NETSCC, HTA

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1 Project title

A randomised controlled trial of alternative treatments to **I**nhibit **V**EGF in **A**ge-related choroidal **N**eovascularisation (**IVAN**) **HTA reference: 07/36/01**

2 Trial summary

Wet or neovascular age-related macular degeneration (nAMD) is a condition which causes severe sight loss in older people. Until recently, available treatments only slowed down the rate of sight loss with most patients becoming moderately or severely visually impaired in the affected eye despite optimal management. Wet macular degeneration is due to a pathological process known as choroidal neovascularisation (CNV) where new blood vessels grow from the choroid breaching the normal tissue barriers and come to lie within the sub pigment epithelial and sub retinal spaces. A variant of this process is also being increasingly recognised in which abnormalities of the microvasculature initially appear in the retina with subsequent appearance of CNV. These abnormalities of the retinal circulation are termed Retinal Angiomatous Proliferation (RAP) but it is as yet unclear whether these are true new vessels or simply represent dilated, tortuous and leaky segments of existing retinal microvasculature. CNV and RAP lesions leak fluid and, because they are fragile, can bleed easily. The collection of fluid and or blood between the tissue layers and within the neural retina is incompatible with normal eyesight.

Very recently a new treatment with a drug known as Lucentis (Ranibizumab) was found to prevent sight loss in over 90% of recipients when given as injections into the eye with CNV for periods of up to two years. Lucentis is extremely expensive (approximately £750 per injection) and wet macular degeneration is common (about 25,000 newly affected people each year in the UK). There is very little evidence on which to base criteria for stopping treatment and so there is considerable uncertainty about precisely how much treatment might cost in the longer term. With respect to possible side effects of treatment, a recent press release from the manufacturer suggests that the currently recommended dose of Lucentis (0.5mg) increases the risk of stroke 4-fold compared with the lower dose (0.3mg) raising concerns about its systemic safety.

Another drug, called Avastin (Bevacizumab) which is licensed for colorectal cancer therapy is similar to Lucentis in its properties. This drug has also been used to treat neovascular AMD patients and also is thought to confer similar benefits but the data come from multiple small uncontrolled studies. This drug is extremely cheap as the dose for ocular injection is small (i.e. the amount of drug needed for one colorectal cancer treatment can be made into very many doses for injection into the eye). With respect to possible side effects of treatment, there is little robust information on the systemic safety of Avastin. The large number of small uncontrolled studies, and an internet survey which compiled information on several thousand treated patients, have not reported any serious adverse effects. The present study is therefore a proposal to undertake a prospective randomised controlled clinical trial which will (a) compare the clinical efficacy of the two drugs; (b) compare a reduced treatment regimen versus two years of continuous treatment; (c) describe the cost effectiveness of different drugs and treatment regimens; (d) describe both eye-related and systemic side effects with different drugs and treatment regimens.

3 Planned Investigation

3.1 Aims and Objectives

The aim of the trial is to investigate alternative VEGF inhibition treatment regimens for the treatment of nAMD. We hypothesise that:

(a) Avastin® is not inferior to Lucentis® with respect to the benefits of VEGF inhibition in maintaining /improving visual acuity in eyes with nAMD.
(b) Treatment with VEGF inhibition can be 'safely' withdrawn at 3 months with monthly review to detect reactivation, i.e. criteria for re-starting treatment can be pre-specified to prevent any difference in average visual acuity compared with continuing monthly treatment.

We do not hypothesise that Avastin® will be more effective than Lucentis® with respect to visual acuity.

The trial has three specific, inter-related objectives:

I To estimate the relative effectiveness of two VEGF inhibitors, i.e. Lucentis® (ranibizumab) and Avastin® (bevacizumab), on visual outcome in patients with nAMD. Existing evidence of the benefit of VEGF inhibitors compared to sham treatment precludes inclusion of a sham VEGF inhibition arm.
II To estimate the effectiveness of more frequent vs. less frequent VEGF inhibition in improving or maintaining visual function, with stringent criteria for restarting treatment to prevent visual acuity loss in patients receiving less frequent treatment.
III To estimate the cost-effectiveness of the alternative treatment strategies outlined above.

3.2 Existing research evidence

Treatments for choroidal neovascularisation and rationale for the IVAN trial

The onset of CNV in an eye with AMD is accompanied by central distortion and blurring which, when left untreated, intensifies into a dense central scotoma **[1]**. These visually disabling effects of CNV are monitored by measuring distance visual acuity which is a surrogate for central visual function; a drop of ≥15 letters in the number of letters read on a logMAR letter chart (equivalent to the loss of 3 lines of letters) is considered to be a visually significant event **[2]**. Until recently all treatments considered beneficial in the management of CNV have merely limited visual acuity loss relative to untreated controls. Until 2005, the best treatment outcomes were observed in the TAP study **[3]**, in a subgroup of people with the predominantly classic type of CNV treated with photodynamic therapy (PDT), and in the VISION trials **[4]** in people treated with Macugen® (pegaptanib). Twelve months after randomisation, visual acuity in about two-thirds of treated eyes remained within 3 lines of the presenting visual acuity, compared to about half of control eyes that were untreated or which had sham treatment.

More recently, the MARINA and ANCHOR trials which investigated Lucentis® (ranibizumab, a monoclonal antibody to VEGF) reported larger treatment benefits **[5-6]**. Lucentis® is administered intraocularly by monthly injection into the vitreous cavity. At 12 and 24 months, more than 90% of eyes treated with Lucentis® (0.5mg) remained within 3 lines of presenting visual acuity compared to fewer than 64% of eyes treated with PDT (ANCHOR) or 62% of eyes treated with sham injections (MARINA). Of equal importance, eyes treated with Lucentis® showed on average an increase in acuity of between 1 and 2 lines and about 25% had visual acuity better than logMAR 0.3 (Snellen equivalent of 6/12), a level of vision which is compatible with visually demanding tasks such as fluent reading and driving. These results exceeded all expectations since trials of other therapeutic agents, including the VEGF inhibitor Macugen® **[3-4]**, showed on average a reduction in acuity in treated eyes of between 2 and 3 lines over 24 months.

While these results are impressive, they were achieved using an intensive dosing schedule of monthly intra-vitreal injections which poses serious challenges for elderly patients who are likely to experience difficulties in attending assessment and treatment clinics frequently for several years. In addition, such intensive treatment regimens also create difficulties in terms of resource implications for health service providers. A small study (PIER) using a less intensive dosing schedule (three 4-weekly injections of Lucentis® 0.5mg followed by re-treatment at fixed 3 monthly intervals) did not yield equivalent visual acuity results as those observed in the MARINA and ANCHOR trials **[7]**. Although visual acuity improved in the PIER study in the first 3 months in a manner similar to that seen in ANCHOR and MARINA, it gradually dropped down to baseline by 12 months (still a 'good' results compared to other treatments, but worse than in ANCHOR and MARINA). By contrast, in PrONTO another ongoing small clinical trial, preliminary analyses suggest that a reduction in treatment frequency can be achieved through rigorous tailoring of treatment to morphological parameters without compromising visual acuity outcomes **[7,8]**. Taken together these findings imply that there is a variable need for re-treatment amongst patients and that any reduction in treatment frequency or alteration of dosing interval will require continuous monitoring and tailoring of therapy.

Existing trial data on Lucentis® do not permit conclusions to be drawn about the total duration of treatment required. However, data from the VISION trials (which also investigated a VEGF inhibitor) showed that regular injection of Macugen® for two years was superior to stopping treatment after one year **[9]**. These data suggest that it may be necessary to continue VEGF inhibition beyond two years in a proportion of patients.

Lucentis® 0.5mg is the most effective and well tested treatment for nAMD. However, a very similar drug (Avastin®, bevacizumab) has been claimed as having equivalent benefits on the basis of uncontrolled case series **[10]**. Remarkable improvements in acuity and morphological findings following intra-vitreal injection of Avastin® have been reported by investigators throughout the world and several thousands of patients have been treated with this drug **[11-12]**, primarily because it is more affordable. Avastin® (also a pan-VEGF monoclonal antibody) is the parent molecule from which Lucentis® was derived and the same manufacturer holds the patents and licences for both drugs. Avastin® is currently licensed for use in colorectal cancer; the therapeutic dose for systemic administration for this condition is approximately 1000 times greater than that required for intraocular use. Thus clinicians have been able to offer a cheap alternative to Lucentis® through off-label use of Avastin®.

There are no randomised controlled trials of the efficacy of VEGF inhibition therapy specifically in the treatment of RAP. It is now recognised that RAP is present in some 20% of patients with neovascular AMD. However to date, most patients with RAP have been excluded in nAMD trials because most trials have had an inclusion criterion which specifies that neovascularisation should occupy at least 50% of the lesion. This criterion was originally developed to exclude eyes where the neovascular lesion was mainly constituted by blood. However this criterion has also resulted in the exclusion of eyes with RAP because the abnormal retinal vessels usually occupy a small area (classified as neovascularisation) and most lesions include a large serous pigment epithelial detachment, The net result is that RAP lesions are usually classified as

having less than 50% neovascularisation and excluded on the basis of angiographic eligibility criteria. Interestingly, none of the trials including the VEGF studies intended specifically to exclude RAP lesions as they are clearly considered part of the nAMD spectrum. With the availability of VEGF therapy, clinicians have used these treatments in eyes with RAP and the consensus is that a clear therapeutic benefit exists. Consequently, it is our view that it is appropriate to include participants with this variant of nAMD in this trial.

By virtue of their ability to inhibit all classes of VEGF, both Lucentis and Avastin have the potential to induce serious ocular and systemic side effects. VEGF is known to have an important growth promoting role in the retina **[13]** and is also thought to maintain the fenestrated phenotype of the choroidal vasculature **[14]**. Therefore there is concern that pan inhibition of VEGF over long periods of time can cause atrophic changes in neural, retinal pigment epithelial and vascular cells and tissues with serious consequences for visual function. Although no such adverse effects have been detected in clinical trials employing VEGF inhibition strategies **[4-9]** the data relate to a relatively short periods of time with few patients having follow up beyond two years. Repeated intraocular penetration for drug delivery carries a risk of endophthalmitis and traumatic retinal detachment. However, as shown by the VISION clinical trials, adherence to protocols that emphasize sterility and administration of the drug by experienced personnel reduces these risks to acceptable levels **[4]**. Systemic side effects remain a concern as the pooled findings from ANCHOR and MARINA trials reveal a slight excess of thromboembolic events in the highest dose of Lucentis arms and a small increase in non-ocular haemorrhages in the treatment arms **[5-7]**. In addition, circulating antibodies to Lucentis were discernible in serum samples in a significant proportion of patients who received ocular administration of the drug **[5-6]**. As Avastin has not been tested in a controlled trial environment there has been no orderly collection of information on its potential to cause systemic drug toxicity. We therefore propose to collect serum samples immediately prior to and at the first post injection visit in participants in the IVAN trial for assay of the VEGF inhibitors themselves and to detect circulating antibodies to the inhibitors.

Advances in pharmacogenomics have notably revealed that genetic variation modifies the therapeutic response to drugs in a number of disease conditions **[15]**. Thus there is increasing enthusiasm for linking DNA biobanks to randomised controlled trials where participants are extremely well phenotyped**.** Trials employing VEGF inhibition strategies in cancer have shown that both survival and toxicity are influenced by genetic variation **[16]**. It is plausible that similar mechanisms may influence visual outcomes following therapeutic VEGF inhibition in choroidal neovascularisation. In addition, evidence is accruing that susceptibility to choroidal neovascularisation is influenced by the carriage of specific polymorphisms in a number of genes which encode proteins involved in immune mediation and regulation **[17-19]**. Together, these findings provide a strong rationale for the establishment of a DNA biobank in the IVAN trial.

IVAN will enrol some 600 participants with neovascular AMD whose phenotypes will be extensively and thoroughly documented by virtue of their participation in this trial. Even though the present funding is only sufficient to enable banking of serum and DNA, we are seeking funding to undertake the serological assays and the genotyping studies concurrently with IVAN, allowing this information to be used in the analysis. Therefore, consent for these aspects of the research will be sought at the time of recruitment.

Summary of existing evidence

There has been no systematic review of VEGF inhibitors in the treatment of CNV due to AMD. There has been no head-to-head comparison of VEGF inhibitors. There are very limited data on the minimum treatment frequency / duration that is required to maintain the maximal visual benefit achieved with either of the drugs studied in IVAN and no trial has compared continuing vs. early cessation of VEGF inhibition. There are no randomised controlled trials addressing the efficacy of any therapy for RAP. Therefore, the research questions that this study will address have not been investigated directly before.

Importance of the health problem to the NHS

Epidemiological studies have shown that there are some 25,000 incident cases of nAMD each year in the UK [**1**]. Randomised controlled trials have now demonstrated the substantial benefit of Lucentis® for all types of CNV; therefore, all of these patients are potential candidates for treatment each year. Avastin® is considerably cheaper than Lucentis®. The drug costs alone for monthly administration of Lucentis® are estimated to be about £11,000 per patient per year and the cost of assessments and treatment delivery about £3500 per year. Thus the total cost for the UK could be up to £300 million per year.

The cost-effectiveness of VEGF inhibitor treatment is influenced greatly by the differential in drug cost (about 20 times) between Avastin® and Lucentis®; total NHS costs of monthly VEGF inhibition treatment for 2 years are estimated to be about £8,250 and £28,600 respectively, i.e. a ratio of 1:3.5. Thus, a comparison of their relative benefits and harms is critically important to publicly funded health services. There is no commercial incentive to undertake such trials because the manufacturer of Avastin® holds the licence for Lucentis®.

However, the costs of administering treatment are also high and at present there are no recommendations about the likely duration of treatment required. Therefore, it is vital to explore strategies to limit the number

of treatments without compromising the visual outcome. Stopping treatment early, with careful review, is one such strategy. For example, we estimate that being able to reduce the number of Lucentis® injections from 24 to 9 would also reduce costs substantially; total NHS costs for 2 years are estimated to be about £14,550 and £28,600 respectively, i.e. a ratio of 1:2.

3.3 Study design

The study will be a multi-centre, randomised, controlled factorial trial. The research objectives (see **3.1**) will be addressed by randomising participants to 1 of 4 combinations of two treatment factors (see **3.4** & **Fig 1**).

Participants, clinicians and trial personnel will be masked to the VEGF inhibitor to which a participant is assigned. Pharmacies will dispense the appropriate drug to the ophthalmic clinic, as a pre-filled syringe for Avastin® or in the commercially available vial for Lucentis®. The drug will be injected by unmasked injectors (ophthalmologists) who will have no other role in the trial. All assessments and treatment management decisions will be made by other trial personnel who will be masked to allocation to drug throughout the trial, and to allocation to treatment frequency until after the third treatment. This method of masking has been used previously in ophthalmic trials in which the treatment modalities differ or where the control is sham treatment.**[4,5,6]**

Figure 1: Factorial study design

	Lucentis®	Avastin®
Continue treatment @ 3 months	A	B
Stop treatment @ 3 months	C	D

We have chosen not to mask participants, clinicians and trial personnel to whether patients are allocated to continue or stop treatment at 3 months. Although this would have been possible (by carrying out real or sham injections at all visits for 2 years), it would have prevented us from investigating participants' views about the acceptability of different treatment regimens (see **3.10**). It would also have been logistically complex for staff at trial centres and more costly. Therefore, we have prioritised investigation of the acceptability to patients of different treatment regimens, an important outcome in the population affected by AMD, over masking of this factor.

Randomisation will be stratified by centre and blocked to ensure approximately equal numbers of participants per group within a centre. Allocations will be generated by computer and concealed using an internet-based system (e.g. Sealed Envelope Ltd). Staff in participating centres will be able to gain limited access to the system using a password. Information to identify a participant uniquely and to confirm eligibility must be entered before the system will assign a study number (and hence the randomised treatment allocation).

Methods to protect against sources of bias

Concealed randomisation will prevent selection bias. Participants, clinicians and trial personnel will be masked to a participant's allocation to VEGF inhibitor, minimising performance and detection biases with respect to this treatment factor. The morphology of nAMD lesions, both at baseline and during follow-up, will be assessed from fundus fluorescein angiograms (FFA) and optical coherence tomography scans (OCT) by experienced graders, masked to treatment allocation, working in an independent 'reading centre'.

Allocation to continuation or cessation of treatment will be masked up to 3 months but not thereafter. However, assessment of the primary outcome (distance visual acuity, see **3.8**) will be as objective as possible. Assessment of logMAR visual acuity uses a 'forced-choice' procedure in which patients are required to read the letter chart (reporting the 'most likely' letter when they are uncertain) until they make 3 errors on one line.

3.4 Planned Interventions

Participants will be randomised to one of 4 combinations of two treatment factors (see **Figure 1**), i.e. VEGF inhibitor drug, and treatment duration of 24 months or 3 months

VEGF inhibitor drug

Participants will be randomised to monthly intra-vitreal injection of Lucentis® 0.5mg [**5,6**] or Avastin® 1.25mg [**10,33**]. Avastin is commonly used in a dose of 1.25 mg. The rationale for its use at this dose is that the molar concentration achieved after intravitreal injection is highly similar to that achieved by the 0.5 mg dose of Lucentis (verbal communication from Professor Rosenfeld, University of Miami, Florida). A review published in the Annals of Pharmacology, [**33**] reported that 1.25mg was the most commonly used dose amongst the 2700 or so persons who had received this therapy. A dose escalation study found no systemic or ocular SAE following a single injection of 1.0, 1.5 or 2.0 mg of Avastin.[**34**]

Treatment duration of 24 months or 3 months

Patients will be randomised to continue treatment or to stop treatment at the 3 month visit (i.e. after 3 treatment visits at 0, 1 and 2 months). Participants allocated to stop treatment will continue to attend monthly for assessment of their visual outcome, in exactly the same way as participants allocated to continue treatment; however, the former will not receive treatment unless the clinician assessing lesion morphology (by OCT) judges against pre-specified criteria (see **Figure 2**) that the CNV lesion has reactivated / treatment has failed. Patients showing signs of relapse / reactivation of the CNV will re-start treatment according to their original treatment allocation (or a treatment regimen found to be superior in an interim analysis) for a further 3 month treatment cycle, and then stop treatment again (see **Figure 3**).

Figure 2: Criteria for treatment failure / restarting treatment

	Yes	No	Not sure
1. Is there evidence from OCT of sub-retinal fluid in the study eye?	☐	☐	☐
2. Is there evidence from OCT of an increase in intra-retinal fluid in the study eye?	☐	☐	☐
3. Is there fresh blood in the lesion in the study eye?	☐	☐	☐
If the answer is YES to any of the above questions, start a new 3 month cycle of treatment.			
4. Is there evidence from OCT of persistent intra-retinal fluid in the study eye?	☐	☐	☐
5. Has the VA dropped by ≥10 letters over the last three months?	☐	☐	☐
If the answer is YES to both of the above questions, start a new 3 month cycle of treatment. (NB. The presence of hyporeflective spaces under the RPE on OCT are not considered an indicator of re-treatment.)			
If uncertain about one or more of the above criteria, carry out fluorescein angiography.			
6. Is there evidence of extension of the CNV?	☐	☐	
7. Is there leakage from >25% of the circumference of the CNV?	☐	☐	
If the answer is YES to either of the above questions, start a new 3 month cycle of treatment regardless of OCT findings.			

OCT – optical coherence tomography; RPE – retinal pigment epithelium; CNV – choroidal neovascularisation.

Further relapses during the first two years' follow-up will be managed in identical fashion. All patients, i.e. including those continuing treatment, will be assessed against these pre-specified criteria at all visits, since lesion reactivation / treatment failure is a secondary outcome and can happen despite continuing treatment.

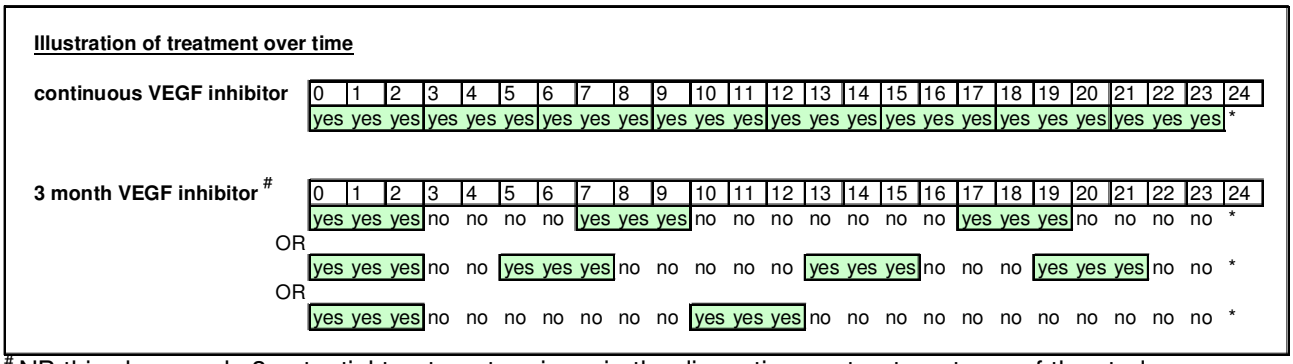
The duration of intervention in the trial is 24 months. After 24 months, treatment will be stopped (unless participants allocated to stop treatment at 3 months are in the middle of a treatment cycle) and all patients will be managed in accordance with guidelines from the National Institute of Clinical Excellence (NICE) which are expected in Oct 2007.

The minimum interval between treatment/review visits will be 28 days. Participating centres will aim for a maximum interval of 35 days (but see below, re. unscheduled breaks in treatment).

Figure 3: treatment over time in patients allocated to continue or stop treatment at 3 months

Notes:

- In continuous groups, VEGF inhibitor is administered at each of 24 visits (from baseline, month 0, to month 23).
- In 3 month groups, VEGF inhibitor is administered at each of 3 visits (from baseline, month 0, to month 2). The patient is then reviewed monthly, receiving a further cycle of three treatments (hatching in Figure 3 indicates initiation of a further cycle of treatment) if the patient satisfies any of the criteria for 'treatment failure' (see Figure 2). Three different possible treatment courses over time are shown for patients in 3 month groups.
- Asterisks (month 24) indicate stopping of treatment in the trial; at this time, the need for treatment will be assessed against guidance in the forthcoming NICE technology appraisal and evidence from the trial.



NB this shows only 3 potential treatment regimes in the discontinuous treatment arm of the study, any combination from no treatment after the initial 3 month cycle to continuous treatment fro 24 months is possible in this arm of the trial.

Treatment stopping rules

In addition to a participant's right to withdraw at any time, there will be provision for a participant to exit early from the trial if the clinician responsible for the care of the participant believes there is no reasonable prospect of future benefit. (The net effect of treatment is harmful in these circumstances, given the potential for serious adverse effects from VEGF inhibitor drugs; see **3.9**.) It is not possible to list all circumstances in which this condition would be considered to be satisfied, but these would include:

- Best corrected distance visual acuity <15 letters (standard ETDRS chart at 1 metre) on two occasions;
- A significant drug-related adverse event which the clinician believes would be likely to worsen or recur if treatment were to be continued, e.g. severe uveitis in either eye.

It is important to note that treatment complications, e.g. endophthalmitis, retinal detachment, traumatic cataract, will not normally be considered absolute contraindications to continue treatment (see below).

Unscheduled breaks in treatment

IVAN is a pragmatic trial which recognises that participants may miss occasional treatment or review visits because of illness or holidays, especially in view of the demanding monthly visit schedule. It is envisaged that participating centres will set the dates of several future visits, to allow participants to plan holidays and to assist clinic planning. Treatment intervals must not be <28 days. The monthly visit schedule means that some visit intervals will be up to 35 days. If a visit is missed and cannot be re-arranged within a week, this visit will be considered to have been missed, with the next visit arranged according to the original schedule. All time references in the protocol refer to calendar months and will not be affected by missed visits. Therefore, if a participant in one of the reduced treatment frequency arms misses treatment visit 2 (see **Figure 3** above), at visit 3 his or her status will still be evaluated against the re-treatment criteria shown in **Figure 2**; the same will be true if a participant misses a visit in a 3 month cycle of treatment.

Unscheduled breaks in treatment may also arise due to ocular or systemic adverse effects. Except for a drug-related adverse effect which restricts the potential for a participant to benefit (see treatment stopping rules, above), no adverse effect will be considered an absolute contraindication to further treatment. In the event of an adverse event such as endophthalmitis, myocardial infarction or stroke, the clinician responsible for the care of the participant will discuss the risk of a further adverse event, and the risk of loss of vision without further treatment, with a view to the participant making an informed decision about continuing treatment. Therefore, there will be no maximum treatment interval and patients will be able to resume treatment according to their allocation after a break of any duration.

3.5 Inclusion/exclusion criteria

Both Lucentis and Avastin are contraindicated in pregnancy, breastfeeding, children and adolescents. While it is highly unlikely that patients with nAMD will be pregnant or will have given birth recently (patients <50 years are ineligible and the average age at presentation of patients with nAMD is approximately 73 years), any woman who fulfils all other criteria for enrolment who has recently given birth and wishes to participate must discontinue breast-feeding during therapy and not breast feed for at least six months following the last dose Avastin. Avastin and Lucentis are contraindicated in those patients known to be hypersensitive to the active compound or excipients. Additionally, Avastin is contraindicated in patients known to be hypersensitive to Chinese hamster ovary (CHO) cell products or other recombinant human or humanised antibodies. IVAN has been designed for participants with a confirmed diagnosis of CNV due to AMD and the study will only enrol patients 50 years and older. IVAN will not enrol children or adolescents in whom both Lucentis and Avastin are contraindicated. Any woman of child-bearing potential (i.e. those not sterilised or postmenopausal) will be advised of the risk of foetal harm. Dosing in male subjects who have a pregnant or lactating female partner could also result in harm to the fetus or neonate. Therefore, male subjects with pregnant or lactating partners who are otherwise eligible and wish to participate should use a condom when engaging in sexual activity for the duration of the trial and for 3 months after the last dose.

Notwithstanding the above caveats, we propose to use eligibility criteria that are as inclusive as possible, to promote the applicability of the evidence obtained during the trial.

Inclusion criteria:

- Adults of either sex aged 50 years and older;
- Newly referred for the treatment of nAMD in the first or second eye;
- Corrected distance logMAR visual acuity (VAlogMAR) ≥25 letters read on a standard ETDRS chart at 1 metre;
- Any component of the neovascular lesion (CNV, blood, serous pigment epithelial detachment, elevated blocked flourescence) involving the centre of the fovea.

If a fellow eye develops CNV from AMD, it will be treated with the optimum locally available treatment.

Exclusion criteria:

- Age less than 50 years
- Corrected VAlogMAR <25 letters at 1 metre;
- Long standing CNV evidenced by the presence of fibrosis in excess of 50% of the total lesion;
- Greatest linear diameter >6000μm (equivalent to about 12 disc diameters)
- Argon laser treatment to the proposed study eye within the last 6 months
- Presence of thick blood involving the centre of the fovea
- Presence of other active ocular disease causing concurrent vision loss, e.g. diabetic retinopathy.
- Patients with 8 or more dioptres of myopia.
- Previous treatment with PDT or a VEGF inhibitor in the eye being considered for inclusion.
- Pregnant and or lactating women
- Women with child bearing potential (i.e. not sterilised or not post menopausal) who are unwilling to use contraception
- Men with a spouse or partner with child bearing potential unless the participant has agreed to use condoms

A past medical history of cardiovascular disease or cardiovascular comorbidity, e.g. previous myocardial infarction or stroke, current angina, will not be an exclusion criterion. However, such factors will be documented carefully at the time of recruitment, and the potential benefits and harms of treatment discussed carefully with potential participants.

3.6 Participating centres

We aim to have 18 to 25 centres, each recruiting about 35 participants over 10-12 months. We will prioritise invitations to centres that have support from their local commissioners, have taken part in controlled clinical trials, have established facilities for study conduct, are part of the existing retinal research network established for the VPDT Cohort Study, and access to the appropriate imaging equipment so that there will be no delay in obtaining the necessary local R and D approvals in the course of initiating the centre as a study site. Centres currently being assessed for participation in the study are listed below.

- Aberdeen
- Aintree
- Belfast
- Birmingham
- Blackburn
- Blackpool
- Bolton
- Bradford
- Brighton
- Bristol
- Cambridge
- Cardiff
- Derby
- Dundee
- Edinburgh
- Frimley Park
- Cheltenham & Glos
- Hillingdon
- Hull & E Yorks
- Kings Coll, London
- King's Lynn
- Leeds
- Liverpool
- Maidstone
- Manchester
- Moorfields, London
- Newcastle
- N Lincs & Goole
- Nottingham
- Oxford
- Plymouth
- Sheffield
- Southampton
- Southend
- Stoke Mandeville
- Torbay
- Western Eye, London
- Wigan
- Wolverhampton

3.7 Ethical arrangements

Ethical approval for the trial will be sought from a NHS Research Ethics Committee (REC).

With respect to equipoise about the main research questions:

- There is evidence of clinical effectiveness for both Lucentis® and Avastin® (see 3.2); therefore, there is no placebo arm in this study. Through adherence to strict protocols, ocular adverse events relating to the injection procedure can be minimised. Many thousands of people have been treated with Lucentis® and Avastin® without any obvious increase in the risk of serious ocular adverse effects.
- Repeated clinic visits (every month) and the method of treatment administration (multiple ocular injections) are sources of anxiety for elderly patients. We believe that uncertainty about the possible risks of stopping treatment (with stringent criteria in place for re-starting treatment), and the possible benefits of less frequent treatment, justifies allocating participants to continue or stop treatment at 3 months.

We have consulted with patient support organisations. The Macular Disease Society strongly supports this trial, will be working with the trial team in developing components of the application to a REC for ethical approval and will be represented on the Trial Steering Committee.

Risks and anticipated benefits for trial participants and society, including how benefits justify risks.

Access to anti-VEGF treatment is not an option currently in the NHS. Given the expensive nature of VEGF inhibition treatments and the limited resources available to the NHS, the finding that Avastin® is as good as Lucentis® might be expected to increase the general availability of VEGF inhibition, both to trial participants in the short term and, in the long term, to future patients.

Potential harms to participants include the possibility of randomisation to an inferior treatment (a possible harm of participating in any trial) and possible side effects of the treatments to which participants are allocated. The 'reasonableness' of asking participants to accept the possibility of randomisation to an inferior treatment, i.e. the prevailing uncertainty about the research questions of interest and the benefits and risk of carrying out the trial to participants, future patients and society, will be judged by our application to a NHS REC for ethical approval for the study, and by our application to the Medicines and Healthcare Products Regulatory Agency (MHRA) for permission to use Avastin® to treat CNV in the trial. Possible adverse effects of VEGF inhibitor treatment (see **3.9** below) include:

> *Local adverse effects:* complications of intra-vitreal injection such as endophthalmitis, traumatic cataract and or retinal detachment and retinal pigment epithelial (RPE) tears. [**20**].
>
> *Systemic adverse effects:* an increased risk of thromboembolic adverse events has been observed after administration of doses of VEGF inhibitor in the therapeutic range required for cancer studies [**21**]; statistically significant increases in risk were not observed in the ANCHOR or MARINA trials [**5,6**], but a larger number of adverse events were seen in the treatment arms. Some reports of such events have been documented in the course of CNV treatment through post-marketing surveillance. We will be extremely vigilant for such adverse events (see **3.8**).

Informing potential trial participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in a Patient Information Leaflet (PIL) given (or read) to patients at the time they are approached to take part. The PIL will be part of our application to a NHS REC and will be written in consultation with members of the Macular Disease Society. We are confident that the trial design need not appear complex to patients and have drafted a PIL that focuses on the following key points:

"There is considerable uncertainty about how best to use the new drug treatments for AMD. There is uncertainty about the best new drug to use and the optimal frequency and duration of treatment:

- Research studies have shown that monthly treatment over 2 years is better than sham treatment but less frequent treatment combined with regular monitoring, re-starting treatment if required, may be equally effective.
- The frequency and duration of treatment is important because treatment may have rare but serious harmful effects (side effects in the eye from the injection, and the possibility of an increased risk of a cardiovascular event such as a heart attack or stroke) as well as benefits.
- The frequency and duration of treatment is also important because less frequent treatment or a shorter overall duration of treatment are expected to be less inconvenient and more acceptable to patients.

We invite you to join a research study to answer some of these questions. Some key features of the trial are as follows:

- You will be allocated by chance (like tossing a coin) to a particular treatment schedule – to one of two anti-VEGF drugs, and to continuous treatment for 2 years or a short period of treatment with careful monitoring of vision afterwards.
- Neither you, nor the doctor managing your treatment, will know which drug you are receiving.
- Whichever group you are allocated to, you will receive active treatment.
- If you are allocated to a short period of treatment, and your vision appears to be deteriorating, you will be put back on to treatment– minimising any potential loss in your vision.
- Whichever group you are allocated to, you will need to make monthly visits for 2 years. Even if you are allocated to a short period of treatment, you need to make regular visits to have your vision checked."

Obtaining informed consent from participants

All participants will be required to give written informed consent. The process for obtaining informed consent, including the information in the PIL, will be described in our application to a NHS REC for ethical approval.

Proposed time period for retention of relevant trial documentation.

We will propose to the NHS REC that we retain all trial documentation for a period of 5 years after the end of the trial, when all patient-identifiable paper records will be destroyed by confidential means. We will also propose to the REC that the fully anonymised dataset be retained in electronic form indefinitely because of the potential for the raw (but anonymised) data to be used in subsequent summary or individual patient data meta-analyses.

Proposed actions to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004'.

Actions to comply with these regulations include:

- Obtain NHS REC approval
- The Royal Group of Hospitals Trust has been declared as the primary sponsor for the trial. As this is a large study with over 20 centres, and because data management will be undertaken at the University of Bristol, co-sponsorship is currently being negotiated with this organisation.
- Obtain written informed consent from all participants
- Record and report serious and other adverse events in accordance with GCP (see **3.9** below)
- Obtain MHRA approval for the use of Avastin®
- Establish Trial Steering (TSC) and Data Monitoring and Ethics Committees (DMEC)
- Comply with Good Clinical Practice (GCP)
- Carry out regular audit of compliance of centres with GCP and data collection procedures

3.8 Proposed outcome measures

Primary outcomes:

The primary outcome is corrected distance visual acuity (VAlogMAR), measured as the number of letters read on a standard ETDRS chart at 1 metre (testing at 4 metres initially and then at 1 metre if <20 letters are read at 4 metres; total letters read are scored 'as it' viewing at 1 metre). The primary end point will be VAlogMAR after two years of follow-up.

Secondary outcomes:

Secondary outcomes will be analysed after one and two years of follow-up, unless otherwise stated.

(a) Frequencies of adverse effects of treatment
(b) Generic and vision-specific health-related quality of life (HRQoL)
(c) Treatment satisfaction
(d) Cumulative resource use/cost, and cost-effectiveness.
(e) Clinical measures of vision
(f) lesion morphology (from masked grading of FFAs and OCTs).
(g) Distance VAlogMAR after all patients have been followed for 1 year after starting treatment.
(h) Survival free from treatment failure (i.e. satisfying one or more of the criteria for re-treatment).

3.9 Safety

Adverse event/reaction reporting procedures

Lucentis® and Avastin® are very similar drugs therefore, expected adverse events are likely to be the same in each arm. Most participants in the study will be elderly, and we anticipate that 50% will be >75 years at the time of recruitment. Therefore, many serious adverse events, including death, are expected.

Adverse event/reactions

Investigators assessing study eyes at each visit will be required to supply data in accordance with GCP about specified (i.e. "expected") serious adverse events (SAEs) in each of the following key areas, as well as reporting any other expected adverse effects that may possibly be associated with treatment.

Serious adverse events (SAEs) are defined as events which result in death, are life threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity. The latter component of this definition is problematic in the context of the IVAN trial because natural progression of CNV usually causes significant disability or incapacity. Therefore, SAEs in the trial will focus on events that are likely to be attributable to treatment, either due to intravitreal injection or systemic effects of VEGF inhibition:

Ocular: Endophthalmitis (confirmed by culture positive vitreous tap)
Severe uveitis (vitreous flare and cells (culture negative or no vitreous tap obtained) using the international uveitis severity classification)
Traumatic cataract (cataract caused by needle trauma)
Retinal detachment (rhegmatogenous detachment following intra-vitreal injection, location associated with the site of needle penetration)
Retinal pigment epithelial (RPE) tears.

Systemic : Death
Permanent stroke (documenting method of diagnosis, e.g. CT/MRI imaging or clinical signs)
Myocardial infarction (diagnosed by ECG changes or elevation in creatine kinase or troponin I cardiac enzymes)
Incident, or worsening of, angina (change of 2 or more classes, or from class 3 to hospital admission for angina, using the Canadian Cardiovascular Society classification)
Deep vein thrombosis of pulmonary embolism (documenting method of diagnosis, e.g. ultrasound or other imaging, biochemical or clinical signs with associated medication)
Non-ocular haemorrhage requiring admission to hospital
Heart failure (As confirmed by reason for admission codes provided by admitting hospital)

We will use a combined safety endpoint of: Cardiovascular death OR non-fatal MI (primary discharge coding) OR stroke (primary discharge coding) OR heart failure (primary or secondary discharge coding). Deaths will be classified as cardiovascular or not on the basis of death certificates, judged by masked assessors. Other elements of the combined safety endpoint will be judged from discharge summary / hospital diagnostic coding.

SAEs will be collated in the same way as SUSARs and will be reported regularly to the Data and Safety Monitoring Committee and to the regulatory authorities.

Occurrence of an SAE between visits will trigger administration of HRQoL and resource use questionnaires at the next visit.

Investigators will also be required to report any of the following other ocular and non-ocular adverse events not considered to be SAEs, many of which were reported with treatment with Lucentis® in randomised trials:

Ocular	*Non-ocular*
Conjunctival haemorrhage	Hypertension
Increased visual disturbance ≤48 hrs of injection	Urinary tract infection
Other retinal detachment	Nasopharyngitis
Ocular pain/irritation	Headache
Increased lacrimation	Arthralgia
Vitreous floaters	Bronchitis
Vitreous detachment	Cough
Intraocular inflammation	Sinusitis
Visual hallucinations	Nausea
Elevated intraocular pressure	Transient ischaemic attack/non-permanent stroke
Immediate post-injection vascular occlusion	Non-ocular haemorrhage (not requiring admission)
Progressive cataract	Upper respiratory tract infection
	Onset of angina or worsening not defined as SAE
	Influenza

Baseline and exit ECGs will also be collected and judged in a masked fashion as a sensitive measure of cardiovascular changes.

Suspected unexpected serious adverse reactions (SUSARs)

GCP will be followed for reporting any SUSAR, i.e. any serious ocular or systemic adverse event not listed above. Responsibility for expedited reporting of SUSARs to regulatory authorities, in accordance with the Medicines for Human Use (Clinical Trials) Regulations will be delegated by the main trial sponsor to the data management centre. Local principal investigators are responsible for informing the data management centre of a SUSAR within 24 hours. The data management centre will then correspond with the local principal investigator and, if necessary with one or more of the clinicians on the trial executive group, to complete and submit a SUSAR report to the REC and to the MHRA within 72 hours of the SUSAR having been notified.

Analyses of serum

Concerns still remain about the potential for systemic adverse events following intravitreal delivery of Lucentis® [**5,6**] and Avastin® [**10**]. Although the doses administered by intravitreal injection are extremely small, both agents are found in detectable levels in serum 4 weeks after administration and antibodies to Lucentis were demonstrated in the sera of patients at the 12 month visit. Serum will be collected from all participants who consent to this aspect of the study at visits 0 and 1, 11 and 12, and 23 and 24; serum samples will be banked for future analysis. An exploratory analysis to investigate the association between serum markers and cardiovascular SAEs will be pre-specified.

An additional blood sample will be taken at months 6 and 18 to monitor serum biomarkers of endothelial health and circulating levels of Lucentis and Avastin.

3.10 Data collection procedures

Responses to generic HRQoL questionnaires will be collected at baseline, 3, 12 and 24 months. We will use the EuroQoL EQ5D [**22**] and Health Utility Index HUI3 to measure generic HRQoL [**23**], since responses to these instruments can be mapped on to 'valuations' for the economic evaluation (see below). These instruments will be administered by a research nurse when participants attend for treatment or assessment. A custom-designed questionnaire to document resource use will also be administered at the same time, except for the baseline visit. HRQoL and resource use questionnaires will also be administered following an SAE so that the HRQoL and resource use consequences of SAEs can be described in detail. Smoking history, the most important risk factor for AMD, will be recorded at the baseline visit.

We will use the MacDQoL to measure disease-specific HRQoL [**24**]. The MacDQol has been developed with the collaboration of members of the UK's Macular Disease Society specifically for patients with AMD. It is designed to assess both the impact of AMD on a respondent's physical and social functioning and the importance of this impact to the respondent. The MacDQoL will be administered by telephone by staff in the coordinating centre in Bristol 1-2 weeks after the 3, 12 and 24 month visits.

As already described (see **3.7**), repeated clinic visits and intra-vitreal injection are inconvenient and unpleasant for elderly patients and cause anxiety. Therefore, we believe it is very important to compare treatment satisfaction between different treatment regimens, especially those which are more or less frequent. For example, it is important to know whether patients prefer less frequent treatment but with the anxiety of possible reactivation of their disease, or frequent treatment in the knowledge that the maximum possible is being done. We will use the MacTSQ (Treatment Satisfaction Questionnaire), which has also been designed by Professor Bradley specifically for this purpose [pers comm, Bradley]. Like the MacDQoL, it has been developed in collaboration with members of the Macular Disease Society. The MacTSQ will be administered at the same time as the MacDQoL (with the order of administration randomised), and administered in addition 1-2 weeks after the baseline visit. Responses to the MacDQoL will also be collected by telephone follow-up, by staff in the trial coordinating centre in Bristol.

We are proposing to split the collection of questionnaire data, based on experience in the VPDT Cohort Study. Clinic assessment and treatment (a whole day's visit for patients having both) will be demanding for patients. Professor Bradley, who developed the MacDQoL and the MacTSQ, has confirmed that telephone administration of these instruments is valid. Participants will be reassured during telephone administration of the MacDQoL and the MacTSQ that their responses are confidential and will not be fed back to the clinical staff responsible for treating them.

A full clinical assessment of vision function (refraction check, distance VAlogMAR [**25**] and near visual acuity using the Bailey-Lovie near reading cards, Pelli-Robson contrast sensitivity [**26**] and reading speed using Belfast reading charts [**27**] will be carried out at 3, 6, 12, 18 and 24 month visits by research staff 'masked' to treatment allocation. (The timing of these assessments will not be affected by treatment that may be received by patients in the groups allocated to stop treatment at 3 months.) Distance VAlogMAR will also be measured at every visit but a refraction to check the optical correction will only be carried out at intermediate visits if the visual acuity has dropped ≥15 letters or a refractive change is suspected.

Centres will maintain detailed logs of all patients approached, and reasons for ineligibility and refusal. Data will be documented on case record forms (CRFs) by staff in participating centres. CRFs will be printed in duplicate ("NCR" forms). After a visit has taken place, centre staff will complete the CRF, separate the duplicate forms and fax the top copy to the trial coordinating centre within 5 working days, or transcribe data into a secure web-based database. We propose that centres should fax forms because of the need for reliable and prompt data submission. The coordinating centre needs to have entered data from the previous visit in advance of the date of the next visit in order to monitor compliance with the follow-up schedule.

In participating centres, there will be seven elements to data collection and the CRF: (a) recruitment form, including check of eligibility (RECT); (b) baseline assessment (BASE); (c) treatment (TREAT); (d) follow-up assessment form (full, fFUA, and partial, pFUA); (e) form to check criteria for treatment failure (CTF; see Figure 3); (f) EQ5D questionnaire (EQ5D); (g) resource use questionnaire (RUQ). Data for the MacDQoL and MacTSQ will be collected by the trial coordinating centre. The schedule of data collection over time is shown in **Table 1**.

In section **3.2**, we outlined the advantages of linking genetic analyses to well phenotyped populations in clinical trials. Therefore, we propose to 'bank' from all study participants who give their consent for us to do so. We will also seek participants' permission to store their DNA and to use it future studies of eye disorders and related conditions.

A blood sample will be taken at the baseline visit from all participants who consent to take part in the genetic aspect of the study. These blood samples will be sent immediately to Prof Lotery's laboratory in Southampton and stored for batched DNA analysis. All stored samples will be fully anonymised and identified only by a unique number. Consenting to the genetic aspect of the study will be sought in a separate question on the consent form, and is not required for participation in the IVAN trial.

In the event that a blood sample for the genetic aspect of the study is spoilt in transit to Professor Lotery's laboratory, or yields insufficient DNA, an aliquot of blood from the samples that are taken at a subsequent visit (there is planned venepuncture with blood collection from participants at 6 IVAN study visits) will be used to re extract DNA.

Table 1: schedule of data collection over time

RECT – recruitment form, including check of eligibility; BASE – baseline assessment; TREAT – treatment; fFUA, pFUA – full/partial follow-up assessment form; CTF – form to check criteria for treatment failure; HRQoL – EuroQol and Health Utility Index questionnaires; RUQ – resource use questionnaire. Administration of MacDQoL and MacTSQ is not included because these instruments will be administered by phone, shortly after clinic visits.

Month	Continue treatment at 3 months	Stop treatment at 3 months	
0	RECT, BASE, TREAT, HRQOL, RUQ	RECT, BASE, TREAT, HRQOL, RUQ	
1, 2	pFUA, TREAT	pFUA, TREAT	
		If CTF <u>not met</u>	**If CTF <u>met</u>**
3	fFUA, CTF, TREAT, HRQOL, submit OCT	fFUA, CTF, HRQOL, submit OCT	
4	pFUA, CTF, TREAT	pFUA, CTF	pFUA, CTF <u>met</u>, TREAT
5	pFUA, CTF, TREAT	pFUA, CTF	pFUA, CTF, TREAT
6	fFUA, CTF, TREAT, HRQOL, RUQ submit OCT	fFUA, CTF, HRQOL, submit OCT	fFUA, CTF, TREAT, HRQOL, submit OCT
7, 8	pFUA, CTF, TREAT	pFUA, CTF	
9	pFUA, CTF, TREAT submit OCT	pFUA, CTF submit OCT	
10, 11	pFUA, CTF, TREAT	pFUA, CTF	
12	fFUA, CTF, TREAT, HRQOL, RUQ submit OCT & FFA	fFUA, CTF, HRQOL, RUQ submit OCT & FFA	
13	As for months 10 & 11	As for months 10 & 11	
14	As for months 10 & 11	As for months 10 & 11	pFUA, CTF <u>met</u>, TREAT
15	As for month 9	As for month 9	pFUA, CTF, TREAT submit OCT
16	As for months 10 & 11	As for months 10 & 11	pFUA, CTF, TREAT
17	As for months 10 & 11	As for months 10 & 11	
18	As for month 6	As for month 6	
19, 20	As for months 10 & 11	As for months 10 & 11	
21	As for month 9	As for month 9	
22, 23	As for months 10 & 11	As for months 10 & 11	
24 (**Exit**)	fFUA, CTF, HRQOL, RUQ submit OCT & FFA	fFUA, CTF, HRQoL, RUQ submit OCT & FFA	

3.11 Methods for independent grading of FFA and OCT

FFAs and OCTs provide essential information on severity and extent of disease at recruitment and for documenting changes in response to therapy. Centres will be required to carry out these investigations and submit digital copies of images for independent assessment as described below:

- FFA at month 0 (the baseline/recruitment visit), months 12 and 24
- OCT every three months (months 0, 3, 6, 9, 12, 15, 18, 21 and 24),
- OCT (and FFA if the decision to re-start treatment was made on the basis of FFA) at the start of a further course of treatment in the "stop treatment" arms

Participating centres will submit digital copies of FFA and OCT images to the study reading centre where skilled graders, masked to treatment allocation, will characterise the CNV subtype and grade the extent and severity of disease according to standardised protocols.

An additional FFA will <u>not</u> be required at 12 months if a FFA has been carried out at month 10 or 11, for example in a patient allocated to stop treatment at 3 months in whom the CNV lesion was judged to have reactivated at 10 months. OCTs will also be carried out every month for people allocated to stop treatment at 3 months in order to assess whether treatment should be re-started (see **3.4** and **Figure 3**). Staff at participating centres will be required to document on patients' CRFs that these investigations have taken place. Staff will also be asked to submit these 'non-assessment' OCTs to the reading centre so that clinical judgements made at centres about re-starting treatment can be validated.

3.12 Economic evaluation methods

Established guidelines will be used for the conduct of the economic evaluation [**28-29**]. The main outcome measure for the economic evaluation will be quality adjusted life years (QALYs) using the EuroQol EQ-5D [**22**] and the HUI3 [**23**], to be administered every 6 months. Respondents will be assigned valuations derived from published UK population tariffs [**30**] and the mean number of QALYs per trial arm and incremental QALYs will be calculated. In addition, data on visual acuity, the MacDQoL and the MacTSQ will act as additional outcome measures, which will then be compared with the QALY results. Data will be collected from the trial centres on health care resource use for treatment (including different types and grades of staff and training), any side effects, subsequent treatments and complications. Resource use will be measured in naturally occurring units; for example, staff time will be measured in terms of length of times for treatments and unit costs will be derived from nationally published sources. Costs for further contact with health care professionals such as GP visits, patient travel costs and time away from usual activities such as paid employment for those who are not retired will be estimated using an existing questionnaire from the VPTD Study. The analysis will calculate the average cost and outcome on a per patient basis and, from this, the incremental cost-effectiveness ratios for the different trial arms will be derived, producing an incremental cost per QALY (and secondary economic outcome measures, such as visual acuity). Probabilistic sensitivity analysis will be used to demonstrate the impact of the variation around the key parameters in the analysis on the baseline cost-effectiveness results. Results will be expressed in terms of a cost-effectiveness acceptability curve, which indicates the likelihood that the results fall below a given cost-effectiveness ceiling. Given that individual patient follow-up will be for 2 years of treatment, the primary focus of the economic evaluation will be on within-trial costs, effects and cost-effectiveness. Therefore, there will be uncertainty over longer-term outcomes from the trial and we will explore the construction of a Markov model to examine potential longer-term costs and effects of treatment, extending to approximately 5 years beyond treatment.

3.13 Proposed sample size

With respect to the primary outcome (distance visual acuity, VAlogMAR), the trial is designed to answer non-inferiority questions.

Objective I

A small target difference is required to determine whether Avastin® is inferior to Lucentis®. We have considered non-inferiority margins of 3 or 4 letters (standardised difference of 0.20 to 0.30, considered "small" [**31**]). To help contextualise these differences, the 95% limits of agreement for test-retest of visual acuity among people with impaired but stable vision is 10 letters [**32**]. We have also considered analyses with one or two post visual acuity measure (i.e. 2 repeated measures), adjusted for a baseline measure of visual acuity in both cases. We have made the following additional assumptions:

- The comparison of Lucentis® vs. Avastin® will combine data for in groups continuing and stopping VEGF inhibition at 3 months.
- SD deviation for VAlogMAR=14 letters (based on baseline visual acuities for treated eyes in the VPDT Cohort Study, restricting to acuities ranging from 85 (6/6) to 25 (6/60) letters).
- 90% power, 2.5% significance, one-sided test (appropriate for a non-inferiority research question).
- Correlations between baseline (pre-) and follow-up (post) acuities = 0.5, and between follow-up acuities (post1 and post2) = 0.8; both of these correlations have been calculated from longitudinal visual acuity data collected at 0, 6 and 12 months for patients treated with PDT at baseline in the VPDT cohort study.

Table 2 below gives the sample size for <u>each</u> of the Lucentis® and Avastin® groups being compared (i.e. for cells [A+C] and [B+D] in **Figure 1** continuing treatment). On the basis of these calculations, we propose to recruit 150 participants to each of the <u>four</u> cells described in **Figure 1**, providing a sample size of 300 vs. 300 (less participants lost to follow-up) for this objective. No adjustment has been made for drop-out, estimated to be <10% per year [**5,6**]. Mixed-models for analysis of repeated measures can include any patient with at least one 'post' outcome measure, although missing data will increase the standard errors for parameters estimated by the models.

Table 2: sample size estimates for Objective I; multiply by 4 for total sample size required

Equivalence margin	1 pre- measure, 1 post measure	1 pre- measure, 2 post measures
<3 letter	344	298
<4 letter	194	168

The same sample size calculations and assumptions apply to other clinical visual function measures, for which non-inferiority is hypothesised. The calculations and assumptions also apply to HRQoL, treatment satisfaction, and resource use/cost (*Objective III*) except that the comparisons will be 2-sided, i.e. the study will be able to detect a standardised difference of 0.20 to 0.30 with 90% power and 5% significance, since we hypothesise that Avastin® will be superior to Lucentis® for these outcomes.

Objective II

Like objective I, this objective is also non-inferiority, since the main concern is that people allocated to stop treatment at 3 months do not suffer a visual function disadvantage. The comparison of stopping vs. continuing VEGF inhibition at 3 months will combine data for groups allocated to Lucentis® and Avastin® (i.e. cells [A+B] vs. [C+D] in **Figure 1**). Other assumptions set out above for objective I also apply to this objective. Therefore, these comparisons will have the same sample size as for objective I, hence the same power.

Objective III

This objective will have the same sample size as for objective I, hence the same power but at a significance level of 5% (2-sided; see above).

We plan to recruit, on average, 35 participants from each of 18 centres, with each recruiting over 10-12 months. Based on data from the VPDT Cohort Study, recruiting 35 participants would require centres to recruit at most about 15% of all AMD patients newly referred with CNV. Loss to follow-up in other trials carried out in the target population has been about 5-10% per year. As described above (see **3.14**), participants with one full follow-up assessment can be included in analyses of continuously scaled outcomes; in survival analyses, those who are lost to follow-up will be censored at the time of their last visits. From the applicants' experience in other trials of treatments for AMD, compliance is high. Intra-vitreal injection is well tolerated. However, people in the target population are elderly, so may miss some treatment visits. There is no reason why loss to follow-up or poor compliance should be differential across treatment groups.

3.14 Statistical analysis

Analyses of visual acuity and other continuously scaled outcomes

Analyses of these outcomes will be adjusted for baseline covariates using mixed-model analysis to analyse repeated measures; these methods do not require complete data at all time points and no attempt will be made to impute missing data. The primary analyses for objectives I and II will include the entire study population and will estimate the main effect of Lucentis® vs. Avastin®. The interaction of VEGF-inhibitor with continue/stop treatment at 3 months will be tested but will only be included in the final model if it reaches a statistical significance ($p<0.05$). Formal subgroup analyses will be carried out for genetic polymorphisms, if funding from another source can be obtained for genotyping of trial participants. The following additional subgroups will be investigated: (i) baseline visual acuity in study eye (<55 vs. ≥55 letters read), (ii) baseline CNV size (<6 vs ≥6 disc areas); (iii) proportion of classic CNV (<50% vs. ≥50%); (iv) presence of RAP; (v) fellow eye status (<75 vs. ≥75 letters read). When interpreting subgroup effects, i.e. interactions, the direction of effects will be compared with those predicted in advance, and a correction will be applied to take into account multiple statistical tests.

Analyses of time to treatment failure / re-starting treatment

Analyses of this secondary outcome will be carried out using Cox regression, censoring participants who drop out at the last known follow-up. The primary analysis will include the entire study population and will estimate the main effects of of Lucentis® vs. Avastin® and continue vs. stop treatment at 3 months. As for visual acuity, the interaction of VEGF inhibitor continue/stop treament at 3 months will be tested but will only be included in the final model if it reaches statistical significance ($p<0.05$). Subgroup analyses and treatment effects will also be estimated as described above.

Analyses of potential adverse effects of treatment

Potential adverse effects of treatment will be tabulated separately for ocular and systemic events, describing the number of events of different types within each category. The trial will not have adequate power to detect differences in the risk of adverse effects that are considered plausible by the investigators at the outset. Therefore, there is no prior intention formally to compare the risks of individual adverse effects between trial arms, although it is proposed that interim analyses should compare the risk of any serious adverse event by drug and treatment frequency. However, a summary of all reported adverse effects (masked by treatment allocation) will be distributed to the Data Monitoring and Ethics Committee (DMEC) every 3 months, and the DMEC will have the authority to request such a comparison at any time.

Frequency of analyses

The primary analysis (all outcomes) will be carried out when outcome data at 2 years are available for all patients. An interim analysis will be carried out when outcome data at 1 year are available for all patients. We also propose to carry out an interim analysis after 50% of the target sample size have reached 3 months follow-up, to check that there is no substantial difference in visual acuity between participants allocated to Avastin® and Lucentis®. The details of these planned interim analyses will be confirmed by the Data Monitoring and Ethics Committee, before starting recruitment.

3.15 Trial management

The trial will be overseen by a Trial Steering Committee and a Data Monitoring and Ethics Committee (see below). Both Committees will be convened before the start of recruitment. The DMEC will be asked to confirm/specify details of planned interim analyses, which will be forwarded to the REC.

Trial Steering Committee (TSC)

Membership (n=8/9) of the TSC will include:

- independent chair (Mr John Sparrow, DPhil, FRCOphth)
- patient representative (Mr Tom Bremridge, chief executive of the Macular Disease Society)
- independent ophthalmologist / vision scientist (Prof Andrew Dick, University of Bristol & United Bristol Healthcare NHS Trust)
- independent statistician (Dr Sue Richards, University of Oxford)
- specialised services commissioner (Mr Simon Banks, Cheshire and Merseyside PCT)
- representative from the funding agency (Dr Peter Davidson, NCCHTA)
- representative of the primary sponsor (Prof Ian Young, Belfast Health and Social Services Trust)
- FFA/OCT reading centre representative (Prof Simon Harding, Royal Liverpool & Broadgreen University Hospitals NHS Trust)
- IVAN representatives (Prof Chakravarthy, Dr Reeves, trial manager)

Data Monitoring and Ethics Committee (DMEC)

Membership of the DMEC will include:

- independent chair/statistician (Prof Sheila Bird, MRC Biostatistics Unit)
- independent cardiologist (Dr Hugh McIntyre, East Sussex Hospitals Trust)
- independent ophthalmologist (Mr Richard Wormald, Cochrane Eyes & Vision Group)
- independent medical retina specialist (Mr Roger Gray, Taunton & Somerset NHS Trust)

The trial will be managed by an Executive group, which will meet face-to-face 4 to 5 times per year and by teleconference approximately fortnightly. The Executive group for the trial will be chaired by the Chief Investigator and will consist of the applicants and the trial manager.

4 Expertise

Prof Chakravarthy is an international expert in the field of AMD and has led or collaborated with previous multi-centre RCTs of treatments for CNV. Profs Harding and Lotery, Ms Downes and Mr Talks are expert medical retina ophthalmologists and have been investigators or have contributed to previous multi-centre RCTs of treatments for CNV. Prof Chakravarthy, Dr Reeves, Prof Harding, Ms Downes and Mr Talks are the executive group for the VPDT Cohort Study for the UK, which has established a large retinal network of treating centres to document the effects of PDT for CNV from AMD in the real-life setting of the NHS. This network is central to the feasibility of the proposed trial. Prof Lotery runs a molecular genetics laboratory focused on the genetics of AMD. He has past experience of performing genotype-phenotype correlations in retinal disorders. Dr Reeves has extensive experience of designing and carrying out RCTs, including multi-centre ones. Dr Rogers has >20 years experience as a medical statistician and has been responsible for analysing many single and multi-centre RCTs. Dr Wordsworth has extensive experience of economic evaluations alongside RCTs. Professor Raftery has extensive experience of economic modelling, including work on VEGF inhibition treatments for NICE.

5 Service users

IVAN will actively engage with service users. The Macular Diseases Society of the UK and the Royal National Institute of the Blind, which are the two largest patient support organisations representing AMD sufferers in the UK, strongly support this trial. At the outline proposal stage, this trial was also submitted to the MRC who sought the opinion of the Macular Diseases Society. The Macular Diseases Society unequivocally confirmed their support of the proposed trial. The Macular Diseases Society have also confirmed their willingness to represent their members through steering committee membership of the IVAN trial and to help the trialists in the construction of the MREC application and patient information leaflets.

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