TANDEM: A randomised controlled Trial of standard and low dose Avastin® for Neovascular macular Degeneration in the East Midlands

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Table of contents

PROTOCOL SYNOPSIS

Title of Study	**TANDEM: A randomised controlled Trial of standard and low dose Avastin® for Neovascular macular Degeneration in the East Midlands**
Chief Investigator:	Alexander Foss
Scientific Rationale:	Bevacizumab (Avastin®) and Lucentis are two very similar drugs which both act by neutralizing VEGF which is a key cytokine in the pathogenesis of Age Related Macular Degeneration. Avastin® is a monoclonal IgG antibody directed against VEGF while Lucentis® is an Fab fragment derived from the same monoclonal antibody. The dosing regime for Avastin® is based on it being the same as Lucentis®. However it has two important structural differences. First it has two active sites, not one and the second is that it retains the Fc portion of the antibody which would be expected to confer a significantly longer half-life – a fact that has been confirmed by measurement. Accordingly a reduced dose and a reduced frequency would be expected to be equally effective.
Clinical Rationale:	Systemic VEGF blockade can lead to serious clinical side effects and in particular CVA. Accordingly, it is desirable to use the smallest effective dose in order to minimise the risk of such complications. Secondly, the standard dosing regimen requires monthly hospital visits, which present a significant challenge both to the hospital services and to the patients (who are elderly). This study will determine if a regimen that is based on half the dose given on a two monthly, rather than monthly regime will prove equally effective clinically. Such a demonstration would benefit both the patients and the health service.
Total Patient Number:	Recruit 2000 patients to obtain 304 separate events
Duration of Study:	48 months
Aims:	To investigate alternative treatment regimens for the treatment of nAMD with Avastin®.
Primary endpoints:	Time to treatment failure to be analysed using Cox regression
Secondary endpoints:	Analyses of this secondary outcome will include the entire study population and will estimate the main effects of standard vs. low dose Avastin® and monthly vs. 2-monthly review. The interaction of Avastin® dose and review interval will be tested but will only be included in the final model if it reaches statistical significance ($p<0.05$). Susceptibility to differential informative censoring will be investigated
Study design:	A factorial multi-centre masked randomised trial using Avastin in standard or low dose with second randomisation to monthly or bi-monthly patient review.
Inclusion criteria:	• Age ≥50 years • Newly referred for treatment of nAMD or reactivation of nAMD • No treatment for nAMD to either eye for the previous 6 months • Eligible for anti-VEGF treatment of nAMD in the NHS
Exclusion criteria:	• Known hypersensitivity to recombinant human or humanised antibodies • Woman of child bearing potential and not willing to use contraception • Male with spouse of child bearing potential not willing to use condoms • Pregnant or breast feeding
Study Drug:	Bevacizumab (Avastin®) administered as an intravitreal injection either standard dose 1.25mg or low dose 0.625mg for loading doses A, B & C and then on a need to treat basis.
Patient care post trial:	All active patients will be treated under routine NHS care.
Safety:	An important part of this study is to obtain further safety data in the use of Avastin for nAMD for differing doses and review intervals.

Glossary

Assessment review - visit at which the patient is treated if necessary and visual acuity data is collected. This falls at every other review visit starting on the 2nd visit after visit C (see Study schema) for patients in the monthly arm alternating with interim visits; and all the visits for the two-monthly review arm of the trial.

Avastin® - *bevacizumab:* anti-VEGF being investigated in this study as an off-label treatment for nAMD

CATT - Comparisons of Age-Related Macular Degeneration Treatments Trials

CNV - *choroidal neovascularisation:* pathological process in which new blood vessels grow from the choroid layer of the eye, breaching the normal tissue barriers and come to lie within the sub-pigment epithelial and sub-retinal spaces.

Endophthalmitis - inflammation or infection of the internal coats of the eye, often as a result of intraocular surgery or injection.

ETDRS letter chart - a type of visual acuity test originally designed as part of the Early Treatment Diabetic Retinopathy Study.

FFA - *Fundus Fluorescein Angiography:* a diagnostic imaging technique in which a dye is injected into a patient's arm and sets of digital photographs are taken to display the blood vessels at the back of the eye.

Interim review - visit at which the patient is treated if necessary but visual acuity data is not collected. This falls at every other review visit starting after visit C (see Study schema). Only patients in the monthly review arm of the trial attend this type of review.

IVAN - A randomised controlled trial of alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN)

Lucentis® - *ranibizumab:* anti-VEGF licensed for treatment of nAMD and is the standard treatment at study sites.

nAMD *or* ***wet AMD*** - *neovascular Age-related Macular Degeneration:* medical condition being investigated in which CNV causes rapid deterioration of central vision.

OCT - *Optical Coherence Tomography:* a diagnostic imaging technique in which infrared light is used to scan the retina to track anatomical changes and disease processes.

PDT - *Photodynamic Therapy:* a treatment for nAMD in which blood vessels are destroyed by a drug which is activated by a laser light directed at the eye.

SAE - *Serious Adverse Event:* any events which result in death, are life-threatening, require hospitalisation or prolongation of hospitalisation, result in persistent or significant disability or incapacity.

SSAR - *Suspected Serious Adverse Reaction:* any SAE that is suspected (possibly or probably) to be related to the study drug.

SUSAR - *Suspected Unexpected Serious Adverse Reaction:* any SSAR that is suspected (possibly or probably) to be related to the study drug but where the nature and severity are not consistent with the expected SARs as defined in this document (see **Section 6.1**).

Uveitis - specifically refers to inflammation of the middle layer of the eye, termed the "uvea" but in common usage may refer to any inflammatory process involving the interior of the eye.

VAlogMAR - measurement of visual acuity using an ETDRS chart, usually described in terms of the number of letters read on the chart (ranging from 0 when the visual acuity is very poor to 100).

VEGF - *Vascular Endothelial Growth Factor:* a protein which stimulates new blood vessel formation and is believed to play a critical role in the development of CNV in nAMD patients. Anti-VEGF drugs have been demonstrated to be effective in treating nAMD.

VPDT - Verteporfin Photodynamic Therapy

1. Summary in plain English

Wet or neovascular age-related macular degeneration (nAMD) causes severe sight loss in older people. Neovascular macular degeneration is due to a pathological process known as choroidal neovascularisation (CNV). It is characterised by the presence of new blood vessels in either the sub-pigment epithelial or sub-retinal spaces. These vessels usually arise from the choroid but a well-recognised variant of this process, termed Retinal Angiomatous Proliferation (RAP), has the vessels arise from the retinal circulation but is still considered part of the nAMD spectrum.

Treatment with a drug known as Lucentis® (Ranibizumab) is now recommended best practice. This treatment prevents sight loss in over 90% of recipients when given as injections into the eye with nAMD 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 little evidence on which to base criteria for stopping treatment and so there is considerable uncertainty about precisely how much treatment may be needed in the longer term. With respect to possible side effects of treatment, recent data from studies sponsored by the manufacturer suggested that the currently recommended dose of Lucentis® (0.5mg) may double the risk of stroke compared with a lower dose (0.3mg) raising concerns about its systemic safety, although this increase was not found to be statistically significant.

Another drug, called Avastin® (Bevacizumab) is licensed for colorectal cancer therapy and has similar properties. This drug has also been used to treat patients with nAMD and is also thought to confer similar benefits, based on multiple uncontrolled studies. Avastin® is extremely cheap relative to Lucentis® because the dose for an 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. Five trials are currently comparing the efficacy of Lucentis® and Avastin® to answer the question of whether Avastin® is not inferior to Lucentis® with respect to visual acuity. Collectively, these trials will also generate important evidence about the relative safety of the two drugs.

There is an urgent need for more evidence about cost-effective ways to treat nAMD. Avastin® is widely used in a clinical context and some European countries have opted to provide Avastin® only. One of the five trials comparing the efficacy of Lucentis® and Avastin®, the Comparisons of Age-Related Macular Degeneration Treatments Trials (CATT), has recently reported its findings one year after randomisation and found that the two drugs "had equivalent effects on visual acuity when administered according to the same [treatment] schedule." The CATT investigators also concluded that "Differences in rates of serious adverse events require further study," which will happen as CATT participants are followed for a second year and the other ongoing head-to-head trials report their findings.

It is important to obtain more information to optimise treatment with Avastin®, given that Avastin® appears to have equivalent effects on visual acuity to Lucentis®. Different doses of Avastin® have not been evaluated and may be important for safety. There is also a pressing need to evaluate different intervals for reviewing eyes that are being considered for re-treatment because monthly review is demanding for elderly patients, resource intensive and expensive.

Therefore, we propose to carry out a factorial, randomised controlled clinical trial which will (a) compare the clinical efficacy of standard versus low doses of Avastin® and (b) compare monthly versus two-monthly review intervals. The trial will also describe both eye-related and systemic adverse effects observed with different Avastin® doses and treatment regimens.

2. Background

2.1. *Treatments for choroidal neovascularisation and rationale for the trial*

The onset of nAMD is accompanied by central distortion and blurring which, when left untreated, results in loss of central vision with a dense central scotoma (blind spot) [1]. These visually disabling effects, such as the inability to read, recognise faces and watch television, 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; VAlogMAR) is considered a visually significant event [2]. Untreated, this disease has a poor visual prognosis with the average visual loss at three months from diagnosis being 1–3 lines and 3–4 lines by one year [3]. Until 2005, the best treatment outcomes were observed in the TAP study [4], in a subgroup of people with the predominantly classic type of CNV (accounting for 30% of the total) treated with verteporfin photodynamic therapy (PDT).

The outlook has been transformed by the introduction of the anti-VEGF-agents. There are several isoforms of VEGF and the first agent of this class to be introduced was Macugen® (pegaptanib) which was active only against the most common 165-isoform. The VISION trial observed visual benefits similar to the TAP study [5]; twelve months after randomisation, VAlogMAR remained within 15 letters (3 lines) of the presenting VAlogMAR in about two-thirds of treated eyes compared to about half of untreated control eyes or control eyes which received sham treatment. However, the different isoforms of VEGF have distinct biological actions [6] and, since pan-VEGF inhibitors have subsequently been shown to be much more effective, it is possible that Macugen® was directed against the wrong isoform.

The introduction of the pan-VEGF inhibitors, Avastin® (bevacizumab) and Lucentis® (ranabizumab), has transformed the prognosis of nAMD. The first to be developed was Avastin®, which was an IgG antibody directed against VEGF. It was shown to have powerful anti-angiogenic effects in an experimental tumour model [7] and was developed as an anti-cancer drug. Lucentis® was derived from the Fab fragment of Avastin® which is a fragment of the antibody that has the VEGF binding site. The claimed impetus for developing Lucentis® is that Avastin, being an intact antibody, would not penetrate the retina and would therefore be clinically ineffective, whereas the Fab fragment would be able to penetrate [8].

2.2. *Effectiveness of Lucentis®*

The landmark phase 3 trials, MARINA and ANCHOR, demonstrated that Lucentis® (ranibizumab, a monoclonal antibody to VEGF) gave large treatment benefits [9, 10]. Lucentis® was administered by monthly intravitreal injection into the vitreous cavity. At 12 and 24 months, more than 90% of eyes treated with Lucentis® (0.5mg) remained within 15 letters (3 lines) of the presenting VAlogMAR 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 VAlogMAR of between 5 and 10 letters (1 to 2 lines) and about 35% had VAlogMAR better than 70 letters (Snellen equivalent of 6/12) compared to eyes that had sham or other treatments; this level of vision 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® [4, 5], showed on average a reduction in VAlogMAR in treated eyes of between 10 to 15 letters over 24 months.

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 showed that regular injection of Macugen® for two years was superior to stopping treatment after one year [11]. These data suggest that it may be necessary to continue VEGF inhibition beyond two years in a proportion of patients.

2.3. *Effectiveness of Avastin®*

The claim that Avastin® will not penetrate the retina [8] has not been replicated and subsequent work has shown that antibodies penetrate the retina well both in rabbits [12] and in primates [13]. Avastin® is still currently licensed only 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, by aliquoting Avastin® into many small doses, clinicians have been able to offer a cheaper alternative to Lucentis® through off-label use of Avastin®.

Evidence of the efficacy of Avastin® was summarised in a systematic review of randomised trials comparing Avastin® with PDT and of uncontrolled case series using Avastin® [14]. Small trials comparing the effectiveness of intravitreal Avastin® injections with PDT showed similar average differences in VAlogMAR between groups to that observed in ANCHOR, and average gains in VAlogMAR in the Avastin® arms were similar to those observed in the Lucentis® arms of the ANCHOR and MARINA trials for different nAMD sub-types [15-17]. In uncontrolled case series with at least 24 weeks follow-up, gains of 5 to 18 letters have been reported,[14] in comparison to average gains over one year of 11 and 7 letters in ANCHOR (predominantly classic lesions) and MARINA (minimally classic and occult lesions) [9, 10]. Remarkable improvements in visual acuity and morphology following treatment with Avastin® have been reported by investigators throughout the world and several thousands of patients have been treated with this drug [18, 19], primarily because it is more affordable. The Pan-American Collaborative Retina Study (PACORES) group reported an average gain over 1 year of about 10 letters in over 1000 patients treated in six countries [20, 21].

Two recent randomised controlled trials support this review. The first is the ABC trial, which provided indirect evidence that Avastin® has similar efficacy to Lucentis® [22]. It compared Avastin® (administered as “three loading injections at six week intervals followed by further treatment if required at six week intervals”) with standard treatment, either verteporfin photodynamic therapy (VPDT), pegaptanib or observation. The benefits of this treatment schedule with Avastin® were similar to those observed in the ANCHOR and MARINA trials [9, 10].

The second trial is the CATT trial, which is the first of five on-going trials comparing the efficacy of Lucentis® and Avastin® to report [23]. It found, at one year after randomisation, that the two drugs "had equivalent effects on visual acuity when administered according to the same [treatment] schedule."

Avastin® is being used widely for the treatment of nAMD and has been adopted by some countries as the primary method of treatment in publicly funded health services [24, 25], since accruing evidence supports the conclusion that it is equally effective as Lucentis® and, being much cheaper, represents much better value for money.

There has been much debate about the consequences of the differences in molecular structure between Avastin® and Lucentis®. Lucentis® was generated from the Fab fragment of the Avastin® molecule. The structure of Avastin® differs from that of Lucentis® in two important respects. First, Avastin® contains the Fc fragment which confers an enhanced half-life. Second, it has two binding sites rather than one. These differences provide the rationale for the comparisons being evaluated in the TANDEM trial.

2.4. ***Rationale for bi-monthly arms and the issues of health care delivery and ocular safety***

The results of the ANCHOR and MARINA trials were impressive, but they were achieved using an intensive dosing schedule of monthly intravitreal injections, which poses serious challenges for elderly patients who are likely to experience difficulties in attending clinics frequently for several years. In addition, such intensive treatment regimens also create difficulties in terms of resource implications for health service providers.

Monthly dosing may not be necessary to achieve good visual results. 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 [26]. 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' result 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 [27, 28]. 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. Consistent with these findings, monthly review with treatment 'as required' is becoming the standard method of administration.

PIER showed that assessment and re-treatment with Lucentis® once every three months still gave good results but not equal to those achieved with monthly review. Bi-monthly review has not been assessed for Lucentis®. The first structural difference between Avastin® and Lucentis® described above, namely that includes the IgG Fc portion of the molecule, means that Avastin® is actively retained by the body and has a much longer in vivo half-life [29, 30]. The half-life of Lucentis® in the vitreous of rabbits is 2.9 days [31, 32] compared to a half-life of 4.3 days for Avastin® [31]. In humans, the reported half-life of Avastin® is 10 days [33] compared to the reported half-life for Lucentis of 3 days in primate eyes [33]. The mean duration of clinical action of Avastin® has been reported to be significantly longer than Lucentis at 100 days [34] and this suggests that monthly assessment and potential treatment may be too frequent and that a review frequency of around every 56 days (eight weeks) should be sufficient. In this context, it also is of interest that the VEGF-trap is a molecule with two active binding sites for VEGF, has the IgG Fc portion and has been shown to be effective with a bi-monthly treatment schedule [35].

Bi-monthly dosing has the additional advantage of less frequent exposure to the risk of local complications related to the injection process. Intra-ocular injection carries the risk of endophthalmitis, traumatic cataract and traumatic retinal detachment (RD) which are potentially blinding complications. These risks are small and can be minimised, as shown by the VISION clinical trials, with adherence to protocols that emphasize sterility and administration of the drug by experienced personnel (1.3% endophthalmitis, lens injury 0.7%, RD 0.6% in 1 year) [5]; similar or smaller risks were observed in the PACORES [21]. Although the risks are small, they can result in severe ocular morbidity and the absolute risk does accumulate with repeat injections.

2.5. ***Rationale for low dose arms and the issue of systemic safety***

The second structural difference between Avastin® and Lucentis® is that Avastin® has two binding sites to VEGF whereas Lucentis®, being the Fab fragment, has only one. Therefore, it is not clear whether an 'equivalent' dose should be calculated on the basis of the number of molecules or the number of active sites.

The most commonly used dose of Avastin®, 1.25 mg, was calculated on the assumption that the dose should be equimolar with respect to Lucentis®, i.e. this calculation did not take into account the fact that Avastin® has two, rather than one, binding sites. Increasing the dose of Avastin offers no increased clinical benefit; doses of both 1.25 mg and 2.5 mg are equally effective in the treatment of AMD [20, 36]. Similarly, no differences in the effectiveness of 1.25 mg and 2.5 mg doses of Avastin® have been reported when used to treat macular oedema from branch retinal vein occlusions [37], central retinal vein occlusions [38] and diabetic macular oedema [39].

Moreover, there is evidence that a lower dose maybe just as effective. In the context of diabetes, Avery has shown that proliferative disease will respond to an injected dose as low of 0.00625 mg (6.25 µg) [40]. A simple calculation shows that the concentration of Avastin® in the eye following a 1.25mg injection is 2.1 µM, assuming a volume of distribution of

4 mls and a molecular weight of an antibody of 150 kdal. The half maximum proliferative response is in the region of 50pM [41] and the standard dose result is 42,000 fold excess. Allowing for whole body dilution (a factor of 20,000) still gives a ten-fold excess in the fellow eye of the VEGF levels that are measured in ocular disease. The VEGF level reported in proliferative diabetic retinopathy is 29pM [42], and 4 pM (assuming a molecular weight of VEGF of 50KDal) for AMD [43, 44] (but note for nAMD that the important form is strongly heparin binding and so it would be expected to be present at a higher level in the tissue compared to either aqueous or vitreous). This fully explains why an injection in one eye has been observed to cause new retinal blood vessels to regress in the fellow eye in diabetics [40] and why intra-ocular injections of anti-VEGF agents would be expected to give rise to systemic VEGF blockade.

A large excess may be necessary with Lucentis® because most peptides are rapidly cleared. However, for Avastin®, the longer half-life may mean that administering a large excess (albeit equimolar with the licensed Lucentis® dose) results in over-dosing and unnecessary increased exposure to dose-related complications. This is important consideration with respect to safety since the ability of Lucentis® and Avastin® to inhibit all classes of VEGF means that they have the potential to induce serious ocular and systemic side effects. VEGF is known to have a neuro-protective effect in the retina [45] and is also thought to maintain the fenestrated phenotype of the choroidal vasculature [46]. Therefore, there is concern that pan-inhibition of VEGF over long periods of time may 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 [5, 9-11, 23], the data relate to relatively short periods of time with few patients having follow up beyond two years. Endothelial cells have a slow turnover and so there is still the risk of delayed side-effects.

Systemic side effects remain a concern as the pooled findings from ANCHOR and MARINA trials revealed a slight excess of thromboembolic events when eyes had been treated with the highest dose of Lucentis® and a small increase in non-ocular haemorrhages in eyes treated with any dose of Lucentis® [9, 10, 47]. An interim analysis of the SAILOR trial, reported in a review [47], found an increased risk of stroke with 0.5mg vs. 0.3mg Lucentis® dose (1.3% vs 0.3%, p=0.02) but this difference reduced and was not statistically significant in the final analysis [48]. A recent systematic review compared the adverse effects of intravitreal injections of Lucentis® or Avastin® in randomised controlled trials (RCTs) [49]. For Lucentis®, the review calculated an annual incidence of arterial thromboembolic events of 2.7%; possible safety signals were observed for thromboembolic events (RR 1.35, 95% CI 0.66 to 2.77) and non-ocular haemorrhage (RR 1.62, 95% CI 1.03 to 2.55). The authors found that studies of Avastin® were methodologically flawed and concluded that they showed “too many methodological limitations to rule out any major safety concerns,” although it should be noted that this review did not consider the ABC or CATT trials [22, 23]. In contrast, an observational analysis of 146,942 Medicare claims files of beneficiaries treated VPDT, pegaptanib, Lucentis® or Avastin® concluded that there was “no evidence of increased risks of mortality, myocardial infarction, bleeding, or stroke among Medicare beneficiaries who received intravitreous ranibizumab or bevacizumab” [50].

The one year findings about adverse events from the CATT trial were equivocal; the proportions of patients with thrombotic events were similar for both drugs but the proportions of patients with one or more serious systemic adverse events were 19.0% for Lucentis and 24.1% for Avastin (p=0.04).[23] However, “No one MedDRA system organ class accounted for the difference between drugs; differences in rates were largest for hospitalizations for infections and gastrointestinal disorders.” These findings were unexpected, of marginal statistical significance and are consistent with chance since the CATT investigators carried out multiple statistical tests of differences in adverse events by drug and treatment schedule. More information about adverse events following multiple intravitreal injections of Lucentis® or Avastin® over time will become available from the second year findings of the CATT and one year findings of the alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN) trial [51]. The IVAN trial will also report information about systemic levels of Lucentis® and Avastin® following multiple intravitreal injections over time, and the development of antibodies to the drugs. It has been hypothesised that these markers will be associated with the risk of systemic adverse effects.

Overall, the evidence has been reviewed by the Cochrane Collaboration and the conclusion was [52] that 1.25mg of Avastin® and 0.5mg of Lucentis® have similar safety profiles but they do carry the risk of systemic side effects, most importantly of stroke. Furthermore, there is evidence that this increased risk of stroke is dose related.

It is desirable to use the lowest effective doses of these agents in order to minimise this risk. Given the concern about possible systemic side effects it is clearly desirable to use the smallest clinically effective dose. The combination of half dose bi-monthly would result in a potential four-fold lowering of the total drug delivered during the maintenance phase. The evidence described above suggests that this is still a large enough dose to give a good clinical response.

2.6. *Summary of existing evidence*

Considerable uncertainty remains about the best way to deploy VEGF inhibitors for the treatment of nAMD. Although Lucentis® is approved for use in the NHS, it is expensive and, because of the need for monthly review during treatment [53], has resource implications affecting the ability of the NHS to provide treatment for all affected patients. Avastin® appears to be equally effective [23], may require fewer treatments [22] and less intensive review. There are other on-going trials of Avastin® (mainly in comparison to Lucentis®) but only the CATT trial has reported to date [23]. There are very limited data on outcomes with different Avastin® doses and on the minimum treatment frequency / duration that is required to maintain the maximal visual benefit. Therefore, the research questions that this study is addressing have not been investigated before.

2.7. ***Need for additional information about outcome in usual NHS clinical practice***

The TANDEM trial builds on successful and complete recruitment in two large randomised controlled trials comparing Lucentis with Avastin® [23, 51]. In the course of the IVAN trial, the IVAN Data and Safety Monitoring Committee (DMSC) has pointed out that high quality safety data regarding Lucentis® have been, or are being, collected only in commercial trials, the IVAN and CATT trials. All of these trials have only recruited and studied one eye.

For patients who have bilateral wet AMD (at least 7% at some stage during the 2 years following treatment to the first eye [53]), it has now become common practice in the NHS to treat both eyes at the same time. Leakage of drug from the vitreous into the circulation would be expected to be similar from either eye, so these patients are being exposed systemically to double the amount of VEGF-inhibitor. This has been true for patients in the IVAN trial, even though each participant has only one eye in trial, because second eyes that have developed wet AMD and require treatment have been treated with standard NHS treatment, i.e. Lucentis®. Half of IVAN participants with bilateral disease receiving two injections at the same time will have had two Lucentis® injections (one into the study eye and one into the NHS-treated eye) and half will have had one Avastin® injection (study eye) and one Lucentis® injection (NHS-treated eye). Therefore, the total number of double injections of the same drug is small. The IVAN DMSC pointed out the urgent need for high quality data to be collected for a larger sample of patients receiving two intravitreal injections of a VEGF-inhibitor at the same time. The TANDEM trial infrastructure, collecting high quality data for adverse events for Avastin® in randomised participants will contribute this data.

A recent publication from a national registry of patients treated with verteporfin photodynamic therapy (VPDT) demonstrated how different treatment in practice can be compared to treatment in trials carried out for marketing authorisation [54]. The IVAN and CATT trials, although more pragmatic in their design than the ANCHOR and MARINA trials, have detailed treatment schedules that do not represent usual NHS practice. Despite the reimbursement scheme put in place by Novartis to satisfy NICE (data held by Novartis and not made public), we are not aware of any process that is collecting high quality data about treatment intervals, frequency and duration of treatment with Lucentis® in the NHS. In order to inform the planning of future services, it is important to describe treatment and review frequency and their association with visual acuity in usual NHS practice.

2.8. ***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® and its longer half-life in the eye, and postulated slower diffusion into the circulation, may permit fewer treatments and less intensive review. On-going trials comparing Lucentis® and Avastin® are designed to test whether Avastin® is not inferior. In the interests of both patients and the NHS, there is a need for further research to inform the best way to treat eyes affected by nAMD with Avastin®, should the ongoing trials find that Avastin® is not inferior to Lucentis®.

3. Aims and objectives

The aim of the trial is to investigate alternative treatment regimens for the treatment of nAMD with Avastin®. We hypothesise that:

(a) Low dose Avastin® is not inferior to standard dose Avastin® with respect to the benefits of Avastin® in maintaining or improving visual acuity in eyes with nAMD.

(b) Following an initial 3-month period of monthly review, eyes treated with Avastin® can be 'safely' reviewed every two months to detect disease activity and the need for retreatment, rather than monthly, i.e. the 2 monthly review interval will not be inferior to the monthly review interval with respect to average visual acuity.

The trial has three specific, inter-related objectives:

I To estimate the relative effectiveness of standard versus low dose Avastin® (bevacizumab) for intravitreal injection 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 describe the adverse effects of different Avastin® doses and review regimens.

4. Plan of Investigation

4.1. *Figure 1a Induction Phase*

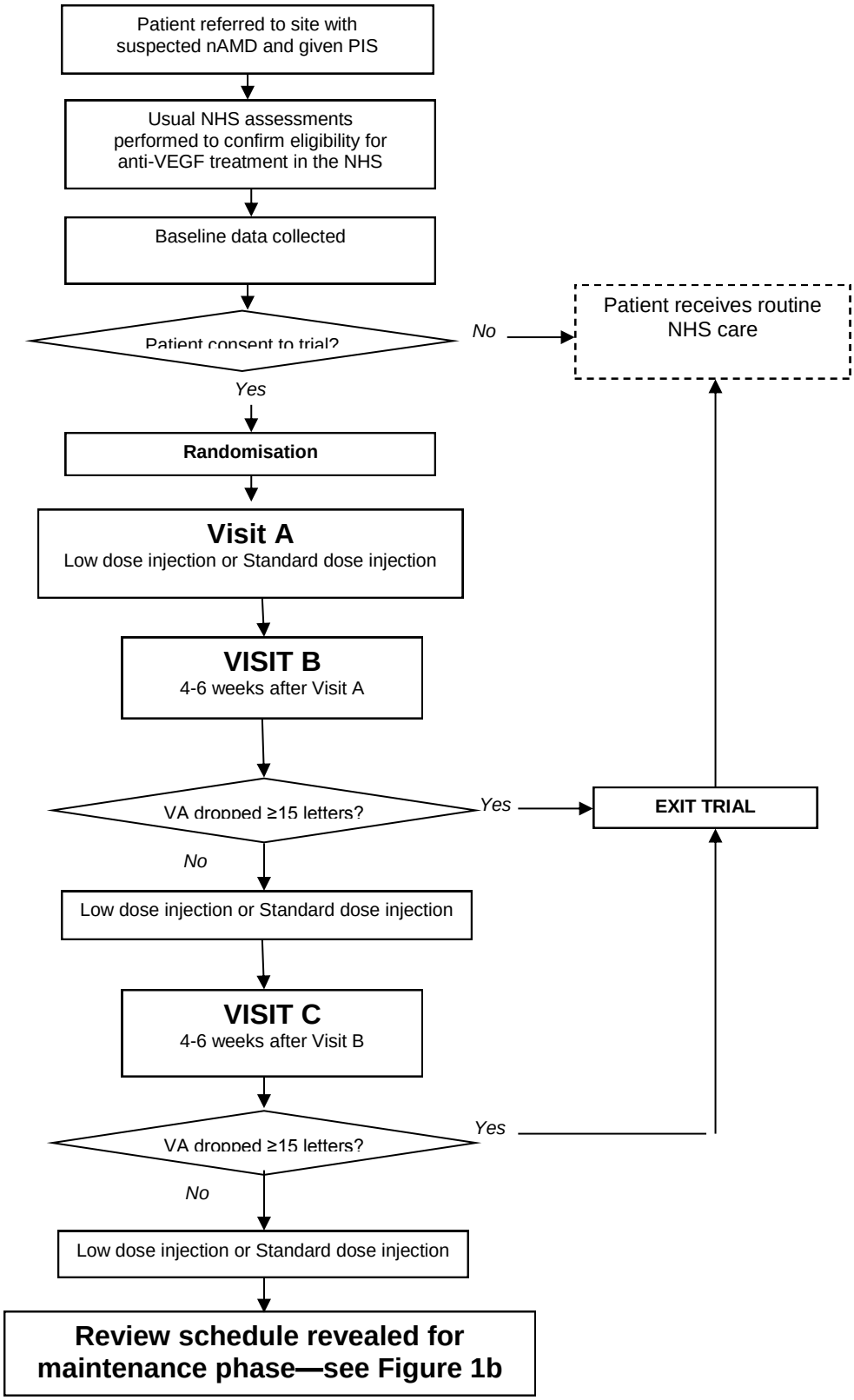
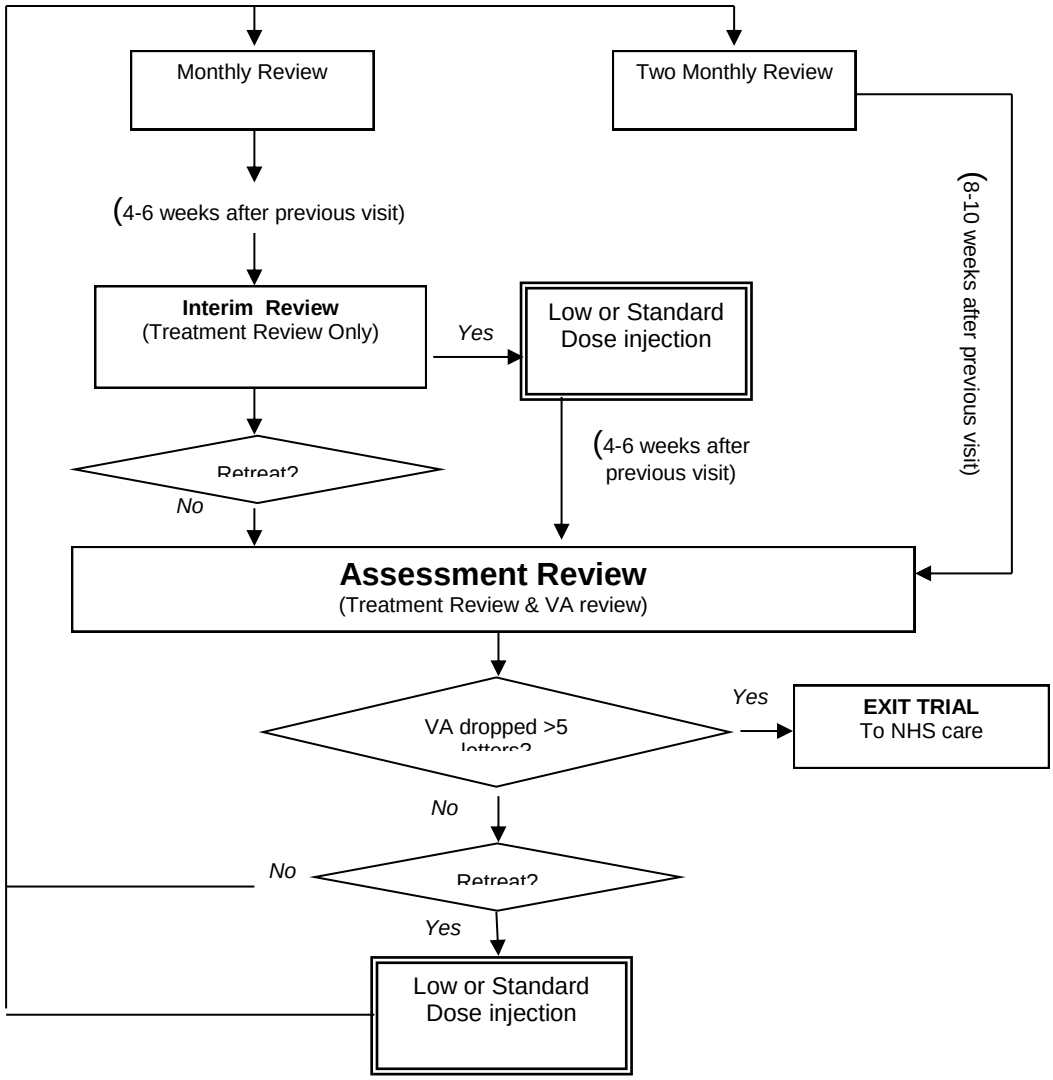


Figure 1b Maintenance phase (Review schedule)



4.2. ***Study design***

The study uses a comprehensive cohort design [57], comprising a multi-centre, factorial RCT Randomisation will be to 1 of 4 combinations of two treatment factors (see **Figure 2** and **section 5.1**).

Participants, clinicians and trial personnel will be masked to the dose of Avastin® to which a participant is assigned. Pharmacies will dispense the appropriate dose to the ophthalmic clinic, as a pre-filled syringe. At randomisation and for the first 3 visits (visits A-C) participants, clinicians and trial personnel will be masked with respect to allocation of patients to monthly or two-monthly review intervals. The review interval allocation will be revealed after assessment and injection at visit C in order that the next visit can be booked.

Figure 2: Factorial study design

	Low dose Avastin® (new dose)	Standard dose Avastin® (currently used dose)
Two-monthly review (new review interval)	L_2	S_2
Monthly review (current review interval)	L_1	S_1

4.3. *Study population*

The trial will be offered to any patient who is eligible for anti-VEGF treatment in the NHS as set out in the final appraisal determination published by NICE for Lucentis® [56].

4.3.1. Inclusion criteria:

- Any patient newly referred for the treatment of nAMD or reactivation of nAMD, i.e. disease stable with no treatment for nAMD to either eye for the previous 6 months, who is considered eligible for anti-VEGF treatment in the NHS.

4.3.2. Exclusion criteria:

- Pregnant and/or lactating;
- Woman of child bearing potential (i.e. not sterilised or post menopausal) who are unwilling to use contraception;
- Male with a spouse or partner of child bearing potential unless the participant has agreed to use condoms;
- Patients with known hypersensitivity to recombinant human or humanised antibodies.

Eligibility for the trial is subject to treating clinician deciding whether the patient will benefit and would receive treatment within the normal NHS environment [56]. There are other prognostic factors, which are not explicitly criteria for exclusion in the TANDEM trial but will be taken into consideration by ophthalmologists.

These include:

- 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 surface areas);
- Presence of thick blood involving the centre of the fovea;

Information about these factors will be collected at the time of recruitment.

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, the potential benefits and harms of treatment will be discussed carefully with potential participants at the time of recruitment by the ophthalmologist initiating anti-VEGF treatment, both in the trial and in usual NHS care.

At all times, the decision to treat remains the clinician's decision, judging if the patient will benefit and receive treatment within the normal NHS environment, whether participating within this trial or not.

Participating centres

We will recruit up to 20 centres at NHS acute hospital Trusts, both in the East Midlands and elsewhere. Centres will be commissioned by local Clinical Commissioning Groups (CCGs) to recruit and treat trial patients alongside provision of a standard NHS anti-VEGF service in accordance with the NICE guidance on Lucentis®.

4.4. *Study interventions*

All participants will initially have three visits at monthly intervals (Induction Phase; visits A, B and C – see **Table 1** and **Figure 1a Induction Phase**) when the allocated dose will be injected. Participants will be allocated to a review interval of one or two months at the time of recruitment but the allocated interval will only come into effect at visit C when the maintenance phase begins.

4.4.1. Avastin® dose

Participants will be randomised to intravitreal injection of Avastin® 1.25mg, the 'standard' dose observed to be effective in clinical practice [14, 22, 23], or Avastin® 0.625mg, the 'low' dose. The rationale for the dose of 1.25mg is that the molar concentration achieved after intravitreal injection is highly similar to that achieved by the 0.5 mg dose of Lucentis® 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® [57].

4.4.2. Review schedule (maintenance phase)

After visit C, patients will be scheduled for review at intervals of one or two months. There will be 2 types of review visits:

- **Interim review visit**: the presence of active nAMD and the need for further treatment will be evaluated against standard OCT or FFA criteria.

- **Assessment review visit**: visual acuity will be measured and the presence of active nAMD and the need for further treatment will be evaluated against standard OCT or FFA criteria.

Patients in the monthly review arm (L_1 and S_1 in **Figure 2**) will alternate between Interim and Assessment review visits. The minimum interval between visits will be 28 days (4 weeks) and the maximum interval will be 42 days (6 weeks) between visits. If a patient is unable to attend for an Interim review visit in this 14 day window, the review visit will be considered to have been missed and the patient will be seen at the next Assessment review visit.

Patients in the two-monthly review arm (L_2 and S_2 in **Figure 2**) will only have Assessment review visits. For patients allocated to a review interval of two months, the next review visit should be scheduled ≥56 days (8 weeks) and ≤70 days (10 weeks) after the previous one. A

At all visits either Interim or Assessments patients showing signs of active nAMD will be re-treated.

4.4.3. Criteria for retreatment

At every interim or assessment visit (and irrespective of allocation to dose), participants will be reviewed and will be retreated if, on the basis of OCT or other investigations, the assessing ophthalmologist considers that retreatment is warranted (see Figure 3b Maintenance Phase). Re-treatment decisions will be made on the basis of:

- the presence of sub-retinal fluid in the study eye, using evidence from the OCT scan
- the presence of fresh blood in the lesion in the study eye on clinical examination
- evidence from OCT of persistent or increasing intra-retinal fluid in the study eye such that the assessing ophthalmologist considers that retreatment is warranted

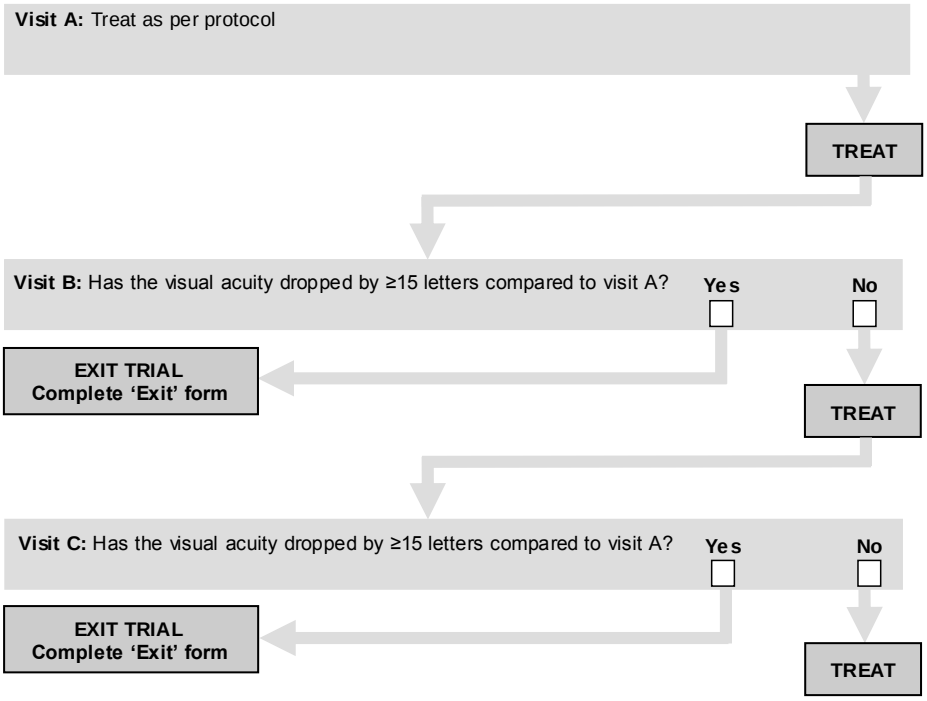
When there is uncertainty about the retreatment decision based on the above information, additional imaging may be performed to guide the decision.

4.4.4. Unscheduled breaks in treatment

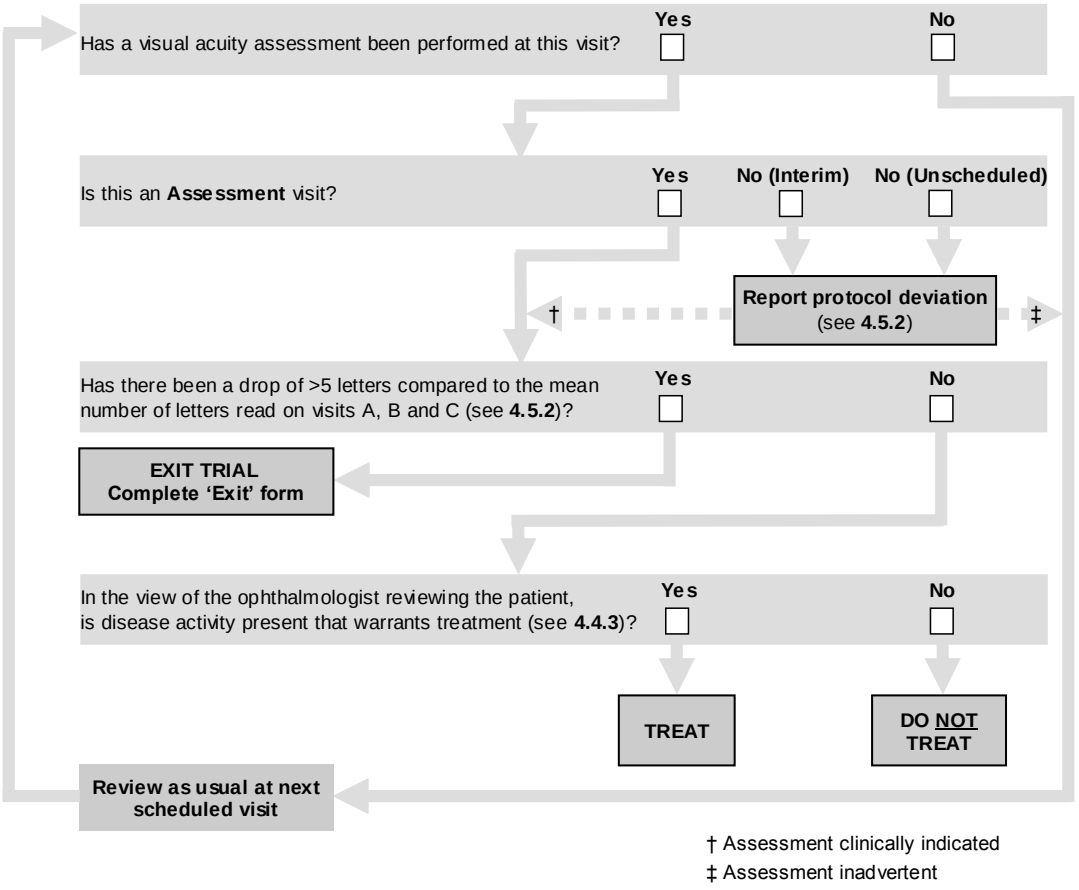
The TANDEM trial aims to reflect usual NHS practice and, therefore, recognises that participants may miss occasional scheduled visits because of illness or holidays, especially in view of the frequency of visits. It is envisaged that participating centres will set the dates of several future visits, to allow participants to plan holidays and to assist clinic planning.

Unscheduled breaks in treatment may also arise due to ocular or systemic adverse effects. 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 original allocation and visit schedule after a break of any duration.

Figure 3: Decision Algorithms (a) Induction phase



(b) Maintenance phase



4.4.5. Treatment of the fellow eye if it becomes eligible

If a fellow eye develops nAMD, it will also be eligible for inclusion in the study and will receive treatment as per randomisation and review schedule for the primary study eye, subject to the agreement of the participant. Confirmation of the diagnosis for the second eye will be provided by FFA at the time of presentation of the fellow eye. If a participant does not wish his or her fellow eye treated within the study, treatment for both eyes will be standard therapy (Lucentis®) within the NHS.

If both right and left eyes are eligible for inclusion at the baseline visit both can be included in the trial, as described above. If one eye is switched to treatment with Lucentis® at any stage of the study, the participant will be withdrawn from the study.

4.5. *Primary and secondary endpoints*

4.5.1. Primary endpoint:

The primary endpoint is time to vision deterioration, as defined in **4.5.2** below. The justification for choosing this primary endpoint is as follows:

- TANDEM is intended to reflect usual NHS practice and, therefore, the primary endpoint has to accommodate the usual management decisions of ophthalmologists, in particular decisions to discharge patients, e.g. because the disease is judged to be stable or treatment is judged to be futile.

- As TANDEM will be set in a pragmatic, routine care setting, there is a higher chance of missing data, missed visits, loss to follow-up, etc.; the primary endpoint has to be able to cope with these limitations without introducing bias. These features of TANDEM preclude the use of a continuously scaled endpoint such as logMAR ETDRS visual acuity.

The proportion of eyes losing ≥15 letters over the first 12 months of follow-up when treated with Lucentis® was reported by the ANCHOR and MARINA as 5-6% [9, 10]. However, the definition of a deterioration of this magnitude was not strictly defined (the method of "last observation carried forward" was used to interpolate missing data). If based on a single baseline visual acuity and visual acuity at 12 months (both subject to considerable measurement error), the endpoint is likely to have been insensitive to small amounts of deterioration. Hence, we have chosen the definition described at **4.5.2**.

The primary endpoint is defined by the time-to-an-event, i.e. vision deterioration, and allows any period of observation in the trial, however short, to contribute to answering the trial objectives. With such an outcome, there is no need to define a primary endpoint in time. Instead, we define the number of events needed to achieve satisfactory power for the main objectives (Section 6). The trial will accrue events over time. The timing of interim analyses will be chosen with respect to the number of events observed (subject to confirmation by the DMSC). Similarly, recruitment will cease and the trial will conclude when the target number of events has been observed. The open-ended duration of the trial, although unconventional, is not problematic given its pragmatic design and method of funding.

4.5.2. Criteria for vision deterioration compared to baseline

It is important to protect participants against vision outcomes worsening more than would be expected using Lucentis®. Therefore, participants' VAlogMAR will be checked for deterioration against stringent exit criteria:

(a) On visits B or C, a drop of ≥15 letters compared to the number of letters read on visit A, **OR**
(b) On assessment visits during the maintenance phase or other unscheduled visits if VAlogMAR was assessed because clinically indicated, a drop of >5 letters compared to the mean number of letters read on visits A, B and C.

These decision rules are shown in **Figure 3**. If criterion (a) or (b) appears to be satisfied, the qualifying visual acuity must be checked by another practitioner, using the most recent refractive correction.

These criteria have been met by about 10-15% of patients in the IVAN trial in the first year of follow-up, but would also have been met by a similar proportion in the Lucentis® licensing trials. Therefore, vision deterioration will not necessarily be attributable to use of Avastin® or 2-monthly review. Nevertheless, participants who experience vision deterioration, as defined above, will be switched to standard anti-VEGF treatment with Lucentis®. .

After visit C, in order to avoid biasing the primary outcome, participants in the monthly review arm should not have their VAlogMAR assessed on an Interim visit (see Figure 3b). Deviation from this rule will be explicitly recorded by the ophthalmologist when carrying out the ocular examination, and will be classified as 'inadvertent' (e.g. accidental measurement of vision at an Interim Visit) or 'clinically indicated', (e.g. if the participant reported having perceived their vision to have worsened). VAlogMAR measured in any participant requesting an unscheduled visit having reported worsening vision will be classified as clinically indicated. Participants will continue in the trial unless they wish to withdraw.

4.5.3. Secondary endpoints:

Secondary endpoints will be analysed 18 months after the start of recruitment, 30 months after the start of recruitment and then annually, unless otherwise stated, using data available at the time.

(i) Frequencies of adverse effects of treatment

(ii) Corrected distance visual acuity (VAlogMAR), measured as the number of letters read on a standard ETDRS chart (testing initially at 3-4 metres depending on the facilities at sites and then at 1 metre if <20 letters are read ; total letters read are scored 'as if' viewing at 1 metre).

4.6. *Sample size calculation*

With respect to the primary outcome (i.e. time to vision deterioration), the trial is designed to answer non-inferiority questions.

4.6.1. Objective I (Avastin® dose)

A small target difference in the proportion of patients who experience vision deterioration is required to determine whether the low dose of Avastin® is inferior to the standard dose. We have made the following assumptions in order to set a target sample size:

- Non-inferiority margin for low dose Avastin® equivalent to a hazard ratio of 1.4 for the primary outcome;
- One study eye per patient (conservative assumption, simplifies the sample size calculation);
- Risk of vision deterioration rate with standard dose Avastin® and monthly review = 10%/year;
- One sided test, 90% power and 5% significance;
- No interaction between drug dose and review interval.

The trial needs to observe 304 eyes (in separate patients) with vision deterioration to satisfy these assumptions. This number of events is expected to accrue over 3 years (see **5.8**).

4.6.2. Objective II (Review frequency)

This objective is also non-inferiority, since the main concern is that participants allocated to a review interval of two months do not have a higher risk of vision deterioration than participants allocated to a review interval of one month. The comparison of different review intervals will combine data for groups allocated to standard or low dose Avastin® (i.e. cells $[L_2+L_1]$ vs. $[S_2+S_1]$ 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.

4.6.3. Objective III (Description of adverse events)

This objective is purely descriptive. No difference in the frequency of SAEs is hypothesised and the trial is not to be powered to detect a difference.

4.6.4. Objective IV (Description of adverse effect profiles in patients receiving treatment for one or both eyes)

This objective is purely descriptive. No difference in the frequency of SAEs is hypothesised between groups of patients receiving treatment for one or both eyes. The group of patients receiving treatment for both eyes will also be <10% of the total.

4.6.5. Objective V (Description of the frequency and duration of treatment and review visits)

This objective is purely descriptive.

5. Trial methods

5.1. *Description of randomisation and code breaking*

5.1.1. Generation of randomised allocations

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. 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).

5.1.2. Masking of randomised allocations

Avastin® will be shipped to sites with a label indicating both possible doses in addition to a tear-off sticker that will indicate the dose of Avastin® in the syringe. On preparing the prescription, the pharmacist will tear this second label off so that the syringe is masked, and place the tear-off label in to the patients prescription record which stays in pharmacy. There will be space on the remaining label to complete the unique identifier for the patient so that the injecting ophthalmologist knows which patient the syringe has been allocated to.

Allocation to monthly or two-monthly review intervals will be masked up to 3 months but not thereafter.

5.1.3. Unmasking of randomised allocation to low or standard dose Avastin®, if required

The Pharmacy at each participating NHS Trust holds the study codes in a study specific file for participants recruited at that Trust. The study file is held in a secure area in Pharmacy with access only provided to those persons whom permission has been delegated, documented on the delegation list. The complete code list for all sites is held by the sponsor's pharmacy at Nottingham University Hospital (NUH).

At the time of recruitment and randomisation, each participant is given a card giving contact details for the trial, including contact telephone numbers for NUH pharmacy. In the event of need for emergency unmasking, the participant or attending doctor is directed to telephone the on-call pharmacist at NUH who will be able to unmask on receipt of the randomisation number recorded on the Contact Information Card. Clinical cover/advice will be provided by the CI and

that the pharmacist will have the 24 hour contact number to contact the CI in the need of clinical input. Each recruiting site should refer to the current version of the 'Unmasking Procedure' for further instruction and relevant contact information.

The study code should only be broken when absolutely necessary for valid medical or safety reasons e.g. in the case of a severe adverse event where it is necessary for the PI or treating physician to know which treatment dose the patient is receiving before the participant can be treated. The TANDEM study pharmacy manual asks the on-call pharmacist receiving an unmasking request to explain that the masked aspect of randomisation (to low or standard dose) concerns two active treatments differentiated only by dose and, in cases of doubt, medical advice can be obtained from the on-call registrar for ophthalmology who is contactable from the NUH switchboard. Therefore, *a priori*, it is considered extremely unlikely that a situation could arise in which unmasking would be necessary for medical or safety reasons.

5.2. *Research procedures*

All patients presenting with nAMD at participating sites will be assessed as usual in the NHS to determine their eligibility for anti-VEGF treatment. Baseline data will be collected (part of routine care, summarised below, section **5.5**). Patients who are eligible and give consent to enter the trial will as part of the study, have their FFA images and colour photography submitted for independent grading (see sections **5.5** and **6.1**). Patients will then be randomised and treated with Avastin® according to a randomly allocated dose regimen and review schedule, both allocations remaining double-masked at this time. Study patients will then receive Induction therapy of three injections of their randomised allocation on visits A, B and C with 4-6 weeks between each visit.

Following visit C and the third injection, the allocated treatment schedule will be revealed, indicating the frequency with which patients should return for future review visits. The details of the procedures carried out at specific visits are listed in **Table 1** below.

Patients who do not consent to the study will be treated in the NHS according to standard care.

5.3. *Duration of study treatment period*

There is no definitive study treatment duration. Patients recruited into the study will receive a minimum of three Avastin® injections one month apart, after which they will be reviewed at monthly or 2-monthly intervals, depending on their allocated review schedule (see **4.4**), for the need to receive further treatment. A patient's participation in the study will continue at these intervals indefinitely, receiving treatment as required, until either:

1. the patient is withdrawn (see **5.9**)
   (a) due to ineffective treatment
   (b) due to some other reason, e.g. adverse event, patient choice
   (c) due to study completion (target number of events reached as defined in **4.6**)

or

2. the patient is deemed by the relevant clinician to require no further treatment (in this case the patient should be continued to be reviewed for 6 months after their last injection).

Patients who end study treatment due to 1(a) will be transferred to alternative treatment. Patients who are still receiving treatment with Avastin® when the study ends, as per scenario 1(c), will be given the option to continue receiving Avastin® or to transfer to routine care with Lucentis®.

5.3.1. Reactivation of disease

It is possible that a clinician will determine that a patient requires no further treatment or reviews due to the apparent resolution of nAMD symptoms, as per scenario 2 above. Should a patient in this situation return to the site at a later date with renewed symptoms in the same eye and meet the study eligibility criteria, the patient can restart treatment with Avastin® under the protocol, following the same regimen as originally allocated. If a patient returns with symptoms in the fellow eye requiring anti-VEGF treatment and once again meets the study eligibility criteria, the patient can also restart treatment with Avastin® under the protocol, following the same regimen as originally allocated. In both cases, the patient will have a repeat induction phase and have a new base line vision established (mean of visits of A, B and C) against which subsequent assessments will be made.

5.4. *Definition of the end of the study*

The end of the trial for an individual participant is defined as whichever of the following occurs latest in calendar time:

- Withdrawal from the trial, or
- Discharge from further review without subsequently restarting treatment in the first treated eye or starting treatment in the fellow eye, or
- Cessation of the trial because the target number of events has accrued.

The definition of the end of the trial is when the trial has accrued the target number of events.

5.5. *Data collection*

Data collection will comprise the following activities:

(i) Baseline data collection (e.g. general and ophthalmic history and examination, baseline morphology of nAMD lesion) – Visit A only
(ii) Refraction – Visit A then at each subsequent visit, if required.
(iii) ETDRS logMAR visual acuity, including checking visual acuity against criteria for vision deterioration – Visits A, B, C and all Assessment reviews. NOT at Interim reviews.
(iv) FFA and colour photography – Visit A (images sent for independent grading) then at each subsequent visit, if required (not sent for grading).
(v) OCT – Visit A and at Assessment and Interim reviews. Only at visits B and C if required.
(vi) Follow-up ophthalmic examination – all visits
(vii) Assessment of need for re-treatment – all visits after visit C.
(viii) Assessment of AEs / SAEs – all visits.
(ix) Injection of trial drug, as required, in accordance with the protocol – Visits A, B and C, and at each subsequent visit if required (as determined by point (vi) above).

Separate screening and enrolment logs will be maintained for all patients screened and/or enrolled into the trial in all participating centres. After a visit has taken place, centre staff will transfer data into a secure web-based database within 5 working days. Baseline FFA and colour images must also be submitted to CARF within 28 working days (details in Trial Manual). The schedule of data collection over time is shown in **Table 1**.

5.6. *Source documents*

Source documents provide evidence for the existence of the participant and permit verification of the data collected. Source documents shall be filed at the investigator's site and may include but are not limited to, consent forms, current medical records, laboratory results and pharmacy records. A worksheet may serve as its own source data, for certain data points. These data points will be specified in the SDV plan. Only trial staff as listed on the 'Site Responsibility Delegation Log' shall have access to trial documentation other than the regulatory requirements listed below.

5.7. *Direct access to source data /documents*

The principal investigators and their institutions will provide direct access when required to all source documents and other trial documentation e.g. signed consent forms, worksheets, for the purpose of trial monitoring and audit and other lawful regulatory inspection. The eCRF and all source documents, including progress notes and copies of laboratory and medical test results shall be made available at all times for review by the trial manager, Sponsor's designee and inspection by relevant regulatory authorities (e.g., MHRA, EMEA).

5.8. *Planned recruitment rate*

The target number of eyes with vision deterioration, i.e. 304 eyes in separate patients, is expected to accrue over 4 years. For illustration, 12 participating centres would be expected to have a catchment population of approximately 6 million which is expected to give rise to ≈2,400 new referrals per year for treatment for nAMD [1]. We expect to recruit 30% of patients newly referred for treatment for nAMD, i.e. 720 participants per year when all participating sites are recruiting. Assuming the rate of vision deterioration is 10% per year (estimated from existing data accruing in IVAN; this proportion is not dissimilar to ANCHOR and MARINA), ≈3,200 person years of observation in the trial and ≈320 eyes with vision deterioration will accumulate over 3 years. Patients' who die, withdraw from the trial or give up treatment without experiencing vision deterioration will cause a reduction in the number of person years; set against this, however, some second eyes will be treated.

Table 1: schedule of data collection over time

1 MONTH REVIEW INTERVAL	Pre-treatment	←	Induction	→	←					Maintenance				→	
Months after first treatment		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Treatment Visit		**A**	**B**	**C**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	
Visit Type		***BL***	***BL***	***BL***	***I***	***A***	***I***	***A***	***I***	***A***	***I***	***A***	***I***	***A***	
Baseline data collection^	**Y**		**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	**N**	CONTINUE TREATMENT SEQUENCE AS REQUIRED
Fundus fluorescein angiography (FFA)^	**Y**		**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	
Colour fundus photography^	**Y**		**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	
Ocular coherence tomography^	**Y**		**IR**	**IR**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	
Submit FFA & colour images	**Within 28 days of recruitment**														
Refraction^	**Y**		**IR**	**IR**	**N**	**IR**	**N**	**IR**	**N**	**IR**	**N**	**IR**	**N**	**IR**	
ETDRS logMAR visual acuity^	**Y**		**Y**	**Y**	**N**	**Y**	**N**	**Y**	**N**	**Y**	**N**	**Y**	**N**	**Y**	
Ophthalmic examination^	**Y**		**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	
Complete Patient Informed Consent		**Y***													
Injection		**Y**	**Y**	**Y**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IR**	**IRI**	**IR**	
Assessment of AEs / SAEs		**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	**Y**	
2 MONTH REVIEW INTERVAL															
Months after first treatment		**0**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	
Treatment Visit		**A**	**B**	**C**		**1**		**2**		**3**		**4**		**5**	
Visit Type		***BL***	***BL***	***BL***		***A***		***A***		***A***		***A***		***A***	
Baseline data collection^	**Y**		**N**	**N**		**N**		**N**		**N**		**N**		**N**	CONTINUE TREATMENT SEQUENCE AS REQUIRED
Fundus fluorescein angiography (FFA) ^	**Y**		**IR**	**IR**		**IR**		**IR**		**IR**		**IR**		**IR**	
Colour fundus photography^	**Y**		**IR**	**IR**		**IR**		**IR**		**IR**		**IR**		**IR**	
Ocular coherence tomography^	**Y**		**IR**	**IR**		**Y**		**Y**		**Y**		**Y**		**Y**	
Submit FFA & colour images	**Within 28 days of recruitment**														
Refraction^	**Y**		**IR**	**IR**		**IR**		**IR**		**IR**		**IR**		**IR**	
ETDRS logMAR visual acuity^	**Y**		**Y**	**Y**		**Y**		**Y**		**Y**		**Y**		**Y**	
Ophthalmic examination^	**Y**		**Y**	**Y**		**Y**		**Y**		**Y**		**Y**		**Y**	
Complete Patient Informed Consent		**Y***													
Injection		**Y**	**Y**	**Y**		**IR**		**IR**		**IR**		**IR**		**IR**	
Assessment of AEs / SAEs		**Y**	**Y**	**Y**		**Y**		**Y**		**Y**		**Y**		**Y**	

***Informed consent must be complete prior to delivery of any treatment**

^May be completed ≤14 days prior to taking of consent and delivering first treatment.

BL= Baseline Visit
I = Interim Review Visit, patient treated if required
A= Assessment Review Visit, visual acuity data collected, patient treated if required.
Y= Yes activity must be carried out
IR= activity only carried out if required
N= not required

5.9. *Patient recruitment*

Potential study participants will be identified from those patients presenting with nAMD at the ophthalmology departments of participating sites and who meet the eligibility criteria for anti-VEGF treatment. Patients will be approached by a member of the local research team study (clinician/research nurse/trial coordinator) and provided with a Patient Information Sheet (PIS) describing the study, with the opportunity to discuss participation with a relevant clinician.

Patients will undergo standard NHS baseline tests and assessments to determine their eligibility for anti-VEGF treatment in the NHS according to NICE guidance [56]. If a patient's ophthalmologist decides the patient is eligible, the patient will be invited to consent to participating in the trial. If a patient gives written informed consent, he/she will be randomised.

In view of the age and study population it will be expected that treating clinicians will consider and ascertain that potential study participants have the capacity to give fully informed consent to enter into the trial. Should there be any degree of doubt, patients should not be recruited to the trial

5.10. *Discontinuation/withdrawal of participants*

5.10.1. Exiting the trial

Each participant has the right to withdraw at any time. If a participant wishes to withdraw, we will continue to analyse any data already collected, unless the participant expresses a wish for their data to be destroyed.

5.10.2. Exiting the trial because the primary endpoint, vision deterioration, has occurred

We expect that vision deterioration, as defined in **4.5.2**, will be the main reason for a patient to exit the trial. It should be noted that different criteria for vision deterioration apply during the first three months of the trial and subsequently (see **Figures 3a & 3b**).

5.10.3. Other reasons for exiting the trial

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.) It is not possible to list all circumstances in which this condition would be considered to be satisfied, but the criteria for vision deterioration and exit from the trial described at **4.5.2** are expected to cover most ocular-related reasons for withdrawal.

A clinician may wish to withdraw a participant from the trial if the participant experiences a significant systemic adverse event which the clinician believes would be likely to worsen or recur if treatment were to be continued.

5.11. *Frequency and duration of follow up*

Following the initial treatment of three monthly intravitreal injections of Avastin®, patients will return to the site for review visits every month or every two months (depending on randomised allocation) until their participation in the study ends (see **5.4**). No follow-up visits are planned after the end of the study.

5.12. *Likely rate of loss to follow-up*

This is a pragmatic trial where some loss to follow-up will be expected due the age of the population being studied. Losses would be of a similar magnitude to patients who withdraw from NHS treatment for nAMD. We would estimate that 10% would be lost from the trial each year, comprising of patients for whom other health concerns prevent them from attending, patients who die, and patients who no longer wish to continue treatment. Bias should not be introduced unless the loss to follow-up is differential across groups.

5.13. *Expenses*

Participants will not be reimbursed for any expenses because they are only attending for scheduled visits comparable to NHS treatment. Their entitlement to existing NHS benefits (such as hospital transport) will not be affected by participation in the trial.

5.14. *Measures taken to avoid bias*

Concealed randomisation will prevent selection bias.

The morphology of nAMD lesions at baseline will be assessed from fundus fluorescein angiograms (FFA) by experienced graders, masked to treatment allocation, working in an independent 'reading centre'.

With respect to masking, participants, clinicians and trial personnel will be masked to the dose of Avastin®, as described in section **5.1.2**. Allocation to monthly or two-monthly review intervals will also be masked up to 3 months but not thereafter.

Assessment of logMAR visual acuity, on which the primary outcome is based, 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. This will help to ensure that assessment of the primary endpoint is as objective as possible despite assessors and patients not being masked to allocation of review interval.

6. Statistical analyses

6.1. *Plan of analysis*

6.1.1. *Analyses of time to vision deterioration*

Analyses of time to vision deterioration, the primary 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 standard vs. low dose Avastin® and monthly vs. 2-monthly review. The interaction of Avastin® dose and review interval will be tested but will only be included in the final model if it reaches statistical significance ($p<0.05$). Susceptibility to differential informative censoring will be investigated. Conventional Cox regression implies that only one treated eye per patient will be used for the hypotheses of data independence. It is estimated that about 20% of patients could have both eyes treated, and the outcome in two eyes of one person will be inevitably correlated. If including both eyes in the conventional Cox regression analysis, the estimated treatment effects will be biased due to the violation of its hypothesis of independence of data. In this case multilevel proportional hazard model with random effects will be considered. This model treats outcomes of two eyes as repeated measures within patient and can estimate variation of between and within patient separately, hence to produce unbiased estimates of the main effects as mentioned above.

6.1.2. Analyses of logMAR visual acuity

Analyses of this outcome will be adjusted for baseline covariates using multilevel 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. In addition, the measure of two eyes for some patients can be included in the analysis with a random effect parameter to take into account the clustering effect in the outcome between two eyes. In this analysis, patients are level 3 units with eyes nested within patient, and visits nested within eye. Susceptibility to differential informative censoring will be investigated.

Analyses of this secondary outcome will include the entire study population and will estimate the main effects of standard vs. low dose Avastin® and monthly vs. 2-monthly review. The interaction of Avastin® dose and review interval will be tested but will only be included in the final model if it reaches statistical significance ($p<0.05$). Susceptibility to differential informative censoring will be investigated.

6.1.3. 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 Safety Committee (DMSC), and the DMSC will have the authority to request such a comparison at any time.

6.1.4. Description of adverse effect profiles in patients receiving treatment for one or both eyes

Potential adverse effects of treatment will be tabulated separately for groups of patients receiving treatment for one or both eyes, describing the number of events of different types within each category. The trial will not have adequate power to detect differences between groups 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 groups.

6.1.5. Description of the frequency and duration of treatment and review visits

Distributions of numbers of treatments and review visits in years 1 and 2 after starting treatment for a new episode of nAMD will be described; the average interval between visits (whether treatment or review) and treatments will be derived.

FFAs provide essential information on the morphology, severity and extent of disease at recruitment. Centres will be required to carry out FFAs at the time of recruitment and submit digital copies of images for independent assessment by the study reading centre. Skilled graders, masked to treatment allocation, will characterise the nAMD subtype and grade the extent and severity of disease according to standardised protocols.

6.2. *Subgroup analyses*

Formal subgroup analyses will be carried out for: (i) baseline visual acuity in study eye (≤44 vs. >44 letters read), (ii) baseline CNV size (≤4 vs >4 disc areas); (iii) nAMD lesion composition (classic no occult, classic and occult, occult no classic); (iv) participants receiving treatment for nAMD the first time and without extreme myopia or any ocular comorbidity (similar to participants in previous trials) vs. participants with reactivation of nAMD or extreme myopia or ocular comorbidity,

accepting that the latter group are heterogeneous. 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.

The subgroup analyses described above will be carried out for objectives I, II and VI.

6.3. *Frequency of analyses*

The primary analysis will be carried out when the target number of events has accrued, i.e. projected to be 3 years after starting recruitment.

6.4. *Criteria for the termination of the study*

The trial may be terminated early on the instruction of the DMSC, e.g. because the result of an interim analysis of the data from this trial or the results of another study indicate that continued participation in this study is unsafe or unnecessary.

6.5. *Economic issues*

The cost-effectiveness of the different treatment strategies using Avastin® is not of particular interest in this trial because the differences in cost will be small relative to the difference in cost between using Avastin® and Lucentis®. The cost of various regimens can be modelled at the end of the trial using existing data without the need for an economic evaluation alongside this trial.

7. Trial Management Group

The Trial Management Group (TMG) will be convened and meet regularly. This group will be in charge of the day-to-day running of the trial.

8. Trial Steering Committee

A trial steering committee (TSC) will be set up which will have overall supervision of the trial. It will meet (in person or by telephone conference) prior to commencement of the trial and then at regular intervals until completion. The steering committee and investigators are responsible for the conduct of the study. The trial will be conducted according to the Good Clinical Practice guidelines. A meeting of the TSC will be held within a month of every data management committee (DMC) meeting to consider their recommendations.

9. Data Monitoring Committee

An independent Data Monitoring Committee (DMC) will be established. The role of the DMC is to assess safety outcomes and efficacy outcomes during the trial. The DMC will receive safety reports every six months, or more frequently if requested. They will report their assessment to the chair of the TSC.

Collaborators, and all others associated with the trial, may write through the trial office to the DMC, to draw attention to any concern they may have about the trial interventions, or any other relevant issues.

10. Trial Monitoring

The trial will be monitored according to a prospectively agreed monitoring plan and using standard operating procedures in order to verify that (ICH GCP SECTION 5.18):

1. The rights and wellbeing of the human subjects are protected
2. The reported trial data are accurate, complete and verifiable from source documents
3. The conduct of the trial is in compliance with the approval protocol, with GCP and with applicable regulatory requirements.

Prior to commencement of enrolment, a site initiation meeting will take place to review the protocol and data collection procedures with key site staff. In addition, the monitor will contact the site to confirm that the necessary organisational preparations have been completed and that the personnel, technical and clinical facilities assigned to the trial are adequate.

The extent, nature and frequency of monitoring while the trial is on-going at the site will be based on such considerations as the study objective and/or endpoints, the purpose of the study, study design, complexity and enrolment rate. During these contacts the monitor will:

- Check the progress of the study
- Review the essential trial documentation, the study data and the Trial Master File
- Conduct source document verification
- Identify any issues and address their resolution

Following completion of the last patient's last visit a final monitoring contact will be arranged to close down the clinical study site.

All data collected on the CRFs must be verifiable against the source data. The Investigator and members of the study team shall ensure that all relevant data is recorded in the medical records.

The investigator agrees to allow the monitor direct access to all relevant documents and to allocate his/her time and the time of his/her staff to the monitor to discuss findings and any relevant issues.

11. Assessment of safety

All patients who receive at least an initial dose of Avastin will be considered evaluable for all safety analyses. The collection of safety data will continue throughout the trial and for 60 calendar days after the final dose of Avastin. This is regardless of whether the event is observed by the Investigator or reported by the patient during the study.

11.1. *Adverse Event Definitions*

11.1.1. Adverse Event

Any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An adverse event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of the medicinal (investigational) product, whether or not related to the medicinal (investigational) product. (For further reference see the ICH Guideline for Clinical Safety Data Management: Definitions and Standards for Expedited Reporting).

11.1.2. Adverse Reaction (AR)

Any untoward and unintended response to a medicinal product related to any dose where a causal relationship between a study medication and an AE is at least a reasonable possibility, i.e., the relationship cannot be ruled out.

All cases judged by either the reporting medically qualified professional or the sponsor as having a reasonable suspected causal relationship to the study medication qualify as adverse reactions.

11.1.3. Serious Adverse Events (SAEs)

A Serious Adverse Event (SAE) or reaction (SAR) is any untoward medical occurrence, regardless of dose, causality or expectedness, that:

- Results in death
- Is life-threatening*
- Requires in-patient hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect
- Other important medical event(s)**

*The term 'life-threatening' in the definition of 'serious' refers to an event in which the participant was at risk of death at the time of the event. It does not refer to an event that hypothetically might have caused death if it were more severe.

**Other events that may not result in death, are not life threatening, or do not require hospitalisation, may be considered a serious adverse event when, based upon appropriate medical judgment, the event may jeopardise the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

11.1.4 Expected Serious Adverse Events/Reactions

Expected adverse events/reactions that meet the definition of serious, identified in the current referenced safety information (SmPC Avastin 25mg/ml concentration for solution for infusion) , together with the expected events related to the mode of administration as follows:-

Mode of administration related events:
Cataract
Traumatic cataract
Endophthalmitis (sterile - includes Uvetitis/Vitritis)
Endophthalmitis (infective)
Infective Keratitis
Optic nerve damage
Optic neuropathy (any cause)
Retinal detachment
Retinal tear

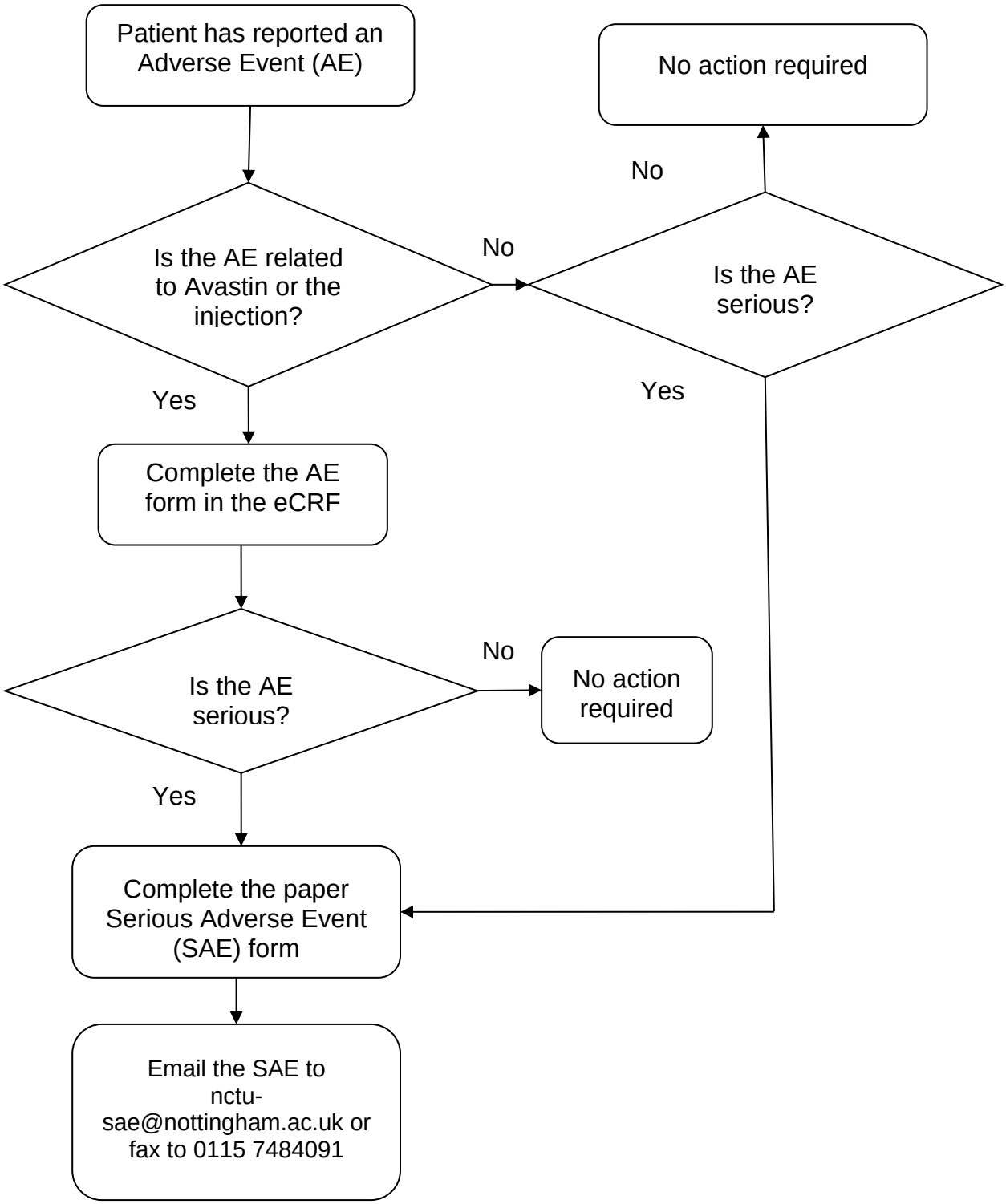
Retinal vein occlusion (branch or central)
Retinal artery occlusion (branch or central)
Venous stasis retinopathy
Vitreous haemorrhage
Glaucoma (any type)

NB: With the agreement of the Sponsor any cancer diagnosis will be reported as an initial SAE with no subsequent treatment related or disease progression hospital admissions being captured as a separate SAE or ongoing reporting.

11.1.5 Suspected Unexpected Serious Adverse Reactions (SUSARs)
A serious adverse reaction, the nature or severity of which is not consistent with the applicable current reference safety information or as defined above.

11.2. ***Adverse Event Reporting Flow Chart***

AE flow chart



11.3. *Adverse Event Reporting*

All possibly, probably or definitely related AEs occurring during the study observed by the investigator or reported by the participant, will be recorded on the eCRF.

The following information will be recorded: description, date of onset and end date, study treatment, assessment of seriousness and outcome. Follow -up information should be provided as necessary.

AEs considered related to the study medication as judged by a medically qualified investigator will be followed until resolution or the event is considered stable. All related AEs that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up for 60 days or resolution whichever is sooner.

It will be left to the investigator's clinical judgment whether or not an AE is of sufficient severity to require the participant's removal from treatment .A participant may also voluntarily withdraw from treatment due to what he or she perceives as an intolerable AE. If either of these occurs, the participant must undergo an end of study assessment and be given appropriate care under medical supervision until symptoms cease or the condition becomes stable.

Any pregnancy occurring during the clinical study and the outcome of the pregnancy should be recorded and followed up for congenital abnormality or birth defect.

11.2.1. Serious Adverse Event Reporting

All SAEs must be reported to Nottingham Clinical Trials Unit (NCTU) within 24 hours of discovery or notification of the event. As Sponsor R&D at NUH will report all SUSARs to the Competent Authorities MHRA and the Research Ethics Committee concerned. Fatal or life-threatening SUSARs must be reported within 7 days and all other SUSARs within 15 days. The CI will inform all investigators concerned of relevant information about SUSARs that could adversely affect the safety of participants.

All Serious AEs should be documented on the Sponsors Serious Adverse Event Report Form (SAE Report Form). These should be either:

- **emailed to** nctu-sae@nottingham.co.uk **or**
- **faxed to 0115 7484091 within 24 hours of site staff becoming aware of the event**

11.4. *Follow-up of all safety events*

Follow up, coordinated by the NCTU, will continue until all the necessary safety data for the event has been gathered and until the SAE has either resolved or stabilised. If new information on a previously reported SAE becomes available, the Investigator should report this to the Sponsor. In addition, the Sponsor may make requests for further information to the study site at regular intervals. Requested follow-up information should be reported in a timely manner and as soon as possible after receipt of the follow up request.

11.5. *Safety updates*

The Chief Investigator is responsible for ensuring that emerging new safety data is reviewed and communicated to the Sponsor, responsible oversight bodies and participating centres as appropriate. Local Investigators will review safety updates and ensure that the information is acted on and retained as instructed in accordance ICH-GCP practice and any local requirements.

11.6. *Annual Progress and Safety Update Reports (ASR and DSUR)*

The Chief Investigator is responsible for drafting Annual Progress and Safety Reports to the MHRA, REC, Sponsor and the R&D department of each participating Trust. The DSUR will be submitted to the applicable bodies by the Sponsor.

12. Ethical considerations

12.1. *Ethical review*

Ethical review of the protocol for the trial will be carried out by a UK NHS Research Ethics Committee (REC).

With respect to equipoise about the main research questions:

- Patients may elect to receive standard Lucentis® treatment under the NHS. The alternative will be treatment with Avastin® in the trial, offering the possibility of less frequent treatment and review. The widespread use of Avastin® internationally, and the finding of equivalence in the CATT trial, justifies the use of Avastin® in the trial. Studying a lower dose of Avastin® is justified because only a few small studies have investigated different doses. Although the standard dose of 1.25mg is effective, a lower dose may be equally effective and safer.
- 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 less frequent review (with criteria in

place for switching to monthly review in the event of an eye a losing vision, i.e. the primary outcome), and the possible benefits of less frequent review, justifies allocating participants to a review interval of one or two months.

We have consulted with patient support organisations. The Macular Disease Society is reviewing its policies in the view of the one-year results from the CATT trial but it has been and currently still is supportive of the trial. It is represented on the Trial Steering Committee.

12.2. *Risks and anticipated benefits*

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 benefit 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 nAMD in the trial. Possible adverse effects of any VEGF inhibitor treatment include:

- Local adverse effects: complications of intra-vitreal injection such as endophthalmitis, traumatic cataract and or retinal detachment.
- 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. Information about systemic adverse effects with intravitreal injection are described in **2.1**. We will be extremely vigilant for such adverse events.

12.3. *Informing potential study participants of possible benefits and known risks*

Information about possible benefits and risks of participation will be described in the PIS given (or read) to patients at the time they are approached to take part in the study. The PIS forms part of our application to a NHS REC and is written in consultation with advisors from the Macular Disease Society. We are confident that the trial design need not appear complex to patients and have drafted a PIS that explains in layman's terms details of the selection process, randomisation, treatment options, study duration and possible complications. Any new information which emerges through publication of other trial results will be updated within subsequent versions of the PIS and submitted through REC as amendments.

12.4. *Obtaining informed consent from participants*

All participants will be required to give written informed consent. This process, including the information about the trial given to patients in advance of recruitment, will be described in our application to a UK NHS REC for ethical approval. All patients will receive information about the trial at least one day before being asked to give informed consent.

13. Research governance

This study will be conducted in accordance with:

- The Medicine for Human Use (Clinical Trial) Regulations 2004
- International Conference for Harmonisation of Good Clinical Practice (ICH GCP) guidelines
- Research Governance Framework for Health and Social Care
- Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004).

13.1. *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
- Nottingham University Hospitals Trust has been declared as the sponsor for the trial.
- Obtain written informed consent from all participants
- Record and report serious and other adverse events in accordance with GCP (see 11 above)
- Obtain MHRA approval for the use of Avastin®
- Establish Trial Steering (TSC) and Data Monitoring and Safety Committees (DMSC)
- Comply with Good Clinical Practice (GCP)
- Audits will be carried out in line with Sponsor audit procedures and through a risk based assessment approach.

13.2. *Investigators' responsibilities*

Investigators will be required to ensure that research governance approvals have been obtained and contractual agreements have been signed off by all parties prior to the start of the study. Investigators will be required to ensure compliance to the protocol and completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor, the trial coordinating centre or any regulatory authorities.

13.3. *Monitoring by sponsor*

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework and the Medicines for Human Use (Clinical Trials) Regulations 2004. All study related documents will be made available on request for monitoring and audit by the sponsor or the Ethics Committee.

13.4. *Indemnity*

This is an NHS-sponsored research study. For NHS sponsored research HSG(96)48 reference No. 2 refers. If there is negligent harm during the clinical trial when the NHS body owes a duty of care to the person harmed, NHS Indemnity covers NHS staff, medical academic staff with honorary contracts, and those conducting the trial. NHS Indemnity does not offer no-fault compensation and is unable to agree in advance to pay compensation for non-negligent harm. Ex-gratia payments may be considered in the case of a claim.

14. Data protection and patient confidentiality

14.1. *Data protection*

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

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14.2. *Data storage*

Paper records will be retained by each recruiting hospital and form part of the patient's hospital record. Paper records should be retained for at least 5 years. After this time the policy for archiving paper records of the participating trust should be followed. In compliance with the MRC Policy on Data Preservation, we will also propose that the fully anonymised dataset, a separate secure electronic 'key' with a unique patient identifier, and relevant 'meta'-data about the trial be retained in electronic form indefinitely because of the potential for the raw data to be used subsequently for secondary research.

15. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

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17. Amendments to protocol

Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
1	29th June 2009	2	2nd July 2010	Amended sample size calculation which resulted in changes to the inclusion/exclusion criteria and sub group analysis. Additional expected ocular and non-ocular AEs/SAEs. Replacement of patient representative from the Macular Disease Society. The Sponsor will retain responsibility for the reporting of SUSARs to the authorities.	09th November 2010
2	2nd July 2010	3	25th February 2011	Changes are required to the protocol to include DNA testing for patients who are randomised to the study. Observational patients are being included in the study. Changes are also required to the initial application to the REC and MHRA on confidentiality	04th April 2011
3	25th February 2011	4	22nd September 2011	The background section has been updated with new scientific evidence. Changes have also been made to: - comply with Sponsor's template. - the description of eligibility and review of patients with respect to criteria of withdrawal from the trial. DNA testing for patients who are randomised to the study has been removed.	07th October 2011
4	22nd September 2011	5	30th March 2012	The protocol reflects the following changes: • Move from Bristol Coordinating Centre to Nottingham Clinical Trials Unit. • Removal of observational study	4th May 2012
5	30th March 2012	6	13th August 2013	Safety section updated following MHRA inspection visit of 30th July 2013. Change of statistician Update of DMC wording to reflect role and remit within the trial.	5th October 2013
6	13th August 2013	7	15th December 2014	Minor wording amendments made to: • 11.2.1 'SAE Reporting'- reporting timeframe	09 January 2015

				has been clarified. • 13.1 'Proposed actions to comply with 'The Medicines for Human Use (Clinical Trials) Regulations 2004': Update of wording to reflect Sponsor audit procedure • Addition of new references.	
7	15th December 2014	7.1	28th October 2015	Minor wording clarifications made to: • Protocol synopsis; study drug low dose weight amended • 4.3 Participating centres; PCTs amended to CCGs • 5.1.3 Unmasking Procedure now referenced Formatting applied throughout protocol	25th November 2015
8	25th November 2015	8.0		Removal of the interim analysis Update of the safety reporting information to reflect the transferring of Safety reporting from NUH (sponsor) to the NCTU	