Verteporfin photodynamic therapy for neovascular age-related macular degeneration: cohort study for the UK

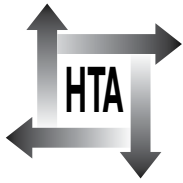BC Reeves, SP Harding, J Langham, R Grieve, K Tomlin, J Walker, C Guerriero, J Carpenter, WP Patton, KA Muldrew, T Peto and U Chakravarthy

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Verteporfin photodynamic therapy for neovascular age-related macular degeneration: cohort study for the UK

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Abstract

Verteporfin photodynamic therapy for neovascular age-related macular degeneration: cohort study for the UK

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Objectives: The verteporfin photodynamic therapy (VPDT) cohort study aimed to answer five questions: (a) Is VPDT in the NHS provided as in randomised trials?; (b) Is 'outcome' the same in the NHS as in randomised trials?; (c) Is 'outcome' the same for patients ineligible for randomised trials?; (d) Is VPDT safe when provided in the NHS?; and (e) How effective and cost-effective is VPDT?

Design: Treatment register.

Setting: All hospitals providing VPDT in the NHS.

Participants: All patients attending VPDT clinics.

Interventions: Infusion of verteporfin followed by infrared laser exposure is called VPDT, and is used to treat neovascular age-related macular degeneration (nAMD). The VPDT cohort study advised clinicians to follow patients every 3 months during treatment or active observation, retreating based on criteria used in the previous commercial 'TAP' (Treatment of Age-related macular degeneration with Photodynamic therapy) trials of VPDT.

Main outcome measures: The primary outcome was logarithm of the minimum angle of resolution monocular best-corrected distance visual acuity (BCVA). Secondary outcomes were adverse reactions and events; morphological changes in treated nAMD (wet) lesions; and for a subset of patients, 6-monthly contrast sensitivity, generic and visual health-related quality of life (HRQoL) and resource use. Treated eyes were classified as eligible for the TAP trials (EFT), ineligible (IFT) or unclassifiable (UNC).

Results: Forty-seven hospitals submitted data for 8323 treated eyes in 7748 patients; 4919 eyes in 4566 patients were treated more than 1 year before the last data submission or had completed treatment. Of 4043 eyes with nAMD in 4043 patients, 1227 were classified as EFT, 1187 as IFT and 1629 as UNC. HRQoL and resource use data were available for about 2000 patients. The mean number of treatments in years 1 and 2 was 2.3 and 0.4 respectively. About 50% of eyes completed treatment within 1 year. BCVA deterioration in year 1 did not differ between eligibility groups. EFT eyes lost 11.6 letters (95% confidence interval 10.1 to 13.0 letters) compared with 9.9 letters in VPDT-treated eyes in the TAP trials. EFT eyes had poorer BCVA at baseline than IFT and UNC eyes. Adverse reactions and events were reported for 1.4% of first visits – less frequently than those reported in the TAP trials. Associations between BCVA in the best-seeing eye with HRQoL and community health and social care resource use showed that the 11-letter difference in BCVA between

VPDT and sham treatment in the TAP trials corresponded to differences in utility of 0.012 and health and social service costs of £60 and £92 in years 1 and 2, respectively. VPDT provided an incremental cost per quality-adjusted life-year (QALY) of £170,000 over 2 years.

Conclusions: VPDT was administered less frequently than in the TAP trials, with less than half of those treated followed up for >1 year in routine clinical practice. Deterioration in BCVA over time in EFT eyes was similar to that in the TAP trials. The similar falls in BCVA after VPDT across the pre-defined TAP eligibility groups do not mean that the treatment is equally effective in these groups because deterioration in BCVA can be influenced by the parameters that determined group membership. Safety was no worse than in the TAP trials. The estimated cost per QALY was similar to the highest previous estimate. Although VPDT is no longer in use as monotherapy for neovascular AMD, its role as adjunctive treatment has not been fully explored. VPDT also has potential as monotherapy in the management of vascular malformations of the retina and choroid and with trials underway in neovascularisation due to myopia and polypoidal choroidopathy.

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Contents

List of abbreviations

AE	adverse event
AMD	age-related macular degeneration
AR	adverse reaction
BCVA	best-corrected monocular distance visual acuity
BSC	best supportive care
CARF	Central Angiographic Resource Facility
CEA	cost-effectiveness analysis
CI	confidence interval
CNV	choroidal neovascularisation
CS	contrast sensitivity
DH	designated hospital
EFT	eligible for TAP trial (as later defined)
EQ-5D	European Quality of Life-5 Dimensions
ETDRS	Early Treatment Diabetic Retinopathy Study
FA	fundus fluorescein angiography
GP	general practitioner
HRQoL	health-related quality of life
HSS	health and social services
HUI3	Health Utilities Index mark 3
IFT	ineligible for TAP trial (as later defined)
IT	information technology
LogMAR	logarithm of the minimum angle of resolution
LSHTM	London School of Hygiene and Tropical Medicine
MCS	mental component score (derived from the SF-36)
MD	macular degeneration
nAMD	neovascular (wet) age-related macular degeneration
NEIVFQ	National Eye Institute Vision Functioning Questionnaire
NetwORC UK	Network of Ophthalmic Reading Centres in the UK
NICE	National Institute for Health and Clinical Excellence (previously National Institute for Clinical Excellence)
PCS	physical component score (derived from the SF-36)
PCT	primary care trust
PIS	patient information sheet
QALY	quality-adjusted life-year
RAP	retinal angiomatous proliferation
RCT	randomised controlled trial
SCG	Specialised Commissioning Group
SD	standard deviation
SF-6D	Short Form questionnaire-6 Dimensions
SF-36	Short Form questionnaire-36 items
SRVF	self-reported visual functioning
TAP	Treatment of Age-related macular degeneration with Photodynamic therapy

UNC	unclassifiable with respect to TAP eligibility (as previously defined)
VEGF	vascular endothelial growth factor
VIP	verteporfin in photodynamic therapy
VPDT	verteporfin photodynamic therapy

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

Executive summary

Introduction

In 2003, the National Institute for Clinical Excellence (NICE; now the National Institute for Health and Clinical Excellence) issued guidance to the NHS for a new, expensive treatment for 'wet' or neovascular age-related macular degeneration (nAMD) called verteporfin photodynamic therapy (VPDT). The guidance recommended treatment for the subtypes of nAMD for which the benefit from VPDT had been observed to be largest in phase 3 licensing trials [the 'TAP' (Treatment of Age-related macular degeneration with Photodynamic therapy) trials] but mandated the collection of robust information on vision, quality of life and the costs of having and treating nAMD for subtypes for which the cost-effectiveness of VPDT was less certain. The VPDT cohort study was set up to provide evidence to inform a future review of VPDT by NICE, to monitor compliance with the NICE guidance and to allow treatment of some subtypes of nAMD in compliance with the 'only-in-research' recommendation of the NICE guidance.

Objectives

The VPDT cohort study aimed to answer the following questions:

(a) Is VPDT in the NHS provided as in randomised trials?
(b) Is 'outcome' the same in the NHS as in randomised trials?
(c) Is 'outcome' the same for patients who would have been ineligible for randomised trials?
(d) Is VPDT safe when provided in the NHS?
(e) How effective and cost-effective is VPDT?

Methods and participants

Study design

Treatment register/longitudinal case series.

Setting and participants

All hospitals providing VPDT in the NHS and all patients attending VPDT clinics, that is including baseline data for patients found to be ineligible for VPDT.

Outcomes

The primary outcome was logarithm of the minimum angle of resolution monocular best-corrected distance visual acuity (BCVA) in the VPDT-treated eye. Secondary outcomes were adverse reactions (ARs) and adverse events (AEs), contrast sensitivity (CS), generic and visual health-related quality of life (HRQoL), resource use and morphological changes in treated nAMD lesions.

Follow-up

The protocol specified that patients should be followed every 3 months during treatment or active observation (a treatment episode) and, at the end of a treatment episode, every 6 months up to 2 years and annually thereafter. Clinicians were advised to base decisions to

retreat on criteria used in the TAP trial. The protocol also specified key data which should be collected [BCVA, fundus colour photography and fundus fluorescein angiography (FA)] at each visit during a treatment episode and at least annually thereafter. CS, HRQoL and resource use data were collected at 6-monthly intervals but only in a subset of hospitals chosen to provide a representative sample of patients. The treatment costs of VPDT were obtained from reference sources.

Grading of neovascular age-related macular degeneration lesions

Colour photographs and FAs were graded by independent, externally accredited personnel within a network of reading centres established for the study. The proportion of classic and occult choroidal neovascularisation (CNV) was measured and lesions were classified into mutually exclusive categories namely predominantly classic, minimally classic or occult no classic. Treated eyes were then classified into one of three categories based on whether or not the treated eye met four key eligibility criteria for the TAP trials (presenting BCVA > 33 and < 74 letters, presence of some classic CNV, total CNV area ≥ 50% of the lesion and CNV under the geometric centre of the foveal avascular zone). Thus, each treated eye was classified as (a) meeting these eligibility criteria ('eligible for TAP'; EFT); (b) not meeting the criteria ('ineligible for TAP'; IFT); or (c) not classifiable owing to the absence of a gradable baseline FA ('unclassifiable'; UNC).

Analyses

Objectives (a)–(d) are descriptive and were addressed by relevant statistical summaries of the data set. Objective (e) required comparisons to be made with untreated patients similar to those treated in the study. We proposed three methods to do this, although only one was possible, namely quantifying the associations between BCVA and HRQoL, and between BCVA and health and social service costs, and combining these associations with information about BCVA benefit from the TAP trials and from the cohort study. Except for objective (d), for which all treated patients were included, the main analyses included only one treated eye per patient for patients with CNV from nAMD who had > 1 year of follow-up or who had completed their treatment.

Results

Data were submitted by 47 participating hospitals for a total of 8323 treated eyes in 7748 patients. Key missing data (e.g. baseline BCVA, no follow-up data) reduced these numbers to 6647 eyes in 6223 patients. Only eyes which were treated > 350 days (1 year) before the most recent data submission, or which had completed treatment, were analysed; 4919 eyes in 4566 patients met this criterion. The number of eyes classified against eligibility for the TAP trial were 1227 EFT, 1187 IFT and 1629 UNC. Responses to at least one HRQoL and resource use questionnaire were submitted for about 2000 patients (the number varied by questionnaire).

(a) Is verteporfin photodynamic therapy in the NHS provided as in randomised trials?

The percentages of treated eyes receiving one, two, three or more than three treatments in year 1 was 25%, 34%, 25% and 16%, falling to 18%, 7%, 2% and 1%, respectively in year 2. The mean number of treatments in years 1 and 2 was 2.3 and 0.4 much lower than in the 'TAP' phase 3 trial on which NICE guidance was mainly based. About 50% of patients had completed their treatment by the end of year 1. Follow-up was incomplete because hospitals discharged patients owing to the introduction of local policies that limited the number of outpatient reviews. Therefore, analyses of outcomes at 1 year (for comparison with 1-year outcomes in the TAP trial) required complex statistical modelling to take into account the missing follow-up data and to allow comparison with 1-year outcomes in the TAP trial.

(b) Is 'outcome' the same in the NHS as in randomised trials?

Analyses of BCVA outcome at 1 year found no difference in the rate at which vision was lost in patients in the different eligibility groups. Patients in the EFT group lost 11.6 letters (95% confidence interval 10.1 to 13.0 letters) by 1 year compared with 9.9 letters in the TAP trial subgroup.

(c) Is 'outcome' the same for patients who would have been ineligible for the TAP trial?

Given that there was no difference in the rate at which vision was lost in the different eligibility groups, patients in the IFT and UNC groups also lost 11.6 letters by 1 year. Note that this does not mean that VPDT is equally effective in these other groups, as the study had no data for the rate of deterioration in BCVA over time without VPDT, which may differ by eligibility group. After adjusting for covariates, patients in the EFT group had, on average, poorer BCVA at baseline (a difference of just over two letters) than patients in the IFT and UNC groups.

(d) Is VPDT safe when provided in the NHS?

Frequencies of ARs (immediately following treatment) and AEs (recorded at the subsequent visit, covering the interval between visits) decreased dramatically after the first treatment visit, either because local investigators did not record adverse effects of the same kind on repeat visits or because adverse effects deterred patients or their ophthalmologists from continuing treatment. ARs were reported on 1.4% of first visits and AEs following 1.9% of first visits; these frequencies were lower than those reported for patients treated with VPDT in the TAP trial.

(e) How effective and cost-effective is verteporfin photodynamic therapy?

Associations between the best BCVA in either eye with (i) HRQoL and (ii) health and social care resource use in the community were estimated from data for visits for which BCVA and HRQoL data were available. These associations allowed the 11-letter difference in BCVA between VPDT and sham treatment in the TAP trial to be 'translated' into a utility difference of 0.012 and into a health and social service resource use difference equivalent to £60 in year 1 and £92 in year 2. The cost-effectiveness of VPDT was estimated on the basis of these quality-adjusted life-years (QALYs) and community cost differences derived for the TAP trial and the costs of the lower frequency of treatment observed in the cohort study, giving an incremental cost per QALY over 2 years' treatment of £170,000.

Comment and conclusions

The main findings were that (i) VPDT was administered much less frequently in routine clinical practice than in the TAP trial; (ii) in routine clinical practice, patients were followed much less frequently than in the research setting of the TAP trial, with attendance tending to stop once BCVA had dropped; (iii) for the EFT group, deterioration in BCVA over time was similar to that in the TAP trial; (iv) there was no evidence that safety was worse than in the TAP trial; and (v) the estimated cost per QALY was similar to the highest previous estimate.

The main limitation was the exclusion and early loss to follow-up of some patients, who are likely to have been those with a worse than average outcome; this limitation would have led treatment frequency to be overestimated and deterioration in BCVA and cost per QALY to be underestimated.

A number of observations on the introduction of this technology into routine clinical practice can be made: (i) there was wide variation in the readiness of centres to follow a proscribed protocol including follow-up; (ii) there was variable engagement by centres with the collection

of data, with improvement in data quality occurring over time only at centres with highly committed research-focused staff; (iii) provider organisations had varying degrees of difficulty in establishing and maintaining consistent provision to the service specification required by the national commissioning and professional bodies.

Implications for practice

Implications for practice do not relate to the use of VPDT to treat nAMD because VPDT has now been superseded by the introduction of new treatments.

- The small number of treatments administered suggests that treatment regimens receiving marketing authorisation may overestimate the intensity of treatment required. This is potentially an important consideration in relation to other new health technologies.
- This limitation of loss to follow-up should be carefully considered in the design of similar studies for interventions requiring treatment or follow-up over many months, especially if the effectiveness of an intervention is not dramatic.
- Use of VPDT should be limited to (a) circumstances in which newer technologies are contraindicated or refused by patients or (b) categories of age-related macular degeneration such as polypoidal choroidopathy or other diseases with neovascularisation arising from the choroid.
- Appraisal of a technology that benefits one eye should evaluate the benefit at the level of a person, not an eye.
- The consequences of the shallow gradients of relationships (a) between BCVA and European Quality of Life-5 Dimensions utility and (b) between BCVA and health and social services resource use/cost need to be considered carefully when appraising other technologies to treat eye diseases that impair vision.

Research recommendations

Similarly, our research recommendations are outside the context of nAMD:

- Further studies are required to investigate the effectiveness and cost-effectiveness of VPDT for neovascularisation due to myopia, inflammation and other choroidal diseases including central serous chorioretinopathy.
- Modification of the effectiveness of new interventions for nAMD by covariates found to influence effectiveness in this study should be studied.
- The relationships between BCVA and HRQoL/health and social services resource use are important for modelling cost-effectiveness. Further research should investigate how widely these relationships can be applied, for example to other diseases that reduce BCVA.

Conclusions

The VPDT cohort study model was successful in establishing a network of research expertise, expanding research capacity, engaging professional bodies and developing purchaser–provider relationships around research and development. It formed a structure for the managed introduction of the technology including the necessary training and service specification development. The success of the model was limited by the freedom of providers to divert investment into other services and to revise care pathways. Improvements in models of the introduction of costly new technology into the NHS are recommended.

Chapter 1

Introduction

Background and rationale

Macular degeneration (MD) is the commonest cause of visual impairment in the developed world.[1,2] It mainly affects central vision, which underpins the ability to do tasks that require fine detail to be resolved, for example reading, watching television and recognising faces. The commonest cause of MD is ageing, although there are many other less frequent causes. Age-related MD (AMD) causes visual loss principally through the development of new vessels, which form in the choroid under the retina and leak fluid, bleed and eventually fibrose (choroidal neovascularisation, CNV). A less frequent site for the development of new vessels is in the retina itself, and this is termed retinal angiomatous proliferation (RAP). The process of neovascularisation is often referred to as 'wet' or neovascular AMD (nAMD) to distinguish it from a less aggressive or 'dry' form. CNV is identified and categorised using fundus fluorescein angiography (FA) into 'classic' and 'occult' forms based on patterns of fluorescence and location under the retina. RAP is identifiable using FA but more readily using indocyanine green angiography. At the onset of nAMD, a progressive fall in vision in the affected eye generally occurs over weeks and months and is more rapid with classic than occult CNV.

Verteporfin is a light-sensitive drug which is used in combination with an infrared laser to treat abnormal blood vessels proliferating under or within the macular retina in patients with nAMD and, less frequently, in some other eye conditions. The drug is injected intravenously and binds selectively to endothelial cells in the abnormal retinal vessels. The drug is activated by low-energy laser radiation, causing the abnormal vessels to regress. These two steps, that is initial infusion of verteporfin followed by laser exposure, are known as verteporfin photodynamic therapy (VPDT). Over time the vessels frequently reopen and so treatment usually needs to be repeated 3-monthly.

Verteporfin photodynamic therapy has been shown in randomised clinical trials to be better than sham treatment in maintaining sight in patients with nAMD. In the clinical trials of VPDT carried out for licensing, the Treatment of Age-related macular degeneration with Photodynamic therapy (TAP) trials and the Verteporfin in Photodynamic therapy (VIP) trials,[3–5] the overall difference between treatment and placebo groups was small except in a subgroup of patients in whom ≥ 50% of the area of CNV was classified as classic by FA; in this subgroup, the benefit was larger.[4]

There are no established criteria for stopping a course of treatment. The treatment protocol used in the TAP trials required 3-monthly reviews of FA for 2 years with retreatment if active CNV was observed.[3]

The cost of a course of therapy has been estimated to be between £6000 and £8000. This relatively high cost arises largely because of the frequency of retreatment episodes in research cohorts. Cost-effectiveness was not estimated alongside the clinical trials used for licensing. In 2003, the National Institute for Clinical Excellence (NICE; now the National Institute for Health and Clinical Excellence) recommended treatment in the UK NHS for patients with nAMD 'who have a confirmed diagnosis of classic with no occult subfoveal choroidal neovascularisation'.[6] However, NICE did not recommend VPDT for people with predominantly classic CNV 'except as part of

on-going 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' (*Box 1*).[6]

Uncertainties about the effectiveness of VPDT were highlighted by the NICE technology appraisal.[6] Around the time of publication of the NICE guidance, the NHS R&D Health Technology Assessment programme, on behalf of the Department of Health, approached potential investigators about carrying out further research on VPDT to address these uncertainties. The overall aim was to characterise the cohort of patients referred for and treated with VPDT and to collect data about their visual acuity outcomes, quality of life and use of health and social care resources.

Initially, it was envisaged that this research should focus on the group of patients referred to in paragraph 1.2 of the NICE guidance (see *Box 1*), that is patients with 'predominantly classic' CNV lesions. However, discussions with the regional NHS commissioners and the Royal College of Ophthalmologists led to the scope of the research being expanded to include all patients treated with VPDT, irrespective of the subtype of the CNV. The VPDT cohort study was set up to meet these objectives. It built on surveillance programmes and research proposals active at the time and allowed patients with nAMD to access VPDT through the NHS.

The VPDT cohort study investigators aimed to address a number of questions which were relevant to NICE and to the NHS which were unanswered at the time of its guidance in 2003. These are set out in *Chapter 2*. However, the study was also of interest to other stakeholders, for example commissioners of NHS care. There is a need to develop robust methods of managing the introduction of new technologies into the NHS, especially when these are expensive, and the VPDT cohort study is one model by which this might be achieved. At the outset, there was the ambition that establishing a treatment register would allow a new technology (in this case, VPDT) to be introduced to a pre-specified service standard ensuring best possible care for patients, its use to be monitored effectively by commissioners and uncommon/rare adverse events (AEs) not identified in pre-licensing trials to be detected. A further benefit might be training clinical sites in research methods and processes to facilitate future clinical trials and research relevant to the NHS.

BOX 1 Extract from NICE guidance to the NHS on VPDT[6]

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) (that is, whose lesions are composed of classic CNV with no evidence of an occult component) and best-corrected visual acuity 6/60 or better. VPDT should be carried out only by retinal specialists 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 on-going 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 VPDT 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.

Visual acuity and health-related quality of life

A limitation of many randomised controlled trials (RCTs) of ophthalmological interventions is that the researchers conventionally choose best-corrected monocular distance visual acuity (BCVA) as the primary outcome. Reporting the effect of a new treatment as the average BCVA benefit relative to a control group allows ophthalmologists to consider the probable value of the new treatment compared with the best existing treatment (or alternative treatments) for the same condition. However, the limitations of clinical measures of outcome are now widely appreciated and many governmental and non-governmental organisations emphasise the importance of patient-reported outcomes or health-related quality of life (HRQoL) for measuring treatment effectiveness and health-care performance.[7,8] Moreover, the benefits of ophthalmic interventions are difficult to compare with other health-care interventions without being able to describe them in a common currency, for example quality-adjusted life-years (QALYs, see below and *The health and social service costs of nAMD and associated treatments*).[9]

Health-related quality of life is a complex concept. A spectrum of instruments have been designed to measure HRQoL, from ones focused closely on functional performance to those assessing broader domains and rating the importance to an individual patient of a perceived loss of physical, social or emotional function.[10] This spectrum can be investigated specifically with respect to the condition affecting a respondent (condition-specific instruments) or to his or her wider life experience (generic instruments). The National Eye Institute Visual Function Questionnaire (NEIVFQ), which lies towards the functional performance end of the HRQoL spectrum, is perhaps the most widely used vision-specific HRQoL instrument.[11]

A subset of generic HRQoL instruments explicitly recognises underlying preferences for different health states. These preference-based measures, such as the European Quality of Life-5 Dimensions (EQ-5D) and the Short Form questionnaire-6 Dimensions (SF-6D),[12,13] report HRQoL on a scale with 'anchors' at 0 for death and 1 for perfect health. Preference-based measures of HRQoL are important because they can be combined with the relative effects of interventions on life expectancy to report QALYs.[9] QALYs allow comparison of interventions that may improve HRQoL but not life expectancy (such as many ophthalmic interventions) with interventions in other disease areas that can improve life expectancy but have little effect on HRQoL (e.g. statins to prevent coronary heart disease). Such comparisons, using HRQoL measures that take preference weights (i.e. societal values) or utilities from the general population,[14,15] underpin health policy in many publicly funded health systems. They enable policy-makers to decide the relative worth of a new treatment in a wider context, that is compared with the value of health-care treatments for all other conditions that compete for funding from a finite budget.

Many studies have examined cross-sectional associations between visual acuity and HRQoL using a variety of HRQoL instruments including preference-based measures.[16,17] However, few have examined these associations longitudinally. Also, several studies that have reported preference-based measures of HRQoL have reported utilities elicited directly from patients[18] rather than by the recommended process of taking these preferences from the general population.[14,15] Previous studies that have attempted to use preference-based measures of HRQoL to assess the gains from ophthalmic interventions for policy-making purposes have highlighted the deficiencies in existing studies.[19]

The VPDT cohort study collected clinical measures of vision, measures of HRQoL and measures of resource use to achieve its principal aims of estimating the effectiveness and cost-effectiveness

of VPDT in routine clinical practice.[20,21] Understanding the relationships between visual function and vision-specific and generic HRQoL was central to achieving these aims.[22]

The health and social service costs of neovascular (wet) age-related macular degeneration and associated treatments

Neovascular AMD is potentially associated with high costs to health services and society.[23–25] Interventions for nAMD may improve HRQoL and reduce the costs associated with declining vision.[26] Cost-effectiveness analysis (CEA) is a powerful tool to evaluate and prioritise health-care interventions according to their relative effectiveness and cost. In many publicly funded health systems, policy-makers require CEA to assess whether or not a new intervention has sufficient gain to justify additional costs before recommending adoption. Decision-makers in predominantly privately funded health systems have recently shown interest in using CEA.[27]

Previous CEAs of VPDT for nAMD have been contradictory. Some studies have reported that VPDT is 'highly cost-effective' and others that it is 'definitely not cost-effective'.[26,28] For CEAs to provide a sound basis for decision-making, they must meet certain methodological standards.[15,29] The previous CEA of VPDT did not meet these standards on three grounds.[19] Firstly, intervention costs were based on treatment frequencies reported in the TAP trial, which are higher than those for routine practice.[3,20,30] Secondly, the HRQoL measures used took inappropriate preference weightings from patients with nAMD rather than generic measures such as the SF-6D that take health-state preferences from the general population.[19,31] Because CEAs are used to compare health gain across disease areas, the HRQoL measures used should weight different health states according to valuations taken from the general population rather than any specific patient group, for example patients with AMD. Thirdly, costing studies have reported that, compared with the general population, patients with AMD are more likely to use residential care and social services and to take antidepressants.[32,33] However, previous CEAs either ignored costs associated with vision loss or relied on expert opinion, rather than collecting appropriate patient-level costs.[19,26,32,33] The VPDT cohort study was commissioned to address some of these limitations.

Chapter 2

Aims and objectives

The overarching aim of the VPDT cohort study was to broaden the understanding of the pathogenesis of CNV and its treatment with VPDT through a longitudinal analysis of outcomes in patients undergoing VPDT for CNV.

The a priori objectives of the study were set out in the manual of operations (see *Appendix 1*). These were:

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

During the first year of the project and following review of progress by the Health Technology Assessment programme, but before any analyses of data collected in the study, these objectives were updated to characterise better the uncertainties experienced by the NICE appraisal committee:

(a) Is VPDT in the NHS provided as in randomised trials?
(b) Is 'outcome' the same in the NHS as in randomised trials?
(c) Is 'outcome' the same for patients who would have been ineligible for randomised trials?
(d) Is VPDT safe when provided in the NHS?
(e) How effective and cost-effective is VPDT?

These objectives will be referred to in sequence in the rest of the report.

Chapter 3

Methods

Study design

The VPDT cohort study was designed as a longitudinal treatment register (case series) of all patients treated with VPDT in the UK. The study received research ethics committee approval (reference MREC/03/11/103).

The manual of operations, describing the study design and methods, including standard protocols for all measurements, was prepared before recruitment started and was updated periodically. The final version of this manual (version 2.1, December 2005) is included as *Appendix 1*.

Setting

When the VPDT cohort study was conceived, VPDT was not widely used in the NHS. Local Specialised Commissioning Groups (SCGs) recommended that VPDT should be provided only in designated ophthalmology departments in NHS hospitals. The Royal College of Ophthalmologists and clinicians involved with the VPDT cohort study took responsibility for providing a training programme for ophthalmologists and other health-care staff in hospitals that were newly implementing the provision of VPDT. Thus, the setting for the study was all designated hospitals (DHs) providing VPDT in the NHS.

After the majority of DHs had been identified and their personnel had been trained, the study team organised meetings of investigators. These meetings described progress with the study, discussed aspects of compliance with the study protocol, data submission and quality, and provided additional training. This training covered:

- for participating ophthalmologists, retreatment decision-making and interpretation of angiograms
- for independent grading for ophthalmic photographers and technicians, acquisition of angiograms and their subsequent submission to the Network of Ophthalmic Reading Centres in the UK (NetwORC UK, see *Network of Ophthalmic Reading Centres in the UK*)
- for nurses, optometrists and site co-ordinators, assessment of visual and other study procedures.

Participants

The manual of operations described the criteria for eligibility for treatment according to the NICE guidance:

- 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 one or more letters on the line corresponding to a logarithm of the minimum angle or resolution (logMAR) of 1.0, or > 30

letters when measured with an Early Treatment Diabetic Retinopathy Study (ETDRS) distance visual acuity chart (see *Outcomes*).

■ Choroidal neovascularisation must be wholly or predominantly classic (i.e. ≥ 50% of the entire lesion must consist of classic CNV).

■ Patients with subfoveal CNV due to nAMD or any other disorder are eligible for inclusion in the VPDT study.

All patients referred for assessment at a VPDT clinic in a designated treatment centre, whether eligible or not, made up the reference population. As part of the assessment, the ophthalmologist in charge of the patient made a decision on eligibility for treatment (above). There were no a priori exclusion criteria for people in the reference population. Participating hospitals were asked to submit a full set of data at the screening visit for all ineligible patients seen in person at the VPDT clinic, together with the FA used for decision-making, irrespective of whether the FA was carried out by the participating centre or by a referring hospital.

The study population consisted of all patients treated with VPDT at participating centres irrespective of CNV aetiology. (The decision whether or not to include all patients treated with VPDT, irrespective of aetiology, was made by the SCGs.) Participants were asked to give written informed consent for the collection of data and use of these data for the research.

Treatment with verteporfin photodynamic therapy

Participating centres were requested to classify CNV as had been done in previous RCTs[3,5,34] in order to decide whether or not patients were eligible for treatment (*Table 1*).

Participating centres were also requested to review patients at 3-month intervals, carrying out ophthalmological and angiographic examinations to determine whether or not repeat therapy was needed. Two algorithms to guide retreatment decisions were included in the study manual (*Figure 1* and *Table 2*). Investigators were also referred to the retreatment criteria developed by an international expert consensus group, the Verteporfin Round Table.[37]

Outcomes

The primary outcome was defined as BCVA, measured on a logMAR scale using the ETDRS distance visual acuity chart.[38]

Secondary outcomes included:

(a) safety, that is adverse reactions (ARs) and AEs
(b) contrast sensitivity (CS) measured with the Pelli–Robson chart at 1 m[39]
(c) generic HRQoL measured using the Short Form questionnaire-36 items (SF-36),[40] from which SF-6D scores were also derived[13]
(d) vision-specific HRQoL measured using the NEIVFQ[11]
(e) independently graded morphological changes in treated lesions, that is total lesion size, total CNV leakage, classic leakage and fibrosis
(f) health and social services (HSS) resource use measured using a custom-designed questionnaire administered to patients at the time of hospital visits for treatment or review.

Collecting data to characterise ARs and AEs was an important objective of the study because, at the outset, there was concern that such events experienced in licensing trials of VPDT may not

TABLE 1 Method for determining the category of CNV from stereoscopic FAs to help in the assessment of suitability of patients for treatment with VPDT according to the NICE recommendations issued in 2003[6]

A. Identify morphological features *Use stereos of colour and angiographic frames to assist in recognition of the following lesion components*	B. Assess total lesion size	C. Categorise lesion subtype
1. *CNV lesion components* Fluorescein leakage associated with CNV ■ Classic CNV ■ Occult CNV: fibrovascular PED; late leakage of undetermined origin Features contiguous to CNV which prevent determination of the extent of leakage and which therefore constitute part of the lesion ■ Blood ■ Elevated blocked fluorescence not due to blood (may be due to RPE hyperplasia, thick exudate, fibrous tissue) ■ Serous PED 2. *Other features associated with CNV which are NOT used to define the boundaries of the lesion* ■ Atrophy: GA and non-GA ■ Flat blocked fluorescence ■ Fibrosis not contiguous to CNV boundary ■ Thick exudate not contiguous to CNV boundary 3. *Other features which help with categorisation of CNV or which may modify natural history* ■ Retinal angiomatous proliferation ■ Chorioretinal anastamoses ■ Idiopathic polypoidal choroidopathy	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 photodynamic therapy if < 50% of lesion is CNV	1. Classic with no occult (NICE FAD 1.1) 1A. Classic leakage accounts for 100% of lesion 1B. Classic leakage accounts for 50–99%, but lesion has no occult component 2. Predominantly classic with occult (NICE FAD 1.2) Classic leakage accounts for 50–99% of lesion with some occult 3. Minimally classic Classic leakage accounts for < 50% of the lesion 4. Occult with no classic Classic is 0%. Any CNV leakage is of the occult variety

GA, geographic atrophy; PED, pigment epithelial detachment; RPE, retinal pigment epithelium.
The decision tree describes terminology from grading centres involved in TAP, VIP and Subfoveal Radiotherapy Study RCTs.[3,35,36]
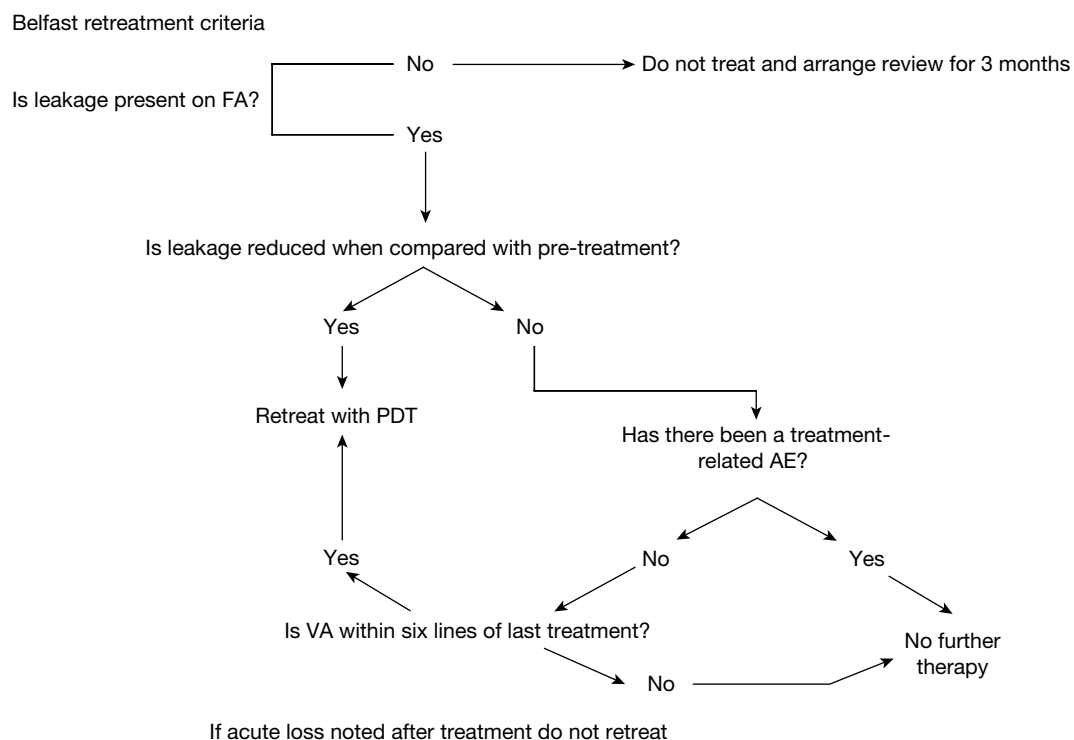
FIGURE 1 Example of flow chart for making retreatment decisions – Belfast retreatment criteria. VA, visual activity.

TABLE 2 Example of flow chart for making retreatment decisions – Liverpool retreatment criteria

Parameter	Retreat	Do not retreat
FA	Leakage	No leakage/no leakage at centre
Visual acuity	Dropping	Stable or < 20 letters
Subretinal fluid	Persistent	Cleared
Haemorrhage	New	Cleared
CNV	Extension	Inactive
Next visit	3 months	≥ 9 months[a]

a   This visit interval was recommended at Liverpool prior to the start of the VPDT cohort study. The schedule of data collection (see *Table 3*) took precedence in the study; this required 3-monthly visits when a patient was being actively treated or received.

be representative of the events observed in usual practice. The manual of operations specified that all ARs (during or just after treatment) or AEs (between treatment visits) should be recorded in the database. Any AR or AE considered to be *serious* and *possibly, probably* or *definitely* associated with treatment had to be reported to the Data Management Centre within 24 hours in accordance with good clinical practice in clinical research.

Other predictors of visual function

Data were collected at baseline to characterise study participants. The data included variables that were considered important for describing the study population and potential predictors of BCVA that might confound associations investigated in the analyses:

- age
- gender
- baseline BCVA and CS
- CNV composition, that is lesion area and proportion of the lesion graded as classic and occult CNV.

The collection of additional potential predictors of visual function was instituted after the study started to recruit (see *Chapter 4, Collection of additional predictors of visual function*).

Network of Ophthalmic Reading Centres in the UK

The baseline morphological characteristics of CNV lesions were defined in the protocol as potentially important covariates/confounding factors (see *Other predictors of visual function*) with respect to the primary outcome of visual acuity (see *Outcomes*). For example, classic compared with occult CNV is associated with more rapid loss of vision but greater responsiveness to treatment.[4] Changes in the morphological characteristics of CNV lesions over time, with or without treatment, were also defined as secondary outcomes (see *Outcomes*).

Considerable training is required to distinguish the various components of CNV lesions reliably, and, although the training put in place by the Royal College of Ophthalmologists and the research team included a session on lesion composition, this was not considered sufficient for research purposes. When designing the study, the research team was concerned that judgements about CNV composition made by the ophthalmologists treating patients might be unreliable and potentially biased. Unreliable judgements about CNV composition would have biased observed

associations to the null. More importantly, given that the study was to some degree the means by which patients with predominantly classic CNV lesions could access treatment, there was a possibility that ophthalmologists might tend to overdiagnose the presence of classic CNV in order to classify patients as eligible.

The research context was also important. The TAP trials that were reporting at the time the study was being designed had taken great care to assure the quality of photographic images and the grading of these images. All photographers were accredited at the outset and reaccredited annually. All photographic images (colour fundus and FA) were submitted to a central reading centre for independent grading.[3] The VPDT cohort study research team wanted to establish the same standards to ensure that the results of the study were credible.

Therefore, NetwORC UK was established with the capacity to carry out independent grading of, potentially, > 5000 angiograms per year. Three geographically distinct centres, in Belfast, London and Liverpool, with facilities to grade stereoscopic fundus colour images and FAs were combined into a single network with a management facility in Belfast (Central Angiographic Resource Facility; CARF) to co-ordinate the administrative and technical issues. CARF managed the collection and archiving of images from designated VPDT treatment centres, performed consistency checks, certification and training of photographers, and transmitted images electronically to the three reading centres using a customised software platform. Regular training and concordance exercises were organised to ensure consistency between the reading centre grading staff and minimise grading protocol discordance.

The large volume of FAs to be graded precluded a double grading. Therefore, quality assurance was built in as an integral feature of the grading process. One in every eight FAs was randomly selected for regrading by the same reading centre, and 1 in 80 FAs was randomly selected for regrading by one of the other reading centres. All graders were masked to whether a particular grading was the original grading or a regrading.

Stereoscopic colour images and FAs were graded by the three reading centres that made up NetwORC UK using previously published definitions and protocols.[35,36] Grading involved the delineation and measurement of the area of classic and occult CNV and other lesion components contiguous to CNV, for example fibrosis and haemorrhage.

Data collection and management

Table 3 shows the schedule of data collection at follow-up visits. A decision was taken to collect HRQoL and HSS data in a subset of centres because of the workload involved and because not all primary care trusts (PCTs) paid the full tariff covering the costs of data collection. There was a strong desire to ensure that these data were collected in a representative population. Therefore, the research team reviewed fully funded sites and their geographic disposition and recommended to the Steering Committee that 18 centres collect these data. The geographic distribution of all sites is shown in *Figure 2*, distinguishing between the sites which collected only the clinical data set and the sites which also collected HRQoL and HSS data.

To meet its objectives, the VPDT study had to collect data from all of the hospitals designated for providing VPDT identified at the outset. These hospitals had been selected to form a network of specialist retinal practitioners. When planning the study, we estimated that these hospitals would enrol about 7000 patients each year and that each patient would make, on average, three clinic visits per year. The study was planned to run for 3 years so that, in total, data would be collected for 21,000 patients who, between them, would make up to 168,000 clinic visits.

TABLE 3 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 data set											
Informed consent	✓										
Clinical history	✓										
Refraction[a]	✓	✓				✓				✓	✓
BDVA in the study eye	✓	✓	✓	✓	✓*	✓	✓*	✓	✓*	✓	✓
Binocular distance visual acuity with habitual correction	✓	✓	✓	✓	✓*	✓	✓*	✓	✓*	✓	✓
Ophthalmic exam	✓										
Stereo colour photography and angiography[c,d]	✓	✓	✓	✓	✓*	✓*	✓*	✓*	✓*	✓*	✓*
Extended data set											
Contrast sensitivity test (Pelli–Robson)	✓			✓		✓		✓		✓	✓
Quality of life and resource use questionnaires		✓		✓		✓		✓		✓	✓

BDVA, binocular distance visual acuity.
a   Protocol refraction was encouraged at every visit, but had to be done at the screening visit, the first treatment visit (month 0) and yearly.
b   Presenting BDVA and BCVA measurements were recorded at every clinic visit; MDVA had to be recorded using forms showing the number of letters read on each line and copies returned to the co-ordinating centre.
c   Stereo colour photography and angiography had to be performed at month 0 and at every visit until the treated eye was considered to be free of leakage on two occasions or until treatment has been stopped for clinical reasons. Photography and angiography were mandatory at treatment-related visits.
d   In years 2 and 3, stereo colour photography and angiography were required on at least one visit, but timing was not critical if the angiography was not treatment related.
The screening/baseline visit and 'month 0' were sometimes the *same visit* if a patient was treated at the screening visit. Three-monthly clinical visits, with distance visual acuity (BDVA and MDVA) checks, were mandatory up to 6 months *after the first PDT treatment* in all treated patients. Three-monthly visits were also required in all patients *continuing to receive treatment*. For patients who did not continue to receive treatment, 6-monthly assessments were required, for example at months 12, 18 and 24 if no treatment was given after month 6. Given that the scheduling of visits after 6 months depended on whether or not a patient was treated, some later visits (with asterisks) could not be specified definitively.

The study aimed to collect data for all patients who were referred to a participating VPDT clinic and who gave consent for their data to be collected. This population included those who were subsequently found to be ineligible for VPDT treatment, so that an accurate estimate could be made of the proportion of all referrals who were subsequently found to be eligible for treatment. This proportion, and the way in which it changed over time, was of interest because of uncertainty about the ability of referring practitioners to diagnose CNV lesions that were eligible for treatment. With experience and training, we expected the proportion of referrals found to be eligible for treatment to increase.

At each patient visit, data had to be collected on BCVA, any VPDT treatment given, ARs resulting from VPDT treatment given at the current visit and any AE possibly resulting from VPDT treatment given at the previous visit. Demographic and referral data were also collected at the patient's first clinic visit.

Imaging of the fundus of the eye was carried out at each clinic visit, yielding colour images and FAs. Grading of these images was co-ordinated by CARF (see *Network of Ophthalmic Reading Centres in the UK*) and the resulting data then had to be transmitted electronically to the London School of Hygiene and Tropical Medicine (LSHTM) and linked with all other data.

FIGURE 2 Map of the UK showing sites which participated in the VPDT cohort study. Sites shown as open circles were selected to collect the extended data set, including contrast sensitivity, HRQoL and resource use.

Based on a previous postmarketing surveillance study sponsored by the manufacturer of verteporfin (Novartis), the cohort study adopted a strategy of requiring ophthalmologists, optometrists, nurses and administrative staff to collect and enter data in the course of providing treatment at each PDT clinic. It was felt that this approach would maximise data quality, reduce the burden of data collection upon a small number of individuals and avoid the need for additional staff to be appointed.

The information technology (IT) strategy for data collection required a robust, networked method of electronic data entry at each site. When the strategy was planned in 2003, web-based methods of longitudinal data collection were not easily available at a reasonable cost and this, combined with the complexity of the clinical data being recorded, meant that a database installed on the local network within each hospital was the preferred solution to allow data entry at multiple points of care. Participating sites were provided with a copy of a uniform Microsoft Access (Microsoft Corporation, Redmond, WA, USA) database developed by a third party. This database was a modification of the database used for the previous postmarketing surveillance study. Where possible, the database was installed on the hospital network. A minority of the initial 30 DHs had taken part in this study and were familiar with the database.

The strategy was based on electronic data entry taking place at each site, in real time, during the course of each patient visit. Thus, records clerks and reception staff would enter initial demographic data, optometrists the BCVA measurements and ophthalmologists the data relating to disease assessment and treatment. The use of paper case record forms would be avoided, and at the end of each session data would be transmitted electronically to the data management centre at the LSHTM. As the number of data entered at each clinic grew, so it was hoped that the data sources would become administrative tools in their own right, and be used routinely to access and review patient information. We expected regular review and appraisal of data to help to improve the accuracy of data collected for the study.

Data transmitted electronically to the LSHTM were placed into a secure central database and were 'queried' extensively with respect to data ranges and consistency. The data queries that resulted from these checks were e-mailed as a report to the relevant centres, which were asked to make corrections to the data held in their own local database or confirm that the original data were indeed correct. Corrections were part of the next data transmission, and queries which had been successfully resolved were labelled as such in the central database and removed from the subsequent data monitoring report.

The majority of data being collected was information that we expected to be collected in the course of usual care, although investigations were required to be carried out according to the manual of operations. Additional data were required about potential predictors of visual function outcome – possible ARs and AEs that might otherwise have been considered 'expected occurrences' (e.g. back pain). Additional data collection (CS, HRQoL and resource use) was carried out in the subset of centres.

Although the data collection strategy strove to avoid using paper case record forms, there were two elements of the study in which these were to be used. The first was the recording of visual acuity onto paper data sheets by optometrists at each clinic. This paper record was intended to act as a validation for the BCVA data (the primary outcome), which were also being collected electronically, and the paper forms were sent directly to the LSHTM for data entry and comparison with the electronic records. Paper forms were also used to collect HRQoL and resource use by the subset of 18 participating centres.

Risk of biases

Risk of bias is described below for the main bias domains identified in the *Cochrane Handbook for Systematic Reviews of Interventions*[41] when reviewing primary studies of the effectiveness of interventions.

Selection bias

The VPDT cohort study focused on patients who were treated with VPDT. Although we attempted to collect baseline data for all patients referred for VPDT, including those subsequently found to be ineligible, ineligible patients were clearly different from treated ones and we never planned to compare outcomes in these groups.

The potential remained for selection bias when comparing outcome between subgroups in the treated cohort, for example according to patients' classification with respect to the inclusion criteria for the TAP trials or baseline measurements of classic and occult CNV. Therefore, we attempted to characterise a range of potential confounding factors in order to minimise the risk of confounding (see *Other predictors of visual function*).

Detection bias

The ophthalmologist collecting clinical data was not masked, so these data were potentially at risk of detection bias. At each visit, the ophthalmologist judged the lesion composition and the change in lesion composition since the previous visit (from a retinal examination or from an FA performed on the day of review), with knowledge of whether or not VPDT had been administered at the last visit. The study manual described a strict protocol (similar to a forced choice psychometric task) for the measurement of BCVA, the primary outcome, to try to minimise detection bias. However, the BCVA was measured by an optometrist or nurse who was not blinded to treatment status and so was also potentially at risk of detection bias for the same reason.

All analyses involving lesion characteristics (including the categorical variable 'TAP eligibility') used the independently graded data provided by NetwORC UK, which were not fed back to participating centres.

Performance bias

Although all clinical staff were aware of treatment status, the study was not described as a treatment comparison to health-care staff, so we judged that the risk of performance bias was low.

Attrition bias

With an elderly study population and a treatment requiring regular review, the risk of attrition bias was high. We used mixed regression models, taking account of the hierarchical nature of the data set, to include data for as many patients as possible (see *Plan of analysis* and *Chapter 4, B: Is 'outcome' the same in the NHS as in randomised trials?*), irrespective of compliance with the data collection schedule. However, this analytic strategy did not remove the risk of informative censoring.

Sample size considerations

Because the UK Specialised Services Commissioning Group originally intended that treatment in the UK should be conditional on recruitment and participation in the study, the study population was defined in the manual of operations simply as the number of patients recruited during the study period. Uncertainties (e.g. about the proportion of patients likely to be referred, the proportion of referred patients found to be ineligible, the proportions of eligible patients categorised as having different CNV subtypes and the precise ways in which control data were to be modelled) made it difficult to provide in advance a clear sample size justification.

For illustrative purposes, we considered a simple comparison of a continuously scaled outcome, that is BCVA, between two subgroups of patients with different types of CNV lesions.[6] The following assumptions were made for this illustration: (a) equal sample sizes for the two groups; (b) analysis adjusted for baseline BCVA; (c) standard deviation (SD) of changes in BCVA = 0.1 logMAR; (d) two-tailed significance level of 0.01; and (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.

We acknowledged that other outcomes might have a larger SD and that subgroups might not have equal sample sizes. For example, comparing a continuously scaled outcome with SD = 0.3 in two subgroups with sample sizes as unequal as 4:1 would require a total of about 1200 (960:240) subjects. These simple illustrations did not take into account the added precision from the longitudinal nature of the data but also did not consider dependencies between patients treated by the same medical retina teams.

Plan of analysis

The manual of operations recognised that the data set for the VPDT cohort study would have a complex structure, with varying numbers of visits/duration of follow-up across patients up to about eight visits/3 years of follow-up. It was also recognised that patients would be 'nested' within groups of retinal specialists and DHs. Therefore, we planned to analyse the data set by mixed regression with multilevel modelling, an extension of conventional regression methods to take into account statistical dependency between observations that are 'clustered' in the data structure, for example observations within patients or patients within retinal teams.

Follow-up of patients throughout the study period allowed repeated measurements of outcomes and changes over time to be described in detail. The main outcomes (BCVA, CS, HRQoL and lesion characteristics) were continuously scaled and could be analysed by mixed regression with multilevel modelling. We also planned to use similar models to quantify associations between clinical outcomes and HRQoL. The analysis plan did not provide details of additional analyses but envisaged that outcomes might also be analysed in different ways, for example by dichotomising the change in BCVA to describe a deterioration of ≥ 15 ETDRS letters or not (a deterioration expected to occur in about 50% of participants) or using survival analysis to describe the cumulative probability of a deterioration of this degree with increasing duration of follow-up.

The analysis plan stated that, because of the complexity of the data set and the likelihood that the composition of the cohort would influence the nature of the analysis, a detailed plan of analyses would be written after carrying out preliminary descriptive analyses. The preliminary descriptive analyses would characterise baseline clinical and treatment characteristics of patients recruited to the cohort but not involve any comparative analyses. A number of baseline factors were expected to influence outcomes independently following photodynamic therapy, including BCVA at presentation, CNV composition and fellow eye comorbidities, and the analysis plan specified that analyses should take all of these factors into account.

Consideration of predictors of outcome in the analyses

As described in *Other predictors of visual function*, known predictors of outcome were identified and collected. The use of adjunctive treatments was also documented, although it was not known if these would influence outcome. The plan of analysis recognised that it would be important to take into account differences in these predictors between subgroups that were of interest to compare.

Estimating the effectiveness and cost-effectiveness of verteporfin photodynamic therapy

The objective of estimating effectiveness and cost-effectiveness required comparisons to be made with untreated patients. At the outset, we recognised that the lack of a concurrent control group was an important limitation of the study and a number of strategies were discussed to estimate outcomes for untreated patients. We proposed 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 VPDT provide estimates of effectiveness. Longitudinal data for BCVA, CS and HRQoL 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.[42] Self-reported use of HSS resources in relation to AMD were also collected in the VPDT cohort study (see *Appendix 2*). We proposed to use

these data, together with the characteristics of participants, to model indirect comparisons between treated and untreated patients.

(b) *Extrapolate use of health and social service resources* The use of health and personal resources can be extrapolated from associations between the use of resources and visual function and other outcomes in the groups documented in the study. For example, if a relationship between the use of resources and amount of deterioration over time were observed in the study, the use of resources could be extrapolated to the level of deterioration in acuity expected without treatment, based on published data for sham/no treatment groups from previous randomised or non-randomised studies.

(c) *Estimate use of health and social service resources from the cohort* This method assumed that resource use for an untreated control group would be similar to that for patients observed in the cohort who received VPDT but who showed no benefit (i.e. whose BCVA and Pelli–Robson Contrast Sensitivity outcomes deteriorate in a similar way to patients in the control groups in trials). This method required estimates to be adjusted for any difference in clinical characteristics between patients who showed no benefit in the cohort study and patients in the control groups of trials.

We stated that cost-effectiveness estimates would be calculated by combining the estimates of effectiveness with utilities derived from SF-6D scores and the association between use of resources and visual function.

Data management and statistical analyses

Treating centres submitted clinical and HRQoL data to an independent data management centre at the LSHTM. The imaging data were submitted to the central angiographic resource facility which managed the grading of the angiograms by NetwORC UK.

Chapter 4

Key changes to the protocol

The scope and duration of the VPDT cohort study were atypical. In particular, its longitudinal nature with visits at regular intervals at which retreatment decisions were made, and the fact that many participating sites had to establish VPDT provision, distinguished it from many earlier treatment registries or comparative outcome studies.[43–45] Its set-up also involved negotiations between many stakeholders, namely ophthalmologists at participating sites, the Royal College of Ophthalmologists, SCGs, PCTs and the Department of Health. Consequently, amendments to the protocol and the study procedures were required during the course of the study. These included the submission to the Ethics Committee for a protocol amendment, addition of study sites, revision of the data set and the methods of data collection, and changes to the image grading procedures.

Protocol amendments submitted to the Research Ethics Committee

One formal protocol amendment was approved by the Research Ethics Committee during the course of the study.

An amendment was submitted for approval in September 2005 requesting approval for five changes:

1. to obtain an anonymised minimum data set for all patients considered for VPDT
2. to include presenting binocular visual acuity as part of the data set
3. to adopt a modified patient information sheet (PIS)
4. to allow nested RCTs as a secondary objective
5. to approve one such trial (comparing combined triamcinolone and VPDT vs VPDT only), for which a detailed protocol was submitted.

The request for an amendment was rejected because of the amendments describing nested RCTs. The amendment was resubmitted without items 4 and 5 in December 2005 and was finally approved in February 2006.

The reasons for seeking these amendments were as follows. Patients receiving VPDT in the NHS had to give informed consent for their data to be included. We wanted to describe the characteristics of all patients considered for VPDT, by eligibility for treatment and by willingness to take part in the study, so that we could comment on the representativeness of the study population. We wanted to collect presenting binocular visual acuity (i.e. binocular visual acuity with a patient's habitual spectacle correction, rather than BCVA) because we reasoned that this was likely to be the visual function parameter most strongly associated with a patient's self-reported vision-specific HRQoL. We requested approval to adopt a much simpler PIS because patients reported to us that the PIS initially approved (which included possible side effects of having VPDT) was too complex and discouraged participation. The proposed simpler PIS distinguished procedural consent for treatment (independent of the study) from research consent to use the data collected in the course of treatment.

These amendments did not alter the overall study design, the setting, the eligible study population or the outcomes.

Changes to study procedures relating to participating sites

As the study progressed, more hospitals were designated to provide VPDT. At the start of the study, because of the novel and complex nature of the treatment, there was professional concern to restrict the provision of VPDT to designated centres in which specified doctors and other personnel had been accredited by attending appropriate training, provided by the Royal College of Ophthalmologists. As time passed, this policy became more difficult to sustain because of the inconvenience to patients in sparsely populated geographic areas. Some hospitals, together with their commissioning PCTs which wanted the hospitals to provide VPDT, were unwilling to participate in the study. Unfortunately, despite the fact that policy-makers provided a lot of the impetus to carry out the study, there was no NHS directive requiring centres to participate. It also became clear at quite an early stage that participating sites were not complying with the follow-up schedule; this required the principal investigators to adapt the planned statistical analyses.

Collection of additional predictors of visual function

The data set being collected for the study was reviewed after 12 months. Because of evidence about the influence of other factors on BCVA, the Steering Committee accepted the recommendation of the principal investigators to ask centres to collect information on additional potential confounding factors:

- smoking status[46–48]
- use of statins[49]
- family history of nAMD[50]
- visual status of fellow eye.[51]

These factors were likely not to vary over time for a participant, and we asked centres to collect the data at the next visit for participants who had already been recruited. At the time of this change to the data set, there was only a small minority of existing participants who had already been discharged from treatment or lost to follow-up.

Smoking status was classified as current smoker, ex-smoker or never smoked. The visual status of the fellow eye (worse or better BCVA) was assigned based on BCVA data collected across the duration of the study. If the better-seeing eye varied across visits, that is both eyes had similar BCVA, the fellow eye status was classified as uncertain.

Network of Ophthalmic Reading Centres in the UK

Images from the VPDT cohort study were graded from 2004 to 2008 by NetwORC UK. Regular training and concordance exercises within the three designated reading centres ensured the reproducibility and reliability of grading outputs. During this period, improvements occurred in image acquisition systems which led to an expansion in the knowledge of the different phenotypes of nAMD. The expanded phenotypic spectrum was incorporated into the grading vocabulary, and the grading protocols were also appropriately amended.

Data collection and management

Changes in the data collection strategy

Several factors were responsible for the study recruiting substantially fewer people than anticipated. However, one was the failure of the original data collection strategy to function in the manner intended. The strategy failed for four main reasons:

- The database supplied by the third party could not be adapted in a satisfactory way to the needs of the study.
- One particular aspect of the inadequacy of the database was the perceived lack of security of electronic data submission. The study coincided with considerable investment in IT modernisation in the NHS and greater awareness among IT managers of national guidance about the confidentiality of patient data held in electronic form.[52]
- Some sites refused to install the local database on their local computer networks.
- Despite the investment in modernising IT in the NHS, many participating sites did not have reliable local computer networks to support data collection at the multiple points of care involved in the management of patients being treated with VPDT. Also, some sites provided VPDT in clinics that were remote from the main ophthalmology department.

There were two main consequences of the failure of the strategy. Data collection at most sites was carried out on paper forms, using forms developed and recommended by the co-ordinating centre (*Figure 3*) or custom forms developed by a site. Using paper forms often represented duplication of the recording of most of the clinical data and required an unexpected time commitment locally for entry of data into the database. There was also a general reluctance to use the adapted database and difficulties in submitting data at some sites.

Concerns about the third-party database became sufficiently grave that, during the summer of 2005, the local database was completely rewritten by LSHTM staff, retaining only the table structure of the original so that data from old and new databases could be combined with relative ease. A new data transmission protocol was also developed by the LSHTM, in which data were transmitted to a secure web address and were, therefore, powerfully encrypted by Secure Socket Layer technology. This revised data transmission protocol met with the requirements of the NHS Information Authority, which the original database could not do, allowing the sites that had refused to submit data electronically to do so; it also persuaded some IT managers who had previously been reluctant to do so to install the database on the local computer network. The revised database and data transmission protocol also allowed implementation of submission of the anonymised minimum data set for patients who had treatment but from whom consent had not been obtained for participation in the cohort study (see *Protocol amendments submitted to the Research Ethics Committee*).

All centres were provided with the revised database. Clinics which had already collected data via the original system were able to retain the original data tables and have the revised database added as a new 'front end'. Setting up the new databases required every site to receive a visit from a member of the LSHTM staff, during which the updated database was installed and staff were trained. The first of these site visits took place in August 2005, with the majority of upgrades taking place during the 12 months from September 2005. The database upgrade also required additional investment by the data management centre at the LSHTM, which had to recruit an extra full-time member of staff for 12 months.

The fundamentally different design of the revised clinical database was welcomed by the vast majority of clinics and overcame a lot of the reluctance to collect data. However, it could not

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)   e. Smoking history
   ☐ Suspected CNV   ☐ Never
   ☐ Predominantly classic CNV   ☐ Current: Number of years smoked............yrs
   ☐ Classic CNV   ☐ Ex-smoker: Number of years smoked............yrs
   ☐ Other   Yrs/mths since last smoked ....yrs ....mths

f . Other health-related information   g. Imaging
   Y / N Cardiovascular disease   ☐ None   ☐ OCT only
   Y / N Use of statins   ☐ ICG only   ☐ Both
   Y / N Family history ....

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   **R** ....   laser photocoagulation   .... **L**
   treatments for CNV   **R** ....   PDT   .... **L**
   (enter 0 if none)   **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, ___/ ___/ ___

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FIGURE 3 Paper data collection forms recommended by the data management centre.

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 <u>one item</u> only)

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

....

b. **AMD characteristics** (tick <u>one</u> only)

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

<u>Location</u> of lesion (tick <u>one</u> only):
☐   Subfoveal   ☐
☐   Juxtafoveal   ☐

7. Features of treated eye
a. Required for **ALL VISITS**
b.& c. Only required if <u>treated at this visit</u>

a. **Additional features (tick <u>all</u> 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: ....

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FIGURE 3 Paper data collection forms recommended by the data management centre. (*continued*)

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 _____

FIGURE 3 Paper data collection forms recommended by the data management centre. (*continued*)

overcome inadequacies in local computer networks or the refusal to install the database at some sites. In two cases the database could be installed only on a stand-alone personal computer with no network/internet connection. Other obstacles which made networking the database difficult included a virtual private network at one clinic, a complex arrangement of virtual servers at another, specialist optometry software which altered the configuration of dates and an unwillingness to install the software which the database required to operate. These cases highlighted that the hardware infrastructure at clinics was far from standard.

Centres generated a data report by executing a standard query on their local database and submitted the data periodically to the co-ordinating centre by the secure internet link, except for the two sites without an internet connection which submitted data by computer disk sent by registered post. The co-ordinating centre implemented data validation checks and sent back data queries to sites centres, as originally planned (see *Chapter 3*, *Data collection and management*).

Collection of health-related quality-of-life data

The protocol specified that participants should complete HRQoL questionnaires in large-print versions at baseline and every 6 months thereafter. An assisted self-administration approach was specified, described in detail in the manual of operations. Some centres were unable to follow this approach because of a lack of resources. Therefore, it was agreed that selected patients who had sufficiently good vision to read the questions and who, for example, had already completed a set of questionnaires using the assisted self-administration method could be given the questionnaires to complete at home and return by post.

Bias

Attrition was very much worse than expected in that many patients were not followed up as described in the protocol. Consequently, we were required to rethink the approach to the analysis plan (see *Chapter 3*, *Plan of analysis*). The revised analysis plan allowed us to include data for all of the observation time/documented visits in the analysis plan, irrespective of compliance with the schedule, but did not address the risk of attrition bias/informative censoring.

Sample size considerations

The sample size considerations remained the same as described in *Chapter 3*, *Sample size considerations*. However, we originally expected the study to document VPDT in about 20,000–25,000 patients over 3 years. Although the rate of recruitment increased substantially over the course of the study, it was quickly apparent that the difficulties in ensuring that DHs participated would mean that the actual sample recruited would be considerably smaller.

Detailed consideration of possible biases also led us to decide to exclude from the main analyses of BCVA patients who were within 1 year of their first treatment, unless their treatment episodes were completed (see *Plan of analysis*). We used this strategy because the TAP trials reported 1-year outcome and suggested that outcomes continue to improve with repeated treatment up to 1 year.

Despite these limitations, the study still had considerable precision (greater than in the TAP trials) when estimating treatment outcomes after 1 year by virtue of the continuously scaled outcomes of BCVA and HRQoL and their repeated measurement over time in the study. These attributes of the outcomes contrast with primary outcome in the TAP trials, namely the percentage of patients losing > 15 ETDRS letters at a particular time point.

Plan of analysis

The objectives of the study were reformulated *prior* to analytical comparisons as described in *Chapter 2*.

A detailed description of our approach to derivation of new variables for the analyses from the data collected and analysis plans to address each of the objectives of the study are described in the ensuing sections. These data management decisions and analysis plans were established by exploring the accumulating data descriptively and before the key analytic comparisons were carried out. Methods of fitting of final models could not be completely pre-specified, but evolved primarily to optimise the fit of the models given the limitations of the data set.

Data analysis decisions and definitions of derived analysis variables

Close of data collection for the data analyses

Centres were told in advance that recruitment to the study and documentation of study visits would stop for the data analyses on 14 September 2007. An exception to this rule was made for centres that did not submit their final data download on or after this date. For these centres, the cut-off date for calculating whether or not a patient had a completed treatment episode was the date of the last data submission.

Because the NICE guidance stated that patients with predominantly classic CNV lesions with some occult CNV should be treated only in a research study, the VPDT cohort study was funded to continue to collect data up to 31 March 2008. This allowed sites to continue to address data validation queries and missing data for visits that took place up to 14 September 2007. Data submitted for visits after 14 September 2007 were excluded from the analyses in this report. Few new patients were recruited, and few additional visits took place during this period for patients who were already recruited, because new treatments, primarily drugs that inhibited vascular endothelial growth factor (VEGF), were supplanting VPDT (*Figure 4*).

Definition of eligible patients and eligible eyes

A patient was eligible for inclusion in the analysis if he/she had at least one eligible eye and had consented to VPDT and to submission of his/her data to the study. Although eligibility for treatment was also defined with respect to visual acuity and lesion composition (see *Chapter 3*, *Participants*), these criteria were not always adhered to (judged by BCVA data submitted by the site and by independent grading of the baseline FA).

An eye was defined as eligible for inclusion in the analysis if it had been treated with VPDT at least once and had BCVA recorded at the first treatment visit and at least one follow-up visit. If a patient had had both eyes treated with VPDT, the first treated eye was included in preference to the second because it was more likely to have longer follow-up, or to have a completed treatment episode, that is to be eligible for inclusion. If the first treated eye of a patient was ineligible, the second treated eye was included if it met the above criteria. If both eyes were treated at same time and both were eligible, one eye was chosen at random. Some treated eyes with missing BCVA at baseline or no BCVA measurements after treatment could not contribute to the analysis and were excluded. Untreated patients were excluded from all analyses, except the description of the overall cohort.

Definition of year 1 and year 2

In order to compare the number of treatments administered in the VPDT cohort study with the number of treatments administered in the TAP trials, we needed to classify visits as occurring
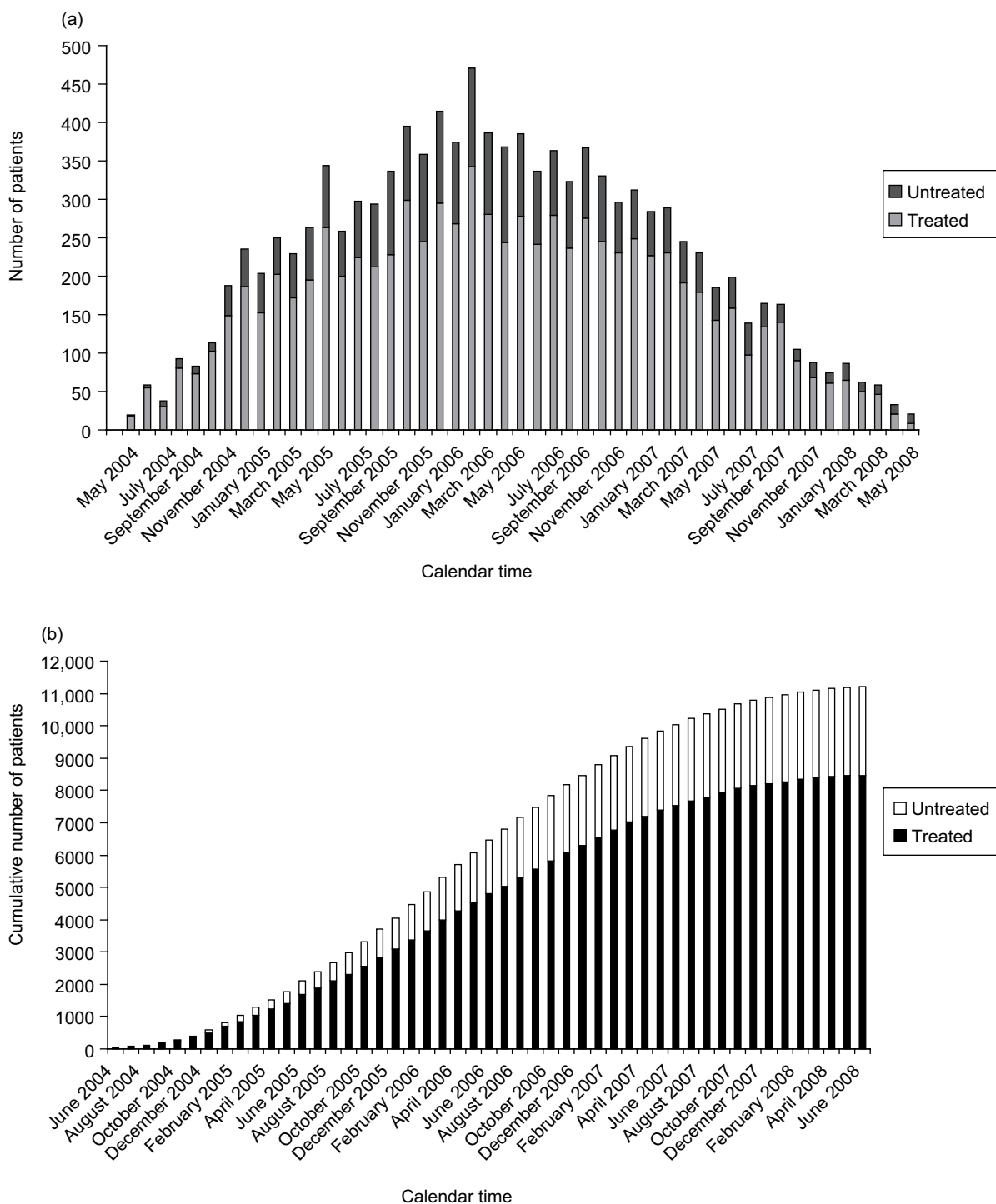
FIGURE 4 Recruitment to the VPDT cohort study for the UK. (a) Monthly recruitment up to the end of June 2008. (b) Cumulative monthly recruitment up to the end of June 2008.

in year 1 or year 2 of follow-up. Cut-off dates for year 1 and year 2 were defined, respectively, as ≤ 350 days and > 350 and ≤ 715 days after the date of first treatment on the assumption that scheduled visits would tend to slip over time, and were unlikely to occur at shorter time intervals than scheduled.

Classification of treatment as active or completed

For objective A (see *Chapter 2*), we needed to define episodes of treatment as active or completed because, by including patients still receiving active treatment, we would have underestimated the number of treatments administered. This distinction was complicated by the fact that many participants were discharged from or lost to follow-up before 1 year. Distinguishing between active and completed treatment was also important when estimating BCVA 12 months after starting treatment (a prerequisite for addressing objectives B, C and E). We wanted to include in these analyses data for patients classified as having completed their treatment before 12 months. However, patients who had not reached 12 months' follow-up and who were still having active treatment could have experienced additional benefit from ongoing treatment up to 12 months.

Patients were classified as having completed treatment for year 1 if they satisfied one of the following sets of conditions:

- visit with BCVA follow-up data ≥ 350 days after the first treatment
- no visit with BCVA follow-up data ≥ 350 days after the first treatment *and* no visit recorded in the 150 days before 14 September 2007 (or the last date of data submission, if earlier)
- no visit with BCVA follow-up data ≥ 350 days after the first treatment *and* visit in the 150 days before 14 September 2007 *and* explicit reason for loss to follow-up (planned discharge, treatment failure, etc.).

Other participants, that is those with *no* data for BCVA follow-up ≥ 350 days after the first treatment *and* a visit in the 150 days before 14 September 2007 *and* a further visit booked (or no reason for not booking a further visit, e.g. explicit reason for loss to follow-up), were classified as having 'active treatment, with continuing follow-up'. Classification as active or completed treatment was mutually exclusive.

Definition of 'TAP eligibility'

We decided that the independent, reading centre gradings of baseline angiograms should be the basis for the classification of patients as 'eligible for the TAP trials' (EFT) or 'not eligible for the TAP trials' (IFT). As described in *Chapter 3*, *Network of Ophthalmic Reading Centres the UK*, this decision was made because the research team was concerned that ophthalmologists' in vivo clinical gradings might be biased in order to allow a patient to be classified as eligible for treatment (e.g. percentage of classic CNV overestimated).

This concern was substantiated by an unpublished interim subanalysis comparing ophthalmologists' classifications with reading centre gradings for 2441 eyes which showed that, on average, the former classified a higher percentage of patients as having predominantly classic CNV lesions (*Table 4*). Agreement was poor (although substantially better than expected by chance: $\kappa = 0.093$, standard error 0.010, $p < 0.0001$). Many more eyes were classified as predominantly classic with occult by ophthalmologists than by independent grading; conversely, fewer eyes were classified as minimally classic (with or without occult) by ophthalmologists, that is as ineligible for VPDT according to the NICE guidance.[6]

At the time of first treatment, eyes were classified into mutually exclusive categories based on the proportion of classic and occult CNV (predominantly classic, minimally classic or occult no classic) as independently graded. We grouped patients into three categories based on whether or not the treated eye met the following eligibility criteria for the TAP trials:

- BCVA > 33 and < 74 letters at first treatment AND
- evidence on FA of at least some classic CNV (> 1% of lesion) AND

TABLE 4 Interim analysis comparing ophthalmologists' classifications of CNV lesions (numbers of eyes) with classifications based on independent reading centre gradings

CNV classification by ophthalmologist	CNV classification by reading centre				
	CNO	PCO	MC	ONC	Total
CNO	1085	29	275	66	1455
PCO	538	22	198	93	851
MC	14	2	18	6	40
ONC	31	1	27	36	95
Total	1668	54	518	201	2441

CNO, classic with no occult CNV; MC, minimally classic CNV with or without occult; ONC, occult with no classic CNV; PCO, predominantly classic with occult CNV.

- total CNV area ≥ 50% of the lesion AND
- CNV under the geometric centre of foveal avascular zone.[3]

Thus, each treated eye was classified as:

- meeting these eligibility criteria (EFT)
- not meeting the criteria (IFT)
- not classifiable owing to the absence of gradable baseline FA ('unclassifiable'; UNC).

A: Is verteporfin photodynamic therapy in the NHS provided as in randomised trials?

We aimed to address objective A by describing the following aspects of VPDT provision:

1. distribution of the number of treatments received in years 1 and 2 by patients classified as having completed their treatment for year 1/2
2. time to stopping treatment among patients classified as having completed their treatment
3. rate of treatment (per eye) among patients classified as having completed their treatment (treatments/year)
4. reasons for loss to follow-up before 1 year.

Item 3 was subsequently omitted because of the substantial loss to follow-up in the first 2 years after starting treatment. Item 4 was omitted because reasons for loss to follow-up were frequently not reported by participating centres.

In order to investigate numbers of treatments administered, we had to distinguish clinical follow-up visits from visits solely for the purposes of the study. In addition to the criteria for a completed treatment episode described in *Classification of treatment as active or completed*, treatment was defined as complete (despite continuing follow-up) if > 150 days (approximately 5 months) had elapsed between subsequent visits, except when a gap of > 150 days occurred between consecutive treatment visits. This criterion allowed for slippage in a scheduled 3-month visit, or one missed 3-month visit, and classified a 6-month follow-up visit without treatment as follow-up for the purposes of the study in accordance with the data collection schedule.

For item 1, the primary outcome was the number of applications of VPDT in years 1 (≤ 350 days) and 2 (> 350 and ≤ 715 days). Treatment frequencies were cross-tabulated with TAP eligibility and tested for significance using chi-squared statistics. We also compared treatment frequencies in year 1 with treatment frequencies reported for the TAP trials.[30] For item 2, we calculated the time until the first treatment episode was completed (see *Classification of treatment as active or completed*) or 350 days, whichever was later. These times were described as a Kaplan–Meier curve (see *Figure 6*), estimating the duration of follow-up when 50% of participants had completed their treatment.

In order to make the comparison with the TAP trials, the cohort for this analysis was restricted to patients with a CNV lesion diagnosed as nAMD and who had completed their treatment or who had completed follow-up for 1 or 2 years after the first treatment. The analysis was also limited to one eye per patient.

B: Is 'outcome' the same in the NHS as in randomised trials?

Objective B focused on patients who would have been EFT. We aimed to address this objective by estimating BCVA 1 year after the first treatment in patients classified as having completed their treatment for year 1. We fitted a mixed regression model to estimate the BCVA trajectory during the first year, using data up to 2 years where available. This method of analysis allowed all visit data for an eligible eye to be included irrespective of adherence to the data collection schedule. The duration of follow-up ('time') was a covariate in the model; interactions of other covariates with time represented non-parallel trajectories.

A single model was used to answer objectives B and C and included the following covariates: age, gender, baseline BCVA, TAP eligibility, CNV composition, smoking status and whether or not the fellow eye was the better-seeing eye. Coefficients from the model were used to estimate BCVA at 1 year for the EFT [objective (B)], IFT [objective (C)] and UNC subgroups. Inclusion of covariates was necessary because they were potential confounding factors when comparing outcome across the EFT, IFT and UNC subgroups. The influence of the covariates in such a large cohort was also intrinsically of interest; inclusion of the UNC subgroup increased the precision of the analysis with respect to estimating the influence of the covariates.

Because of substantial loss to follow-up in year 2, we again restricted our main analysis to estimating BCVA at 12 months for the cohort of patients described above for objective A (see *A: Is verteporfin photodynamic therapy in the NHS provided as in randomised trials?*).

C: Is 'outcome' the same for patients ineligible from randomised trials?

Objective C focused on patients who would have been IFT. A single model was used to address objectives B and C (see *B: Is 'outcome' the same in the NHS as in randomised trials?*).

D: Is verteporfin photodynamic therapy safe when provided in the NHS?

Adverse reactions and AEs were not classified as required for good clinical practice, although such events were promptly notified to the Data Management Centre at the LSHTM in accordance with good clinical practice. Attribution of ocular AEs to VPDT is difficult because such events may occur as part of the natural history of nAMD. An AR was defined as an ocular or systemic reaction at the time of treatment which was recorded on the same day as treatment with

other clinical data for that visit. An AE was defined as any other ocular or systemic AE reported at the next visit after a treatment or retreatment visit. The association of an AE with the previous treatment visit was coded during data management and, therefore, was associated with the corresponding treatment visit, not the visit on which it was reported.

The probability of a treatment visit giving rise to an AR or AE by site and visit was estimated using a logistic regression model, fitting participating site as a random effect. The distributions of centre-specific probabilities were examined carefully because of concern about the extent to which sites had adhered to the instructions for collecting data about ARs and AEs. To contextualise the overall probability of an AR or AE, we also described the probabilities for a site which had the largest number of treated patients and which we believed had collected such data better than average. We also investigated whether any site had a site-specific upper 95% confidence limit below the lower 95% confidence limit for the *entire* cohort; where this was the case, a sensitivity analysis was rerun omitting the site.

E: How effective and cost-effective is verteporfin photodynamic therapy?

Different approaches to estimate effectiveness were proposed in the manual of operations (see *Chapter 3, Estimating the effectiveness and cost-effectiveness of verteporfin photodynamic therapy*). For reasons outside our control, we were able to use only the second of these methods, that is to investigate associations between the use of resources and visual function and other outcomes in the study. This method is described in more detail in *How effective is verteporfin photodynamic therapy?*, below. This method also underpinned the second element of objective E, that is estimation of the cost-effectiveness of VPDT.

The first method depended on obtaining individual patient data from other researchers, including the TAP triallists. We were able to obtain some data for studies which had academic or public sponsors, but were unable to obtain the data for the key RCTs of VPDT (TAP and VIP trials[3,5]), even though the manufacturer of verteporfin (Novartis) was represented on the Steering Committee. Without these data, we judged that the first method was not feasible.

The third method depended on being able to characterise an untreated control group in the cohort of patients recruited for the study. However, it quickly became apparent that we were not capturing adequate data for patients who were not treated (either by choice or because of ineligibility) and that untreated patients represented in the database were not similar across sites because of the varied arrangements in place for triaging patients before referral to VPDT clinics.

How effective is verteporfin photodynamic therapy?

The estimates of BCVA outcome at 1 year were used to derive indirect estimates of the effectiveness of VPDT by comparing the estimates with the reported BCVA outcomes at 1 year in the treatment and sham treatment groups of the TAP trials.

The strategy for estimating the HRQoL benefit from VPDT was as follows:

1. to estimate the extent to which HRQoL changes per unit change in BCVA
2. to 'translate' the observed difference in BCVA in the TAP trials into HRQoL, based on the association quantified by step 1
3. to 'translate' the observed change in BCVA in the VPDT cohort study over time minus the change in BCVA observed in the sham treatment arms of the TAP trials into HRQoL, based on the association quantified by step 1.

In addition to estimating the overall associations between BCVA and HRQoL, we also sought to test two pre-specified subhypotheses. One concerned the shape of the association. We hypothesised that the associations would be sigmoid, with a relatively shallow gradient at the extremes of the visual function continuum. We reasoned that HRQoL would vary a relatively small amount (shallow gradient) among people above and below visual function thresholds for being easily able, and completely unable, to carry out tasks that depend on vision; conversely, we reasoned that HRQoL would drop sharply over the range of visual function when people's ability to do such tasks also deteriorated markedly. The second subhypothesis concerned adaptation over time to poorer visual function. We hypothesised that the gradients of the relationships would decrease with increasing time from first treatment, as patients adapted to their residual vision.

We used BCVA and CS measurements from the better-seeing eye and HRQoL data for corresponding visits. Visits were classified using the following time intervals: 0 months (first treatment date), 3 months (>77 to ≤168 days), 6 months (>168 to ≤259 days), 9 months (>259 to ≤350 days), 12 months (>350 to ≤442 days), 15 months (>441 to ≤533 days), 18 months (>533 to ≤624 days), 21 months (>624 to ≤715 days) or 24 months (>715 to ≤807 days) after the date of first treatment. Intervals were not symmetrical around the 3-monthly schedule because follow-up visits tended to shift towards longer rather than shorter intervals.

Mixed regression models were used to allow all available visits to contribute to the analysis, taking into account multiple visits by the same patients and visits without HRQoL data. To allow for the correlation of the data, an unstructured covariance matrix was used where possible, otherwise random intercepts and slopes were fitted.

To address our second objective, that relationships are sigmoid, we fitted a range of putative models; these included linear, quadratic, cubic and spline functions. We addressed our third objective, that gradients decrease with time since first treatment, by modelling time in 3-month intervals (see above). The analyses investigated both time interval and the interaction between BCVA and time, allowing the gradient of the relationship to vary with time.

We also fitted a range of covariates (including age, gender, participating centre, smoking status and whether or not the fellow eye was the better-seeing eye). Covariates did not materially alter the shape or gradient of the relationships between visual function and HRQoL, and their effects are not described.

We judged that the cause of CNV was very unlikely to influence the association between BCVA and HRQoL. There was also no reason why the association would be influenced by whether or not a patient had completed treatment. By virtue of modelling BCVA in the better-seeing eye, the issue of treatment in both eyes did not arise. Therefore, the cohort for this analysis included all patient visits for which visual function data (BCVA or CS) and HRQoL data (NEIVFQ or SF-36) were reported.

How cost-effective is verteporfin photodynamic therapy?

The CEA element of objective E consisted of three parts: (a) estimation of the costs of delivering VPDT in routine clinical practice; (b) development of a regression model to quantify changes in HSS for a given change in visual function (i.e. BCVA); and (c) assessment of the cost-effectiveness of VPDT versus best supportive care (BSC) using the findings from (a) and (b).

Overview of the cost-effectiveness analysis

The VPDT cohort study was designed to assess the costs and HRQoL of VPDT and to report the cost-effectiveness of VPDT versus BSC. The CEA was undertaken in accordance with current methodological standards. It took a health and personal social services perspective and so

included all relevant costs to HSS.[28] The main assumptions underlying this CEA are reported in *Box 2*.

The study used the BCVA measures reported in the TAP trial to assess the cost-effectiveness of VPDT versus BSC.[3] The effect of VPDT on BCVA was taken from the subgroup of eyes with predominantly classic lesions in the TAP trials; the effectiveness of VPDT was largest in this subgroup of eyes (mean difference in BCVA letters lost from baseline of 11 letters at 2 years), which was the basis for the previous NICE recommendations.[3,6,30] This report combines these data from the TAP trials with estimates from the VPDT cohort study of (a) the relationship between BCVA and HRQoL (see *How effective is verteporfin photodynamic therapy*?), (b) treatment frequency in routine practice (see *A: Is verteporfin photodynamic therapy in the NHS provided as in randomised trials?*) and (c) the relationship between BCVA and HSS cost (using the same methods as when estimating the relationship between BCVA and HRQoL, described in *How effective is verteporfin photodynamic therapy*?). This report also estimates the costs of VPDT in routine practice and the cost-effectiveness of PDT versus BSC over 2 years.

Costs of verteporfin photodynamic therapy and best supportive care

The VPDT cohort study recorded the number of outpatient visits, tests performed (colour photography or FA) and VPDT treatments administered. For each patient, the treatment costs were measured from the date on which the first eligible eye was treated for up to 2 years. Costs were categorised as falling in year 1 or year 2 (*Definition of year 1 and year 2*). Because the probability of receiving one FA for each visit (whether a treatment or follow-up visit) exceeded 0.95 for > 90% of study centres, it was assumed that there was one FA for each visit.

We assumed that one vial of verteporfin was used per treated eye as stipulated in the licence. Verteporfin costs were taken from the *British National Formulary* (£860 per treatment) and excluded value added tax.[53] The numbers of treatment and follow-up visits were combined with national unit costs (£113 and £67 for treatment and follow-up visits respectively).[54]

The costs of BSC were estimated by assuming plausible costs for follow-up without VPDT. In the base-case analysis, it was assumed that there would be on average 1 and 1.5 low-vision assessments scheduled in years 1 and 2 respectively.

Health and social sciences use and costs related to vision loss

The cost of HSS for patients affected by nAMD was estimated from the HSS use questionnaires which were administered every 6 months to patients attending a subset of 18 of the participating

BOX 2 Assumptions made in the CEA

The target population was patients treated with VPDT in routine NHS practice

VPDT treatment was given to the better-seeing eye

nAMD costs and HRQoL only varied according to BCVA which, in turn, depends on whether treatment is or is not given and changes over time as described in the TAP trials

Treatment frequency was as observed in VPDT study

For patients having both eyes treated, the treatment costs were assumed to be the twice the costs for patients having a single eye treated

To calculate QALYs from HRQoL, it was assumed that there was no mortality

Costs and QALYs in year 2 were discounted at 3.5%

sites. The questionnaires elicited the use of HSS relating to the patient's eye condition in the preceding 3 months. This included unscheduled low-vision appointments, use of antidepressants, visits to the general practitioner (GP), visits from social services (mainly home carers) and time in nursing homes, residential care or sheltered housing. The patient-reported HSS use at each time point was combined with national unit costs to give an estimate of the costs in the 3 months preceding the visit that were 'attributable' to the patients' vision.[54] All costs (inflated to 2007 prices) were summed across years 1 and 2 to give total costs per patient and were reported in UK pound sterling.[55]

Estimating incremental quality-adjusted life-years, and incremental costs for verteporfin photodynamic therapy versus best supportive care

The incremental costs of VPDT versus BSC comprised the mean differences in both intervention and HSS costs between the VPDT and BSC groups. The association of BCVA with HSS cost was estimated using regression models, following the same strategy used to measure the association between BCVA and HRQoL. Estimates for the CEA were taken from a model which included just BCVA (or CS) as an independent variable because other covariates did not improve model fit.

Because a substantial proportion of the sample of patients incurred zero HSS costs, we used a 'two-part' model.[56] The first part modelled all observations in a logistic regression, with use (or not) of any service in the 3 months preceding the visit as the dependent variable and BCVA as the independent variable. The second part of the model included only those observations for which HSS was used and fitted a linear regression with the HSS cost per user as the dependent variable and BCVA as an independent variable. The resultant conditional probabilities of HSS use and HSS costs per user were combined to predict overall HSS costs with varying BCVA.

The CEA then combined the 3-monthly BCVA data from the TAP trial with the association between BCVA and HSS cost to report the incremental HSS costs for VPDT versus BSC. These costs were added to the incremental intervention costs of VPDT and BSC to give the overall incremental costs of VPDT at 1 and 2 years.

This association between BCVA and SF-6D was combined with the differential decline in BCVA from baseline for the VPDT and placebo groups in TAP to derive differences in HRQoL between VPDT and BSC at 3-monthly intervals. The incremental QALYs for VPDT versus BSC were calculated as the average HRQoL difference for each 3-monthly time point multiplied by 0.25 years and summed over 1 or 2 years. The CEA reported incremental (mean VPDT – mean BSC) costs, QALYs and costs per QALY.

Sensitivity analyses

A probabilistic sensitivity analysis was undertaken to recognise the sampling uncertainty surrounding the key parameters (BCVA, association between BCVA and HRQoL, intervention costs and association between BCVA and HSS costs), and to report the probability that VPDT is cost-effective compared with BSC at different levels of willingness to pay for a QALY gain (e.g. £20,000 per QALY).[28,57]

Further sensitivity analyses assessed the robustness of the results to the main methodological assumptions and data sources used in the base case. Five alternative scenarios were considered:

1. The treatment frequency was taken from TAP trials rather than the VPDT cohort study.
2. BCVA data for the VPDT group were taken from the cohort study (post- vs pre-VPDT) rather than TAP.

3. The relationships of cost and HRQoL with CS rather than BCVA were used.
4. To assess whether or not the results were sensitive to the costs of BSC, which may be higher when financed under private health insurance, the BSC costs were assumed to be 10-fold higher than in the base case.
5. Cost-effectiveness was estimated over 5 rather than 2 years, assuming that the difference in BCVA between the treatment groups observed at 2 years applied for years 2–5.

As when quantifying the association between BCVA and HRQoL, the analysis to quantify the relationship between BCVA and resource use included all patient visits for which visual function data (BCVA or CS) and resource use data (NEIVFQ or SF-36) were reported. The treatment frequency data were restricted to the group of patients with predominantly classic lesions who had completed treatment or who had follow-up data to 1 year.

Chapter 5

Results (1) – study cohort

Participating centres

The number of participating sites increased over time. We originally planned for 30 but, by the time that data collection started, 48 DHs had been identified by SCGs. A few more DHs were identified as the study progressed; this number is imprecise because, if DHs refused to register for the study, we sometimes did not receive definitive information about whether or not a prospective DH actually started to provide VPDT. Additional DHs joined the study up until May 2007. A total of 49 sites registered to take part in the VPDT service but only 47 contributed data to the study (see *Figure 2*). The first participating site gained the necessary approval to enrol patients on 21 May 2004. Approval for other sites progressed steadily throughout 2004–5. Twenty-one sites were submitting data by May 2005, 38 by May 2006 and 45 by May 2007. Some sites submitted data early during the course of the study but did not continue to do so throughout.

Study population

The first patient was enrolled on 3 June 2004. The rate of recruitment increased to a peak in April 2006 and then declined steadily (see *Figure 4*). The numbers of patients recruited by each site are shown in *Table 5*. The numbers ranged from 5 to 593 for all patients treated at any time, but only from 3 to 351 for patients with CNV caused by nAMD, baseline BCVA and at least one follow-up BCVA assessment and not under active treatment or > 1 year since the first treatment (i.e. patients included in the main analyses; *Figure 5* and *Chapter 4*, *Definition of 'TAP eligibility'* and *B: Is 'outcome' the same in the NHS as in randomised trials?*).

The flow of recruited patients in the study with respect to consent, treatment, inclusion of one or both eyes and whether or not an eye was considered under active treatment when the database was locked is shown in *Figure 5*. Between June 2004 and September 2007, data on 11,727 patients were submitted. A total of 7748 patients were recorded as having been treated at any time; 575 patients were treated and contributed data for both eyes, giving a total of 8323 eyes. Data were submitted for 31,640 clinic visits in these 7748 patients. The referral mechanisms adopted by sites varied considerably; for example, some had systems for initial triaging of patients with respect to criteria determining eligibility for treatment. Therefore, the data on patients found to be ineligible when attending VPDT clinics could not be interpreted and were not analysed further.

Missing BCVA for 1527 patients resulted in the exclusion of 1676 eyes (142 missing at baseline and 1534 at follow-up). The characteristics of the remaining 6221 patients are shown in *Table 6*. Their median age was 78 years (interquartile range from 72 to 83 years). The majority were female (3620/6202, 58.4%). The majority (55.4%) were current (832/5282, 15.8%) or ex-smokers (2092/5282, 39.6%).

Of the 6221 patients, 426 (6.8%) were treated and contributed data for both eyes, giving a total of 6647 eyes treated at least once with valid BCVA data at baseline and at least one follow-up assessment; 1728 eyes in 1655 patients had been first treated ≤ 350 days (study definition

TABLE 5 Numbers of patients recruited by centres

Centre	All patients treated at any time		Patients treated at any time with BCVA		Patients with BCVA and not under active treatment[a]		Patients with AMD, BCVA and not under active treatment[a]	
	Number of patients	%	Number of patients	%	Number of patients	%	Number of patients	%
1	52	0.67	42	0.68	21	0.46	19	0.47
2	106	1.37	90	1.45	56	1.23	51	1.26
3	39	0.50	35	0.56	22	0.48	21	0.52
4	5	0.06	3	0.05	3	0.07	3	0.07
5	165	2.13	147	2.36	102	2.23	92	2.28
6	186	2.40	155	2.49	128	2.80	94	2.33
7	84	1.08	61	0.98	16	0.35	14	0.35
8	566	7.31	457	7.35	355	7.77	307	7.59
9	134	1.73	115	1.85	90	1.97	84	2.08
10	125	1.61	114	1.83	93	2.04	89	2.20
11	60	0.77	44	0.71	31	0.68	25	0.62
12	55	0.71	39	0.63	39	0.85	37	0.92
13	117	1.51	95	1.53	62	1.36	58	1.43
14	49	0.63	24	0.39	10	0.22	8	0.20
15	255	3.29	224	3.60	161	3.53	153	3.78
16	114	1.47	1	0.02	–	–	–	–
17	281	3.63	215	3.46	130	2.85	119	2.94
18	23	0.30	19	0.31	14	0.31	14	0.35
19	46	0.59	12	0.19	7	0.15	7	0.17
20	292	3.77	194	3.12	148	3.24	129	3.19
21	101	1.30	90	1.45	55	1.20	48	1.19
22	42	0.54	28	0.45	5	0.11	4	0.10
23	133	1.72	117	1.88	111	2.43	105	2.60
24	113	1.46	92	1.48	65	1.42	64	1.58
25	110	1.42	80	1.29	61	1.34	57	1.41
26	258	3.33	227	3.65	179	3.92	151	3.73
27	586	7.56	513	8.25	399	8.74	344	8.51
28	77	0.99	49	0.79	48	1.05	43	1.06
29	263	3.39	221	3.55	120	2.63	105	2.60
30	323	4.17	263	4.23	232	5.08	202	5.00
31	593	7.65	536	8.62	393	8.61	351	8.68
32	50	0.65	28	0.45	27	0.59	23	0.57
33	320	4.13	282	4.53	195	4.27	180	4.45
34	76	0.98	38	0.61	35	0.77	33	0.82
35	168	2.17	141	2.27	98	2.15	76	1.88
36	48	0.62	30	0.48	23	0.50	23	0.57
37	360	4.65	329	5.29	247	5.41	225	5.57
38	102	1.32	48	0.77	34	0.74	31	0.77
39	192	2.48	123	1.98	100	2.19	88	2.18
40	88	1.14	83	1.33	63	1.38	55	1.36
41	147	1.90	128	2.06	104	2.28	95	2.35
42	14	0.18	7	0.11	–	–	–	–
43	209	2.70	184	2.96	156	3.42	127	3.14
44	126	1.63	113	1.82	82	1.8	78	1.93
45	350	4.52	297	4.77	187	4.1	157	3.88
46	60	0.77	24	0.39	7	0.15	7	0.17
47	85	1.10	64	1.03	52	1.14	47	1.16
Total	7748	100	6221	100	4566	100	4043	100

a   Not under active treatment, or first treatment >350 days before the study was closed.

	Eligible for TAP trials	Ineligible for TAP trials	Eligibility for TAP trials unclassified	Total
All eyes	1268	1487	2164	4919
One eligible eye/patient	1227	1435	1904	4566
One eligible eye with nAMD/patient	1227	1187	1629	4043
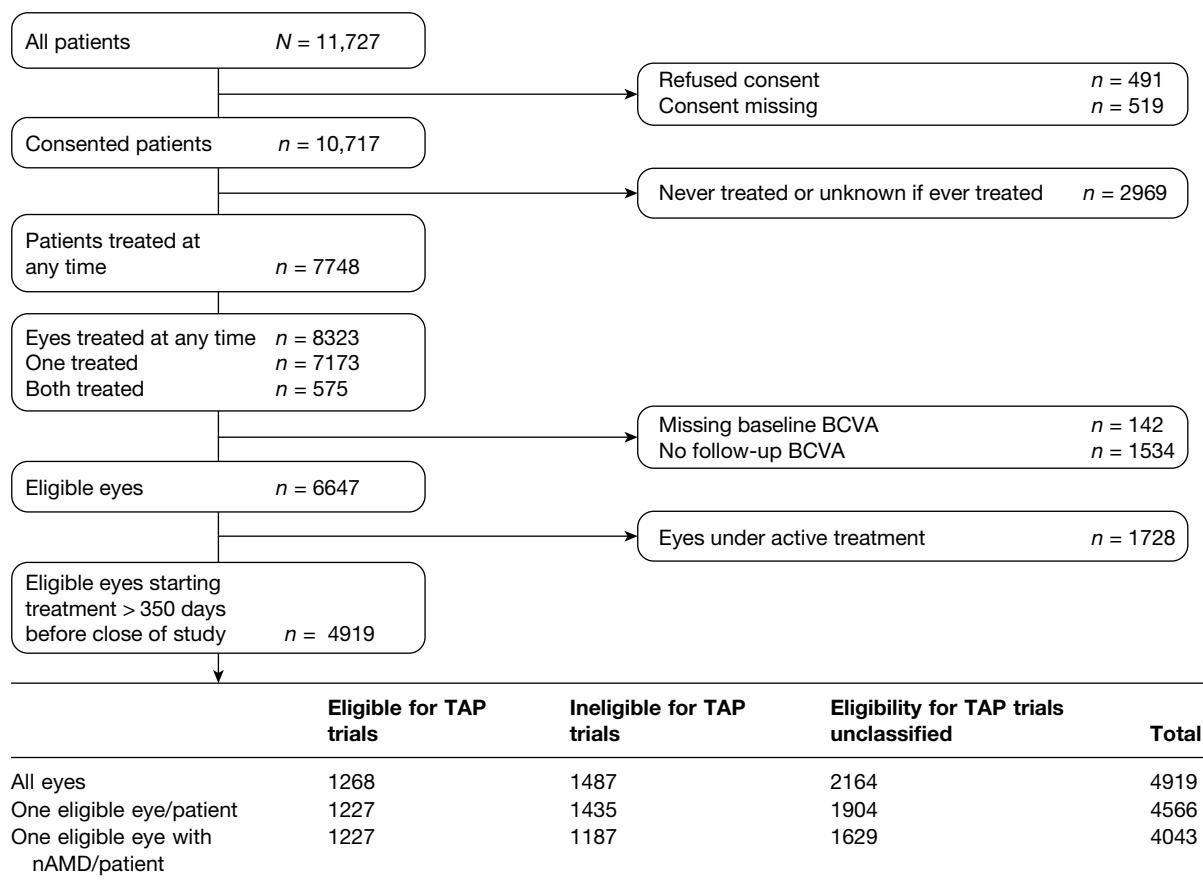
FIGURE 5 Consolidated Standards of Reporting Trials style diagram showing the patients and eyes treated in the VPDT cohort study.

equivalent to < 1 year) before the database was locked and the study was closed, leaving 4919 eyes in 4566 patients. Patients with CNV caused by nAMD made up 88.5% of these. The characteristics of the 6647 eyes are summarised in *Table 7*. Very few had had prior laser photocoagulation. The mean BCVA at baseline was 50.4 letters and the mean CS was 22.7 letters. The characteristics of the treated CNV lesions that were independently graded are summarised in *Table 8*. The majority of lesions had a greatest linear dimension of fewer than three disc areas (1892/2957, 64.0%), were subfoveal or juxtafoveal (2459/2756, 89.2%), were composed of > 50% classic CNV (1943/2777, 70.0%) and were without occult CNV (2243/2773, 80.9%).

Subgroup of patients with choroidal neovascularisation caused by neovascular (wet) age-related macular degeneration

As described previously (see *Classification of treatment as active or completed*), patients still under active treatment when the study closed were not included in the main analyses because of the risk of bias. It was challenging to include second eyes in the main analyses because most second eyes developed nAMD and received a first treatment at varying times after the first. Thus, a second eye was often still under active treatment or it was ≤ 350 days since the first eye had completed treatment or underwent a first treatment > 350 days before the study was closed. Restricting the analysis to one eye per patient excluded a further 8% of treated eyes. Given the marketing authorisation for verteporfin, CNV lesions caused by nAMD were of particular interest; after excluding treated eyes with non-AMD aetiology, a total of 4043 eyes remained.

TABLE 6 Baseline characteristics of eligible patients (column percentages within characteristic unless otherwise stated)

Patient characteristic	Number of patients first treated > 350 days before the end of the study	Number of patients first treated ≤ 350 days before the end of the study	Total
Total eligible patients (see *Figure 3*)	4566	1655	6221
Gender			
Male	1893 (41.5%)	689 (41.6%)	2582 (41.5%)
Female	2658 (58.2%)	962 (58.1%)	3620 (58.2%)
Missing	15 (0.3%)	4 (0.2%)	19 (0.3%)
Age (years)			
Median	78	79	78
Interquartile range	72–83	73–84	72–83
Range	8–102	14–102	8–102
Age group			
< 50 years	203 (4.6%)	61 (3.7%)	264 (4.2%)
≥ 50 to < 65 years	345 (7.6%)	120 (7.3%)	465 (7.5%)
≥ 65 to < 75 years	993 (21.7%)	319 (19.3%)	1312 (21.1%)
≥ 75 to < 85 years	2180 (47.7%)	805 (48.6%)	2985 (48.0%)
≥ 85 years	845 (18.5%)	350 (21.1%)	1195 (19.2%)
Smoking history			
Unknown	775 (17.0%)	164 (9.9%)	939 (15.1%)
Current smoker	617 (13.5%)	215 (13.0%)	832 (13.4%)
Ex-smoker	1543 (33.8%)	549 (33.2%)	2092 (33.6%)
Never smoked	1631 (35.7%)	727 (43.9%)	2358 (37.9%)

The baseline characteristics of this subset of patients and eyes are shown in *Table 9*, which breaks down the data according to whether patients/eyes were classified as EFT, IFT or UNC. In the EFT group, predominantly classic CNV was present in 86.7% (1064/1227) and minimally classic in 13.3% (163/1227). In the IFT group, predominantly classic CNV was present in 52.9% (628/1187) and minimally classic in 47.1% (559/187). The mean baseline logMAR BCVA was 50 letters (20/100) in the treated eye, which was very similar to study eyes of patients randomised in the TAP trials (53 letters).[3]

TABLE 7 Baseline characteristics of eligible eyes (column percentages within characteristic unless otherwise stated)

Visual function measure	Number of eyes first treated > 350 days before the end of the study	Number of eyes ≤ 350 days before the end of the study	Total
Total eligible eyes (see *Figure 3*)	4919	1728	6647
Visual acuity at baseline (first treatment visit)			
Mean BCVA (SD)	50.4 (16.0)	50.6 (15.5)	50.4 (15.9)
Median (interquartile range)	51 (39–62)	51 (40–62)	51 (40–62)
Number of ETDRS letters read			
> 73	356 (7.2%)	122 (7.1%)	478
> 53 to ≤ 73	1838 (37.4%)	640 (37.0%)	2478
> 33 to ≤ 53	2089 (42.5%)	767 (44.4%)	2856
≤ 33	626 (12.7%)	195 (11.3%)	821
CF, HM, PL, NPL	10 (0.2%)	2 (0.1%)	12
Contrast sensitivity			
Mean contrast sensitivity (SD)	22.8 (7.6)	22.4 (7.6)	22.7 (7.6)
Median (interquartile range)	24 (18–28)	24 (18–28)	24 (18–48)
Number of CS letters read			
0	45 (0.9%)	26 (1.5%)	71
> 0 and ≤ 18	684 (13.9%)	224 (13.0%)	908
> 18 and ≤ 24	828 (16.8%)	300 (7.2%)	1128
> 24 and ≤ 28	580 (11.8%)	188 (17.4%)	768
> 28	679 (7.2%)	210 (12.1%)	889
Missing	2103 (13.8%)	780 (45.1%)	2883
Evidence of prior laser photocoagulation	12	3	15

CF, counting fingers; HM, hand movements; NPL, no perception of light; PL, perception of light.

TABLE 8 Lesion characteristics for eligible eyes from independent grading of FA (column percentages within characteristic unless otherwise stated)

Lesion characteristic	Number of eyes first treated > 350 days before the end of the study	Number of eyes first treated ≤ 350 days before the end of the study	Total
Total eligible eyes (see *Figure 3*)	4919	1728	6647
Eligible eyes with an independently graded baseline angiogram	3182 (64.7%)	943 (54.6%)	4125 (62.1%)
Lesion area, disc areas			
≤ 3	2225 (69.9%)	669 (70.9%)	2894 (70.2%)
> 3 to ≤ 6	400 (12.6%)	140 (14.8%)	540 (13.1%)
> 6 to ≤ 9	94 (3.0%)	33 (3.5%)	127 (3.1%)
> 9	54 (1.7%)	18 (1.9%)	72 (1.7%)
Missing or could not be graded	409 (12.9%)	83 (8.8%)	492 (11.9%)
Greatest linear dimension, disc area			
≤ 3	1892 (59.5%)	549 (58.2%)	2441 (59.2%)
> 3 to ≤ 6	966 (30.4%)	310 (32.9%)	1276 (30.9%)
> 6 to ≤ 9	90 (2.8%)	26 (2.8%)	116 (2.8%)
> 9	9 (0.3%)	4 (0.4%)	13 (0.3%)
Missing or could not be graded	225 (7.1%)	54 (5.7%)	279 (6.8%)
Lesion area composed of CNV			
0%	1 (0.0%)	0 (0.0%)	1 (0.0%)
> 0% and < 50%	355 (11.2%)	121 (12.8%)	476 (11.5%)
≥ 50% and < 100%	1305 (41.0%)	377 (40.0%)	1682 (40.8%)
100%	1031 (32.4%)	352 (37.3%)	1383 (33.5%)
Missing or could not be graded	490 (15.4%)	93 (9.9%)	583 (14.1%)
CNV location			
Extrafoveal	297 (9.3%)	99 (10.5%)	396 (9.6%)
Juxtafoveal	408 (12.8%)	94 (10.0%)	502 (12.2%)
Subfoveal	2051 (64.5%)	660 (70.0%)	2711 (65.7%)
Missing or could not be graded	426 (13.4%)	90 (9.5%)	516 (12.5%)
Lesion area composed of classic CNV			
≥ 50% to < 100%	1943 (61.1%)	585 (62.0%)	2528 (61.3%)
> 0% to < 50%	588 (18.5%)	200 (21.2%)	788 (19.1%)
0%	246 (7.7%)	75 (8.0%)	321 (7.8%)
Missing or could not be graded	405 (12.7%)	83 (8.8%)	488 (11.8%)
Evidence of occult CNV			
≥ 50%	402 (12.6%)	142 (15.1%)	544 (13.2%)
> 0 and < 50%	128 (4.0%)	22 (2.3%)	150 (3.6%)
0%	2243 (70.5%)	696 (73.8%)	2939 (71.2%)
Missing or could not be graded	409 (12.9%)	83 (8.8%)	492 (11.9%)

TABLE 8 Lesion characteristics for eligible eyes from independent grading of FA (column percentages within characteristic unless otherwise stated) (*continued*)

Lesion characteristic	Number of eyes first treated > 350 days before the end of the study	Number of eyes first treated ≤ 350 days before the end of the study	Total
Lesion included blood			
Yes	1285 (40.4%)	367 (38.9%)	1652 (40.0%)
No	1647 (51.8%)	522 (55.4%)	2169 (52.6%)
Questionable	34 (1.1%)	7 (0.7%)	41 (1.0%)
Missing or could not be graded	216 (6.8%)	47 (5.0%)	263 (6.4%)
Lesion with blocked hypofluorescence not caused by visible blood			
Yes	655 (20.6%)	154 (16.3%)	809 (19.6%)
No	2298 (72.2%)	740 (78.5%)	3038 (73.6%)
Questionable	13 (0.4%)	2 (0.2%)	15 (0.4%)
Missing or could not be graded	216 (6.8%)	47 (5.0%)	263 (6.4%)
Serious pigment epithelial detachment			
Yes	117 (3.8%)	44 (4.7%)	161 (3.9%)
No	2842 (89.3%)	852 (90.3%)	3694 (89.6%)
Questionable	7 (0.2%)	0 (0.0%)	7 (0.2%)
Missing or could not be graded	216 (6.8%)	47 (5.0%)	263 (6.4%)

TABLE 9 Baseline characteristics of patients with nAMD, categorised by eligibility for the TAP trials

Baseline characteristics	EFT[b] (*n* = 1227)	IFT (*n* = 1187)	UNC (*n* = 1629)	Total (*n* = 4043)
Mean age, years (SD)	78.8 (7.17)	78.3 (8.31)	78.7 (8.66)	78.6 (8.13)
Male, *n* (%)	513 (41.9%)	612 (42.8%)	768 (40.5%)	1893 (41.6)
Smoking status, n *(%)*				
Current smoker	170 (16.4%)	158 (16.5)	211 (15.5)	539 (16.1)
Ex-smoker	437 (42.1%)	415 (43.5)	574 (42.1)	1426 (42.5)
Never smoked	432 (41.6%)	382 (40.0)	579 (42.5)	1393 (41.5)
BCVA, letters (SD)	50.6 (10.4)	50.2 (19.0)	48.7 (15.7)	49.7 (15.5)
BCVA group, n *(%)*				
> 73 ETDRS letters	–	144 (12.1)	79 (4.9)	223 (5.5)
73–34 ETDRS letters	1227 (100%)	766 (64.5)	1311 (80.5)	3304 (81.7)
< 34 ETDRS letters	–	277 (23.3)	239 (14.7)	516 (12.0)
CS, letters (SD)[a]	22.4 (6.89)	23.0 (7.67)	22.1 (7.59)	22.5 (7.38)
Lesion area, median mm² (interquartile range)				
All lesions	*n* = 1215	*n* = 1158	*n* = 25	*n* = 2398
	3.81 (1.8–6.8)	2.58 (0.9–6.4)	4.20 (1.8–5.0)	3.28 (1.4–6.6)
Predominantly classic	*n* = 1058	*n* = 621		
	3.46 (1.7–6.2)	1.80 (0.6–4.7)		
Minimally classic	*n* = 157	*n* = 537		
	6.66 (4.2–11)	3.90 (1.6–8.4)		

continued

TABLE 9 Baseline characteristics of patients with nAMD, categorised by eligibility for the TAP trials (*continued*)

Baseline characteristics	EFT[b] (*n* = 1227)	IFT (*n* = 1187)	UNC (*n* = 1629)	Total (*n* = 4043)
Lesion area, n *(%)*				
Predominantly classic	*n* = 1064	*n* = 628		
≤ 3 DA	868 (81.6%)	557 (88.7%)		
> 3 DA ≤ 6 DA	152 (14.3%)	56 (9.0%)		
> 6 DA ≤ 9 DA	28 (2.6%)	13 (2.1%)		
> 9 DA	16 (1.5%)	2 (0.3%)		
Minimally classic	*n* = 163	*n* = 559		
≤ 3 DA	90 (55.2%)	389 (69.6%)		
> 3 DA ≤ 6 DA	50 (30.7%)	114 (20.4%)		
> 6 DA ≤ 9 DA	14 (8.6%)	35 (6.3%)		
> 9 DA	9 (5.5%)	21 (3.8%)		
CNV location, n *(%)*				
	n = 1227	*n* = 1187		*n* = 2414
Subfoveal	1227 (100%)	586 (49.4%)		1813 (75.1%)
Juxtafoveal	0 (0%)	349 (29.4%)		349 (14.5%)
Extrafoveal	0 (0%)	252 (21.2%)		252 (10.4%)
Lesion % classic CNV, n *(%)*				
	n = 1227	*n* = 1187		*n* = 2414
≥ 50%	1064 (86.7%)	628 (53.0%)		1692 (70.1%)
> 0% < 50%	163 (13.3%)	351 (29.6%)		514 (21.3%)
0%	0 (0.0%)	208 (17.5%)		208 (8.6%)
Occult CNV present, *n* (%)	*n* = 1227	*n* = 1187		*n* = 2414
	197 (16.1%)	303 (25.5%)		500 (20.7%)
Blood present in lesion, *n* (%)	*n* = 1227	*n* = 1187		*n* = 2414
	600 (49.9%)	532 (44.9%)		1132 (46.9%)
SPED present in lesion, *n* (%)	*n* = 1227	*n* = 1187		*n* = 2414
	11 (0.9%)	86 (7.3%)		97 (4.0%)

DA, disc areas; SPED, serous pigment epithelial detachment.
Contrast sensitivity was assessed by only 18 centres. Therefore, the averages and SDs are calculated for a sample of 2289 patients (797, 654 and 838 in EFT, IFT and UNC groups respectively).
Eyes classified as EFT met the following eligibility criteria for the TAP trials: aetiology AMD; BCVA 73–34 letters; subfoveal CNV; CNV comprising ≥ 50% of lesion; classic CNV > 0%.

Chapter 6

Results (2) – objectives A, B, C and D

A: Is verteporfin photodynamic therapy in the NHS provided as in randomised trials?

The analysis for objective A focused on provision of VPDT in the year following the first treatment. Given that TAP trials required prospective participants to have CNV from nAMD, the analysis was based on only the subgroup of patients with CNV from nAMD who were classified as having completed their treatment ($n = 4043$), with one eye per patient.

Is treatment administered at the same frequency as in the randomised trials?

The numbers of VPDT treatments administered in years 1 and 2 by TAP eligibility status (i.e. groups EFT, IFT and UNC) are shown in *Tables 10* and *11*. In year 1 of the VPDT cohort study (≤ 350 days after the first treatment), fewer treatments were administered (average 2.35) than in year 1 in the TAP trials (average 3.4). We compared the numbers of patients having one, two, three and four treatments in year 1 in the VPDT cohort study and in the TAP trials, which differed significantly ($\chi^2 = 615.2$, degrees of freedom 4, $p < 0.0001$).[4,30] The average number of treatments for each of the TAP eligibility groups in the VPDT cohort study was EFT 2.47, IFT 2.31 and UNC, 2.29. The numbers of patients having one, two, three and four treatments in year 1 also differed significantly between groups ($\chi^2 = 364.3$, degrees of freedom 8, $p < 0.0001$).

When considering treatment frequencies in year 2, we had data on 1611 patients who had completed treatment for year 2 of study (see *Chapter 4, Definition of year 1 and year 2*). The average number of treatments administered to these patients was 0.40, compared with 2.2 in the TAP trials. In year 2, the numbers of treatments administered cannot be compared because the distribution of treatments in the TAP trials in year 2 was not reported. The average number of treatments for each of the TAP eligibility groups was EFT 0.40, IFT 0.37 and UNC, 0.43. Unlike year 1, the numbers of patients having one, two, three and four treatments in year 2 did not differ significantly between groups ($\chi^2 = 6.62$, degrees of freedom 6, $p = 0.36$).

Is treatment duration the same as in the randomised trials?

As described in *Chapter 3*, *Data collection and management*, the VPDT manual of operations set out a schedule for follow-up and retreatment. This schedule was intended to approximate the follow-up and retreatment guidance provided in the TAP trials, that is patients should be expected to be observed over a period of 2 years with retreatment every 3 months if required. The treatment frequencies described in *Is treatment administered at the same frequency as in the randomised trials?* show that much less treatment was administered in the study than would have been expected on the basis of the TAP trials.

Based on our definition of a completed treatment episode (see *Chapter 4*, *Classification of treatment as active or completed*), we constructed a Kaplan–Meier curve describing 'survival' until completion of the treatment episode for the 4566 patients who had data for one eye starting treatment > 350 days before the close of the study, shown in *Figure 6*. This figure shows that just over 50% of eyes completed the treatment episode in < 1 year. Thus, not only were fewer treatments administered in the study than in the TAP trials, but also the duration of review of patients' CNV status was shorter than in the TAP trials for the majority of treatment episodes.

TABLE 10 Numbers of treatments in year 1 (≤ 350 days) in patient groups categorised by eligibility for the TAP trial (i.e. EFT, IFT, UNC)

Treatments in year 1	EFT (N = 1227)		IFT (N = 1187)		UNC (N = 1629)		Total patients (N = 4043)	
	n	%	n	%	n	%	n	%
1	255	20.8	307	25.9	425	26.1	987	24.4
2	377	30.7	400	33.7	571	35.1	1348	33.3
3	364	29.7	292	24.6	384	23.6	1040	25.7
4	224	18.3	181	15.3	229	14.1	634	15.7
5	6	0.5	7	0.6	18	1.1	31	0.8
6	1	0.1	0	0.0	2	0.1	3	0.1

TABLE 11 Numbers of treatments in year 2 (> 350 and ≤ 715 days) in patient groups categorised by eligibility for the TAP trial (i.e. EFT, IFT, UNC)

Treatments in year 2	EFT (N = 533)		IFT (N = 478)		UNC (N = 600)		Total patients (N = 1611)[a]	
	n	%	n	%	n	%	n	%
0	392	73.6	348	72.8	425	70.8	1165	72.3
1	90	16.9	89	18.6	112	18.7	291	18.1
2	33	6.2	35	7.3	46	7.7	114	7.1
3	14	2.6	4	0.8	14	2.3	32	2.0
4	4	0.8	2	0.4	3	0.5	9	0.6

a   The total number of patients (1611) represents those among the 4043 patients who had their first treatment > 2 years before the date of last data submission.
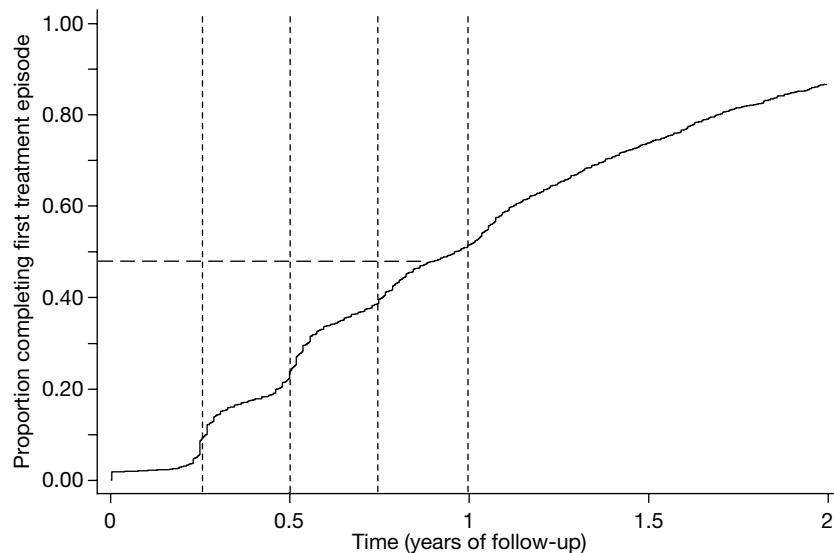
FIGURE 6 Time to completion of treatment episode; Kaplan–Meier graph showing the cumulative proportion of eyes completing the first treatment episode.

B: Is 'outcome' the same in the NHS as in randomised trials?

This analysis included 4043 eyes of the 4043 patients who had a diagnosis of nAMD and a first treatment > 350 days before the close of the study. As described in *Chapter 4*, *Definition of 'TAP' eligibility*, eyes were classified as EFT, IFT or UNC. BCVA outcome in the EFT subgroup was of primary interest in addressing objective B. In order to maximise the power of the analysis, all three subgroups were included in one mixed regression analysis that included the TAP eligibility subgroup and baseline lesion classification (predominantly classic, minimally classic, occult only; *Table 12*). The possibility of a differing gradient of change over time by subgroup was tested by fitting an interaction of TAP eligibility subgroup and time, but this was found to be non-significant and was excluded from the final model.

We compared descriptively the change in BCVA in the two angiographic subtypes in our study with those previously reported for treatment and sham treatment arms in the TAP trials (*Figure 7*).[4,30] Both the fitted trajectory and the absolute changes in BCVA over time for patients with predominantly classic lesions in the EFT group were similar to those for patients in the TAP treatment arm. For eyes with minimally classic lesions in the EFT group, the *trajectory* of BCVA was parallel to that observed for the minimally classic subgroup of the TAP treatment arm but showed less absolute loss of BCVA (*Figure 8*).[4,30]

Baseline lesion classification influenced outcome. Within the EFT group, eyes with minimally classic CNV had better BCVA at baseline (+1.13 letters; see *Table 12*) and deteriorated more slowly than eyes with predominantly classic CNV (+1.13 + 2.08 = +3.2 letters at 1 year; see *Table 12*).

The influences of several covariates on BCVA were also investigated, partly because the covariates could have confounded the influences of the TAP eligibility subgroup and baseline lesion classification, and partly because their possible influences were of interest in their own right. The coefficients from the final mixed regression model, shown in *Table 12*, show that a number of baseline covariates did indeed influence BCVA. None of these statistically significant covariates interacted with the TAP eligibility subgroup, so they can be considered to apply equally to the EFT, IFT and UNC subgroups.

The rate of deterioration of BCVA was influenced by baseline acuity, with faster decline in BCVA over time in eyes with better starting acuity; a patient who read five letters more than average at baseline read only 2.7 letters more at 1 year. BCVA deteriorated faster in older patients; after 1 year of follow-up, BCVA was two letters worse for a person 10 years older than average (88 vs 78 years). Women presented with better baseline BCVA and maintained this difference during follow-up (+1.8 letters). Ex-smokers and those who had never smoked presented with better baseline BCVA (+1.6 and +1.8 letters respectively) and deteriorated more slowly than current smokers. The decrease in BCVA by 1 year was one letter fewer in treated eyes of ex-smokers, and three letters fewer in treated eyes of never smokers, than in treated eyes of current smokers. If the fellow eye had better BCVA than the treated eye, BCVA in the treated eye was worse at baseline (+2.6 letters) and deteriorated faster; the decrease in BCVA by 1 year was five letters worse than if the treated eye was classified as the better-seeing eye. The decrease in BCVA over 1 year was 8 to 16 letters depending on patients' characteristics and lesion factors (see *C: Is 'outcome' the same for patients excluded from randomised trials?* below).

TABLE 12 Influence of covariates on baseline BCVA and change in BCVA over time

Covariate	Regression coefficient	95% CI	*p*-value
Time (per year)	−15.68	−17.78 to −13.59	<0.0001
Time^2 (per year)	3.33	2.74 to 3.92	<0.0001
TAP eligibility			
EFT group	0.00	–	
IFT group	1.42	0.17 to 2.67	0.026
% of lesion classified as classic			0.014[b]
≥50%	0.00	–	–
>0% and <50%	1.13	−0.44 to 2.70	0.158
0%	3.43	1.04 to 5.83	0.005
Unknown % classic	1.50	0.29 to 2.72	0.016
% of lesion classified as classic×time[a]			0.031[b]
≥50%	0.00	–	–
>0% and <50%	2.08	0.38 to 3.77	0.016
0%	2.79	0.20 to 5.38	0.035
Unknown % classic	0.77	−0.45 to 1.98	0.218
Age (year)	−0.20	−0.26 to −0.14	<0.0001
Age×time[a]	−0.29	−0.36 to −0.22	<0.0001
Baseline ETDRS[7] (per letter)	0.743	0.70 to 0.77	<0.0001
Baseline ETDRS[7] (per letter)×time[a]	−0.20	−0.23 to −0.16	<0.0001
Gender			
Male	1.00	–	–
Female	1.76	0.85 to 2.67	0.0002
Smoking status			0.091[b]
Never smoked	1.00	–	–
Ex-smoker	1.89	0.34 to 3.44	0.017
Current smoker	1.59	0.01 to 3.18	0.049
Unknown smoking status	2.03	0.10 to 3.96	0.039
Smoking status×time[a]			0.002[b]
Never smoked	1.00	–	–
Ex-smoker	1.09	−0.66 to 2.83	0.223
Current smoker	3.03	1.28 to 4.78	0.0007
Unknown smoking status	1.21	−0.78 to 3.20	0.233
BCVA in fellow eye			<0.0001[b]
Fellow worse	1.00	–	–
Fellow similar to treated eye	−2.12	−3.46 to −0.77	0.002
Fellow better	−2.57	−3.73 to −1.40	<0.0001
BCVA in fellow eye x time[a]			<0.0001[b]
Fellow worse	1.00	–	–
Fellow similar to treated eye	−1.53	−3.04 to −0.02	0.0471
Fellow better	−5.16	−6.52 to −3.79	<0.0001

CI, confidence interval.
a   Interactions with time, implying that the rate of change in BCVA over time was influenced by the baseline line covariate.
b   *p*-value for overall factor (i.e. across multiple categories).
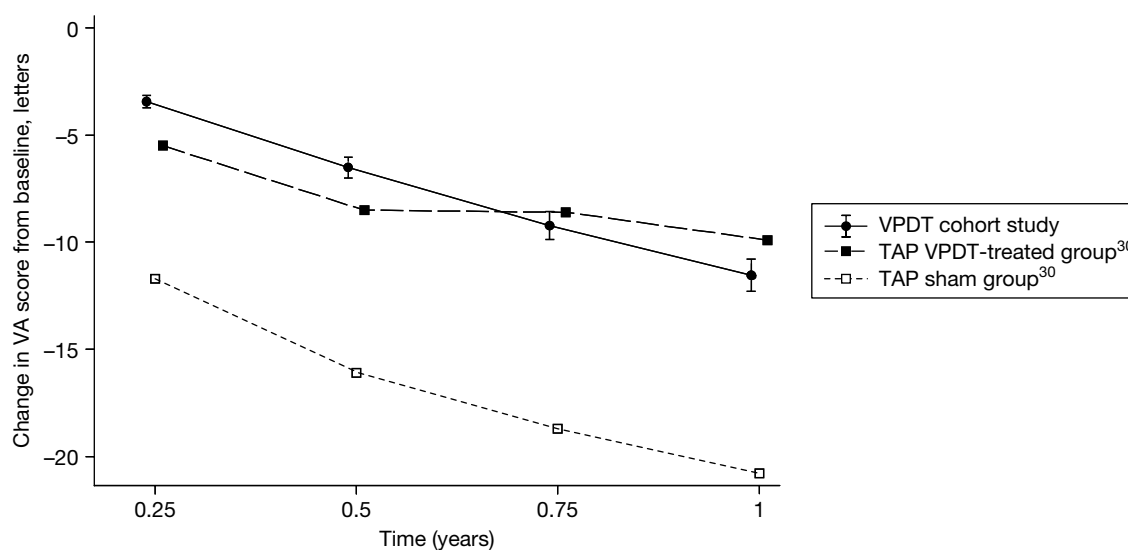
FIGURE 7 Change in BCVA from baseline in eyes classified as EFT with predominantly classic CNV. Confidence intervals are not shown for TAP groups because they were not reported.[30]
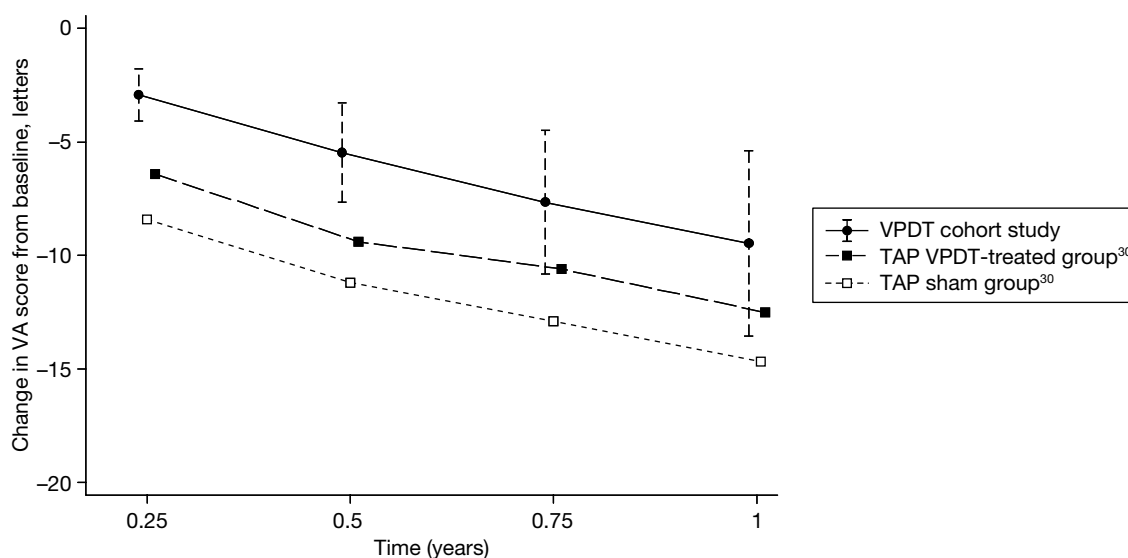
FIGURE 8 Change in BCVA from baseline in eyes classified as EFT with minimally classic CNV. Confidence intervals are not shown for TAP groups because they were not reported.[30]

C: Is 'outcome' the same for patients ineligible from randomised trials?

The mixed regression analysis addressing this objective was the same as the one used to address objective B given that we did not find an interaction of TAP eligibility subgroup and time. BCVA outcome in the IFT subgroup, and to a lesser extent the UNC subgroup, was of primary interest in addressing objective C.

Eyes classified as IFT presented with better BCVA (+1.4 letters; see *Table 12*) than EFT eyes with predominantly or minimally classic CNV; UNC eyes also presented with better BCVA (+1.5 letters) than EFT eyes and deteriorated more slowly (+1.50 + 0.77 = +2.3 letters at 1 year; see *Table 12*); these eyes were UNC because there were no corresponding independently graded FA findings, and so, by definition, they had unknown lesion percentages classified as classic and occult. Eyes with occult only lesions (a subgroup of IFT eyes) were better by +3.4 letters at baseline and were observed to deteriorate more slowly (+3.43 + 2.79 = +6.2 letters at 1 year).

D: Is verteporfin photodynamic therapy safe when provided in the NHS?

The analysis was carried out on the cohort of patients who were treated at any time, that is $n = 7748$ (see *Figure 5*). This larger cohort was used to address objective D because ARs and AEs were collected at all visits and did not require patients to have achieved a particular duration of follow-up. If a patient had only one treatment, then an AR documented at the time of treatment or at a subsequent follow-up visit was considered relevant. Despite defined fields in the database and on the data collection form provided (see *Figure 2*), and a stated requirement in the manual of operations that these fields should be completed at all visits, information about ARs and AEs was often missing. For example, question 8 ('Has there been an AE since the last visit or an AR at this visit?') was often not completed or, when one of these fields was ticked 'yes', the specific AR/ AE form was not completed.

The analysis of safety was complex because both ARs (at the time of treatment) and AEs (documented at the subsequent visit and attributed to the previous treatment) could in principle be either 'systemic', affecting the whole patient, or 'ocular', affecting a particular eye. However, ARs tended to be systemic (e.g. systemic AR = back pain, a known side effect of VPDT and an AR that was documented in the TAP trials) and AEs tended to be ocular (e.g. ocular AE = drop in BCVA > 20 letters within 7 days of treatment or intraretinal haemorrhage).

The cohort of 7748 patients had a total of 31,640 visits documented. Treatment was administered at 17,809 (56.3%) visits. ARs and AEs were reported infrequently, with total numbers of 216 (1.2%) and 253 (1.4%) respectively. The distributions of ARs and AEs by visit (with AEs attributed to the previous treatment visit) are shown in *Figures 9* and *10*. The high frequency of ARs and AEs associated with the first treatment is, to some extent, explained by the fact that the number of patients having a first treatment was higher than the number of patients having a subsequent visit. However, the proportion of treated visits at which ARs and AEs were reported/ attributed declined from a maximum of 1.4% and 2.0%, respectively, for visit 1 to 0.3 and 0.9%, respectively, by visit 4 with no ARs or AEs being reported beyond visit 8. Thus, an AR or AE was much more likely to be reported or attributed to visit 1 than to subsequent visits. Therefore, analysis focused only on ARs and AEs reported at visit 1 because treatments on visit 1 were most numerous and most likely to be representative of the reference population of patients who were eligible for VPDT.

The proportion of first treatment visits at which an AR was reported varied from 0% to 7.8% across centres (*Figure 11*); the overall proportion was 1.4% [exact 95% confidence interval (CI) 1.2% to 1.6%]. Back pain was documented in 86 of 7748 first treatments (1.1%); 58% of these reactions were mild, 27% moderate and 15% severe. Pain at the injection site ($n = 2$) and extravasation ($n = 1$) were rarely reported. Fifteen centres (albeit with relatively few documented treatment visits) reported no AR.

We were concerned about the compliance of centres with reporting ARs and, consequently, the danger of underestimating the risk of an AR. For comparison, the probability of an AR in the
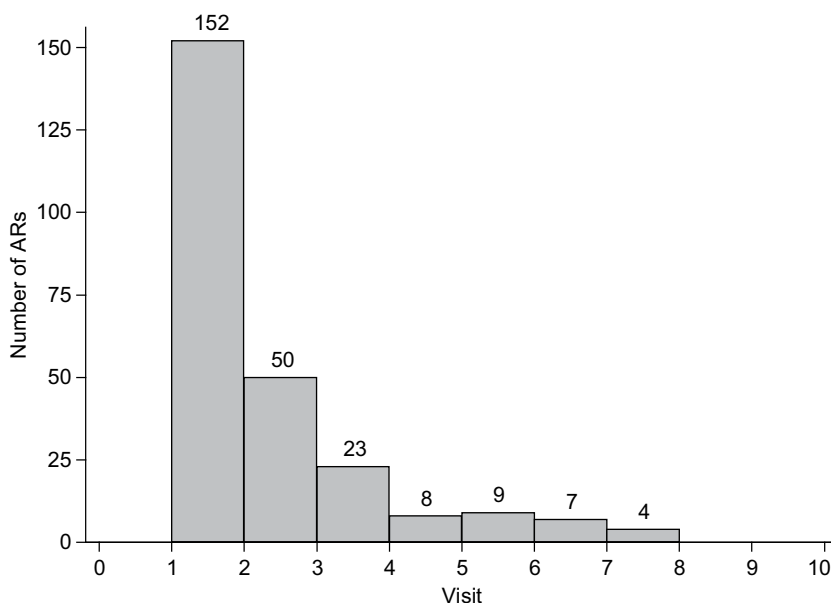
FIGURE 9 Distribution of all ARs over time since eyes were first treated.

FIGURE 10 Distribution of all AEs over time since eyes were first treated.

centre with the most documented treatment visits (1603) was 2.6% (exact 95% CI 1.8% to 3.5%). ARs were reported less frequently than in the TAP trials in which, for example, back pain was documented in association with 2.2% of VPDT treatment administrations, photosensitivity reactions with 3.0% and 'adverse events at the site of injections'[3] with 13.4% (compared with 3.4% for sham treatments).

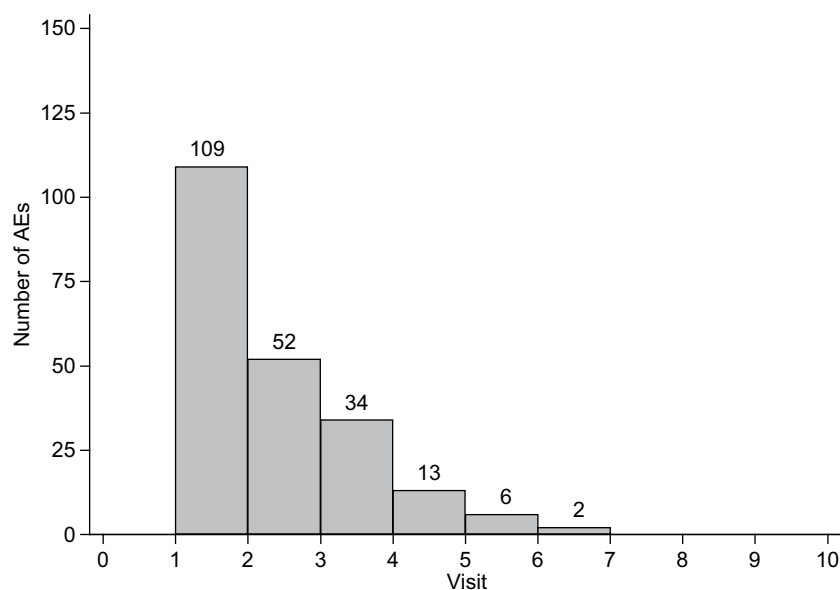Ocular AEs were also reported infrequently. The proportion of first treatment visits at which an AE was reported varied from 0% to 14.3% across centres (*Figure 12*); the overall proportion was 2.0% (exact 95% CI 1.7% to 2.2%). AEs included a sudden fall in vision reported by the patient or a documented loss of ≥ 20 letters within 7 days of treatment in 25 of 7748 first treatments (0.3%), a tear of the retinal pigment epithelium in 5 (0.1%) and diverse other AEs in 121 (1.6%).
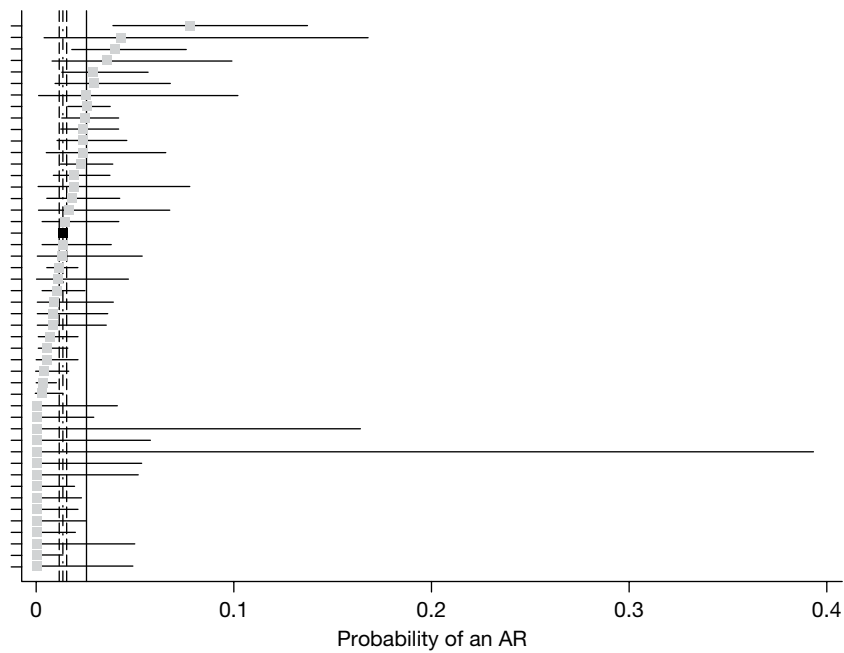
FIGURE 11 Probability of an AR at the time of the first VPDT administration. Each line represents one participating site, ordered by the mean site-specific probability. The vertical dashed lines represent the overall mean probability and 95% confidence interval across all participating sites. The solid vertical line represents the mean probability for the site which submitted data for the most treated patients and which was judged to have complied relatively well with the instructions for recording AEs.
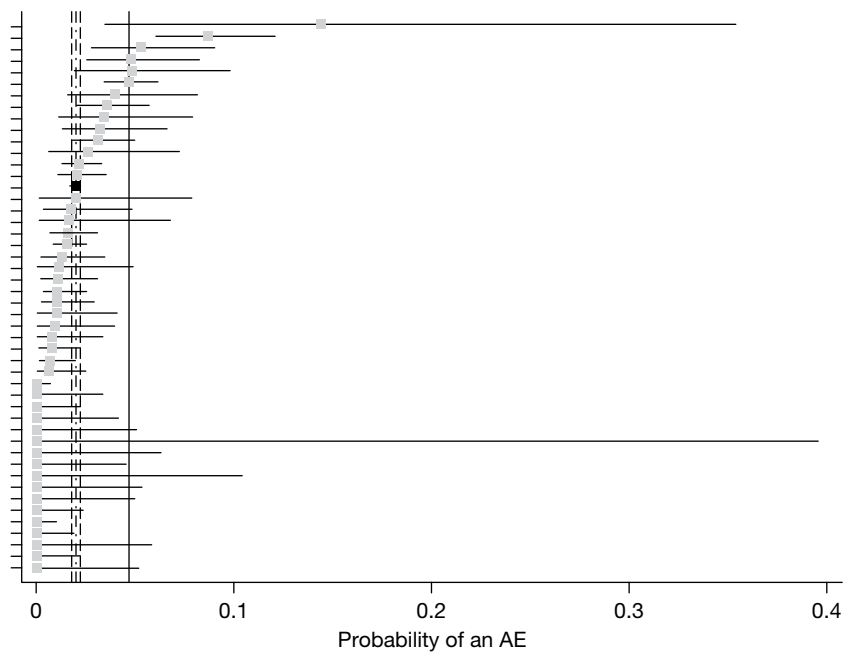
FIGURE 12 Probability of an AE associated with the first VPDT administration. Each line represents one participating site, ordered by the mean site-specific probability. The vertical dashed lines represent the overall mean probability and 95% CI across all participating sites. The solid vertical line represents the mean probability for the site which submitted data for the most treated patients and which was judged to have complied relatively well with the instructions for recording AEs.

AEs, like ARs, were reported less frequently than in the TAP trials, in which 'visual disturbance' was documented in association with 17.7% of VPDT treatment administrations compared with 11.6% of sham treatments, and vitreous haemorrhage with 1.0% (compared with 0.5% of sham treatments).[3]

The variation between centres in the proportion of treatment visits in which an AE was reported was greater than expected; 70% (33/47; 95% CI 55% to 83%) had a centre-specific proportion below the overall proportion. We attributed this to poor compliance in reporting AEs that would have biased downwards the overall estimate of the probability of an AE. In order to estimate a more representative overall proportion, we excluded data for two centres which reported a proportion for visit 1 with a *centre-specific* upper 95% confidence limit below the lower 95% confidence limit for the *entire* cohort. The overall proportion increased to 2.1% (exact 95% CI 1.9% to 2.4%). For comparison, the probability of an AE in the centre with the most documented treatment visits (1603) was 4.6% (exact 95% CI 3.6% to 5.8%).

Chapter 7

Results (3) – objective E

How effective is verteporfin photodynamic therapy with respect to best-corrected monocular distance visual activity?

Chapter 6 reports outcomes of VPDT in comparison with the TAP trials, that is the change in BCVA over time. As the VPDT cohort study did not have a control group, effectiveness could be estimated only indirectly. Although we considered three ways to do this, we were able to apply only the second method (see *Chapter 4*, *E: How effective and cost-effective is verteporfin photodynamic therapy?*).

In terms of BCVA, this method was, in effect, the comparison in change in BCVA over time reported in *Chapter 6*. Both the fitted trajectory and the average absolute change in BCVA over time for patients with predominantly classic lesions in the EFT group were similar to those for patients in the TAP treatment arm. For eyes with minimally classic lesions in the EFT group, the trajectory of BCVA was parallel to that observed for the minimally classic subgroup of the TAP treatment arm, but showed less absolute loss of BCVA (see *Figures 7* and *8*).

For HRQoL outcomes, no similar comparison could be made because HRQoL data were not reported for participants in the TAP trials.

How effective is verteporfin photodynamic therapy with respect to health-related quality of life?

Absence of HRQoL outcome in the TAP trials was a major limitation with respect to the NICE technology appraisal of VPDT. Therefore, describing the change in HRQoL with treatment was a key objective of the study. We aimed to do this by quantifying the extent to which BCVA predicted HRQoL.

The subgroup of 18 centres collected and submitted BCVA, CS and HRQoL data for 3262 visits for 1829 patients (*Tables 13* and *14*). Most data were available for visits at 0, 6 and 12 months, as planned, but data for many patients were also available for 3 and 9 months; 53% of patients had data for two or more visits [one visit, 47%; two visits, 33%; three visits, 16%; more than three visits (maximum six), 4%].

Generic health-related quality of life

Best-corrected monocular distance visual acuity: in the better-seeing eye strongly predicted SF-6D, physical component score (PCS) and mental component score (MCS) ($p < 0.0001$ for all three HRQoL measures). For each HRQoL measure, the best-fitting models were linear. No evidence was found to support the hypothesis of a sigmoid relationship. We also did not observe any tendency at all for gradients to decrease with the duration of follow-up. The relationship between BCVA in the better-seeing eye and the SF-6D utility score is shown in *Figure 13*, with the fitted regression superimposed on a scatterplot of the raw data. Predicted changes in SF-6D, PCS and MCS for 5- and 100-letter reductions in BCVA are shown in *Table 15*.

TABLE 13 Numbers of patients with data for BCVA in the best-seeing eye and HRQoL instrument for different HRQoL instruments and durations since first treatment

HRQoL instrument	Duration of follow-up in months						Total
	0	3	6	9	12	>12	
SF-36 – PCS	1196	116	680	158	459	383	2992
SF-36 – MCS	1196	116	680	158	459	383	2992
SF-6D	1156	117	683	152	469	385	2962
NEIVFQ – composite	1270	130	739	174	504	435	3252
NEIVFQ – distance activities	1267	129	736	174	504	434	3244
NEIVFQ – near activities	1268	130	739	174	504	435	3250

TABLE 14 Numbers of patients with data for CS in the best-seeing eye and HRQoL instrument for different HRQoL instruments and durations since first treatment

HRQoL instrument	Duration of follow-up (months)						Total
	0	3	6	9	12	>12	
SF-36 – PCS	1122	82	599	108	392	320	2623
SF-36 – MCS	1122	82	599	108	392	320	2623
SF-6D	1084	81	605	104	401	325	2600
NEIVFQ – composite	1187	89	649	119	428	356	2828
NEIVFQ – distance activities	1184	88	647	119	428	355	2821
NEIVFQ – near activities	1185	89	649	119	428	356	2826
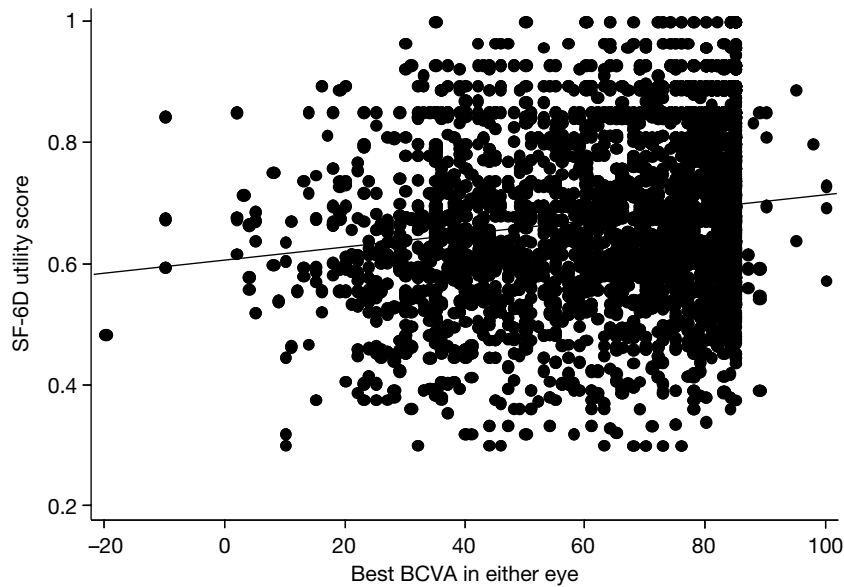
FIGURE 13 Scatterplot showing SF-6D preference-based measure of health (equivalent to utility score) compared with better-seeing eye BCVA. The fitted regression line (see *Table 15*) is superimposed on a scatterplot of the raw data. Values of BCVA <0 (–10 and –20) represent 'counting fingers' and 'hand movements' levels of vision respectively.

TABLE 15 Relationships between visual function and SF-6D/SF-36

HRQoL score	HRQoL scale	Linear regression coefficient (95% CI)	Quadratic regression coefficient (95% CI)	HRQoL change per five letters (≡ one chart line)[a]	HRQoL change per 100 letters (i.e. whole chart range)[a]
BCVA					
SF-6D	0–1	0.0012 (0.0009 to 0.0014)	–	0.0058	0.116
SF-36 PCS[b]	Mean = 50	0.049 (0.025 to 0.073)	–	0.245	4.906
SF-36 MCS[b]	Mean = 50	0.109 (0.078 to 0.140)	–	0.546	10.920
				HRQoL change per three letters (i.e. one contrast sensitivity triad)[a,c]	HRQoL change per 48 letters (i.e. whole chart range)[a]
CS					
SF-6D	0–1	−0.0016 (−0.0041 to 0.0009)	0.0001 (0.00003 to 0.00015)	0.014	~0.14
SF-36 PCS	Mean = 50	−0.269 (−0.476 to −0.062)	0.008 (0.003 to 0.013)	0.792	~7.7
SF-36 MCS	Mean = 50	−0.120 (−0.382 to 0.143)	0.008 (0.002 to 0.016)	1.155	~12.1

a Estimated HRQoL change assumes the change in BCVA CS occurs in the better-seeing eye.
b PCS and MCS: scored on a scale with a mean of 50 and an SD of 10. PCS and MCS are also normalised, i.e. 50 represents the mean for the reference (i.e. 'normal') population.
c Change in HRQoL estimated for a three-letter contrast sensitivity triad from 35 to 32 letters for relationships.

Contrast sensitivity in the better-seeing eye predicted SF-6D, PCS and MCS ($p < 0.01$ for all three HRQoL measures) but less strongly. The relationship between CS and the SF-6D utility score is shown in *Figure 14*, with the fitted regression superimposed. For all HRQoL measures, the best-fitting models were positive and quadratic, with the fitted values tending to an asymptote when < 15 letters could be read (see *Figure 14*). As with BCVA, no evidence was found to support the prior hypothesis of a sigmoid relationship. Predicted changes in SF-6D, PCS and MCS for three-letter (one 'triad') and 48-letter reductions in BCVA are shown in *Table 15*. The latter predicted changes are described as approximate because the quadratic models sometimes caused fitted values to increase slightly when very few letters were read. The predicted changes reported are the fitted value for 48 letters minus the minimum fitted value.

For predominantly classic nAMD lesions, VPDT was observed to confer a net benefit of 11 ETDRS and 5 CS letters after 1 year.[4,30] Based on the best-fitting model for SF-6D, these visual function benefits 'translate' into utility differences of 0.013 and 0.022 respectively (on a scale of 0–1). In the VPDT cohort study, the net BCVA benefit compared with the TAP sham VPDT group was slightly smaller, at about nine letters (see *Figure 7*); this BCVA benefit 'translates' into a utility difference of about 0.011.

For minimally classic nAMD lesions, VPDT was observed to confer a net benefit of four ETDRS letters after 1 year.[4,30] Based on the best-fitting model for SF-6D, these visual function benefits 'translate' into a utility difference of 0.005. The net BCVA benefit observed in the study, of about five letters (see *Figure 8*), 'translates' into a utility difference of about 0.006.

Vision-specific health-related quality of life

In the better-seeing eye, BCVA also strongly predicted the composite total NEIVFQ score, and the distance and near activity subscales ($p < 0.0001$ for all three NEIVFQ scores). The relationship between BCVA in the better-seeing eye and NEIVFQ composite total score is shown in *Figure 15*;
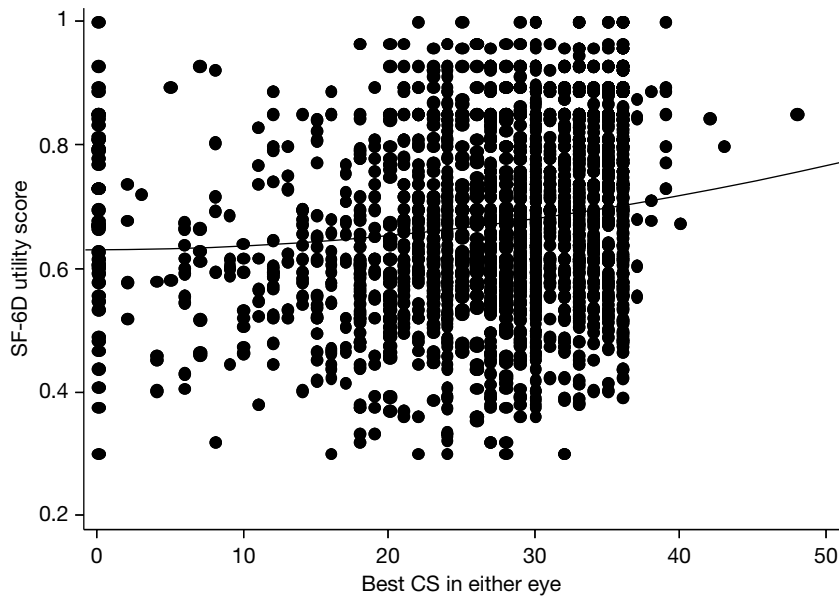
FIGURE 14 Scatterplot showing SF-6D preference-based measure of health (equivalent to utility score) compared with better-seeing eye CS. The fitted regression line (see *Table 13*) is superimposed on a scatterplot of the raw data.
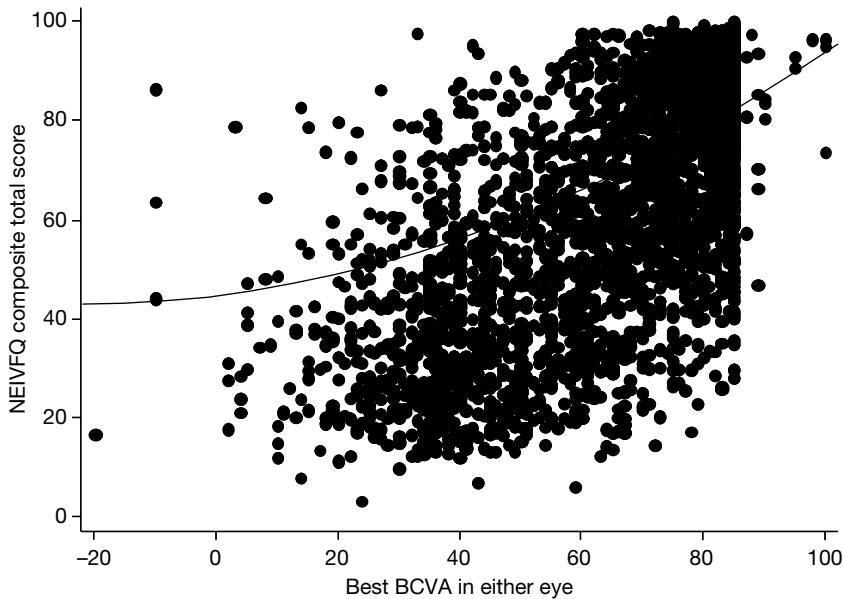
FIGURE 15 Scatterplot showing the NEIVFQ composite total score compared with better-seeing eye BCVA. The fitted regression line (see *Table 16*) is superimposed on a scatterplot of the raw data. Values of BCVA < 0 (–10 and –20) represent 'counting fingers' and 'hand movements' levels of vision respectively.

similar relationships were observed for distance and near NEIVFQ scores. Relationships were positive and quadratic and had steeper gradients (in relation to the range of BCVA) than those seen for SF-6D and SF-36 component scores. Gradients were steeper for the distance and near activities subscores than for the composite total score. Predicted changes in composite total, distance and near NEIVFQ scores for 5- and 100-letter reductions in BCVA are shown in *Table 16*. Because the functions were quadratic, the predicted NEIVFQ changes for 100-letter reductions are described as approximate.

TABLE 16 Relationships between visual function and NEIVFQ scores

| HRQoL score	HRQoL scale	Linear regression coefficient (95% CI)	Quadratic regression coefficient (95% CI)	HRQoL change per five letters (≡ one chart line)[a,b]	HRQoL change per 100 letters (i.e. whole chart range)[a]
BCVA					
NEIVFQ composite	0–100	−0.129 (−0.342 to 0.083)	0.0067 (0.0049 to 0.0085)	3.90	~55.0
NEIVFQ distance activities	0–100	0.00002 (−0.236 to 0.236)	0.0075 (0.0054 to 0.0096)	5.08	~72.5
NEIVFQ near activities	0–100	0.397 (−0.626 to −0.127)	0.0111 (0.0090 to 0.0131)	5.48	~72.8
				HRQoL change per three letters (≡ one contrast sensitivity triad)[a,b]	**HRQoL change per 48 letters (i.e. whole chart range)[a]**
CS					
NEIVFQ composite	0–100	−1.285 (−1.646 to −0.924)	0.0540 (0.0454 to 0.0625)	6.99	~44.4
NEIVFQ distance activities	0–100	−1.737 (−2.181 to −1.292)	0.0694 (0.0589 to 0.0799)	8.74	~57.6
NEIVFQ near activities	0–100	−1.967 (−2.406 to −1.527)	0.0757 (0.0653 to 0.0860)	9.32	~64.7

a　Estimated HRQoL change assumes the change in BCVA occurs in the better-seeing eye.
b　Changes in HRQoL estimated for a 5-letter drop in BCVA from 70 to 65 letters, and a 3-letter drop in CS (one triad) from 35 to 32 letters.

Similarly, CS in the better-seeing eye strongly predicted the composite total, distance and near activity NEIVFQ score ($p < 0.0001$ for all three HRQoL measures, but less strongly than BCVA). The relationship between CS and NEIVFQ core total is shown in the scatterplot in *Figure 16*; the relationships were similar for distance and near NEIVFQ scores. As for BCVA, the relationships were positive and quadratic and had steeper gradients than those observed for SF-6D, PCS and MCS scores. Predicted changes in composite total, distance and near NEIVFQ scores for 3-letter (one triad) and 48-letter reductions in CS are shown in *Table 16*. Because the functions were again quadratic, the predicted NEIVFQ changes for 48-letter reductions are again described as approximate.

Based on the best-fitting model for the NEIVFQ composite total score and an average presenting BCVA of 50 letters and CS of 23 letters, the differences in BCVA and CS observed in the TAP trials for predominantly classic nAMD lesions (11 ETDRS and 5 CS letters, respectively)[4,30] 'translate' into differences in score of about 9 and 12 respectively (on a scale of 0 to 100). In the VPDT cohort study, the net BCVA benefit was slightly smaller, at about nine letters (see *Figure 7*); this BCVA benefit 'translates' into a difference in NEIVFQ composite total score of about 7.

For minimally classic nAMD lesions, the visual benefit observed in the TAP trials of four ETDRS letters after 1 year[4,30] 'translates' into a difference in NEIVFQ composite total score of about 3. The larger net BCVA benefit observed in the study, of about five letters (see *Figure 8*), 'translates' into a difference in NEIVFQ composite total score of about 4.
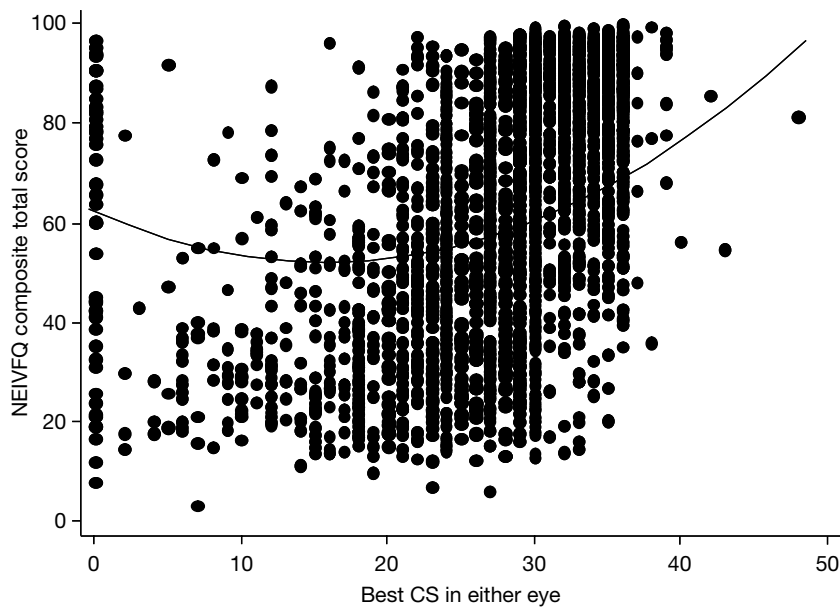
FIGURE 16 Scatterplot showing the NEIVFQ composite total score compared with better-seeing eye CS. The fitted regression line (see *Table 16*) is superimposed on a scatterplot of the raw data.

How cost-effective is verteporfin photodynamic therapy?

Verteporfin photodynamic therapy and best supportive care costs

Data describing VPDT treatments were available for 4566 patients in year 1 and 1834 patients in year 2 (*Table 17*). The mean number of VPDT treatments per patient was 2.4 in year 1, falling to 0.4 in year 2. The mean intervention cost of VPDT was £3026 in year 1 and £845 in year 2. The main cost component was the drug cost, which, on average, was 60% of the year 1 costs. The corresponding mean intervention costs for BSC were £166 for year 1 and £101 for year 2, giving incremental intervention costs of £2860 and £744 respectively.

Health and social services use and costs related to vision loss

Health and social services and BCVA costs were available for a total of 3435 visits in 1764 patients. As in the case of HRQoL data, most resource use questionnaires were completed in association with visits at 0, 6 and 12 months (*Table 18*). All visits with data were included in the analysis. Only about 10% of patients reported using a health service, such as an unscheduled low-vision appointment or seeing their GP, while < 0.5% of patients reported moving into a nursing home, residential home or sheltered accommodation (*Table 19*). The mean annual total costs related to the patients' eye conditions were low (approximately £300) relative to the VPDT intervention costs. Although the highest cost item was social service costs, the mean cost for this item was driven by the 1% of patients who received high levels of support from social service home carers costing > £3500 per year.

There was a negative relationship between BCVA and annual HSS cost. *Figure 17* shows that the gradient of this relationship, like that for HRQoL, was shallow. For example, for a five-letter decrease in BCVA for patients with baseline of 50 letters, the predicted increase in mean annual costs was about £28. For those patients who used a service, a five-letter decrease in BCVA was associated with a statistically significant increase in mean annual costs of £111 (95% CI ~£48 to ~£174). This association between BCVA and SF-6D was combined with the differential decline in BCVA from baseline for the VPDT and placebo groups in TAP to derive differences in HRQoL between VPDT and BSC at 3-monthly intervals (*Figure 18*).[30]

Cost-effectiveness

There was a small reduction in vision-related HSS costs following VPDT compared with BSC because of the smaller vision loss (year 1: mean costs of £320 for BSC group vs £260 for VPDT group; year 2: £382 vs £290). This reduction in vision-related costs offsets the additional costs of the intervention only to a small extent, and the incremental total costs of VPDT were positive (*Table 20*). The incremental QALYs for VPDT versus BSC were positive but small (*Table 20*). The base-case cost-effectiveness results showed that combining the small positive incremental QALYS gained for VPDT with the relatively high additional costs gave a cost per QALY of £170,000 over 2 years (i.e. £3514/0.0207).

TABLE 17 Mean resources used for interventions and associated costs (£) per patient for VPDT in year 1 (≤350 days) and year 2 (>350 and ≤715 days)

| Item	Year 1 (*n*=4566)		Year 2 (*n*=1834)	
	Mean	SD	Mean	SD
VPDT resource use				
VPDT treatment visits	2.41	1.17	0.43	0.81
Follow-up visits	1.30	1.02	1.59	1.25
VPDT costs (£)				
FA	591	152	325	234
Verteporfin and disposables	2074	1003	365	698
VPDT treatment visit	272	132	48	92
Follow-up visit	87	69	107	83
Total	3026	1182	845	944

TABLE 18 Distribution of visits for which visual function and resource use data were available

| Parameter	Duration of follow-up (months)						Total
	0	3	6	9	12	>12	
Resource use and BCVA	1350	136	848	171	528	402	3435
Resource use and CS	1276	96	764	127	466	356	3085

TABLE 19 The percentage of patients using each HSS item, unit costs (£) and HSS costs (£)

Item	% using service in last 3 months	Unit cost	Mean (SD) annual cost per patient (£)
Low vision appointment	9.96	83	51.2 (259.2)
Visits to GP	10.88	44	22.1 (70.5)
Social services	1.14	35	129.0 (1531)
Day centre	1.21	32	26.3 (256)
Nursing home stay	0.06	648	19.6 (812)
Residential care	0.12	443	26.8 (785)
Sheltered housing	0.20	140	14.8 (328)
Antidepressant use	0.52	10	0.64 (8.8)
Other	NA	NA	10.0 (53)
Total	NA	NA	297 (2078)

NA, not applicable.
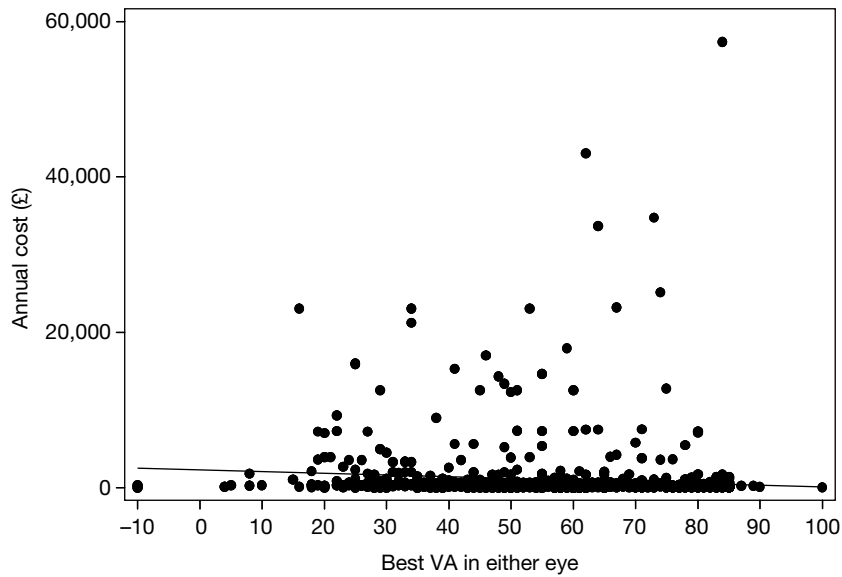
FIGURE 17 Scatterplot showing the annual cost of HSS resource use compared with better-seeing eye BCVA. The regression line superimposed on a scatterplot of the raw data is derived from fitting the two-part model. Values of BCVA <0 (–10 and –20) represent 'counting fingers' and 'hand movements' levels of vision respectively.
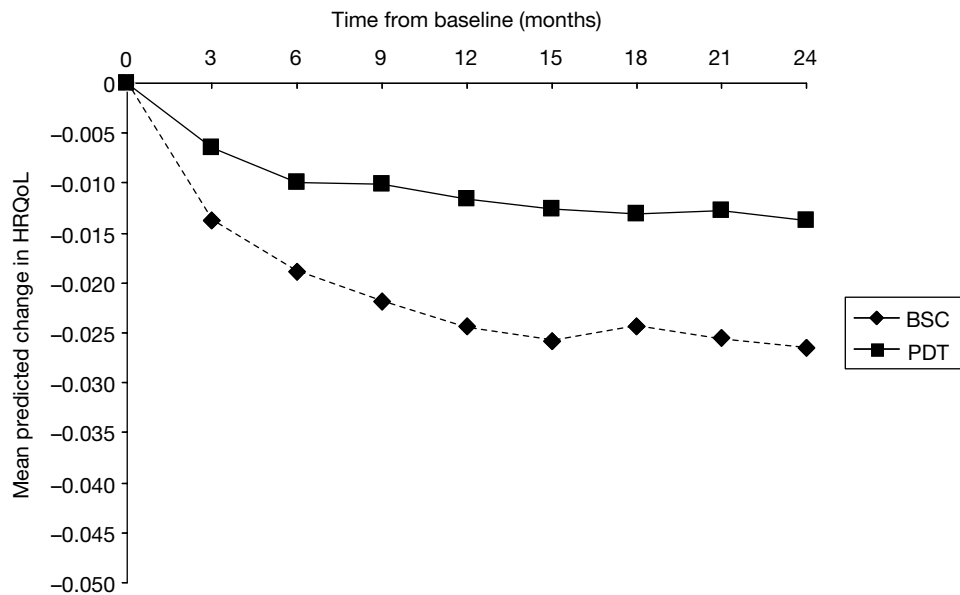
FIGURE 18 Mean predicted change in HRQoL at 3-monthly time points for VPDT vs BSC for eyes with predominantly classic lesions that would have been EFT. Predictions combine VPDT map of HRQoL and visual acuity with visual acuity for VDPT treatment and placebo groups reported in the TAP study.

TABLE 20 Incremental costs, QALYs and costs per QALY results (VPDT vs BSC)

Item	Year 1	Year 2	(Year 1 + 2)
Incremental intervention costs (£)	2860	744	3604
Incremental costs of HSS (£)	−59	−92	−151
Incremental total costs (£)	2884	630	3514
Incremental QALY	0.00866	0.01212	0.02071
Incremental cost/QALY (£)	333,000	52000	170,000

Sensitivity analyses

The sensitivity analyses found that the results were robust to the methodological assumptions and data sources used in the base-case analysis (*Table 21*). The probability that VPDT is cost-effective is zero unless the willingness to pay for a QALY gain exceeds £100,000 per QALY (*Figure 19*). The further sensitivity analyses showed that:

(i) If the treatment frequency was taken from TAP rather than the VPDT cohort study, the incremental costs increased to £5946 and the cost per QALY rose to £288,000.

(ii) If the pre–post BCVA difference from the cohort study was used rather than the difference between arms in the TAP trials, then the estimated QALY gain was higher (0.0212 vs 0.0207), but the cost per QALY gained still exceeded £150,000.

(iii) If the relationships of cost and HRQoL with CS rather than BCVA were used, this led to a small increase in QALY gain compared with the base case (0.0220 vs 0.0207), but again the cost per QALY exceeded £150,000.

(iv) If the costs of BSC were 10-fold those assumed in the base case, the cost per QALY was £91,000.

(v) If the difference in BCVA observed for VPDT compared with BSC at 2 years was maintained until 5 years, the cost per QALY was £94,000.

TABLE 21 Sensitivity analyses on incremental cost (£) per QALY for VPDT vs BSC according to different assumptions

Sensitivity analysis	Incremental QALY	Incremental cost	Incremental cost/QALY[a]
Base case	0.02066	3514	170,000
TAP study treatment frequency	0.02066	5946	288,000
VPDT cohort study VA results	0.02122	3511	165,000
Contrast and sensitivity map	0.02201	3412	155,000
10-fold increase in BSC costs	0.02066	1891	91,000

VA, visual acuity.
a   Values rounded to the nearest 1000.
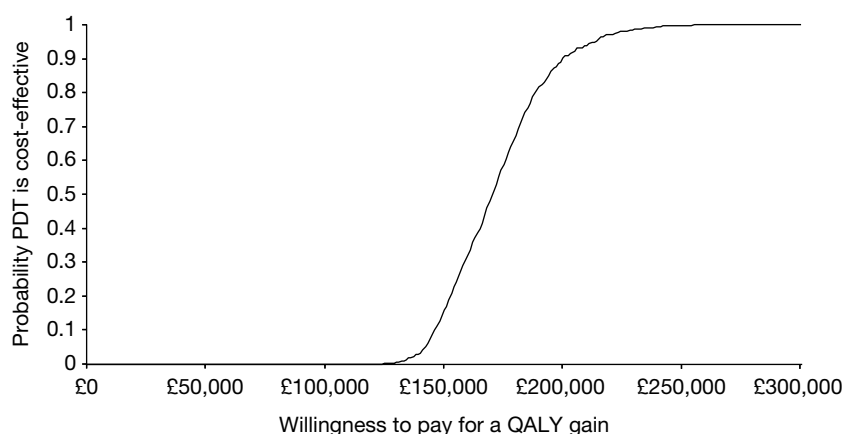
FIGURE 19 Cost-effectiveness acceptability curve for VPDT vs BSC.

Chapter 8

Discussion of results

The VPDT cohort study broke new ground in that it was a publicly funded postlicensing study of an expensive new technology that was beneficial in the management of subfoveal nAMD. Previously, this condition had been largely untreatable. The technology involved the use of the drug verteporfin (a photosensitiser) and its activation within the eye with an infrared non-thermal laser (thus avoiding direct physical injury to the neural retina). Its application to routine practice necessitated significant investment in expensive equipment and dissemination of new knowledge to ophthalmologists in the interpretation of retinal imaging outputs for diagnosis, case selection, treatment initiation and retreatment decision-making.

Although the appraisal by NICE found the treatment to be clinically effective, there was a recognition that evidence about its cost-effectiveness was based on multiple assumptions which were not robust. Hence, the Department of Health recommended a limited and managed introduction of this technology with collection of robust visual function and resource utilisation data to assess whether or not its clinical effectiveness and cost-effectiveness matched those observed in the licensing trials; it was also recommended that a measure of its impact on HRQoL should be obtained.

Thus, the size and the scope of the VPDT study was far more extensive than any previous study of nAMD and acted as a treatment registry containing data acquired on patients receiving VPDT in the clinical sites that were selected to provide VPDT. Protocol-based BCVA and CS were measured at multiple time points and HRQoL instruments were administered to patients at about half of the clinical sites. Collection of these data made it possible to investigate relationships between clinical measures of vision and HRQoL as continuous scales (in contrast to many previous studies).

Key findings

The key findings from the VPDT cohort study are outlined below:

- The change in BCVA was similar to that observed in the treatment groups in the pivotal licensing trials, although the deterioration in BCVA over time may have been underestimated (see *Strengths and weaknesses of the verteporfin photodynamic therapy cohort study*).
- The BCVA benefit was achieved with fewer treatments.
- In addition, non-treatment-related baseline covariates influenced change in BCVA over the study period.
- In the better-seeing eye, BCVA and CS were highly significant predictors of SF-6D utility, SF-36 component scores and NEIVFQ scores. The change in utility for a unit change in BCVA was less than several previous estimates.
- Realistic estimates of the cost-effectiveness of VPDT were obtained and were consistent with higher previous estimates, although these high estimates are almost certainly too low because of the assumption (common to all CEAs) that the better-seeing eye is being treated.

Strengths and weaknesses of the verteporfin photodynamic therapy cohort study

Despite its observational nature, the VPDT cohort study has many strengths. These include its size, pragmatic nature, and systematic collection of standardised data on acuity and lesion characteristics. This was the largest study of its kind to date, giving new insights into the HRQoL of people with nAMD and new data that will be pivotal to future studies of effectiveness in this population. Many aspects of the data collected in this study were robust. Protocol-based BCVA and CS were measured and HRQoL instruments administered at multiple time points, which allowed us to investigate in detail the relationships between clinical measures of vision and HRQoL. The large sample gave us reasonable power to test secondary hypotheses about the shape of the relationships and adaptation to vision loss over a 2-year period, even though the proportion of patients with data for more than three visits was small.

The VPDT cohort study was the first with concurrent concurrent collection of data on HRQoL and patient-level data on HSS resource use, and, hence, first to have undertaken a systematic CEA using data acquired during treatment rather than data stipulated by a trial protocol. Our CEA also tackled three major methodological concerns not previously addressed in CEAs of interventions for nAMD. Thus, our work extends the literature on the costs and cost-effectiveness of interventions for nAMD, and its findings will assist future CEA.

Set against these strengths, there were a number of limitations. These include the observational nature of the study, the loss to follow-up of large proportions of the original sample, missing data and the lack of a BSC comparison group of current relevance. There were major logistical challenges in establishing the study, which were discussed at a project review meeting about 18 months after the contract for the study started; key observations and recommendations from this meeting are set out in *Appendix 3*.

Unlike the pivotal trials, in which almost all patients were followed up for 24 months,[3,4,30] about half of the patients included in our analyses did not have 1-year follow-up. Because poor data quality is a well-recognised limitation of observational studies, we undertook computerised data validation checks on an on-going basis and when compiling the final data set. We checked whether or not data were missing for some visits by (a) matching records from paper and electronic systems for collecting BCVA and (b) requesting that centres should check explicitly whether or not additional visits had taken place for selected patients. The results from these checks implied that data had been submitted for > 95% of completed visits.

The exact reasons for loss to follow-up are not known. We attempted to collect information about reasons for completing a treatment episode early or for patients being lost to follow-up, but participating centres did not report reasons reliably. Anecdotally, we became aware that some hospitals had a policy of not rebooking appointments for patients who missed a visit, and some ophthalmologists were put under pressure to discharge patients who did not require active treatment rather than to continue to review them. The context for these policies was the extremely overstretched nature of macular clinics. It should be remembered that providing VPDT required hospitals to make regular appointments (up to four per year) to review a large number of patients who had previously had fewer than one; reviewing a patient required FA and, if treatment was required, administration of VPDT. Irrespective of whether or not funding was available to pay for these resources, the expert workforce needed to provide VPDT could not be expanded rapidly.

Patients who were not followed lost the opportunity to be retreated if reactivation occurred; this could have led to worse BCVA outcomes with treatment in everyday practice than with treatment in the licensing trials. However, the BCVA outcome in the VPDT cohort study was generally similar to that observed in the treatment arm of the TAP trials.

The loss to follow-up introduced uncertainty to the data analyses, which was taken into account by using a mixed regression model to predict BCVA at 1 year in different subgroups. This approach allows all of the available data to be modelled but does not prevent attrition bias. We observed that patients who were lost to follow-up tended to have poorer BCVA at baseline (data available from the authors). Because follow-up data were more likely to be missing with increasing duration after first treatment, and patients with a poor outcome were more likely to be lost to follow-up, the model may have tended to underestimate deterioration in BCVA over time. The regression model for BCVA trajectory assumed that BCVA deteriorated steadily (on the principles of parsimony and 'best fit'); this assumption is unlikely to be valid when BCVA is poor because the neovascular process burns out, causing a 'floor' effect. Attrition bias and a floor effect would have affected the results in opposite directions. Consequently, it is uncertain whether or not the BCVA deterioration over time in the study was truly similar to that observed in the TAP trials or underestimated because of selective attrition.

Although loss to follow-up is a scientific limitation, our experience also demonstrates vividly the difficulties associated with follow-up when treatments requiring multiple visits over an extended period of time in an older age group are introduced into routine clinical practice. Such data are invaluable to health service planners and are rarely available. We believe that patients and ophthalmologists became disheartened with eyes that experienced deterioration of vision during treatment and follow-up, causing treatment to be discontinued before the recommended time point of 2 years. We did not attempt to predict outcome at 2 years because the data were sparse.

A further limitation of the study was the inability to classify 40% of the lesions at baseline with respect to TAP eligibility (eyes classified as UNC), either because an angiogram was not submitted or because the submitted angiogram could not be graded. This group was retained in the model and had parameter estimates which tended to lie between those for EFT and IFT groups and between those for predominantly and minimally classic lesions. Thus, there was no reason to believe that these eyes represented a biased selection with respect to eligibility for the TAP trials or their lesion composition.

In the CEA, we were unable to use a direct control group, instead we relied on the control group in the TAP trials. Extrapolating relative effects across different populations is potentially problematic; for example, trials often report different estimates of effect from those given by observational studies.[58] Nevertheless, in this cohort study, BCVA at first treatment and at 1 and 2 years were similar to the predominantly classic subgroup studied in the TAP trials.

Interpretation

Comparison of outcomes in the verteporfin photodynamic therapy cohort study versus TAP

Visual acuity outcome

The effectiveness of VPDT in reducing deterioration in BCVA in the context of RCTs has been confirmed by a systematic review in which the chosen outcomes were step changes in BCVA over 24 months, for example loss of three or more lines of visual acuity.[59] VPDT was estimated to reduce the risk of losing more than three lines by 20% (risk ratio 0.80, 95% CI 0.73 to 0.88).

The VPDT study protocol specified that BCVA should be measured at 3-monthly intervals. We could not express the outcomes of treatment with VPDT in the study with the outcomes of treatment in the systematic review because of the loss to follow-up. Instead, we estimated the change in BCVA over time (modelling baseline BCVA as a covariate) and observed that at 12 months it was not dissimilar to that reported in the key licensing trials, although we may have underestimated BCVA deterioration at 1 year because of attrition. Notably, for the participants in the VPDT study who would have qualified for entry into the TAP study, the trajectory of change in BCVA was highly similar to that observed in the TAP trials.[4,30] This finding may be interpreted as providing some corroboration of the clinical effectiveness of the technology in terms of better preserved BCVA in the treated eye.

Factors not related to treatment that influenced change in visual acuity over time

Overall in the VPDT cohort study, BCVA in the treated eye declined over time. This finding was consistent with the outcomes observed in the key licensing trials. However, the size of the cohort study allowed us to examine with high statistical power the influence of a number of baseline covariates on the change in BCVA. Although treatment was associated with a lower rate of decline of BCVA, several other factors influenced change in BCVA. Those that contributed to deterioration included older age, poorer BCVA at commencement of treatment and being a current or ex-smoker. One factor was associated with a better outcome and this was having a fellow eye with better vision than the treated eye.

Although our findings are consistent with clinical wisdom, experience and intuition, this is the first study to quantify the effects of these factors on visual change. For example, the eyes of older participants tended to deteriorate faster than those of younger participants with better BCVA. The magnitudes of the interactions between smoking status and vision in the fellow eye with time, estimated here for the first time, are quite striking. Also, our finding of a better outcome when the treated eye is the better-seeing eye is important and has been overlooked in previous studies. This finding is consistent with a previous report that suggested that an eye with nAMD does not achieve its full visual potential unless it is the better-seeing eye,[51] and with previous findings of improvements in adult amblyopic eyes when vision in the fellow eye is lost.[60] The modest size of the effect, and its consistency across conditions, suggests that it may arise from a shift in decision criterion.[61]

The number of verteporfin photodynamic therapy treatments administered

A striking feature of the VPDT cohort study was the much smaller number of treatments that were administered, an average of 2.3 and 0.4 treatments respectively in years 1 and 2, even though it was specified that ophthalmologists should retreat as in the TAP trials. By comparison, in the TAP trials[30] an average of 3.4 treatments were administered in the first year and 2.2 in the second year; these frequencies are not surprising because treatment was mandated if leakage was judged to be present on an FA at the 3-monthly review visits. It is also notable that in the TAP trials the FAs had to be performed to standardised protocols and scrutinised by an accredited angiogram-reading centre, thus ensuring consistency of interpretation for retreatment decision-making.

Our findings suggest that ophthalmologists do not adhere to treatment algorithms that are used in key licensing trials and that decisions to treat are influenced more by subsequent experience gained from treating large numbers of patients. Thus, a matter of increasing unease is the applicability to routine practice of the treatment protocols specified in pivotal licensing trials and subsequent marketing authorisations. The need for regular review combined with invasive and time-consuming imaging procedures followed by administration of treatment can impose significant burdens on already stretched health-care systems. Traditionally, these factors have not been considered when implementing new therapies into routine practice. With VPDT, however, the question was raised about whether or not efficacy might be diminished if treatment

was not administered at the recommended frequency or under the conditions determined by the licensing trials. Even minor diminution of efficacy could have resulted in VPDT becoming cost-ineffective given the borderline benefit of VPDT. Thus, providers and purchasers of health care need to be aware that the characteristics of treatment in routine practice may be substantially different to the treatment recommendations made on the basis of licensing trials. Our findings also highlight that commercial trials may recommend more treatment than necessary or at a treatment frequency that is not deliverable across eligible populations. This fact is also of importance to researchers when designing pragmatic phase 3 trials.[62,63]

Visual function and health-related quality of life

The large sample in the VPDT study gave us adequate power to test the secondary objectives on HRQoL relationships and adaptation to vision loss over a 2-year period, even though the proportion of patients with data for more than three visits was small. Approximately half of the centres provided data on a second measure of vision, namely CS, and also administered structured and validated instruments to ascertain visual functioning, HRQoL and resource utilisation. Thus, only a subset of participants in the VPDT study contributed the data for the analysis of the secondary outcomes as they were necessarily a selected sample and had to be attending one of these centres. These limitations may have led to selection in terms of socio-economic status or age. However, previously published work shows that these factors do not influence HRQoL or visual functioning.[18,31]

Our analyses of the associations between BCVA and HRQoL identified three main features:

- Health-related quality of life (SF-36 and the NEIVFQ) decreased with deteriorating visual function (BCVA or CS in the better-seeing eye) over a wide range of visual function.
- The relationship between visual function and HRQoL measures was not sigmoid but tended to plateau at low levels of visual function.
- The gradient of the relationships did not change over time up to 2 years after first treatment.

Health-related quality of life is a 'whole-patient' outcome, which is dependent on patients' binocular visual experience on a day-to-day basis using their habitual correction (if any) and in their customary environment. Previous studies have demonstrated weak relationships between declining visual function and generic HRQoL instruments and stronger relationships with visual functioning instruments such as the NEIVFQ. However, the association between the most commonly used surrogate marker for visual function, that is BCVA, and the NEIVFQ is at best moderate, with the majority of the variation remaining unexplained. Reasons for the lack of a strong association include that (a) BCVA itself is a psychophysical test and is influenced by patient factors; (b) BCVA subserves only foveal function and does not reflect the more complex aspects of overall vision such as reading text, depth perception, movement detection, colour and contrast processing and field of vision; and (c) self-reported HRQoL has an in-built variability which is dependent on the respondent's mood and emotional status.

Clinical tests to obtain estimates of additional or more global aspects of visual function are not easily measured in routine practice and were beyond the scope of the VPDT study. Instead, we attempted to collect presenting binocular BCVA with the participant wearing the habitual correction, if any. We reasoned that this measure would better reflect the usual state of visual functioning and, thus, the HRQoL response. However, one-third of the data describing presenting binocular BCVA were missing and many of the remaining data were collected in a variety of formats, making meaningful interpretation of the findings difficult. Therefore, like previous researchers, we were forced to select BCVA in the better-seeing eye as the proxy for binocular visual performance.[18,31,64] Validation of the BCVA data showed that BCVA had been collected in a far more robust and reproducible manner.

Our analyses revealed that the decrease in generic HRQoL for a clinically significant deterioration in vision, as measured by BCVA, was small. The predicted decreases for a five-letter drop in BCVA in the better-seeing eye were 0.0058, 0.245 and 0.546 for the SF-6D, PCS and MCS respectively (all $p < 0.0001$). We also had CS data from a subset of participants and therefore were able to estimate changes in HRQoL for both BCVA and CS and relate these to the findings observed in the TAP trial. However, when interpreting these associations, it is very important to recognise that the predicted HRQoL changes do not describe the average benefit in a representative sample of patients, given that a proportion (47% of the VPDT cohort) will have had treatment to the first affected eye and had a normally sighted fellow eye.

The gradient of change in visual functioning measured by the NEIVFQ instrument was not influenced by the duration of follow-up. Models predicting distance, near and composite NEIVFQ scores from BCVA were quadratic. The predicted decreases for a five-letter drop in BCVA in the better-seeing eye were 5.08, 5.48 and 3.90 for the distance and near domains and for the composite instrument respectively. The Submacular Surgery Trials Research Group quantified the association between BCVA and NEIVFQ scores using the change in BCVA.[65] The observed change in NEIVFQ composite score per 100 letters was 18 points, very much less than our estimate of 55 letters. Their lower estimate may be due, in part, to the assumption of a linear relationship or to their much smaller sample size. The VPDT cohort study has enabled more precise quantification of these relationships, particularly those between BCVA and HRQoL. These relationships constitute an important source of robust information for modelling the cost-effectiveness of current and future interventions for nAMD.

The shape of the relationship between visual function and HRQoL had also not been previously investigated. Even in a study as large at the VPDT cohort study, the analyses had limited power to detect departures from a linear relationship. The tendency for some functions to plateau with severe loss of visual function is clearly not a floor effect and supports the prior hypothesis that HRQoL decreases less steeply when visual function is very poor. Our failure to observe a plateau when vision is excellent may have arisen because few patients achieved BCVA < 0.0 logMAR (6/6 Snellen) in the best-seeing eye, either because patients could not achieve better acuity or because they were not encouraged to do so. However, this explanation is not consistent with the observation that visually demanding tasks such as fluent reading and driving ability can be performed with BCVA = 0.3 logMAR (6/12 Snellen) in the best-seeing eye.

Previous researchers have investigated which of BCVA or CS in the better-seeing eye is the stronger predictor of HRQoL. Based on a multivariable regression, Bansback et al.[66] reported that CS was a better predictor of HRQoL than BCVA and, using the Health Utilities Index mark 3[67] (HUI3), estimated a change in utility of 0.14 per log unit. In contrast, we found that, in this large data set, BCVA was a consistently stronger predictor of HRQoL than CS.

Patients' adaptation to loss of visual function was investigated by Brown.[31] In a sample of 237 patients with mixed causes of visual loss there was a tendency for those who had had visual loss for longer (over a time frame of 5 years) to report better HRQoL.[31] In a sample of 72 patients who had had AMD for up to 20 years (35 for < 1 year, 19 for 1–3 years and 18 for 3–20 years), patients with durations of visual loss ≥ 1 year had better HRQoL than those with durations < 1 year ($p < 0.005$).[18] This association was potentially affected by the small number of patients with very longstanding disease. Also, these studies did not assess HRQoL longitudinally in the same patients, so the observed finding is less confidently attributed to the duration of disease and it is not clear whether or not the differences in HRQoL with duration of visual loss were adjusted

for the extent of visual loss, that is BCVA. However, our data were obtained over relatively short durations of follow-up and it is possible that adaptation occurs only over longer periods of time.

Narrative reviews have concluded that utility decreases with deteriorating visual function,[16,17,68] but few studies have systematically quantified the relationships between these measures for patients with nAMD (*Table 22*).[18,64] Our estimate of ~0.1 change in utility per 100 letters is consistent with utility estimates based on the SF-6D or the EQ-5D. It is lower than the estimates based on the HUI3[64] (see below) and those based on preferences elicited directly from patients.[18,65] The distributions of preferences elicited directly from AMD patients were markedly skewed in contrast to scores on preference-based utility measures derived from societal valuations (acknowledging that this contrast is both between source of valuation, i.e. patients vs society, and between measure, i.e. directly elicited preference by time trade-off vs preference-based utility measure). This observation is consistent with some patients refusing to trade years of life for improved vision,[18,31] and raises concern about the validity of the method. More fundamentally, as generic measures of HRQoL are used to make broad comparisons across interventions in different disease areas, it is more appropriate to value health states with preference weights from the general population rather than specific groups.[13]

Is the Short Form questionnaire-6 Dimensions an appropriate measure of generic health-related quality of life?

A generic HRQoL measure chosen for comparing health gain across disease areas should have a descriptive system that covers all the important dimensions of health. The SF-6D, like the EQ-5D, has a descriptive system that purports to meet the World Health Organization definition of health: 'complete physical, mental and social well-being and not merely the absence of disease or infirmity'.[69] Utilities measured using the SF-6D are similar to those measured using the EQ-5D.[70] By contrast, the HUI3 is based on a narrower, 'within the skin' definition of health focusing on impairment and not on the social context of the impairment.[71] Thus, the HUI3 consists of items that tap self-reported functioning more directly than the EQ-5D and SF-6D. The HUI3 is, therefore, likely to be 'more sensitive'[71] to visual loss than the SF-6D.[64] However, the HUI3 has been criticised for using this relatively narrow description of health.[9]

TABLE 22 Estimates of utility from different studies

Study	Instrument/method used	Source of utility values	Visual acuity and utility observations	Approximate utility change per 100 letters
Brown *et al.*, 2000[18]	Time trade-off	Patients	20/20 to 20/400 (0.0–1.3 logMAR or 70 letters ≈ utility 0.89 to 0.52 ≈ 0.47 difference	0.67
Espallargues *et al.*, 2005[64]	EQ-5D	General population	≤ 0.3 to > 2.0 logMAR or 120 letters ≈ utility 0.75–0.63 ≈ 0.12 difference	0.10
Espallargues *et al.*, 2005[64]	SF-6D	General population	≤ 0.3 to > 2.0 logMAR or 120 letters ≈ utility 0.70–0.63 ≈ 0.07 difference	0.06
Espallargues *et al.*, 2005[64]	HUI3	General population	≤ 0.3 to > 2.0 logMAR or 120 letters ≈ utility 0.50–0.10 ≈ 0.40 difference	0.33
Espallargues *et al.*, 2005[64]	Visual analogue scale	Patients	≤ 0.3 to > 2.0 logMAR or 120 letters ≈ utility 0.71–0.59 ≈ 0.12 difference	0.10
Espallargues *et al.*, 2005[64]	Time trade-off	Patients	≤ 0.3 to > 2.0 logMAR or 120 letters ≈ utility 0.73–0.47 ≈ 0.26 difference	0.22
VPDT cohort study	SF-6D	General population	Regression coefficient, 0.0012 per letter	0.12

0.1 logMAR, i.e. five letters.

A further concern that has been previously expressed is that the utilities for the HUI3 have been derived from a power transformation of values from a visual analogue scale,[72] rather than by direct valuation with choice-based methods such as the standard gamble (used for the SF-6D) or the time trade-off (used for the EQ-5D). Our approach of using the SF-6D follows the recommendations of policy-makers such as NICE.[15] Therefore, it is not surprising that our findings are consistent with previous studies that have used the EQ-5D.[64]

In terms of an internationally recognised measure of HRQoL appropriately based on societal preferences, the gradient of the decrease in HRQoL with deteriorating visual function is small. The estimated gain in HRQoL (utility) from VPDT is about 0.02 (in terms of BCVA, a difference of about 11 letters after 2 years, assuming that only the best-seeing eye is being treated), and from ranibizumab is about 0.04 (a difference of about 21 letters after 2 years,[73,74] under the same assumption). Gains in utility (over varying time horizons) for other common interventions for chronic conditions (*Table 23*) show that the utility gain associated with VPDT is relatively small compared with other competing interventions.[75,76] These utilities measured over the appropriate time horizon, and combined with relative effects on life years gained, translate into QALYs and inform health policy decisions.

Cost of illness and resource utilisation

The VPDT cohort study, unlike most other studies used to estimate cost-effectiveness, collected data concurrently on both resource utilisation and HRQoL. Thus, it was able to report on the cost-effectiveness of VPDT versus BSC under the assumption that BSC involved scheduled visits to the ophthalmology clinic to monitor patients' vision and no other treatment.

The main empirical finding from the CEA is that the costs of providing VPDT for patients included in the UK VPDT cohort study were relatively high compared with the projected QALY

TABLE 23 Utility gains of VPDT compared with other common interventions

Intervention[a]	Utility gain[b]	Duration of follow-up[c]	Measure used[d]
Cataract surgery	0.03	3 months	EQ-5D
Groin hernia repair	0.06	3 months	EQ-5D
Total hip replacement	0.42	6 months	EQ-5D
Varicose vein surgery	0.10	3 months	EQ-5D
Total knee replacement	0.31	6 months	EQ-5D
Coronary artery bypass grafting	0.21	6 years	EQ-5D
VPDT[e]	Year 1: 0.009; year 2: 0.012; total: 0.021	2 years	SF-6D

a   The utility gains shown were selected as comparators because the data were collected when the interventions were provided in usual health-care clinical settings. Utilities for five surgical interventions (cataract, hernia, varicose veins, knee replacement surgery and total hip replacement) were obtained from the Patient Reported Outcome Measures (PROMs II) project.[75] Utilities before and after coronary artery bypass grafting were elicited from patients rated clinically appropriate for both bypass surgery and percutaneous management in the Appropriateness of Coronary Revascularisation (ACRE) study.[76]

b   All of the utilities were measured before and after the intervention.

c   The utility gains are reported for different durations of follow-up after an intervention, so they are not directly comparable. In general, one would expect the utility gain to be larger with a longer duration of follow-up. Note that the 2-year utility gain from VPDT is still lower than the utility gains achieved over a shorter durations for the interventions studied in the PROMs II project.

d   The PROMs II and ACRE studies measured utility gains using the EQ-5D,[75,76] whereas the VPDT cohort study measured utility using the SF-6D. The EQ-5D and SF-6D have been shown to differ when used to report extreme health states;[70] the EQ-5D appears unable to discriminate health states close to full health (ceiling effect), whereas the SF-6D seems unable to discriminate health states close to zero (floor effect). However, on average the two instruments generate utilities that are very similar each other, with a mean difference of only 0.05,[70] so the differences shown in the table cannot be explained by the use of different utility measures.

e   The estimate for photodynamic therapy assumes that the better-seeing eye is being treated (see text).

gain. The incremental cost per QALY was £170,000 over 2 years for the base case. Even if the gain from the intervention was extrapolated over 5 years, the incremental cost per QALY was still approximately £100,000, five times higher than the threshold that NICE uses to identify interventions that are 'relatively cost-effective'.[15] The cost-effectiveness ratios reported in previous CEA of VPDT for nAMD have ranged from US$30,000 to US$250,000 (£20,000 to £166,667 assuming an exchange rate of US$1.5 to the UK pound).[26,28] Unlike previous CEA of VPDT for patients with predominantly classic CNV secondary to nAMD, we were able to include all appropriate costs and account for HRQoL associated with vision loss. This resulted in improved patient-centred estimates that showed that VPDT is unlikely to be cost-effective.

There are three other features of our CEA that are relevant to future CEA of interventions for nAMD. Firstly, the study used data on the use of a treatment in routine practice rather than data collected in accordance with a trial protocol. Despite the much lower treatment frequency, we observed similar visual outcomes to those observed in the TAP trials. In the case of our CEA, it was more appropriate to use the lower treatment frequency observed in the VPDT cohort study, and previous CEAs that used treatment frequencies from the TAP trials overstated the incremental costs of the VPDT intervention compared with BSC.[19,26,77] The lesson for future CEA is that treatment intensities observed in licensing trials may overestimate the treatment intensity used in routine practice and, hence, overestimate the costs of treatment in the usual care setting.

Second, previous CEAs either excluded costs associated with declining vision or estimated these costs based on expert opinion.[19,26,28,77–79] By contrast, by collecting patient-level data on HSS resource use and BCVA, our CEA was able to incorporate the cost of declining vision. Our data showed that the HSS costs for patients with nAMD were low (e.g. a mean of £320 for BSC group in year 1), and hence the reduction in these costs after VPDT was relatively small (£151 over 2 years). The costs were lower than those reported by a recent observational study assessing the economic burden of nAMD by self-reported use from 400 patients across five different countries[23] and from studies of Medicare costs based on claims data.[80,81] However, these studies were based on aggregated costing approaches, which tend to overstate costs. The morbidity costs observed in the VPDT cohort study relied entirely on patient recall and therefore may have under-represented the true cost, and also they may reflect the relatively poor availability of low-vision services in the UK; previous studies have found a similarly low use of vision-related services in the UK.[82,83] However, this low use of vision services has been reported in other countries that have used patient-level data, which suggests that the current findings may be more widely applicable.[24] The lesson for future CEA is that the source and robustness of data describing costs associated with declining vision need to appraised with care.

The third feature of our CEA that is relevant to future CEA concerns the importance of using HRQoL measures based on preference weights from the general population rather than patients with nAMD.

A final issue for future CEAs which emerged from the VPDT study but which was not incorporated into our CEA was the relationship between BCVA and HRQoL. The regression models which investigated this relationship found that the rate of change in HRQoL with varying BCVA was not influenced by whether the better- or the worse-seeing eye was being treated. However, a key assumption in this and other CEA is that it is always the better-seeing eye that is being treated, as the HRQoL gain is 'credited' for all treated eyes. Unless policy-makers rule that worse-seeing or 'first' eyes should not be treated (an option considered but rejected by NICE during its deliberations prior to issuing its technology appraisal[6]), the worse-seeing eye will be treated in a proportion of patients (48% in the VPDT cohort study). Therefore, the CEA reported here (and other CEAs) has overstated the QALY gain and the cost-effectiveness of

VPDT. It is important for future CEAs to assess the proportion of worse-seeing eyes that present for treatment in routine practice. We did not incorporate the proportion from the cohort study because it will almost certainly have changed over time as treatments and referral pathways for nAMD became more established.

Implications for practice

The main implications do not relate to the use of VPDT to treat nAMD because VPDT has now been superseded by the introduction of new treatments (see *Current status of verteporfin photodynamic therapy and future research*).

- The fact that a much smaller number of treatments was administered than in the TAP trials suggests that treatment regimens receiving marketing authorisation may overestimate the intensity of treatment required. This observation may apply to other new health technologies.
- Our ability to estimate effectiveness was limited by substantial loss to follow-up, which prevented comparisons with outcomes in RCTs and a systematic review of RCTs. This limitation should be carefully considered in the design of similar future studies if the effectiveness of an intervention is not dramatic and treatment or follow-up is scheduled over many months (conditions which we suspect may cause clinicians or patients not to adhere to the treatment regimen).
- Verteporfin photodynamic therapy is less effective than newer technologies in treating nAMD. Its use should be limited to circumstances in which these newer technologies are contraindicated or refused by patients, and to categories of AMD such as polypoidal choroidopathy or other diseases with neovascularisation arising from the choroid, for example high myopia.
- Licensing trials generally involve only one eye, and the benefit to a person from effective treatment for an eye will depend on whether or not the person's visual function is limited by the vision in the treated eye. In terms of cost-effectiveness, an appraisal of a technology that benefits one eye should evaluate the benefit at the level of a person, not an eye.
- The gradients of the relationships (a) between BCVA and EQ-5D utility and (b) between BCVA and HSS resource use/cost were shallower than most previous estimates. The consequences of these relationships for the appraisal of other technologies to treat eye diseases that impair vision need to be considered carefully.

Current status of verteporfin photodynamic therapy and future research

Verteporfin photodynamic therapy as a monotherapy for nAMD has been superseded by the introduction of molecular biologicals that target VEGF, a key molecule that promotes neovascularisation in AMD. The latter technology was introduced in 2006 following demonstration that monthly intravitreal injections of ranibizumab, a monoclonal antibody that inhibits VEGF, is vastly superior to both BSC and PDT.[72,73] Anti-VEGF therapies have also been shown to result in discernible improvements in HRQoL, outcomes which were not demonstrable with VPDT. VPDT combined with anti-VEGF therapy has been investigated, but the results suggest only a marginally improved benefit in terms of fewer treatments and no benefit in terms of visual acuity for nAMD.[84]

Research recommendations outside the context of nAMD are:

- Benefit from VPDT has been shown for visual acuity outcomes in specific nAMD variants such as polypoidal choroidopathy. VPDT continues to be used as first-line treatment in the

management of other conditions such as neovascularisation due to myopia, inflammation and certain other choroidal diseases including central serous chorioretinopathy. Further studies are required to investigate the effectiveness of VPDT in these disease conditions. Similarly, the methods used in this study could be applied, cautiously, in order to estimate the cost-effectiveness of VPDT for these other eye conditions.

■ We observed differences in the rate of change in BCVA over time for a number of covariates. It would be interesting to investigate whether or not the effectiveness of new interventions for nAMD also varies in a similar way in relation to these covariates.

■ The study demonstrates the value of estimating the relationship between a common clinical outcome, that is BCVA, and other outcomes less often measured in RCTs but which are important for technology appraisals, for example HRQoL or HSS resource use. Because of the size of the study population, these relationships were estimated relatively precisely. Once established, relationships of this kind should be able to be applied to modelling of the effectiveness of other technologies, on the basis of estimates of effect from RCTs for the common clinical outcome. Further research could investigate how widely these relationships can be applied, for example to other diseases that reduce BCVA.

Chapter 9
Conclusions

The most notable finding of the VPDT cohort study was that a visual outcome comparable to that reported in the licensing trial was achieved, although we may have underestimated BCVA deterioration at 1 year because of attrition. This visual outcome was achieved despite a considerably lower retreatment frequency. This finding highlights that treatment regimens that receive marketing authorisation may overestimate the intensity of treatment required. Similar questions have arisen in the last 5 years about other technologies, for example the duration of treatment with Herceptin® (Roche) that women require after primary surgery and chemotherapy to achieve the benefits seen in licensing trials.

The VPDT study clearly showed that the small beneficial differences in BCVA between the treatment and control groups in the TAP licensing trials would translate into small gains in generic and vision-specific HRQoL and that the cost of achieving these outcomes was similar to the largest previously published estimate. The associations between BCVA and HRQoL, and between BCVA and HSS costs, represent an enduring legacy of the VPDT cohort study that are likely to be applicable to future evaluations of interventions to treat nAMD.

Even though VPDT is no longer the first line of treatment for nAMD, our findings continue to have relevance to clinical practice. In particular, the quantification of the influence of key covariates of age, cigarette smoking and status of the fellow eye on the trajectory of vision loss has added to our knowledge and suggests that these factors should be considered in the design and analysis of trials of treatments for nAMD. The findings will also continue to be of relevance and provide a reference framework for the estimation of cost-effectiveness in future trials and technology appraisals.

The future role of studies like the VPDT cohort study needs to considered carefully. The authorities that desired the VPDT cohort study did not state its purpose clearly in advance of commissioning the study, unlike other research commissioned by the National Institute for Health Research. For example, there was ambiguity in the wider health community about whether the study was being set up (a) to allow selected ophthalmologists, with the resources to participate, to treat patients with predominantly classic CNV lesions or (b) to provide a vehicle to allow such patients to receive treatment given the guidance by NICE. Despite a strong desire by the authorities for the study to achieve its aim of providing a quality-controlled implementation of VPDT, this was not matched by unequivocal guidance to commissioners, designated hospitals and ophthalmologists that participation was not voluntary. This lack of direction meant that the flow of resources needed to carry out the study at a participating site was perceived to be discretionary by some PCTs and hospital managers. Some ophthalmologists were also hostile to the study despite strong support from the Royal College of Ophthalmologists. If in the future the introduction of a new technology is made contingent on undertaking postlicensing data collection and research, a more explicit commitment from commissioners and policy-makers is needed.

The model of the VPDT cohort study can be used to meet the many needs of the NHS when considering how to implement an expensive therapy, for example provision of the education and training required to implement the therapy, treatment protocols to assure the quality of treatment, infrastructure for auditing implementation through standardised data acquisition

and measures of the amount of treatment given and safety in routine practice. During the implementation of the cohort study, significant weaknesses in the capabilities of clinicians, clinical teams and trusts to understand the principles and practicality of gathering systematic information were identified. However, undertaking the study has created a network of resources and research competent sites currently participating in other portfolio studies.

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Contribution of authors

- Professor BC Reeves designed the study with Professors U Chakravarthy and SP Harding and Dr R Grieve. He led the Data Management Centre at the LSHTM and oversaw the data analyses and their interpretation from an epidemiological perspective. He drafted the report with Professors Chakravarthy and Harding.
- Professor SP Harding designed the study with Professors Chakravarthy and Reeves and Dr Grieve. He contributed to the initiation and recruitment of sites and the management of the project, including the training of research staff at sites. With colleagues, he led the establishment and management of NetwORC UK, developed specifically for this project. He contributed to the interpretation of the results and drafted the report with Professors Chakravarthy and Reeves.
- Ms J Langham was the study manager at the Data Management Centre. She liaised with sites about protocol or data queries and managed the study on a day-to-day basis. She contributed to data management and descriptive statistics about the study cohort.
- Dr R Grieve designed and conducted the CEA, interpreted the cost-effectiveness study and drafted this section of the report. He also contributed to the design of the overall study, and to the interpretation and reporting of the analysis of HRQoL.
- Mr K Tomlin designed and developed the databases used for VPDT data collection at each of the participating hospitals and provided technical and data management support to each of the clinical teams. He contributed to data management, especially linking the clinical and grading data from NetwORC UK, and descriptive statistics about the study cohort.
- Ms J Walker carried out the regression modelling of visual outcomes and the relationships between visual outcomes, HRQoL and resource use under the supervision of Dr Carpenter.
- Dr C Guerriero helped to design the CEA and to interpreting and drafting the sections of the report on the CEA.
- Dr J Carpenter advised on the statistical aspects of the study, at both the design and analysis stages, especially the regression modelling and the handling of missing data.
- Dr WP Patton contributed to the setting up of NetwORC UK and managed all of the data coming from the reading centres to the Data Management Centre. He worked on the quality assurance processes, training and validation exercises, and contributed to the analyses.

- Dr KA Muldrew contributed to the setting up of NetwORC UK. She designed the grading protocols with clinician colleagues, developed training and validation programmes and trained staff employed in the reading centres. She worked on the quality assurance processes and contributed to the analyses.
- Dr T Peto is Head of the Moorfields Eye Hospital Reading Centre, part of NetwORC UK. She was involved in the setting up, design and execution of the imaging and grading protocol. She also contributed to the training and certification of graders, and advised clinicians about image interpretation, together with the clinical leads from the Belfast and the Liverpool reading centres.
- Professor U Chakravarthy designed the study with Professors Harding and Reeves and Dr Grieve. She was the principal applicant in the effort to secure funding. She led the study and, with colleagues, the establishment and management of NetwORC UK, developed specifically for this project. She contributed to the interpretation of the results and drafted the report with Professors Harding and Reeves.

All authors contributed to the reporting of the study through this report and other peer-reviewed publications arising from the study.

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Publications

1. Harding SP, Tomlin K, Reeves BC, Langham J, Walker J, Carpenter J, *et al.* Verteporfin photodynamic therapy cohort study: report 1: effectiveness and factors influencing outcomes. *Ophthalmology* 2009;**116**:e1–8.

2. Grieve R, Guerriero C, Walker J, Tomlin K, Langham J, Harding S, *et al.* Verteporfin photodynamic therapy cohort study: report 3: cost effectiveness and lessons for future evaluations. *Ophthalmology* 2009;**116**:2471–7.

3. Reeves BC, Langham J, Walker J, Grieve R, Chakravarthy U, Tomlin K, *et al.* Verteporfin photodynamic therapy cohort study: report 2: clinical measures of vision and health-related quality of life. *Ophthalmology* 2009;**116**:2463–70.

References

1. Klein R, Klein BE, Linton KL. Prevalence of age-related maculopathy: the Beaver Dam Eye Study. *Ophthalmology* 1992;**99**:933–43.

2. Vingerling JR, Dielemans I, Hofman A, Grobbee DE, Hijmering M, Kramer CF, *et al.* The prevalence of age-related maculopathy in the Rotterdam study. *Ophthalmology* 1995;**102**:205–10.

3. TAP Study Group. Photodynamic therapy of subfoveal choroidal neovascularisation in age-related macular degeneration with verteporfin: one-year results of 2 randomised clinical trials. TAP report 1. *Arch Ophthalmol* 1999;**117**:1239–45.

4. TAP Study Group. Photodynamic therapy of subfoveal choroidal neovascularisation in age-related macular degeneration with verteporfin: two-year results of 2 randomised clinical trials. TAP report 2. *Arch Ophthalmol* 2001;**119**:198–207.

5. Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in pathologic myopia with verteporfin. 1-year results of a randomized clinical trial – VIP report no. 1. *Ophthalmology* 2001;**108**:841–52.

6. National Institute for Clinical Excellence. *The clinical effectiveness and cost effectiveness of photodynamic therapy for age-related macular degeneration;* 2003. URL: www.nice.org.uk/guidance/TA68 (accessed 30 November 2010).

7. Bren L. The importance of patient-reported outcomes … It's all about patients. *FDA Consumer Magazine* 2006;**40**(6).

8. UK Department of Health. *Guidance on the routine collection of Patient Reported Outcome Measures (PROMs);* 2009. URL: www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_092647 (accessed 30 November 2010).

9. Brazier J, Ratcliffe J, Saloman JA, Tsuchiya A. Introduction to the measurement and valuation of health. In *Measuring and valuing health benefits for economic evaluation.* Oxford: Oxford University Press; 2007. pp. 7–36.

10. Bradley C. Importance of differentiating health status from quality of life. *Lancet* 2001;**357**:7–8.

11. Mangione CM, Lee PP, Gutierrez PR, Spritzer K, Berry S, Hays RD, *et al.* Development of the 25-item National Eye Institute Visual Function Questionnaire. *Arch Ophthalmol* 2001;**119**:1050–8.

12. EuroQol Group. EuroQol – a new facility for the measurement of health-related quality of life. *Health Pol* 1990;**16**:119–208.

13. Brazier J, Roberts J, Deverill M. The estimation of a preference-based measure of health from the SF-36. *J Health Econ* 2002;**21**:271–92.

14. Gold M, Siegel J, Russel L, Weinstein M. Theoretical foundations of cost-effectiveness analysis. In Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. *Cost-effectiveness in health and medicine.* New York, NY: Oxford University Press; 1996. pp. 82–134.

15. National Institute for Clinical Excellence. *Updated guide to the methods of technology appraisal;* 2008. URL: www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp (accessed 4 October 2009).

16. Stelmack J. Quality of life of low-vision patients and outcomes of low-vision rehabilitation. *Optom Vis Sci* 2001;**78**:335–42.

17. Margolis MK, Coyne K, Kennedy-Martin T, Baker T, Schein O, Revicki DA. Vision-specific instruments for the assessment of health-related quality of life and visual functioning: a literature review. *Pharmacoeconomics* 2002;**20**:791–812.

18. Brown GC, Sharma S, Brown MM, Kistler J. Utility values and age-related macular degeneration. *Arch Ophthalmol* 2000;**118**:47–51.

19. Colquitt JL, Jones J, Tan SC, Takeda A, Clegg AJ, Price A. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2008;**12**(16).

20. Harding SP, Tomlin K, Reeves BC, Langham J, Walker J, Carpenter J, *et al.* Verteporfin photodynamic therapy cohort study: report 1: effectiveness and factors influencing outcomes. *Ophthalmology* 2009;**116**:e1–8.

21. Grieve R, Guerriero C, Walker J, Tomlin K, Langham J, Harding S, *et al.* Verteporfin photodynamic therapy cohort study: report 3: cost effectiveness and lessons for future evaluations. *Ophthalmology* 2009;**116**:2471–7.

22. Reeves BC, Langham J, Walker J, Grieve R, Chakravarthy U, Tomlin K, *et al.* Verteporfin photodynamic therapy cohort study: report 2: clinical measures of vision and health-related quality of life. *Ophthalmology* 2009;**116**:2463–70.

23. Cruess AF, Zlateva G, Xu X, Soubrane G, Pauleikhoff D, Lotery A, *et al.* Economic burden of bilateral neovascular age-related macular degeneration: multi-country observational study. *Pharmacoeconomics* 2008;**26**:57–73.

24. Garattini L, Castelnuovo E, Lanzetta P, Viscarra C, Ricci E, Parazzini F, *et al.* Direct medical costs of age-related macular degeneration in italian hospital ophthalmology departments. A multicenter, prospective 1-year study. *Eur J Health Econ* 2004;**5**:22–7.

25. Greiner RA. Cost of care for patients with age-related macular degeneration in Switzerland and cost-effectiveness of treatment with verteporfin therapy. *Semin Ophthalmol* 2001;**16**:218–22.

26. Meads C, Salas C, Roberts T, Moore D, Fry-Smith A, Hyde C. Clinical effectiveness and cost-utility of photodynamic therapy for wet age-related macular degeneration: a systematic review and economic evaluation. *Health Technol Assess* 2003;**7**(9).

27. Stirling B, Shoshanna S, Taryn S, Gold M. Has the time come for cost-effectiveness analysis in US health care? *Health Econ Pol Law* 2009;**4**:425–43.

28. Brown GC, Brown MM, Campanella J, Beauchamp GR. The cost–utility of photodynamic therapy in eyes with neovascular macular degeneration – a value-based reappraisal with 5-year data. *Am J Ophthalmol* 2005;**140**:679–87.

29. Gold MR, Patrick DL, Torrance GW, Fryback DG, Hadorn DC, Kamlet MS, *et al.* Identifying and valuing outcomes. In Gold MR, Siegel JE, Russell LB, Weinstein MC, editors. *Cost-effectiveness in health and medicine.* New York, NY; Oxford University Press; 1996. pp. 82–134.

30. Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in patients with age related macular degeneration: additional information regarding baseline lesion composition's impact on vision outcomes. TAP report no. 3. *Arch Ophthalmol* 2002;**120**:1443–54.

31. Brown GC. Vision and quality-of-life. *Trans Am Ophthalmol Soc* 1999;**97**:473–511.

32.　Meads C, Hyde C. What is the cost of blindness? *Br J Ophthalmol* 2003;**87**:1201–4.

33.　Wright SE, Keeffe JE, Thies LS. Direct costs of blindness in australia. *Clin Exp Ophthalmol* 2000;**28**:140–2.

34.　Hart PM, Chakravarthy U, Mackenzie G, Chisholm IH, Bird AC, Stevenson MR, *et al.* Visual outcomes in the subfoveal radiotherapy study: a randomized controlled trial of teletherapy for age-related macular degeneration. *Arch Ophthalmol* 2002;**120**:1029–38.

35.　Ali F, Chan WC, Stevenson MR, Muldrew KA, Chakravarthy U. Morphometric analysis of angiograms of exudative lesions in age-related macular degeneration. *Arch Ophthalmol* 2004;**122**:710–15.

36.　Hogg R, Curry E, Muldrew A, Winder J, Stevenson M, McClure M, *et al.* Identification of lesion components that influence visual function in age-related macular degeneration. *Br J Ophthalmol* 2003;**87**:609–14.

37.　Verteporfin Roundtable 2000 and 2001 Participants. Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group principal investigators; Verteporfin in photodynamic therapy (VIP) study group principal investigators. Guidelines for using verteporfin (visudyne) in photodynamic therapy to treat choroidal neovascularization due to age-related macular degeneration and other causes. *Retina* 2002;**22**:6–18.

38.　Early Treatment Diabetic Retinopathy Study Research Group. Early Treatment Diabetic Retinopathy Study design and baseline patient characteristics: ETDRS Report Number 7. *Ophthalmology* 1991;**98**:741–56.

39.　Pelli DG, Robson JG, Wilkins AJ. The design of a new letter chart for measuring contrast sensitivity. *Clin Vis Sci* 1988;**2**:187–99.

40.　Ware JE, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36):I. Conceptual framework and item selection. *Med Care* 1992;**30**:473–83.

41.　Higgins JPT, Altman DG. Assessing risk of bias in included studies. In Higgins JPT, Green S, editors. *Cochrane handbook for systematic reviews of interventions.* Chichester: John Wiley; 2008. pp. 187–242. URL: www.cochrane-handbook.org (accessed 31 August 2010).

42.　Stevenson MR, Hart PM, Chakravarthy U, Mackenzie G, Bird AC, Owens SL, *et al.* Subfoveal radiotherapy study. Visual functioning and quality of life in a randomised controlled clinical trial SFRADS report 2. *Br J Ophthalmol* 2005;**89**:1045–51.

43.　Desai P, Minassian DC, Reidy A. *National cataract survey* 1997–8: a report of the results of the clinical outcomes. *Br J Ophthalmol* 1999;**83**:1336–40.

44.　Browne JP, Hopkins C, Slack R, Topham J, Reeves BC, Lund V, *et al.* Health-related quality of life after polypectomy with and without additional surgery. *Laryngoscope* 2006;**116**:297–302.

45.　Langham J, Reeves BC, Lindsay KW, van der Meulen JH, Kirkpatrick PJ, Gholkar AR, *et al.* Variation in outcome after subarachnoid hemorrhage: a study of neurosurgical units in UK and Ireland. *Stroke* 2009;**40**:111–18.

46.　Maguire MG, Klein ML, Chamberlin JA. Recurrent choroidal neovascularization after argon laser photocoagulation for neovascular maculopathy. Macular Photocoagulation Study Group. *Arch Ophthalmol* 1986;**104**:503–12.

47.　Vingerling JR, Hofman A, Grobbee DE, de Jong PT. Age-related macular degeneration and smoking. The Rotterdam Study. *Arch Ophthalmol* 1996;**114**:1193–6.

48.　Thornton J, Edwards R, Mitchell P, Harrison RA, Buchan I, Kelly SP. Smoking and age-related macular degeneration: a review of association. *Eye* 2005;**19**:935–44.

49. Guymer RH, Chiu AW, Lim L, Baird PN. HMG CoA reductase inhibitors (statins): do they have a role in age-related macular degeneration? *Surv Ophthalmol* 2005;**50**:194–206.

50. Smith W, Assink J, Klein R, Mitchell P, Klaver CC, Klein BE, *et al.* Risk factors for age-related macular degeneration: pooled findings from three continents. *Ophthalmology* 2001;**108**: 697–704.

51. Doris H, Hart PM, Chakravarthy U, McCleland J, Stevenson M, Hudson C, *et al.* Relation between macular morphology and visual function in patients with choroidal neovascularisation of age related macular degeneration. *Br J Ophthalmol* 2001;**85**:184–8.

52. Hendy J, Fulop N, Reeves BC, Hutchings A, Collin S. Implementing the National Programme for Information Technology: a qualitative study of progress in acute trusts. *BMJ* 2007;**334**:1360–4.

53. British Medical Association and Royal Pharmaceutical Society of Great Britain. *British national formulary.* No. 57, March 2009. London: BMA and RPS; 2009.

54. Department of Health. *NHS Reference Costs 2002. Appendix 1E. National Schedule of Reference Costs: NHS Trust Outpatient HRG Data. Ophthalmology HRG Label.* London: Department of Health; 2002. pp. 136.

55. Curtis L. *Unit costs of health and social care.* University of Kent, Canterbury: Personal Social Service Research Unit; 2008. pp. 35–178.

56. Mullahy J. Much ado about two: reconsidering retransformation and the two-part model in health econometrics. *J Health Econ* 1998;**17**:247–81.

57. Doubilet P, Begg CB, Weinstein MC, Braun P, McNeil BJ. Probabilistic sensitivity analysis using Monte Carlo simulation: a practical approach. *Med Decis Making* 1985;**5**:157–77.

58. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, *et al.* Evaluating non-randomised intervention studies. *Health Technol Assess* 2003;**7**(27).

59. Wormald R, Evans JR, Smeeth LL, Henshaw KS. Photodynamic therapy for neovascular age-related macular degeneration. *Cochrane Database Syst Rev* 2007, Issue 3. Art. No. CD002030. DOI: 10.1002/14651858.CD002030.pub3.

60. El Mallah MK, Chakravarthy U, Hart PM. Amblyopia: is visual loss permanent? *Br J Ophthalmol* 2000;**84**:952–6.

61. Swets J, Tanner WP Jr, Birdsall TG. Decision processes in perception. *Psychol Rev* 1961;**68**:301–40.

62. Thorpe KE, Zwarenstein M, Oxman AD, Treweek S, Furberg CD, Altman DG, *et al.* A pragmatic-explanatory continuum indicator summary (PRECIS): a tool to help trial designers. *J Clin Epidemiol* 2009;**62**:464–75.

63. Zwarenstein MJ, Treweek S. What kind of randomized trials do we need? *CMAJ* 2009;**180**:998–1000.

64. Espallargues M, Czoski-Murray CJ, Bansback NJ, Carlton J, Lewis GM, Hughes LA, *et al.* The impact of age-related macular degeneration on health status utility values. *Invest Ophthalmol Vis Sci* 2005;**46**:4016–23.

65. Submacular Surgery Trials Research Group. Evaluation of minimum clinically meaningful changes in scores on the National Eye Institute Visual Function Questionnaire (NEI-VFQ) SST Report Number 19. *Ophthalmic Epidemiol* 2007;**14**:205–15.

66. Bansback N, Czoski-Murray C, Carlton J, Lewis G, Hughes L, Espallargues M, *et al.* Determinants of health related quality of life and health state utility in patients with age

related macular degeneration: the association of contrast sensitivity and visual acuity. *Qual Life Res* 2007;**16**:533–43.

67. Health Utilities Inc. *Health Utilities Index Mark 3;* 2008. URL: www.healthutilities.com/hui3. htm (accessed 30 November 2010).

68. Chakravarthy U, Stevenson M. Self-reported visual functioning and quality of life in age-related macular degeneration. *Curr Opin Ophthalmol* 2005;**16**:179–83.

69. World Health Organization. *Constitution of the World Health Organization. Basic Documents.* 45th edn. Supplement, October 2006. URL: www.who.int/governance/eb/who_constitution_ en.pdf (accessed 30 November 2010).

70. Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and the SF-6D across seven patient groups. *Health Econ* 2004;**13**:873–84.

71. Feeny D, Furlong W, Torrance GW, Goldsmith CH, Zhu Z, DePauw S, *et al.* Multiattribute and single-attribute utility functions for the Health Utilities Index Mark 3 system. *Med Care* 2002;**40**:113–28.

72. Stevens KJ, McCabe CJ, Brazier JE. Mapping between Visual Analogue Scale and Standard Gamble data: results from the UK Health Utilities Index 2 valuation survey. *Health Econ* 2007;**15**:527–33.

73. Rosenfeld PJ, Brown DM, Heier JS, Boyer DS, Kaiser PK, Chung CY, *et al.* Ranibizumab for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1419–31.

74. Brown DM, Kaiser PK, Michels M, Soubrane G, Heier JS, Kim RY, *et al.* Ranibizumab versus verteporfin for neovascular age-related macular degeneration. *N Engl J Med* 2006;**355**:1432–44.

75. Browne J, Jamieson L, Lewsey J, Van der Meulen J, Black N, Cairns J, *et al. Patient Reported Outcome Measures (PROMs) in elective surgery.* Report to the Department of Health; 2007. URL: www.lshtm.ac.uk/hsru/research/PROMs-Report-12-Dec-07.pdf (accessed 4 October 2009).

76. Griffin SC, Barber JA, Manca A, Sculpher MJ, Thompson SG, Buxton MJ, *et al.* Cost effectiveness of clinically appropriate decisions on alternative treatments for angina pectoris: prospective observational study. *BMJ* 2007;**334**;624.

77. Smith DH, Fenn P, Drummond M. Cost effectiveness of photodynamic therapy with verteporfin for age related macular degeneration: the UK case. *Br J Ophthalmol* 2004;**88**:1107–12.

78. Fletcher EC, Lade RJ, Adewoyin T, Chong NV. Computerized model of cost-utility analysis for treatment of age-related macular degeneration. *Ophthalmology* 2008;**115**:2192–8.

79. Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2001;**108**:2051–9.

80. Coleman AL, Yu F. Eye-related Medicare costs for patients with age-related macular degeneration from 1995 to 1999. *Ophthalmology* 2008;**115**:18–25.

81. Smiddy WE. Relative cost of a line of vision in age-related macular degeneration. *Ophthalmology* 2007;**114**:847–54.

82. Birchall W. Minimising the impact of visual impairment: training in use of low vision aids is important. *BMJ* 1999;**319**:707.

83. Margrain TH. Minimising the impact of visual impairment: low vision aids are a simple way of alleviating impairment. *BMJ* 1999;**318**:1504.

84. Kiss CG, Simader C, Michels S, Schmidt-Erfurth U. Combination of verteporfin photodynamic therapy and ranibizumab: effects on retinal anatomy, choroidal perfusion and visual function in the protect study. *Br J Ophthalmol* 2008;**92**:1620–7.

Appendix 1

Protocol

THE VERTEPORFIN PHOTODYNAMIC THERAPY COHORT STUDY FOR THE UNITED KINGDOM

Manual of Operations

Version 2.1

23 December 2005

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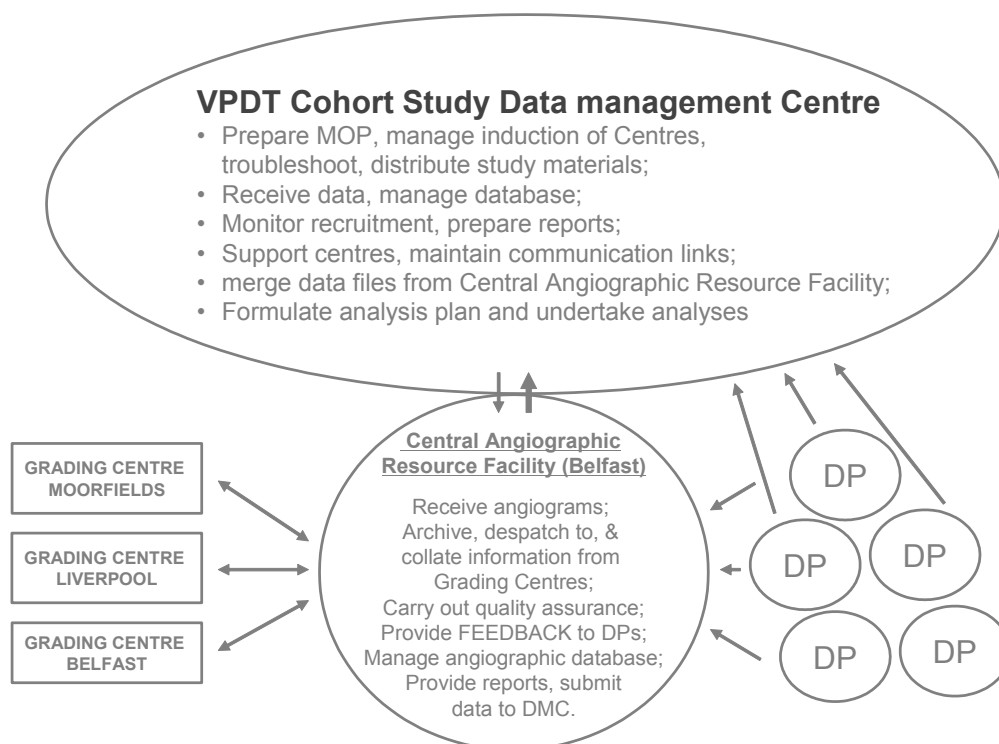
MOP – manual of procedures; DP – designated provider of PDT; DMC – Data Management Centre

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 <u>not</u> 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)
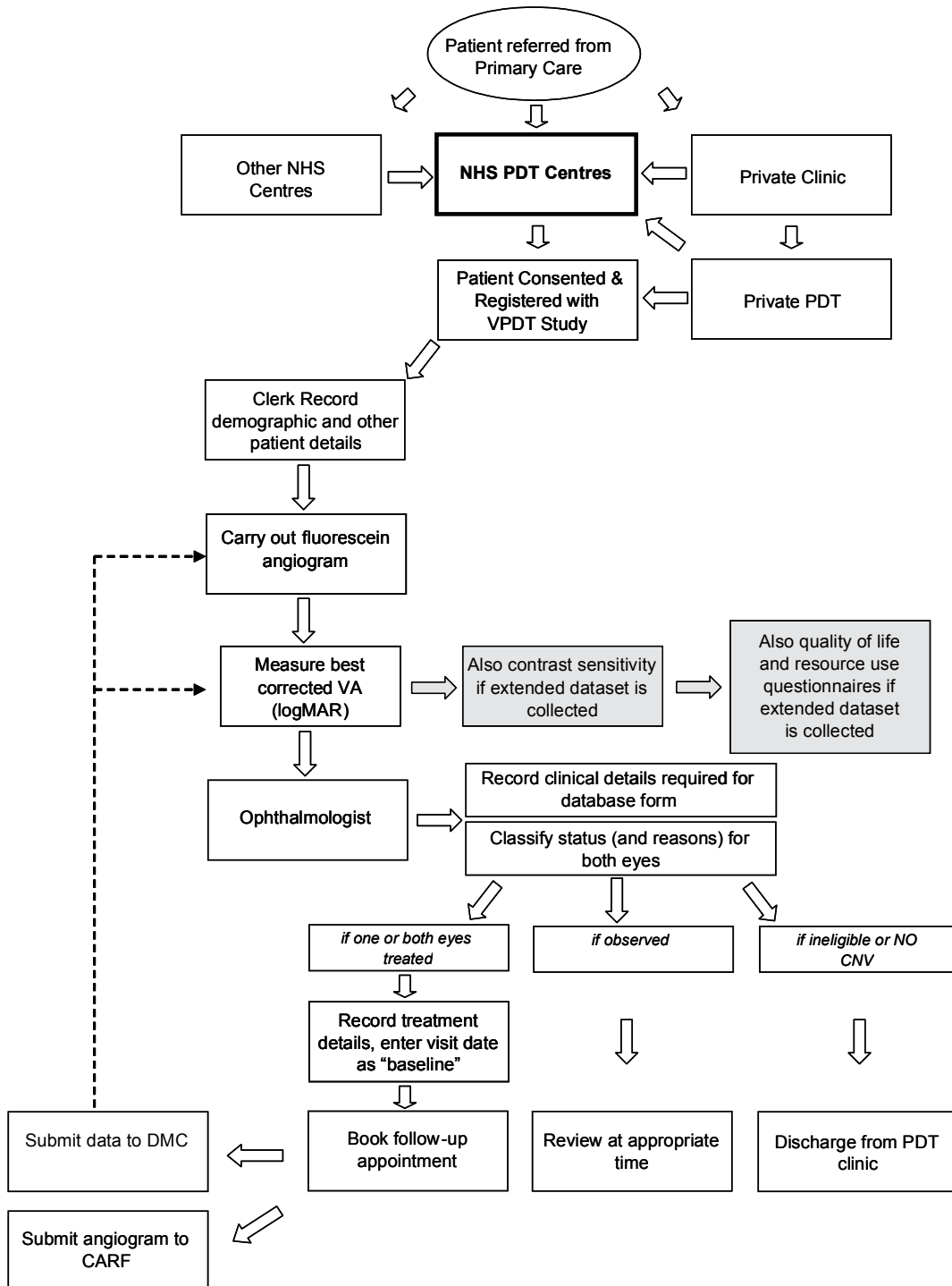
- Contrast sensitivity (CS); CS need only be collected by DPs who have been nominated to collect the extended dataset. CS must be assessed using Pelli Robson CS charts, with precise details of the letters seen/not seen on each line being recorded on the paper form supplied by the Data Management Centre. 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

14. References

[1]   References from the 'Treatment of Age-related macular degeneration by photodynamic Therapy' (TAP) and 'Visudyne In Photodynamic therapy' (VIP) studies

Treatment of age-related macular degeneration with photodynamic therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: one-year results of 2 randomized clinical trials--TAP report. *Arch Ophthalmol* 1999;**117**:1329-45. (Erratum in: *Arch Ophthalmol* 2000;**118**:488.)

Bressler NM; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Photodynamic therapy of subfoveal choroidal neovascularization in age-related macular degeneration with verteporfin: two-year results of 2 randomized clinical trials-TAP report 2. *Arch Ophthalmol* 2001;**119**:198-207.

Bressler NM, Arnold J, Benchaboune M, Blumenkranz MS, Fish GE, Gragoudas ES, *et al*.; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in patients with age-related macular degeneration: additional information regarding baseline lesion composition's impact on vision outcomes-TAP report No. 3. *Arch Ophthalmol* 2002;**120**:1443-54.

Rubin GS, Bressler NM; Treatment of Age-Related Macular Degeneration with Photodynamic therapy (TAP) study group. Effects of verteporfin therapy on contrast on sensitivity: Results From the Treatment of Age-Related Macular Degeneration With Photodynamic Therapy (TAP) investigation-TAP report No 4. *Retina* 2002;**22**:536-44.

Blumenkranz MS, Bressler NM, Bressler SB, Donati G, Fish GE, Haynes LA, *et al*.; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group. Verteporfin therapy for subfoveal choroidal neovascularization in age-related macular degeneration: three-year results of an open-label extension of 2 randomized clinical trials--TAP Report no. 5. *Arch Ophthalmol* 2002;**120**:1307-14.

Blinder KJ, Bradley S, Bressler NM, Bressler SB, Donati G, Hao Y, *et al*.; Treatment of Age-related Macular Degeneration with Photodynamic Therapy study group; Verteporfin in Photodynamic Therapy study group. Effect of lesion size, visual acuity, and lesion composition on visual acuity change with and without verteporfin therapy for choroidal neovascularization secondary to age-related macular degeneration: TAP and VIP report no. 1. *Am J Ophthalmol* 2003;**136**:407-18.

Barbazetto I, Burdan A, Bressler NM, Bressler SB, Haynes L, Kapetanios AD, *et al*.; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group; Verteporfin in Photodynamic Therapy Study Group. Photodynamic therapy of subfoveal choroidal neovascularization with verteporfin: fluorescein angiographic guidelines for evaluation and treatment--TAP and VIP report No. 2. *Arch Ophthalmol* 2003;**121**:1253-68.

Arnold JJ, Blinder KJ, Bressler NM, Bressler SB, Burdan A, Haynes L, *et al*.; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy Study Group; Verteporfin in Photodynamic Therapy Study Group. Acute severe visual acuity decrease after photodynamic therapy with verteporfin: case reports from randomized clinical trials-TAP and VIP report no.3. *Am J Ophthalmol* 2004;**137**:683-96.

Azab M, Benchaboune M, Blinder KJ, Bressler NM, Bressler SB, Gragoudas ES, *et al*.; Treatment of Age-Related Macular Degeneration with Photodynamic Therapy (TAP) Study Group; Verteporfin in Photodynamic Therapy (VIP) Study Group. Verteporfin therapy of subfoveal choroidal neovascularization in age-related macular degeneration: meta-analysis of 2-year safety results in three randomized clinical trials: Treatment Of Age-Related Macular Degeneration With Photodynamic Therapy and Verteporfin In Photodynamic Therapy Study Report no. 4. *Retina* 2004;**24**:1-12.

Bressler SB, Pieramici DJ, Koester JM, Bressler NM. Natural history of minimally classic subfoveal choroidal neovascular lesions in the treatment of age-related macular degeneration with photodynamic therapy (TAP) investigation: outcomes potentially relevant to management--TAP report No. 6. *Arch Ophthalmol* 2004;**122**:325-9.

[2] National Institute of Clinical Excellence

Technology appraisal 68: Full guidance on the use of photodynamic therapy for age-related macular degeneration. 24 Sep 2003. http://www.nice.nhs.uk/pdf/68_PDTGuidance.pdf

[3] Other references relating to the Verteporfin Photodynamic Therapy

Harding S. Photodynamic therapy in the treatment of subfoveal choroidal neovascularisation. *Eye* 2001;**15**:407-12.

Sharma S, Brown GC, Brown MM, Hollands H, Shah GK. The cost-effectiveness of photodynamic therapy for fellow eyes with subfoveal choroidal neovascularization secondary to age-related macular degeneration. *Ophthalmology* 2001;**108**:2051-9.

Sharma S, Hollands H, Brown GC, Brown MM, Shah GK, Sharma SM. Improvement in quality of life from photodynamic therapy: a Canadian perspective. *Can J Ophthalmol* 2001;**36**:332-8.

Haddad WM, Coscas G, Soubrane G. Eligibility for treatment and angiographic features at the early stage of exudative age related macular degeneration. *Br J Ophthalmol* 2002;**86**:663-9.

Verteporfin Roundtable 2000 and 2001 Participants; Treatment of age-related macular degeneration with photodynamic therapy (TAP) study group principal investigators; Verteporfin in photodynamic therapy (VIP) study group principal investigators. Guidelines for using verteporfin (visudyne) in photodynamic therapy to treat choroidal neovascularization due to age-related macular degeneration and other causes. *Retina* 2002;22:6-18.

Keam SJ, Scott LJ, Curran MP. Verteporfin: a review of its use in the management of subfoveal choroidal neovascularisation. *Drugs* 2003;**63**:2521-54.

Meads C, Hyde C. Photodynamic therapy with verteporfin is effective, but how big is its effect? Results of a systematic review. *Br J Ophthalmol* 2004;**88**:212-7.

Keam SJ, Scott LJ, Curran MP. Spotlight on verteporfin in subfoveal choroidal neovascularisation. *Drugs Aging* 2004;**21**:203-9.

Barnes RM, Gee L, Taylor S, Briggs MC, Harding SP. Outcomes in verteporfin photodynamic therapy for choroidal neovascularisation-'beyond the TAP study' Eye. 2004 Feb 13 [Epub ahead of print]

[4] National Eye Institute Visual Functioning Questionnaire

Mangione CM, Berry S, Lee PP, *et al*. Identifying the content area for the National Eye Institute Vision Function Questionnaire (NEI-VFQ): Results from focus groups with visually impaired persons. *Arch Ophthalmol* 1998;**116**:227-238.

Mangione CM, Lee PP, Pitts J, *et al*. Psychometric properties of the National Eye Institute Visual Function Questionnaire, the NEI-VFQ. *Arch Ophthalmol* 1998;**116**:1496-1504

Mangione CM, Lee PP, Gutierrez PR, *et al*. Development of the 25-item National Eye Institute Visual Function Questionnaire (VFQ-25). *Arch Ophthalmol.* 2001 (in press).

[5] Short-Form 36-item health survey

Ware JE, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36):I. Conceptual framework and item selection. *Medical Care* 1992; **30**: 473-483.

See also. http://www.qualitymetric.com/products/SFSurveys.shtml

[6] Sample size calculation

Machin D, Campbell M, Fayers P, Pinol A. *Sample Size Tables for Clinical Studies* (2nd ed.). Blackwell Science, Oxford, 1997.

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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)

A. Identify morphological features	B. Assess total lesion size	C. Categorise lesion subtype
Use stereos of colour and angiographic frames to assist in recognition of the following lesion components		
1. CNV Lesion Components	1. Define the boundaries of the lesion	**1. Classic with no occult (NICE FAD 1.1)**
Fluorescein leakage associated with CNV		1A. Classic leakage accounts for 100% of lesion
Classic CNV		
Occult CNV: fibrovascular PED; late leakage of undetermined origin		1B. Classic leakage accounts for 50-99% but lesion has no occult component
Features contiguous to CNV which prevent determination of extent of leakage and which therefore constitute part of the lesion	2. Define the boundaries of the area of classic leakage	2. Predominantly classic with occult (NICE FAD 1.2)
Blood		
Elevated Blocked Fluorescence (EBF) not due to blood		Classic leakage accounts for 50-99% of lesion with some occult
- may be due to RPE hyperplasia, thick exudate, fibrous tissue	3. Estimate proportion of classic relative to total lesion size	**3. Minimally classic**
Serous PED		Classic leakage accounts for less than 50% of the lesion
2. Other features associated with CNV which are NOT used to define the boundaries of the lesion	4. Ineligible for PDT if less than 50% of lesion is CNV	**4. Occult with no classic**
Atrophy: geographic atrophy (GA) and non GA		Classic is 0%. Any CNV leakage is of the occult variety
Flat blocked fluorescence		
Fibrosis not contiguous to CNV boundary		
Thick exudate not contiguous to CNV boundary		
3. Other features which help with categorisation of CNV or which may modify natural history		
Retinal angiomatous proliferation		
Chorio-retinal anastamoses		
Idiopathic polypoidal choroidopathy		

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

Belfast re-treatment criteria

Is leakage present on FA

No → Do not treat and arrange review for 3 M

Yes → Is leakage reduced when compared with pre-treatment

No → Has there been a treatment related adverse event

Yes → Retreat with PDT

Has there been a treatment related adverse event
- Yes → No further therapy
- No → Is VA within 6 lines of last treatment
  - Yes → Retreat with PDT
  - No → No further therapy

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
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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   Tel: 01903 851951
16, Winston Business Centre,   Fax: 01903 767732
Chartwell Road, Lancing,
West Sussex, BN15 8TU

Schematic showing how to refine the spherical correction during refraction
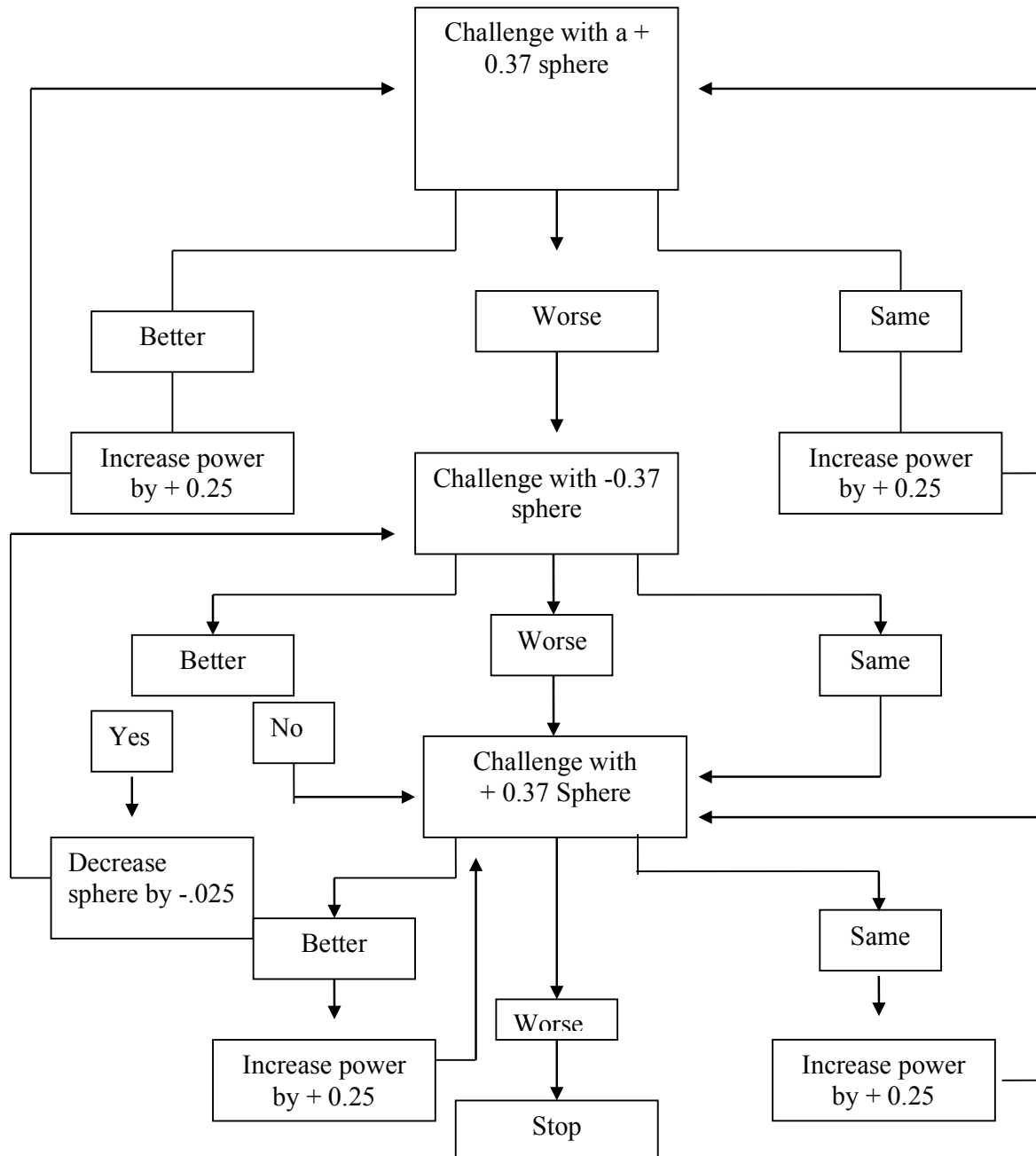
Appendix 6:   Protocol for Pelli-Robson Contrast Sensitivity Assessment

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.
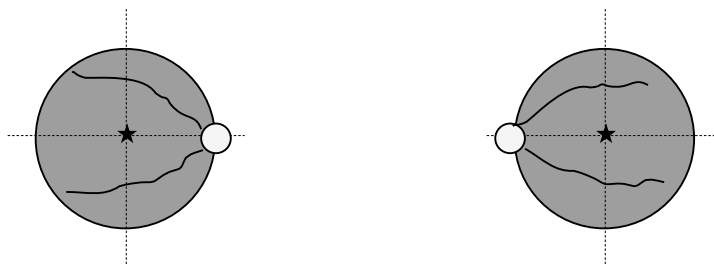
Field 3 - Temporal to Macula: Macula at the nasal edge of the field. Again, the position may be achieved by rotating the camera without making any vertical adjustment or movement of the fixation device. However it may be easier to achieve using the internal fixator and then removing it just prior to taking the photograph.
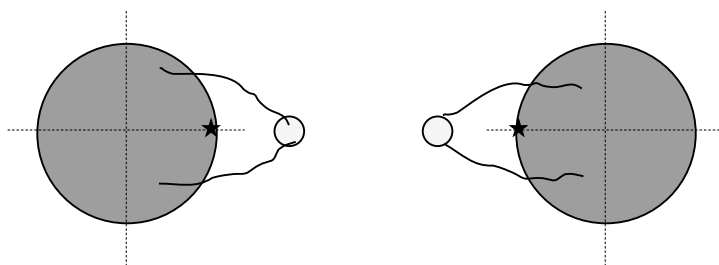
A stereoscopic fundus reflex (FR) photograph should also be taken to document media opacities. To obtain the largest possible FR image the photographer should turn the focusing knob all the way forward and then adjust focus by manually moving the camera closer or further away from the patient.

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 <u>must</u> 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 <u>must</u> include the following information about each patient:
- Centre ID
- Hospital number
- Date of birth
- Date of angiogram

Right Eye

Field 2	Field 2	Field 1	Field 1
Field 3	Field 3	Fundus Reflex	Fundus Reflex
		Identification Label	

Left Eye

Field 1	Field 1	Field 2	Field 2
Fundus Reflex	Fundus Reflex	Field 3	Field 3
		Identification Label	

Fluorescein Page Label Here

End Injection	Begin Injection Time "0"	LE Red-Free LS	LE Red-Free RS	RE Red-Free LS	RE Red-Free RS
Study Eye Early Phase LS	Study Eye Early Phase RS	Study Eye Early Phase LS	Study Eye Early Phase RS	Study Eye Early Phase LS	Study Eye Early Phase RS
Study Eye Early Phase LS	Study Eye Early Phase RS	Study Eye Early Phase LS	Study Eye Early Phase RS	Study Eye Early Phase LS	Study Eye Early Phase RS
Study Macula 60-90 sec.	Study Macula 60-90 sec.	Study Eye Early Phase	Study Eye Early Phase – 45 sec.	Study Eye Early Phase LS	Study Eye Early Phase RS
Study Macula 2-3 min.	Study Macula 2-3 min.	Fellow Eye Macula 2 min.	Fellow Eye Macula 2 min.	Study Disc 60-90 sec.	Study Disc 60-90 sec.
Fellow Macula 10 min.	Fellow Macula 10 min.	Study Macula 10 min.	Study Macula 10 min.	Study Macula 5 min.	Study Macula 5 min.

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 <u>each</u> 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.

> ## <u>Notes:</u>
>
> 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).

<u>Central Angiographic Resource Facility Contact Details:</u>

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)   e. Smoking history
   ☐ Suspected CNV   ☐ Never
   ☐ Predominantly classic CNV   ☐ Current: Number of years smoked............yrs
   ☐ Classic CNV   ☐ Ex-smoker: Number of years smoked............yrs
   ☐ Other   Yrs/mths since last smoked ....yrs ....mths

f . Other health-related information   g. Imaging
   Y / N Cardiovascular disease   ☐ None   ☐ OCT only
   Y / N Use of statins   ☐ ICG only   ☐ Both
   Y / N Family history ....

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   **R**............   laser photocoagulation   .... **L**
   treatments for CNV   **R**............   PDT   .... **L**
   (enter 0 if none)   **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 <u>one item</u> only)

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

....

b. **AMD characteristics** (tick <u>one</u> only)

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

<u>Location</u> of lesion (tick <u>one</u> only):

- ☐   Subfoveal   ☐
- ☐   Juxtafoveal   ☐

7. Features of treated eye

a. Required for **ALL VISITS**
b.& c. Only required if <u>treated at this visit</u>

a. **Additional features (tick <u>all</u> 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: ....

Page 2

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. <u>Ask the patient</u> 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.*

Appendix 2

Verteporfin photodynamic therapy cohort study for the UK

RESOURCE USE QUESTIONNAIRE (administered)

PATIENT SURNAME:_____   DATE OF BIRTH:_____

HOSPITAL NO:_____   DATE OF VISIT: _____

Interviewer to say:

"We are conducting a study to assess the benefits of a new treatment for **macular degeneration**, called **photodynamic therapy**. Part of the study involves finding out about the costs of the illness to you. This questionnaire aims to find out about the costs involved in having macular degeneration. All the answers given will be kept confidential and only used for research purposes. They will not affect your care in any way".

TREATMENT AT AND VISITS TO THE HOSPITAL

Q1	Did you experience any serious complications when you last had either angiography or photodynamic therapy treatment that resulted in:		
	Your treatment being stopped?	yes	no
	Being admitted to hospital?	yes	no

Q2	During the last three months, have you had to make any extra visits to your **eye consultant**?	yes	no

Q3	a) During the past three months, have you **telephoned the Eye Hospital help-line**, or another member of staff at the Eye Hospital, **because of your eye condition**? b) **If yes**, how often? (Tick boxes to indicate member of staff telephoned)						yes	no
		Call 1	Call 2	Call 3	Call 4	Call 5		Call 6
	Help-line							
	Ophthalmologist							
	Optometrist							
	Other staff							
	(if other, who?)							

Q4	a) During the past three months, have you **visited the Eye Hospital** for a low vision appointment (vision rehabilitation, appointment to see whether magnifiers can help your vision)? **b) If yes**, how many times?					yes no	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	Low vision appointment						

PLEASE COMPLETE QUESTIONS 5-7, EVEN IF ANSWERED 'NO' TO Q4

Q5	When you visit the Eye Hospital, does someone usually come with you, for example your husband/wife, a relative or a friend?	yes no

Q6	When you visit the Eye Hospital, how long does your visit take in total (including time travelling to and from the Eye Hospital and waiting time to see the consultant or other members of staff in the hospital)	(hrs/mins)

Q7	When you visit the Eye Hospital, how much does it cost you and anyone who comes with you?*****	(enter total cost, £)
	Interviewer comments about mode of travel and availability of concessions, e.g. bus pass:	

* Note: if the patient comes by car and is unaware of the cost, ask him/her what the total miles taken for the visit was (to and from the clinic)

VISITS TO OR FROM GENERAL PRACTICE

Q8	a) During the past three months, have you **visited your GP**, or other staff in the GP surgery, **because of your eye condition**? b) **If yes**, how often? (Tick boxes to indicate staff seen on each visit.)					yes no **If no, go to Q12**	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	GP						
	Practice nurse						
	Other staff						
	(if other, who?)						

Q9	When you visit your GP surgery, does someone usually come with	yes no

	you, for example your husband/wife, a relative or a friend?	

Q10	When you visit your GP surgery, how long does your visit take in total (including time travelling to and from the surgery and waiting time to see the GP or other member of staff in the surgery)?	(hrs/mins)

Q11	When you visit your GP surgery, how much does it cost you and anyone who comes with you?*****	(enter total cost, £)
	Interviewer comments about mode of travel and availability of concessions, e.g. bus pass:	

* Note: if the patient came by car and is unaware of the cost, ask him/her what the total miles taken for the visit was (to and from the clinic)

Q12	a) During the past three months, have you **been visited at home** by your GP, or another member of staff from the GP surgery, **because of your eye condition**? If yes, how often? (Tick boxes to indicate staff seen on each home visit.) b) **If yes**, how often? (Tick boxes to indicate staff seen on each visit.)					yes no	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
	GP						
	Practice nurse						
	District nurse						
	Other staff						
	(if other, who?)						

Q13	a) During the past three months, have you **telephoned your GP**, or another member of staff in the GP surgery, **because of your eye condition**? If yes, how often? (Tick boxes to indicate staff member telephoned on each occasion.) b) **If yes**, how often? (Tick boxes to indicate staff seen on each visit.)					yes no	
		Call 1	Call 2	Call 3	Call 4	Call 5	Call 6
	GP						
	Practice nurse						
	Other staff						

	(if other, who?)						

VISIT FROM OCCUPATIONAL THERAPIST

Q14	a) During the past three months, have you been visited at home by an occupational therapist **because of your eye condition** (to find out if you need any changes to your home because of your eye condition)? b) **If yes**, how many times?	yes no No. times _____

Q15	During the past three months, have you had any changes done to your home **because of your eye condition** (improved lighting, other methods for enhancing contrast, changes to cooker, etc.)?	yes no **If no, go to Q17**
	Interviewer comments about any changes described:	

Q16	**If yes**, did you have to pay for the changes? How much did they cost?	(enter cost, £)

HOME HELP / SOCIAL SERVICES

Q17	a) During the past three months, have you had **social services** home help because of your eye condition? b) **If yes**, how many hours per week has the home help done?	yes no (hrs/week)

Q18	a) During the past three months, have you had **a private** home help because of your eye condition? b) **If yes**, how many hours per week has the home help done?	yes no (hrs/week)

Q19	a) During the past three months, have you had **meals on wheels** because of your eye condition? b) **If yes**, how many times per week have you had meals on wheels?	yes no (meals/week)

| Q20 | a) During the past three months, have attended a **Day Centre** because of your eye condition? | yes   no |
| | b) **If yes**, how many times per week have you attended? | (times/week) |

| Q21 | a) During the past three months, have you had **regular help** from a member of your family or a friend? | yes   no |
| | b) **If yes**, how many hours per week have they helped you? | (hrs/week) |

Q22	a) During the past three months, have you had regular help from anyone else (private or social services)?	yes no
	b) **If yes**, how many hours per week have they helped you?	(hrs/week)
	Name of professions / service:	

EMPLOYMENT

Q23	a) Are you fully retired?	Yes No
		If yes, go to Q25
	b) **If No**, how many hours per week are you in paid employment?	Hours/week

| Q24 | During the past three months, how many hours per week have you had to take off work because of your eye condition? | hrs/week |

Q25	a) If your husband/wife, a family member or friend accompanies you to hospital or surgery visits, or helps you in other ways, is this person/are these people in paid employment?	yes no **If no, go to Q27**
	b) **If yes**, how many hours per week do they work?	Hours/week

| Q26 | During the past three months, how many hours per week has your husband/wife, a family member or friend had to take off work because of your eye condition? | Hours/week |

Q27	a) During the last past three months, have you incurred **any other costs** because of your eye condition? (covering hospital, community or personal service use e.g. use of residential care, hospital episodes, use of anti-depressants)	yes no
	b) **If so**, please document name of service use/resource use and number of units. E.G. moved into residential care: 90 days, or started on Prozac 10 days, saw social worker 3 times etc.	

Q28	Any other comments/issues of clarification:

Thank you for answering these questions

Appendix 3

Key observations and recommendations arising from an interim project review of the study (1 July 2005)

It is worth noting that it was not possible to undertake a truly comprehensive review. In the writing up of this report, a number of other issues have come to light and been discussed but these have not been included. If the NCCHTA wish to further explore some of these issues then it would be possible to seek additional feedback from the individuals most closely involved both in the implementation of the Cohort Study and the service within the NHS.

Key observations

1. This is an example of how a number of influential people and organisations anticipated that there could be major problems with the introduction of a new treatment and aimed to deal with the issues proactively. Despite this foresight and attempts to avoid problems arising, introducing both the treatment and the cohort study has been one of the most difficult exercises.
2. The model developed in the cohort study can be used to meet many of the needs of the NHS in the introduction of an expensive therapy by providing postmarketing surveillance, a managed introduction to standard treatment protocols, evidence of effectiveness in routine clinical practice and data for optimisation of treatment protocols.
3. Two important communications problems arose which complicated implementation:
   a. The NICE guidance did not explicitly refer to the cohort study.
   b. The Department of Health did not explicitly support the cohort study nor did it issue clear directions in relation to it. In particular, this left those tasked with setting up the cohort study without any mandate to implement it in the NHS.

   It is not clear why NICE and the DOH did not feel able to provide this explicit support.
4. It is not clear:
   a. Why NICE did not recommend a RCT and why the National Coordinating Centre for Health Technology Assessment was willing to support a cohort study instead of a RCT.
   b. Why the cohort study was seen as the best option.
5. There was initial hostility to the cohort study from many of the clinicians, in part because of their general reluctance to gather clinical data and in part because they perceived the cohort study to be a threat to their clinical freedom. Many, but not all, have since changed that view.
6. During the implementation of the cohort study, significant weaknesses in the capabilities of clinicians, clinical teams and trusts in understanding the principles and practicality of gathering systematic information were identified.
7. Commissioners were initially unsupportive of the cohort study. This probably stemmed from a lack of understanding of what it was trying to achieve. Some have remained indifferent to it. The lack of clarity about the aims and objectives of the cohort study meant that interests of commissioners were never made explicit.
8. Both patient groups and the manufacturer (Novartis) were also initially hostile to the cohort study, although patient groups were not initially averse to the idea of a RCT. From the

manufacturer's perspective, the findings of the cohort study could at best only confirm the status quo; at worst, the findings could seriously damage their commercial interest.

9. The size of the task was underestimated by all.
10. The designation processes undertaken locally were very confused and varied greatly.

Recommendations

1. The NHS needs to better anticipate the requirements needed to manage the introduction of new treatments particularly where establishing a new treatment is likely to be complex. (Note that a recommendation has already been made through the Specialised Commissioning Group. This recommendation proposes that NICE, for example, involves 'on the ground' NHS staff from both commissioning and provider organisations in discussion of the practical issues that may arise from specific pieces of guidance.)
2. Establishing postlicensing studies to evaluate the introduction and use of new treatments should not be considered without the explicit support of the Department of Health. This support needs to be transparent and public.
3. A clear set of aims and objectives must be published and made widely available before commencement of any cohort study to ensure that all stakeholders are fully informed and take ownership.
4. There needs to be better understanding of the role of cohort studies together with that of registries and databases.
5. Clinicians should be better informed of the need for robust, continuing postmarketing evaluation of clinical therapies after marketing authorisation in order to ensure that results from RCTs carried out for the purposes of licensing are generalizable in everyday clinical practice after the RCTs have ended. The importance of continuing to acquire data on the use of treatments in everyday practice must be stressed and clinicians strongly encouraged to collect these data particularly when introducing high cost medicines into the NHS.
6. The NHS could benefit from the development of good practice guidance in relation to designation and accreditation processes. (Some work on this has already begun in the West Midlands.)
7. The NHS could benefit from the development of good practice guidance on postlicensing collection of data on new treatments.

Overall, despite very serious obstacles, the cohort study has been established and has achieved the majority of its objectives with a large number of trusts providing good data. Wide geographical access is being provided to a high standard.

The review group strongly supports the development of on-going assessment of new treatments and for the health community and policy-makers to gain as much experience from the cohort study as possible. In spite of a complex set of problems that have been overcome to lesser or greater extent, the model that has been developed by the cohort study team provides a useful model for the future.

Current status of the cohort study

The study is running effectively with good rates of recruitment and data being submitted by most designated providers.

There has been slippage estimated at around 1 year at present. It was expected to reach a full recruitment rate by June 2004 but in reality only a handful of patients had been recruited by

then. A year later, 1200–1500 patients had been recruited. Since the project review, a year's extension to data collection has been provisionally funded. The study is expected to recruit until November 2007.

The study team continue to deal with issues around NHS implementation requiring a major time investment to sort out on-going problems.

Funding for treatment was not considered a major issue at the time of the review other than for the establishment of some dedicated clinics to promote rapid referral. However, since then it has become apparent that the current financial situation has resulted in clinical and nursing posts being frozen, waiting lists being allowed to develop and planned service developments being put on hold. In addition, the effects of national tariffs under Payment By Results are causing concern and generating uncertainties in the minds of managers in designated provider trusts. Indeed the whole issue of funding flows is confused. It is likely that there are problems at all levels: failure of some commissioners to fully fund the cohort study, failure of some trusts not to forward funds given for the cohort study and treatment to clinical teams and also some trusts receiving money for the cohort study but not entering patients into the study.

Compliance among clinicians with respect to the collection and submission of high-quality data continues to be an important problem. Some providers are receiving funding to provide photodynamic therapy but are not participating in the study. The Steering Group constantly monitor this situation.

Data collection is still being established at some sites.

A number of centres are reporting considerable delays in getting patients to treating centres – such that a significant percentage of referrals are deemed ineligible for treatment owing to the poor level of visual acuity in the eye being assessed, suggesting that earlier referral would have resulted in the patient receiving treatment.

Alternative treatments with antiangiogenic drugs with equivalent efficacy to VPDT and, potentially, wider application are due to be licensed for use in this condition during 2006–7. It can be anticipated that the implementation of these new treatments will present a major problem for the NHS as well as a threat to the cohort study.

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