individually for each examination. 1 or 2 metre sticks are ideal for this purpose.

6 Refraction

- All tests of visual function should be performed by a visual acuity examiner who has been appropriately trained.

6.1 Equipment

The equipment required for refraction is:

- Retroilluminated ETDRS chart set.
- Trial lens frames
- Trial lens set, with positive or negative cylinder lenses.
- +0.37 and –0.37 spherical lenses. (+ and -0.50 are adequate if 0.37 are not available)
- Jackson cross-cylinders of 0.25, 0.5, and 1.00 dioptres.
- Pinhole occluder.

Ideally full aperture lenses and the appropriate wire trial frame should be used to improve the patient's ability to eccentrically fixate during the test. However for the cohort study reduced aperture lenses will be acceptable if a full aperture set cannot easily be obtained.

6.2 Subjective Refraction

The following refraction protocol is adapted from those used in previous landmark clinical trials. It was written to ensure standardisation of vision testing by technicians who often were not optometrically trained. For the purposes of the VPDT Cohort Study it should be viewed as a guide when testing is being performed by optometrists. However non-optometrists are advised to strictly follow the protocol.

- Always start with chart R. This is the chart used for refraction ***and for recording presenting BDVA***, which must be measured before carrying out the refraction and measuring monocular DVA (see **7** below).
- At the initial/first visit, the patient's spectacles for distance viewing (if worn) should be measured with a lensometer, and these measurements used as the beginning approximate refraction.
- Refractions may be performed with minus or plus cylinders.
- If the patient does not wear spectacles for distance vision, retinoscopy or autorefraction may be used.
- Ensure that the patient does not lean forward and is using only the eye being tested.
- When no correction is needed, start with plano.
- If correction is needed start with current spectacle correction, retinoscopy result or autorefractor result (i.e. appropriate sphere, appropriate cylinder in measured axis)
- Check which line of the chart the subject is able to read

6.2.1 Refining the spherical correction

- Subject looks at lowest line that he/she can read confidently
- Hold challenge lens in front of trial frame over eye to be tested (range between + 0.37 and + 1.00 depending upon acuity) and ask if this makes the lowest line seen better, no difference or worse.
- If subject indicates better or no difference increase the sphere power in the trial lens frame and repeat with a plus challenge lens.
- If better by reading additional letters, again increase the sphere in the trial frame and repeat these steps until there is no further improvement or a definite reduction in number of letters read.
- If no change in number of letters read repeat challenge with a plus sphere. If subject indicates better increase sphere power, and if no different again increase sphere power. Repeat these steps until performance shows worsening and then stop
- If subject indicates vision is worse offer a minus challenge lens. If patient reads better then change sphere power accordingly using an equivalent minus correction.
- Repeat cycle until subject indicates definite worsening.

6.2.2 Refining the axis of the cylinder

- Ask the subject to view a letter 1 line above the smallest line they can read
- Hold the + 0.5 Jackson's cross cylinder in front of the trial frame straddling the axis of the cylinder and flip to each side. Ask the subject to indicate which is clearer or whether they are equally clear.
- Move axis in the direction of reduced blur if subject indicates reduced blur with a flip.
- Repeat this until subject indicates equal blur on both sides of the flip

6.2.3 Refining the power of the cylinder

- Align the Jackson's cross cylinder with the power meridian of the lens in the trial frame and flip to present either the + 0.50 or the – 0.50.
- Ask the subject to indicate which is better, flip 1 or flip 2.
- If no difference is indicated, stop here

- Adjust the power accordingly if one of the flips is indicated as better.
- If + 0.50 is indicated as better reduce the power of the sphere in the trial lens by – 0.25 and repeat until no difference is indicated.
- If – 0.50 is indicated as better, increase power of the sphere in the trial lens by +0.25 and repeat until no difference is indicated.

6.2.4 Final steps in refraction

- As a final check, repeat a round of the steps used to get the spherical correction
- The best correction for each eye is determined from the subjective refraction should be entered in the *Record of Subjective Refraction*.

7 Recording of VA

The logMAR chart was designed for the recording of vision as a log of the Minimum Angle of Resolution. This is identified as the lowest line on which 3 letters are read and is recorded in a Snellen notation. An adaptation of the testing method is simply to record the number of letters read. Alternatively, acuities can be recorded in logMAR notation where each full line read is recorded as 0.1 (0.0, 0.1, 0.2 …..1.0, etc.) and each letter as 0.02 (0.60, 0.62. 0.64…etc.). For the VPDT Cohort study the number of letters read is the preferred recording method but logMAR conversion is acceptable.

Before carrying out a refraction or measuring MDVA according to this protocol, the patient's presenting *logMAR BDVA* must be measured. Record the patient's presenting binocular logMAR acuity using chart R, with the patient wearing the distance spectacles that they usually wear. Record the number of letters read on the logMAR acuity form in the relevant box (and in the database). It is preferable to measure the BDVA at 4M, but measuring at 2M is acceptable.

In the VPDT Cohort Study the main outcome variable is the visual acuity measured at 1 metre. To speed up the process the test takes place in two parts with initial testing at 2 or 4 metres, depending on unit preference, followed by testing at 1 metre only if insufficient numbers are read at the initial test distance. (DPs must inform the Data Management Centre whether they wish to test at 4M or 2M. Appropriate forms for recording logMAR acuities at 2M or 4M will be provided to centres.)

A full refraction protocol is encouraged at every clinic visit, but must be done at the screening visit, the visit when a patient is first treated (0 months), and yearly (12, 24 and 36 months). When this is not possible, it is acceptable to record logMAR acuities using the trial lenses of the prescription most recently used for vision testing. All logMAR acuities must be recorded in accordance with the following steps.

- If possible, carry out a refraction according to the protocol described above (see 6), using chart R. If not possible, proceed as described below.
- Each eye should be tested separately at a specified distance (or distances, if insufficient letters are seen at the longer viewing distance)
- Make sure that the form used to record the logMAR acuities is appropriate for the testing distance (this will be clearly marked on the VPDT Cohort Study approved logMAR acuity form)
- Use chart 1 to test the RE and chart 2 to test the LE
- Place the appropriate correction in the trial frame on the eye to be tested (see above) and ensure that the fellow eye is occluded properly.
- Ask the patient to read steadily line by line.
- The examiner can make reassuring comments but should not tell the patient whether a letter is correctly or incorrectly identified.

- The patient should be encouraged to guess letters and use eccentric fixation. If letters are missed the examiner may point to the row of letters to aid eccentric fixation.
- If less than 20 letters are read at the initial testing distance (2M or 4M) then testing should be repeated at 1 meter with the 1 metre letters scored separately on logMAR acuity recording form.
- In order to accurately test at 1 M a small addition to the sphere is required. If the patient was refracted at 2 M add +0.5 D to correction or if at 4M add +0.75 D.
- If a patient is unable to read any letters on the largest line at 1 meter, vision should be checked with a pinhole to assess whether reduced vision is due, at least in part, to a very large refractive error.
- For the purposes of recording VA, each letter read correctly should be circled.
- Cross out letters incorrectly identified.
- If a patient skips a letter leave this unmarked, though the patient may be encouraged to reattempt the line on which the letters were missed.
- Patients are also encouraged to guess and the examiner should continue the test until a minimum of 4 letters on one row are incorrectly identified.

8 Scoring

Standardised recording forms for the two stage vision testing procedure are provided separately. Versions for initial measurement at 2 metres and 4 metres are available.

- VA should be recorded on the appropriate form as the number of letters read.
- If 20 or more letters are read at the initial 2M or 4M it is not necessary to proceed with testing at 1M. A correction is added to the number of letters read as follows:
  2M test distance: total score = letters read + 15
  4M test distance: total score = letters read + 30
- If fewer than 20 letters are read at the initial 2M or 4M test distance, testing at 1M should be performed. The total score is then calculated as follows:
  total score = letters read at 2M or 4M + letters read at 1M
- If a visual angle is required, the lowest line on which a minimum of 4 letters are correctly identified is entered as the visual acuity.

9 Follow-up

- LogMAR BDVA on presentation should be recorded on each visit
- At each follow-up visit, the refraction recorded at the previous visit may be used as the beginning approximate refraction for each eye. There is no need to perform full refraction protocol. The refraction details should be present on the record of refraction. Simply place the appropriate refraction in the trial frames, refine the sphere and cylinder and proceed with testing. We suggest that optometrists perform the VA testing at every visit. They are more reliable than a nurse.
- Full refraction is required at least every 12 months.

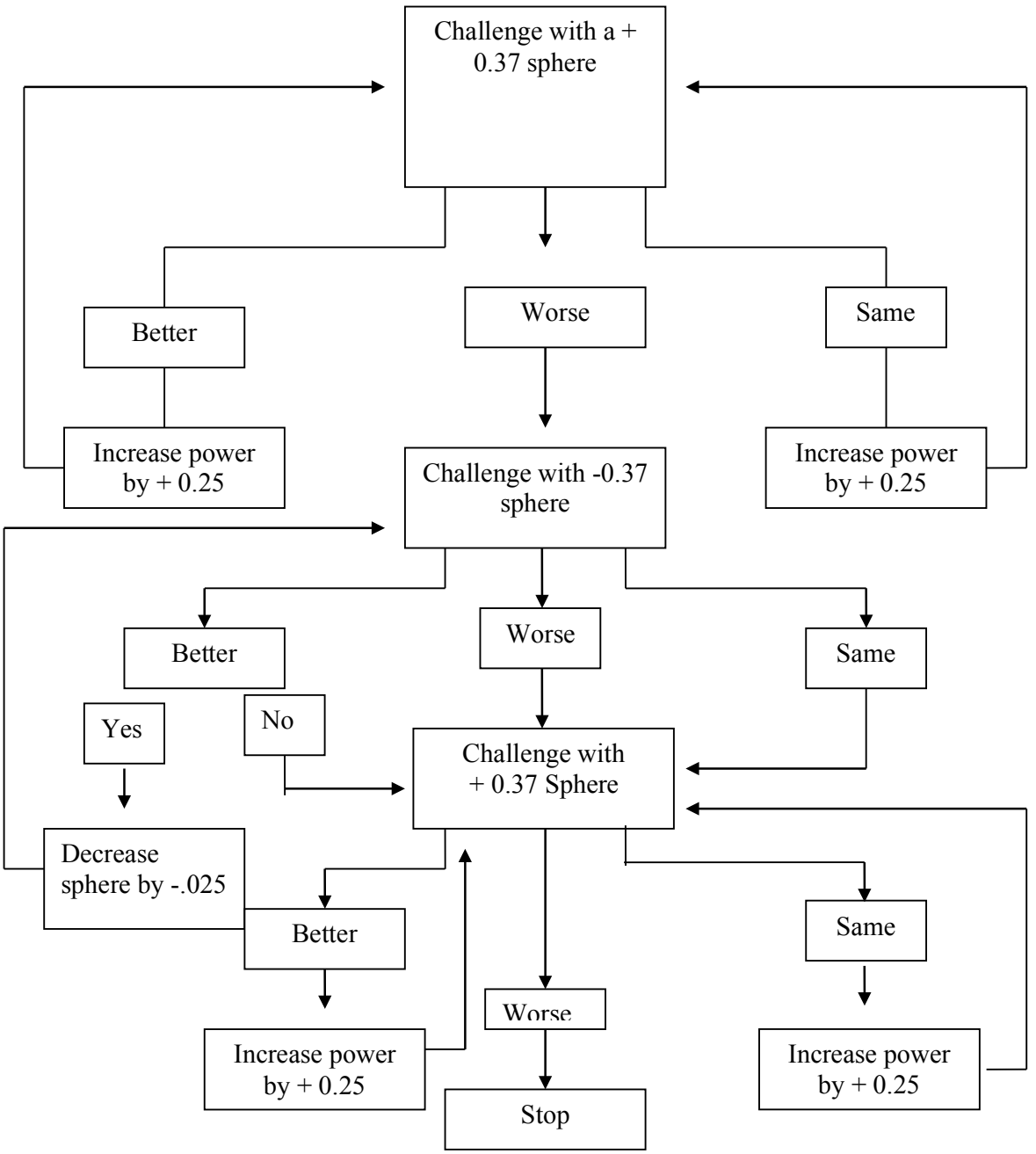
10 Supplier of ETDRS charts

LogMAR ETDRS Charts can be obtained from:

Sussex Vision
16, Winston Business Centre,
Chartwell Road, Lancing,
West Sussex, BN15 8TU

Tel: 01903 851951
Fax: 01903 767732

Schematic showing how to refine the spherical correction during refraction



Appendix 6: Protocol for Pelli-Robson Contrast Sensitivity Assessment

Test Conditions

The Chart.

- There are two charts to be used on each eye separately.
- Each chart has different letter sequences but are otherwise identical.
- The letters on the chart are organised into groups of three (i.e. triplets) there being two per line.
- Within each triplet all letters have the same contrast.
- The contrast decreases from one triplet to the next.
- The division into triplets is indicated on the scoring sheet but not on the chart itself.
- Unlike an acuity chart, in which the difficulty increases from line to line, in the Pelli-Robson chart the difficulty increases in the middle of each line as well.

Mounting the chart.

- The chart should be hung so that the centre of the chart is at the level of the patient's eyes.
- The patient should be seated on a chair that can have the height adjusted or the chart can be moved up or down based on the height of the patient.

Illuminating the chart.

- The chart should be illuminated as uniformly as possible, so that the luminance of the white areas is between 60 to 120 foot candles.
- Measure the illumination in all four corners of the chart to ensure that this is uniform.
- The chart should be used in the same setting for all patients and at every visit i.e. located within a specified area or hung within a illuminated frame.
- Avoid glare.

Supplier of ETDRS charts

Pelli-Robson LogMAR ETDRS Chart Panels can be obtained from:

Clement Clarke International
Edinburgh Way,
Harlow,
Essex
Tel: 01279 414969
Fax: 01279 635232

Contrast Sensitivity Testing

- Test patients before adding drugs to the conjunctival sac.
- Test CS after logMAR visual acuity testing has been completed.
- If the patient was refracted at 2 M add +0.5 D to correction, or if refracted at 4M add +0.75 D.
- The patient must sit one metre from the chart.
- Test the right eye then the left eye.
- The eye not being tested must be covered.
- Test the right eye with the chart V, R and S as the first triplet.
- Test the left eye with the chart that contains H, S and Z as the first triplet.
- The charts should remain hidden from view until the eye is ready for testing.

Recording the patient's performance.

- Complete the header of the record worksheet.
- Ask the patient to name each letter on the chart starting with the dark letters on the upper left-hand corner and reading horizontally across the entire line.
- The lighter letters can take some time to appear so ask the patient to keep looking and not give up too soon
- Do not agree or disagree with the patient. You may encourage the patient to continue to read.
- Circle each letter read correctly and cross out each letter read incorrectly.
- Leave letters not attempted unmarked.
- Test the right eye then the left eye.

Do not let the patient give up too soon. Patients should be made to guess even if they believe the letters are completely invisible. Always allow several seconds for the faintest letters to appear, but do not let the patient give up until he or she has guessed incorrectly 2 of 3 letters in a triplet. The reliability of the results depend on the consistency of the examiner's approach.

Scoring the test. The patient's sensitivity is indicated by the faintest triplet for which 2 of the 3 letters are named correctly. The log contrast sensitivity for this triplet is given by the number on the worksheet nearest to the triplet. Enter this number as the Log Contrast Sensitivity Score.

8. It is customary to take the left member of the pair first, but this is optional.

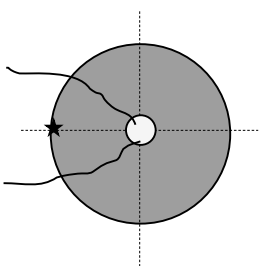
9. To get the maximum stereo effect; first line up and focus on the central image. Then move the joystick left until a crescent of light just appears on the left of the viewfinder. This is the maximum that you are able to move to the left with the dilation achieved. Move back to the right just a little to remove the crescent of light and take the left member of the pair. Repeat this for the right side.

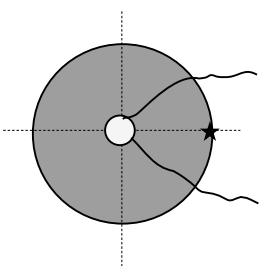
2. Standard Field Colour Fundus Photography

If using analogue systems the recommended film for the procedure is Kodak Professional Ektachrome 100 daylight balanced. This should preferably be processed by any certified “Q-Lab” to ensure consistent quality.

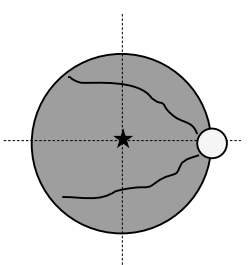
For either digital or analogue capture the following fields are required:-

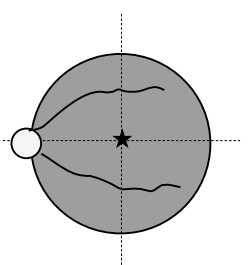
Field 1 - Disc: Centre the optic disc at the intersection of the cross hairs in the ocular.



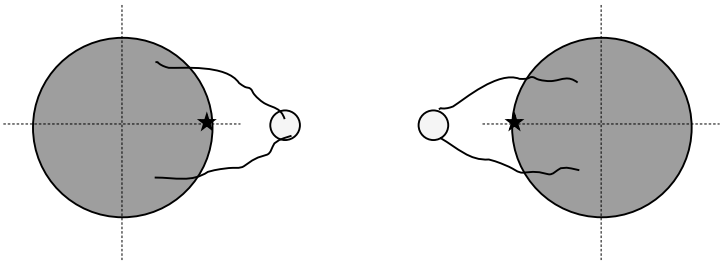


Field 2 - Macula: Centre the macula at the intersection of the cross hairs in the ocular. A suitable position can often be obtained by rotating the camera temporally from the Field 1 position, without vertical adjustment or movement of the fixation device.





Field 3 - Temporal to Macula: Macula at the nasal edge of the field. Again, the position may be achieved by rotating the camera without making any vertical adjustment or movement of the fixation device. However it may be easier to achieve using the internal fixator and then removing it just prior to taking the photograph.



A stereoscopic fundus reflex (FR) photograph should also be taken to document media opacities. To obtain the largest possible FR image the photographer should turn the focusing knob all the way forward and then adjust focus by manually moving the camera closer or further away from the patient.

3. Digital Fluorescein Angiography

For fluorescein angiography only Fields 1 and 2 (F1 & F2) as described above in the colour fundus photography section are required. It is important that good even illumination is used at all times and that the flash settings are kept at the correct levels to ensure this.

The timing for the procedure is as follows: -

1. Before the injection of the fluorescein dye, stereoscopic red-free photographs are taken of Field 2 of both eyes.

2. Position camera on F2 of eye to be treated (index eye) prior to injection. 5ml of fluorescein is injected rapidly (in less than 5secs if possible).

3. THE entire PROCEDURE should be SHOT IN STEREO

Early or Transit Phase

4. The 1st photograph of F2 of the index eye is taken at the start of the injection and the 2nd at the end of the injection. The purpose of this is to document the time taken to inject the dye.

5. 15-30 sec (F2 index eye) : - Take a rapid series of about 10-16 exposures at intervals of about 1 to 2 seconds.

Mid Phase

6. 30 - 45 seconds :- F2 and F1 of the index eye
7. 50 seconds - 1 min :- F2 and F1 of the fellow eye
8. 2 min : - F2 of the index and fellow eye
9. 2½-3 min : - F2 of index eye

Late Phase

10. 5 min : - F2 of index eye and fellow eye
11. 10 min : - F2 of index eye and fellow-eye

Using the appropriate software, the entire angiogram should be copied to a study drive on the system. This is simply a partition of the main hard drive. As these images are a copy of those already on the main hard drive, the patients ID number, and name can be modified to protect their identity before the CD is burned. Only CD-Rs (not CD-RWs, re-writable discs) must be used.

Digital files must include the following information about each patient:

- Centre ID
- Hospital number
- Date of birth
- Date of angiogram

Using CD burning software such as “Easy CD Creator” or “Gear Pro” burn the CD and label it with the patients study ID.

4. Film Fluorescein Angiography

Fluorescein angiography may be captured on film if digital facilities are not available.

- The recommended film is Kodak T-Max or Ilford 400 speed film.
- The film may be processed by clinic staff or at a local processing laboratory.
- The use of Kodak D-11, or similar developer, is recommended.
- Any processing procedure that produces good quality negatives may be used.
- Proper care should be taken to adequately fix the film to insure archival stability.

The timing for analogue fluorescein procedures is the same as for digital.

Although it is customary to take the left member of a stereo pair first, when shooting with film you ***must*** take the right side first.

5. Mounting and Labelling of colour slides

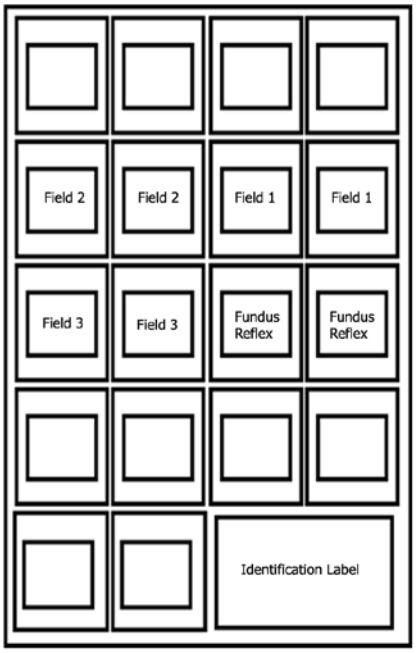
After the slides are returned from the processing lab they must be sorted into their stereo sets and each correctly labelled, with the centre and patient IDs. The labelled slides are then placed into transparent plastic sheets in the correct order for each eye (see diagram below). Use one sheet for each eye. An identification label is completed and attached to the front of each plastic sheet.

- The original negatives are cut into strips of six images per strip and are placed in a transparent plastic sheet with six strips per sheet (see diagram below).
- A page identification label is attached to each page of negatives.
- When cutting the film into strips, the photographer should take care not to separate the members of a stereo pair.
- Clinical centres should retain a copy of the angiogram by making a duplicate of the original negatives.

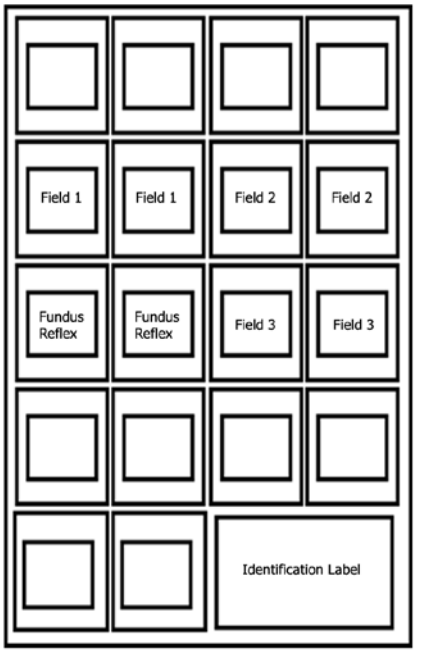
As for digital files, films must include the following information about each patient:

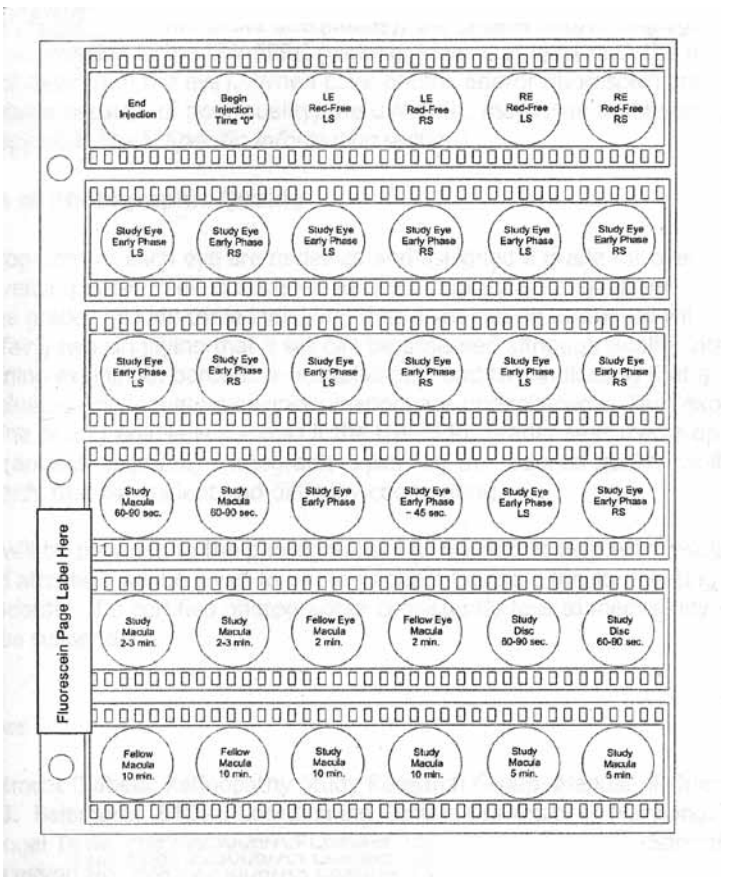
- Centre ID
- Hospital number
- Date of birth
- Date of angiogram

Right Eye



Left Eye





Appendix 8: Submission of angiograms to the Central Angiographic Resource Facility (CARF)

Please contact CARF as soon as your designated provider (DP) site is ready to commence recruitment.

The Data Management Centre (DMC) will have already noted the preferred method for angiogram submission of your DP.

[Practical details of stereo image capture for Colour and Fluorescein angiography are provided in Appendix 7 of the Manual of Operations (pages 65-70)].

Any changes to this MUST be discussed & agreed with the DMC in advance. CARF should also be informed in advance.

As soon as you have been confirmed by the DMC as ready to proceed, CARF will contact the nominated photographer / site coordinator to ascertain a few facts. This interview will be very short and aims simply to establish the best mode of communication with your centre, and to allow CARF team members to familiarize themselves with your specific requirements.

Please do NOT submit any angiograms until this has been accomplished.

Procedures for the Submission of Angiograms:

It is the responsibility of EACH DP to ensure that the details logged for each patient at the first visit remain consistent throughout the study.

Thorough checks of each patient's information must *always* be made prior to submission of any images to CARF.

CARF will accept no responsibility for rectifying any discrepancies that arise from such errors at DP level. This should be done at DP level, & in conjunction with the DMC.

If a DP requires an urgent grading, please contact the CARF Administrator, providing the Hospital Number of the Patient, Date of Angiogram & DP name. CARF will place such requests in an 'URGENT' grading list, addressing each in turn. When the grading process is complete, the CARF Administrator will contact the originating DP with the outcome.

NB: Only in exceptional circumstances will CARF be operational at weekends.

Digital Angiogram Systems:

Photographs captured by digital acquisition systems can be submitted in two formats:
(i) CD-R, or
(ii) On-line

(i) CD-R Submission:

- Only CD-R's will be accepted by CARF.

BRIEF GUIDE TO DIGITAL IMAGE TRANSFER:

1. Select patient using the copy/edit/delete facility
2. Edit patient details: delete name and address.
3. Enter 3 letter site ID in the patient name field
4. Ensure that hospital number and date of birth fields are complete and accurate
5. Copy the angiograms to a CD-R

NB: Step 1 may vary depending upon the acquisition
(Guide is based upon Topcon Imagenet capture systems)

- Each DP should keep an ongoing record of the following details:
  - CD-R number [allocated chronologically, & starting at No.1]
  - Hospital numbers for Patient's held on each CD-R
  - Photographic date range of photographs burned to a CD-R
  - Identity of Person who checked, & verified, CD-R contents
  - Date of Postage to CARF

The *Do's* for Successful Digital Submission:

- **Do** ensure that CD-R's are created and sent in chronological order.
- **Do** use clear writing & permanent markers to identify the CD-R. This should include the DP site ID (3 letters) [the facility to create site-specific ID labels will be included with the preparatory CD issued by the DMC],

CD-R number (in chronological order), photographic date range of photographs burned to a CD-R, date of burning.

- **Do** send the CD-R(s) as close as possible to the capture date, and *definitely* **within two weeks of capture.**

- **Do** send the CD-R(s) (& appropriate documentation) to CARF within 24 hours of being burned.

- **Do** submit a hard copy list of the patient identification numbers stored on the CD-R. Please keep one copy of this log in the DP.

- **Do** use toughened envelopes or bubble-wrap to protect the CD-R(s) when preparing for posting.

- **Do** use the full address of CARF (as shown on page 76). The DP name and site ID should be marked clearly on the back of the envelope(s).

- **Do** notify CARF of CD-R dispatch.

Using transmittal logs, CARF will confirm receipt of the CD-R(s), and will also confirm that images are retrievable, and that all contents are in the appropriate protocol format to be graded.

Any problems will be relayed back to the DP for amendment, and the submission process repeated until ALL problems have been resolved.

(ii) On-Line Submission: **Details to follow.**

Analogue Angiogram Systems:

(i) Film Submission:

- Film received by CARF will be scanned for digital conversion, and posted back to the originating DP.

- Each DP should keep an ongoing record of the following basic details:

    - The hospital number of patient's captured using film format.

    - Transparent plastic sheet identification label details for EACH patient [for BOTH Colour & Fluorescein images in BOTH eyes] (recorded as per photographic protocol: Appendix 7, section 5) [It may be possible to print ID labels from the DMC preparatory CD].

    - Identity of person who checked, and verified, the contents of the transparent plastic sheet.

    - Date of Postage to CARF.

The *Do's* for Successful Film Submission:

- **Do** ensure that slides have been sorted into their stereo pair sets and that each is correctly labelled and positioned inside the transparent plastic sheets, as per study photographic protocol.

- **Do** ensure that each transparent plastic sheet is appropriately labelled.

- **Do** send the transparent plastic sheets (& appropriate documentation) to CARF **within 48 hours** of being processed & mounted, and as close to the capture date as possible (**preferably within one week of date of capture**).

- **Do** submit a hard copy list of the patient identification numbers packaged.
    - Please keep one copy of this log in the DP.

- **Do** insert transparent plastic sheets for postage into the envelope in chronological photographic order (most recent at the top).

- **Do** ensure that ALL transparent plastic sheets for EACH patient [Colour & Fluorescein images for both eyes] are inserted into the envelope in the following order:
  - For EACH patient, the transparent plastic sheets for the Colour images should be placed at the top (Right Eye first), with Fluorescein images underneath (Right Eye first).
  - **Transparent plastic sheets *must not* be folded.**
- **Do** use toughened envelopes or bubble-wrap to protect the transparent plastic sheets when preparing for posting.
  - If large numbers of transparent plastic sheets are to be sent at one time, the use of a small box may be advised (following the same postal safeguards).
- **Do** use the full address of CARF (as shown below). The DP name should be marked clearly on the back of the envelope(s).
- **Do** notify CARF of parcel dispatch.

Using transmittal logs, CARF will confirm receipt of the transparent plastic sheets, and will also confirm that images have been successfully scanned & converted to digital format, and are suitable for grading.

Any problems will be relayed back to the DP for amendment, and the submission process repeated until ALL problems have been resolved.

Notes:

If digital images from a DP need to be retrieved, it will be the responsibility of the originating Treating Centre to ensure that adequate photographic tracking information has been recorded.

It is the responsibility of EACH DP Clinician to ensure that photographers are trained to a standard that will furnish images of the standard required for image grading.

If a Clinician has any concerns about photographer competency, additional photographic training may be available from CARF (for a fee).

If it is found that photographs from a DP consistently do not meet the standards required for grading, the DP will be contacted.

Postage costs **to** CARF will be borne by the originating DP.

CD-R's will be stored at CARF.

CARF will return transparent plastic sheets to the originating DP (postage costs will be borne by CARF).

Central Angiographic Resource Facility Contact Details:

Contact:	Nicola Duff
E-mail:	CARF@qub.ac.uk
Contact Address:	Central Angiographic Resource Facility (CARF) Ophthalmic Research Centre Queen's University of Belfast Royal Victoria Hospital Grosvenor Road Belfast, Northern Ireland BT12 6BJ
Telephone:	028 90 632516
Facsimile:	028 90 632699

Summary: Steps for the Successful Capture and Transfer of Fundus photographs and Angiograms:

Please contact CARF as soon as your site is ready to commence enrolment.

Practical details of stereo image capture for colour and fluorescein angiography are provided in Appendix 7 of the Manual of Operations (pages 65 to 70).

Details of the procedures to be followed for submission of angiograms to the Central Angiographic Resource Facility (CARF) are to be found in Appendix 8 (pages 71-75)

The following steps are a brief guide to the transfer of images captured digitally and step 1 may vary depending upon the acquisition system:

- Select the angiograms to be submitted using the copy/edit/delete facility
- Edit patient details: delete name and address.
- Enter site ID in the patient name field
- Ensure that hospital number and date of birth fields are complete and accurate
- Copy the angiograms to a CD-R
- Label the CD-R with the site ID and the dates spanning the intervals of capture
- Ensure that only the correct side of the CD-R is labelled using a marker pen
- Record postal details
- Email staff at CARF to alert them to CD-R despatch

The following steps are a brief guide to transfer of film angiograms:

- Ensure that colour slides are sorted into their stereo pair sets and that the film strips are properly positioned in their jackets.
- Label the transparent plastic sheet with the 3 letter site ID, patient hospital number and date of birth only.
- Generate a site log showing the 3 letter site ID, hospital numbers and dates of birth for all submitted angiograms and copy to CARF.

CARF study team Contact Details: carf@qub.ac.uk,

Tel: 02890632516 **(Fax**: 028 9063 2699

Appendix 9: Site implementation and training

Background

Nearly a year's experience with the three pilot installations (Liverpool: S Harding, L Gee; Wolverhampton, YC Yang; Newcastle: J Talks) has shown the benefit of a personalised on-site approach to training. In particular, it is now clear that the instructions on the use of the software must be followed up immediately by practical use of the software in the 'live' environment. This might be within the clinic itself, as practised in Liverpool, or after the clinic as in Wolverhampton or a mix of the two as in Newcastle.

In either case, it is now certain that there is considerable value to be gained by supervising the use of the database software and correcting any mistakes or oversights in manipulation as they first arise. The return, in terms of the reduced need for on-line support and recovery, is considerable. With this in mind the following proposal has been drawn up.

Commitment of the Participating Unit

It has proven difficult, with the pilot centres, to obtain a commitment of more than an hour from the ophthalmologists to receive training. This is understandable given the time pressure under which most are operating.

However, it is clear that adequate time must be spent with every person who will be entering data on the system, both clinical and nursing staff. This commitment must include time for instruction and for the input of real locally generated data in addition to test data provided as part of the course material. For each individual this will take between one and a half and two hours in total. Some of this time could include real data entry in the live clinic situation.

Because of the importance of training in the continuance of the project, if any clinic is unable or refuses to commit to the necessary time to train, the software will not be installed at their DP.

Local Project Management Team

In order to smoothly introduce the VPDT Cohort Study into any site, a local project management team will be established to include:

- Lead clinician(s)
  - To advise on clinic set-up and implementation
- Directorate manager or nominated deputy
  - To provide financial and trust authority, staff allocation, etc
- IT lead
  - To provide links with hardware purchasing and software installation, network issues, data transfer
- Data manager
  - A full time post funded within the Cohort Study with responsibility for all data processes including data entry, error checking, queries and liaising with Strategen and LSHTM
- Representative from Strategen (John Fullarton, Scot Buchan, Mark Howland)
- Contact from VPDT Investigators / Data Management Centre (Usha Chakravarthy, Simon Harding, Barney Reeves, Sonia Dhiman, Julia Langham).
- Contact from Digital Healthcare (Rob Stitchbury, Simon Edwards)

The Local Project Management Team should be established prior to site implementation and training with hardware and software issues resolved.

Training Curriculum

Stage 1 – Basic Use of Software

Stage 1 training must cover the following elements:

Software Manipulations

- Familiarity with ACCESS – starting, main sections, closing down
- (For existing pilot centres: familiarisation with the new screen layouts)
- Sequence of data entry, nurse fields and clinician fields
- Manipulation of fields, free text, drop down lists, mandatory fields
- Subsidiary window buttons
- Data display, scrolling keys
- Short cuts

Finding Patients

- Using patient codes, understanding coding practice
- Using search window
- Scrolling records
- Identifying the correct patient
- New patients; existing patients

Entering Visit Data (using fictitious data)

- New patients, existing patients
- Study eye, non-study eye, new study eye
- Correcting data, deleting records
- Signing off, data quality

Sending data

- E-mail links and manipulation
- Record locking

Reports

- Standard reports
- Bespoke reports

These basic training elements will be supported by the User Guide, which will be left with the unit, and the Training manual, which will be used as guidance for the trainer.
It is anticipated that Stage 1 of the training curriculum will take a half day for each DP on-site and involve a further half day for Strategen in the preparation of course materials to ensure smooth implementation on the day.

Stage 2 - Practical Use of Software

The second part of the training will involve the use of the software in entering real data. Most conveniently this could happen on the same day as the training in a routine clinic later in the day. Alternatively it should take place within two or three days. In either case data-entry must be supervised by the trainer on-site.

Option 1 – units intending to use live data capture in clinic

This is the ideal method of data collection but it is recognised that not all DPs will have the necessary IT infrastructure to implement it.

Data entry will be observed in the live clinic environment.
The observations will ensure that:

- Routine software manipulations are carried out correctly (as under Stage 1 above)
- Data capture is accurate – compared to the clinic notes
- Errors/potential errors of manipulation are caught and corrected

Option 2 – units intending to use paper-based data capture
This is the alternative training format, to be implemented where live clinic data capture will not be used.

In this instance, paper based records will be entered under supervision at the end of the basic training session.
The observations will again ensure that:

- Paper-based record keeping is accurate and well-organised
- Routine software manipulations are carried out correctly (as under Stage 1 above)
- Data capture is accurate – compared to the paper record
- Errors/potential errors of manipulation are caught and corrected

In each case, live transmission of data will be carried out at the end of the session.
It is anticipated that Stage 2 of training will involve a further half day for each DP on-site.

Follow up

A member of the local unit will be nominated as the key point of contact for following up the training session (the 'Data Manager'). The hot-line telephone number will be provided to this person in case of immediate need. This individual will be contacted by the training team within 10 days of training (or at least one data transmission after training) to ensure that any residual issues are cleared up.
Additionally a member of the local IT department will be identified as the key contact (IT Lead) for support issues. This person to be present at the time of software installation.

Implementation

It is envisaged that the study will be implemented in established DPs from March to end April 2004. DPs include the following: Belfast, Bristol, Birmingham, Cardiff, Hillingdon, Leeds, Liverpool, Manchester, Moorfields, Newcastle, Sheffield, Southampton, Torbay, Wolverhampton. Invitations will be issued to all established DPs registered on the existing surveillance programme and via the RCOphth website.

This schedule ensures that there will be good early geographical coverage as well as bringing the existing pilot centres on line with the new software as soon as practicable. Roll out will continue throughout the year with the aim of bringing at least 25 sites on board by August 2004 and 40 by December 2004.

Template for Site Visit

Pre visit planning
Invitation Questionnaire completed
Project Planning Team established
Email correspondence to confirm hardware and software capacity
Day 1
Day 2

The details above refer to initial site implementation and training for the Strategen database. For most DPs, the revised database (see 12.3) will not appear dissimilar and training requirements will be identified at time of installation

Appendix 10: Instructions for completing and administering quality of life and resource use questionnaires

The NEIVFQ(25), the SF-36 and the questionnaire with additional items about living circumstances are designed to be self-completed. Some patients will have normal fellow eyes or adequate binocular vision to read the large print questionnaires that have been prepared and will be able to complete their responses themselves. Other patients will be unable to complete the questionnaires themselves. For these patients, an accompanying person can read out the questions and fill in the questionnaires, but they must be told that they should attempt to answer the question on behalf of the patient. Alternatively, a member of staff can administer the questionnaires.

NEIVFQ(25):

Please see instructions at the beginning of the questionnaire.

SF-36:

The following is an extract from the Manual for the SF-36 Health Survey

Introducing the SF-36 Health Survey

- The questionnaire can be introduced with these words: "We are conducting a study to assess the benefits of a new treatment for macular degeneration, called photodynamic therapy. We would like to better understand how you and other persons in this study feel, how well you are able to do your usual activities, and how you rate your own health. To help us better understand these things about you and other persons, please complete this questionnaire about your general health".
- The patient should also be told: "Be sure to read the instructions on the top of the first page. This is not a test and there are no right or wrong answers. Choose the response that best represent the way you feel".
- Respondents must be informed that they should answer these questions by themselves. Spouses, or other family members, or visitors, **should not** assist them in completing the questionnaire*.

Closing

- When the respondents returns the SF-36, check the questionnaire for completeness. If it is not complete, ask the respondent whether he/she had any difficulty completing it and record the reasons for non-completion.

*These instructions relate to people with normal vision completing the SF-36. Spouses, other family members or friends should not answer the questions for the person completing the form, but may read out the questions and help to record the responses.

Dos and Don'ts

Dos	Don'ts
Do have the respondents fill out the questionnaire before they fill out any other health data forms and before they see their physicians (if possible)	Do not discuss respondents' health, health data, or emotions with them before they fill out the questionnaire
Do be warm, friendly, and helpful	Do not force or command respondents to fill out the questionnaire
Do request and encourage respondents to fill out the questionnaire	Do not accept an incomplete questionnaire without first encouraging the respondent to fill out unanswered questions
Do read and repeat a question verbatim for the respondent	Do not interpret or explain a question
Do tell respondents to answer a question based on what they think the question means	Do not force or command respondents to fill out a particular question
Do have respondents fill out the questionnaire by themselves	Do not allow spouses or gamily members to help the respondent fill out the questionnaire
Do encourage the respondents to fill out all questions	Do not minimize the importance of the questionnaire
Do thank respondents for filing out the questionnaire	
Do inform respondents if they will be asked to fill out the same questionnaire again at other clinic visits	

Addressing Problems and Questions

What should I do if the respondent refuses to fill out the SF-36?
If the respondent is able to self-administer the SF-36 but *refuses* to participate, tell the respondent that completion of the questionnaire is voluntary, but that it will provide helpful health-related information. In clinical settings, this will help their physician better understand their health problems. If the respondent still refuses, take back the questionnaire, record the reason for refusal, and thank the respondent.

What if a respondent does not complete the SF-36?
If non completion is a result of the respondent having trouble understanding particular items, ask the respondent to explain why they had difficulty responding to those items. Reread the question for them verbatim, **but do not rephrase the question.** If the respondent is still unable to complete the survey, accept as incomplete, and indicate that the respondent is unable to self-administer the questionnaire, document the reason. If the reason is health related, indicate the specific conditions.

What should I do if the respondent asks for clarification of an item?
While completing the questionnaire, some respondents might ask for clarification of *specific items* so that they can better understand and respond to a question. If this happens, the staff member can assist the respondent by rereading the question for them verbatim. If the

respondent asks what something means, **do not try to explain what the question means**, but suggest that the respondent use his or her own interpretation of the question. **All respondents should answer the questions based on what they think the questions mean.**
If the respondent has trouble with the response choices , it is important to guide him/her to respond in one of the pre-set categories by saying something like: "*I know that it may be hard for you to think this way, but which of these categories most closely expresses what you are thinking or feeling?*"
If the respondent doesn't like a question, or thinks it is unnecessary or inappropriate, emphasize that all questions are in the survey for a reason that is very important to the study. **They should try to answer all of the questions**.
If the respondent has repeated difficulties filling out the questionnaire which you cannot address with the above direction, take back the questionnaire, record the difficulty, and thank the respondent.

What should I do if a respondent wants to know what his/her answers mean?
If a respondent asks for interpretation of their responses or asks for their score on the questionnaire, tell respondents that you are not trained to score or interpret the questionnaire. Emphasize that their answers are to be kept confidential.

What should I do if the respondent is concerned someone will see the answers?
Emphasize that all respondents' **responses to the SF-36 are to be kept confidential**. You are not allowed to read the responses other than to check that all questions are answered.

What should I do if a respondent asks why the SF-36 must be filled out more than once?
Explain that respondents must fill out the same questionnaire at additional visits in order to see if their answers change over time.

Visual Independent Living Questionnaire:

This questionnaire can be introduced with these words:
"Now I would like you to answer some questions about your living circumstances, and some additional questions about problems which involve your vision. Please choose the response that best describes your situation".

Please take as much time as you need to answer each question. All your answers are confidential. In order for this survey to improve our knowledge about vision problems and how they affect your quality of life, your answers must be as accurate as possible.

Resource use questionnaire:

September 2005: Please note that questions 5, 6 and 7 should be answered by all patients for the extended dataset is being collected. There was an error in question 4 of the questionnaire originally distributed to DPs collecting the extended dataset. (This item stated that the person administrating the questionnaire should jump to question 8, if the patient had not visited the hospital for a low vision appointment in the last 3 months.) The database has been amended to allow the answers to these questions to be entered when a patient answers "no" to question 4.

- The questionnaire should be **administered either by a nurse or a health care professional**, by interviewing the patient.
- The patient should be asked each of the 27 questions listed, and **a response should be given for each question and sub-question**, except on **the first screening visit when questions 1 and 2 should be omitted**.
- Where a sub-question is not relevant, rather than leaving it blank it should be stated to be not relevant (NA). e.g. for Q3 if the patient has not used the helpline, then for Q3(b) rather than leaving the question blank NA should be circled. Q28 allows the interviewer to record any additional information that the interviewers considers may be important for estimating or interpreting costs.
- Make sure that the answers for a particular question are **consistent**, e.g. if a patient has said they have visited the GP's surgery during the last three months for reasons related to their eye condition, then make sure that there is tick in the relevant box(es) corresponding to **each visit made**.
- For certain questions it may be necessary to **prompt the patient** and give further information about what to consider when answering the question. For example, Q6 requires the **total time associated** with the visit to be recorded. This requires the patient to consider travel time, waiting time, consultation time etc, and it would be helpful for the interviewer to explain this.
- For **Qq 7** and **11** the interviewer may need to enter additional details to interpret the costs given. For example the mode of transport, cost of parking or use of a travel car or concessionary pass may all determine the cost, so listing them provides important information for estimating the travel costs.
- Note that patients have to consider services use **over the previous three months**. Any appointment, visit, etc. that occurred more than three months ago are not relevant, and should not be included.
- Each question refers to **resource use related to the eye condition**. Unrelated resource use should not be included. There may be instances where the patient is unclear whether the services used were related to the eye condition or not, in such cases the resource use should be included, but it would be helpful if the interview could describe any uncertainty by using the open-ended question at the end of the questionnaire (**Q28**).
- For Question 1, **if the patient is unsure what a fluorescein angiography is**, an explanation should be offered, e.g. angiography is when several photographs are taken of the eye. Similarly for PDT: e.g. PDT is when a doctor shines a laser light in your eye to treat your eye problem. For this question we are only interested in the rare circumstances where a complication is sufficiently serious to cause the treatment to be stopped/the patient admitted to hospital.
- **Q25** is only applicable to patients who are accompanied. The answer "no" should be recorded in part (a) if a spouse, relative or friend accompanies the patient but is not in paid employment. The answer "N/A" should be recorded if the patient is not accompanied. If the answer to **Q25 (a)** is "no" or "N/A", go to **Q27.**
- **Q27** should be used to capture any cost not previously covered. Again only resource use related to the eye condition during the previous three months should be included.

Examples of resource use or costs are: use of residential care, hospital episodes, use of anti-depressants.

- **Q28** should be used to add any points of clarification the interviewer feels would be helpful, e.g. any resource use that has been included but which may not definitely be attributable to the patient's eye condition.
- In month 0, the first two questions from the Resource Use Quesionnaire should be left blank.

Appendix 11: Recommended paper data collection forms and notes about data collection

These forms are available from the Data Management Centre as a pdf file.

Centre code _____ **VPDT DATASHEET** version 2.1

1. Patient details

a. Name ..... b. DOB ___ / ___ / ___ c. Gender M / F

d. Hospital number ..... e. NHS number .....

f. PCT ..... g. Phone number .....

h. Address .....

..... Postcode .....

2. Referral Details – NEW PATIENT ONLY

(all 'screened' patients, irrespective of whether subsequently treated or not)

a. Primary care (optometrist/GP) referral date ___ / ___ / ____ (dd/mm/yy) ☐ tick if approximate

b. Ophthalmologist referral date ___ / ___ / ____ (dd/mm/yy) ☐ tick if approximate

c. Referring hosp:..... First PDT centre:.....

d. Diagnosis at referral (tick one box only)
- ☐ Suspected CNV
- ☐ Predominantly classic CNV
- ☐ Classic CNV
- ☐ Other

e. Smoking history
- ☐ Never
- ☐ Current: Number of years smoked .....yrs
- ☐ Ex-smoker: Number of years smoked .....yrs

Yrs/mths since last smoked .....yrs .....mths

f. Other health-related information
- **Y / N** Cardiovascular disease
- **Y / N** Use of statins
- **Y / N** Family history .....

g. Imaging
- ☐ None ☐ OCT only
- ☐ ICG only ☐ Both

h. Consultant name: ..... i. Consent: ☐ Full ☐ Partial ☐ No

j. Duration of symptoms **R** ..... weeks ..... **L**

k. VA at referral (Snellen) **R** ____ / ____ ____ / ____ **L**

l. Number of previous treatments for CNV (enter 0 if none)
- **R** ..... laser photocoagulation ..... **L**
- **R** ..... PDT ..... **L**
- **R** ..... Intravenous drug injection ..... **L**

m. Cataract surgery (inc date) **R PHA /ECC /NONE** ___ /___/ ___ ___/ ___/ ___ **PHA / ECC / NONE L**

3. Visit details (every visit)

a. Date ___ / ___ / ___ b. Type of visit: ☐ Interim ☐ Scheduled

c. Number of missed appoints since last visit ..... Reason .....

4. Assessment (every visit)

a. Binocular logMAR VA .....

b. Mths since first treated **R** ..... (1.5, 3, 4.5, 6, 9, 12, 15, 18, etc.) ..... **L**

c. LogMAR VA **R** .... **L** ☐ refracted this visit

d. Contrast sensitivity **R** .... **L**

e. Date of VA test: ☐ this visit ☐ = 1 week ago ☐ > 1 week ago, ___/ ___/ ___

f. Angiogram type: ☐ film ☐ digital ☐ SLO

g. Date of angiogram: ☐ this visit ☐ = 1 week ago ☐ > 1 week ago, ___/ ___/ ___

5. Eye status

Tick ONE status only (and related options) for each eye on each visit

RIGHT EYE **LEFT EYE**

a. ☐ **No CNV** ☐

If no CNV **and** VA<65 letters (>0.4 logMAR), please indicate reason for reduced VA:

☐	AMD	☐
☐	Amblyopia	☐
☐	Other	☐

b. ☐ **Ineligible** ☐

Please indicate main reason(s) for being ineligible, and related options:

i. ☐ **Vision below minimum standard** ☐

Delay (weeks) .....

Reasons for delay .....

ii. ☐ **Ineligible because of lesion characteristics** ☐

☐	Minimally classic with occult	☐
☐	Occult / no classic	☐
☐	Lesion too large	☐
☐	Lesion >50% blood	☐

iii. ☐ **Lesion inactive** ☐

☐	No SRF	☐
☐	No blood	☐
☐	No exudates	☐
☐	Lesion fibrosed	☐
☐	Stable vision	☐

iv. ☐ **Other (specify below)** ☐

.....

c. ☐ **Observed** ☐

Reason for observation:

☐	No recent drop in VA	☐
☐	Borderline lesion charact'cs	☐
☐	50% haemorrhage	☐
☐	Bilateral CNV, treat next visit	☐
☐	Other	☐

d. ☐ **Treated at this visit** ☐

e. ☐ **Previously treated but not at this visit** ☐

8. Adverse effects of treatment

Adverse event since last visit: ☐ **Y** ☐ **N**

Adverse reaction during this treatment: ☐ **Y** ☐ **N**

If yes to either, **FILL IN** an **adverse events form**

6. Lesion characteristics

Only required for treated eye at the time of the FIRST treatment

RIGHT EYE **LEFT EYE**

a. **Aetiology** (tick one item only)

☐	AMD	☐
☐	AMD recurrence after laser	☐
☐	Pathological myopia	☐
☐	Juxtapapillary	☐
☐	Angioid streak	☐
☐	Idiopathic	☐
☐	PIC/POHS	☐
☐	Uveitis	☐
☐	RAP	☐
☐	IPCV	☐
☐	Other (specify)	☐

.....

b. **AMD characteristics** (tick one only)

☐	Classic / no occult	☐
☐	Predominantly classic	☐
☐	Minimally classic with no occult	☐
☐	Occult / no classic	☐

Location of lesion (tick one only):

☐	Subfoveal	☐
☐	Juxtafoveal	☐

7. Features of treated eye

a. Required for **ALL VISITS**

b.& c. Only required if treated at this visit

a. **Additional features (tick all that apply)**

☐	Symptomatic drop in VA	☐
☐	Angiographic leakage	☐
☐	Subretinal fluid (any)	☐
☐	Subretinal fluid (at centre)	☐
☐	Cystoid macular oedema	☐
☐	Blood	☐

Fibrosis

..... 1-24%, 25-49%, 50-74%, >75% .....

☐	RPE tear	☐
☐	Chorioretinal anastomosis	☐

b. |__|__|__|__| **GLDµm** |__|__|__|__|

c. **Treatment protocol deviation**

☐	Drug dosage	☐
☐	Infusion rate	☐
☐	Infusion interruption	☐
☐	Delay in light application	☐
☐	Light exposure/laser failure	☐
☐	Other	☐

Next scheduled visit: _____ weeks/months

Ophthalmologist responsible for tx decisions .....

Signature: .....

ADVERSE REACTION AND EVENT FORM

Centre Code_____ Surname_____ Date of Birth__/__/__/

Part 1: Adverse reaction during or just after treatment (Tick and add details if necessary)

Date of Treatment __/__/__/

□ **Back pain during infusion** □ mild □ moderate □ severe

time of onset _____ (minutes since infusion start)

further details_____

□ **Pain at the injection site** further details_____

□ **Extravasations at injection site** further details_____

□ **Other events details** further details_____

Date of onset I___I___I / I___I___I / I___I___I

Date of resolution I___I___I / I___I___I / I___I___I

Reaction attributable to Visudyne treatment? □ definitely; □ probably; □ possibly; □ no (tick one only)

Part 2: Adverse event since last visit

(Tick and add details if necessary)

Date of last treatment __/__/__/

□ **Transient visual loss** Date of onset I___I___I / I___I___I / I___I___I

Date of resolution I___I___I / I___I___I / I___I___I

□ **Loss of ≥ 20 letters** Onset within 7 days of treatment / last visit? Y / N

Was deterioration? Sudden / Gradual

further details_____

□ **RPE tear** further details_____

□ **Haemorrhage** further details_____

□ **Photosensitivity** Date of onset I___I___I / I___I___I / I___I___I

Date of resolution I___I___I / I___I___I / I___I___I

□ **Other** further details_____

Date of onset I___I___I / I___I___I / I___I___I

Date of resolution I___I___I / I___I___I / I___I___I

Event attributable to Visudyne treatment? □ definitely; □ probably; □ possibly; □ no (tick one only)

Ophthalmologist _____ Signature _____

NOTES FOR MAIN DATA COLLECTION SHEET		
Number	**Data item**	**Notes**
1	**Patient details**	
1a	Name	*Self-explanatory*
1b	Date of Birth	*Self-explanatory*
1c	Gender	*Self-explanatory*
1d	Hospital Number	*Self-explanatory*
1e	NHS number	*CHI (Community Health Index) number should be used for Scottish patients.* *We recognise that this number can be difficult for clinicians to obtain, but it should be readily available in the Trust, for example to clerical staff. This number is very important for linking data for patients to the national ONS population register.*
1f	PCT	*Again, we recognise that this can be difficult for clinicians to obtain, but it should be readily available in the Trust, for example to clerical staff. This information is very important for understanding patterns of referral and for reporting to commissioners.*
1g	Phone number	***This is optional.*** *It may be useful for clinicians and other NHS staff to have a record of the patient's phone number on the database for reference.*
1h	Address	*Please pay particular attention to the postcode.*
2	**Referral details**	*Only complete for new patients*
2a	Primary Care Referral Date	*This should be the date when the patient was referred (or first presented) to a primary care health professional (optometrist or GP) with symptoms. The date will not necessarily be documented in correspondence associated with a new referral, especially if a patient has been referred to a designated provider from an ophthalmic department in another acute Trust. If it is not documented,* ***it is very important to ask the patient****.* *The 'approximate' box should be used if the patient cannot remember the exact date. Where the patient self presents to a hospital eye service A&E/casualty department enter this date.*
2b	Ophthalmologist Referral Date	*This should be the date when the patient was referred to the designated provider from an ophthalmic department in another acute Trust, or from another clinic in the designated provider Trust. If a patient has been referred directly to the designated provider from primary care, enter the same date as for 2a. This date should be documented in correspondence associated with a new referral. If it is not documented,* ***it is very important to ask the patient****. The 'approximate' box should be used if the patient cannot remember the exact date.*
2c	Referring Hospital; First PDT Centre	*Write 'Not applicable' for:* • *patients who have not been referred from an ophthalmic department in another acute Trust;* • *patients who have not had PDT before either privately or in an ophthalmic department in another*

		acute Trust; note that treatment in a private clinic should be recorded.
2d	Diagnosis at Referral	*The intention here is to record as best as possible how specific the referral was (other – non-specific; suspected CNV; moderately specific; predominantly classic or classic CNV – most specific), as a surrogate measure of the prevailing expertise of people who are referring to the designated provider. Only one option should be ticked. Actual referral diagnoses may not fall neatly into one or other category but please use your judgement in line with the intention aim of the field described above.*
2e	Smoking History	*Self-explanatory*
2f	Other health related information	*Please circle Y or N for each option*
2g	Imaging	*This field is intended for recording imaging investigations other than fluorescein angiography. Please tick only one box.*
2h	Consultant name	*Self-explanatory*
2i	Consent	*Full consent refers to patients who have agreed to give both clinical and Quality of Life data, whereas Partial consent refers to patients who only agree to give clinical data.*
2j	Duration of symptoms	*Self-explanatory*
2k	VA at referral (Snellen)	*Self-explanatory*
2l	Number of previous treatments for CNV	*Self-explanatory. Please write 0 if the patient has not missed any appointments.*
2m	Cataract surgery	*Please circle either PHACO, ECCO or none. For PHACO and ECCO please record date of surgery.*
3	**Visit details**	*Complete for all visits for all patients*
3a	Date of visit	*Self-explanatory*
3b	Type of visit	*Self-explanatory*
3c	Number of missed appointments & reason(s)	*Self-explanatory*
4	**Assessment**	*Complete for all visits for all patients*
4a	Binocular VA	*To be recorded on every visit, as well as monocular VA.*
4b	Mths since first treated	*For scheduled visits, please enter 'number of months' to indicate how the current visit fits in with the planned follow-up sequence. For interim visits, enter the nearest number of whole months.*
4c	LogMAR VA	*To be recorded on every consultation. For eyes treated on the previous visit, note carefully whether the VA has deteriorated by ≥20 letters; if yes, complete the adverse event form.*
4d	Contrast Sensitivity	*Not applicable if not collecting the extended dataset.*
4e	Date of VA test	*If more than one week ago, please specify date.*
4f	Angiogram type	*Self-explanatory*
4g	Date of angiogram	*If more than one week ago, please specify date.*

5	**Eye status**	*This information is vital. Please tick only one of the 'outer' boxes to indicate the eye status for each eye, then complete the additional information corresponding to each status as indicated below.* ***No CNV** – tick this box if no CNV, even if vision is poor for some other reason;* ***Ineligible** – tick this box if a patient has CNV but is not eligible for treatment (patient would not be expected to be followed up in the PDT clinic);* ***Observed** – tick this box if a patient has CNV, a definitive decision about eligibility cannot be made or treatment is delayed for some reason;* ***Treated** – tick this box if a patient has CNV and is given PDT on the visit being documented;* ***Previously treated** but not at this visit – tick this box if a patient has CNV, has been given PDT previously, but **not** on the visit being documented (e.g.. follow-up visit).*
5a	No CNV, reason for reduced VA	*Tick one reason*
5b	Ineligible	*Tick as many as apply of: (i) vision below minimum standard, (ii) lesion characteristics, (iii) lesion inactive, (iv) other. Within each of these sub-categories, also tick as many of the additional details as apply.*
5c	Observed	*Tick as many as apply.*
5d	Treated at this visit	*See 5 above. If first treatment, please make sure you complete details at 6.*
5e	Previously treated but not at this visit	*See 5 above*
6	**Lesion Characteristics**	*To be completed for the treated eye for all first treatments; complete both 6a and 6b*
6a	Aetiology	*Tick one box only, i.e. main cause of CNV.*
6b	AMD characteristics	*Tick one box only for type of CNV (classic, predominantly classic, etc.) **and** one box to indicate whether subfoveal or juxtafoveal.*
7	**Treatment details**	
7a	Follow up: Additional features	***Complete for all visits**. Tick all that apply. If **Not Applicable** then please indicate by putting a line through the box.*
7b	Follow up: GLDμm	***Only to be completed if treated at this visit**. If **Not Applicable** then please indicate by putting a line through the box.*
7c	Follow up: Treatment protocol deviation	***If treated**, tick all that apply.*
8	**Adverse effects of treatment**	*It is very important to complete a separate adverse events form if **either** an adverse reaction at the time of treatment **or** an adverse event between visits occurs.*
	Next scheduled visit	*Please make sure this is completed. The information is important since it allows to 'look' in the database for*

		another visit at the expected time. It also allows us to check for people who may have died or have been lost to follow-up.
	Ophthalmologist responsible for treatment decisions	*The name of the **ophthalmologist responsible** for the treatment decisions on the visit being recorded must be documented for all visits, not just visits on which patients are treated.*
	Signature	*The **ophthalmologist responsible** must sign the completed form.*

NOTES FOR ADVERSE REACTION / EVENT FORM		
	Centre code	*Please ensure this information is recorded – so that reactions/events can be reliably linked to other clinical information for the same patient*
	Patient's surname	*Please ensure this information is recorded – so that reactions/events can be reliably linked to other clinical information for the same patient*
	Date of birth	*Please ensure this information is recorded – so that reactions/events can be reliably linked to other clinical information for the same patient*
Part 1	**Adverse reaction**	***Complete if a patient experiences an adverse reaction before leaving hospital***
	Back pain during infusion	*Tick the left hand box if patient reports back pain. Based on patient report, classify as mild, moderate or severe. Record how long (in minutes) after the start of the infusion the back pain was reported. Write down any further relevant details*
	Pain at site of injection	*Tick the left hand box if patient reports pain at the site of injection. Write down any further relevant details*
	Extravasation at injection site	*Tick the left hand box if extravasation occurs at the site of injection. Write down any further relevant details*
	Other events	*Tick the left hand box if patient reports any other adverse reaction, or if the doctor attending the patient notices any adverse signs. Write down any further relevant details*
	Adverse reaction attributable to Visudyne treatment?	*For all adverse reactions, the doctor attending the patient must indicate whether the adverse reaction was definitely, probably, possibly, or not attributable to the **visudyne treatment**. Use the text field, details of other of adverse reaction, to attribute an adverse reaction to some other part of the process of having PDT, e.g. reaction to fluorescein, etc.*

Part 2	**Adverse event since last visit**	***Complete if a patient experienced an adverse event between leaving hospital after the previous visit and returning for the current visit. Note carefully whether loss of VA ≥20 letters has occurred. Ask the patient about possible adverse events (i.e. transient visual loss, details of VA loss ≥20 letters, photosensitivity, other events).***
	Transient visual loss	*Ask the patient if he/she noticed a transient loss of vision following the previous visit. If yes, tick the left hand box, and record dates of onset and resolution (to within 1-2 days).*
	Loss of VA ≥20 letters in the treated eye	*Check carefully whether the VA has deteriorated by ≥20 letters in the treated eye. If yes, tick the left hand box, and ask the patient whether the deterioration occurred within one week (yes or no), and whether the deterioration was sudden or gradual (one of these options must be ticked). Write down any further relevant details.*
	RPE tear	*Check whether a RPE tear developed following treatment. If yes, tick the left hand box, and record dates of onset and resolution (to within 1-2 days).*
	Haemorrhage	*Check whether a RPE tear developed following treatment. If yes, tick the left hand box, and write down any further relevant details.*
	Photosensitivity	*Ask the patient whether he/she noticed photosensitivity following treatment. If yes, tick the left hand box, and record dates of onset and resolution (to within 1-2 days).*
	Other	*Ask the patient if he/she has noticed any other vision problem since the previous visit. Tick left hand box if patient reports some other adverse event, or if the doctor attending the patient notices any adverse signs. Write down any further relevant details*
	Adverse event attributable to Visudyne treatment?	*For all adverse events, the doctor attending the patient must indicate whether the adverse reaction was definitely, probably, possibly, or not attributable to the **visudyne treatment**. Use the text field, details of other adverse event, to attribute an adverse event to some other part of the process of having PDT.*