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List of abbreviations

Acronym	Details
SAP	Statistical analysis plan
RCT	Randomised controlled trial
MI	Myocardial infarction
QoL	Quality of life
ITT	Intention to treat
CRF	Case report form
SD	Standard deviation
IQR	Inter quartile range
OR	Odds ratio
CI	Confidence interval
HR	Hazard ratio
MAR	Missing at random

Acronym	Details
SAE	Serious adverse event
MD	Mean difference
nAMD	neovascular age-related macular degeneration
CNV	Choroidal neovascularisation
RAP	Retinal Angiomatous Proliferation
LLIO	Late leakage of indeterminate origin
FPED	Fibrovascular pigment epithelial detachment
SPED	Serious detachment of the retinal pigment epithelium
logMAR	Log(minimum angle of resolution)
ETDRS	Early treatment of diabetic retinopathy study
VAlogMAR	Visual acuity, measured as the number of letters read on a standard ETDRS chart (testing at 4 metres initially and then at 1 metre if <20 letters are read at 4 metres; total letters read are scored 'as if' viewing at 1 metre).
BCVA	Best corrected VAlogMAR
VEGF	Vascular endothelial growth factor
FFA	Fundus fluorescein angiography
OCT	Optical coherence tomography
IOP	Intraocular pressure
Lucentis	Ranibizumab
Avastin	Bevacizumab
CATT	Comparison of age-related macular degeneration treatment trials
AIC	Akaike information criterion
DIC	Deviance information criterion
OHRB	Outer high reflectivity band
MedDRA	Medical Dictionary for Regulatory Activities
CCS	Canadian cardiovascular score
NYHA	New York heart association
MacDQoL	A measure of the impact of macular degeneration on quality of life
MacTSQ	A measure of treatment satisfaction in patients with macular degeneration

1. INTRODUCTION TO STATISTICAL ANALYSIS PLAN

1.1 Scope

This document details information regarding the statistical analysis of the IVAN trial and covers the formal 2 year analyses of trial data for primary publication. It does not include the health economic evaluation or additional analyses not listed in the study protocol.

1.2 Editorial changes

Any changes made to this statistical analysis plan (SAP) after approval must be clearly justified and documented as an amendment at the end of this document.

1.3 SAP document approval

The trial statistician should authorise this document.

1.4 Template tables and figures

Throughout this document references are made to any skeleton tables and figures to be used in the reporting of the trial (e.g. **Figure F1** or **Table T1**). Such tables and figures can be found in the appendix of this document, and are intended as a guide for study reporting. Final versions of the tables/figures may differ: tables may be combined, and/or their layout or numbering may differ. However the content should be consistent with the appendix**.**

2. STUDY OBJECTIVES

IVAN is a multi-centre double blind randomised controlled trial (RCT). Two alternative treatments to inhibit VEGF in wet or neovascular age-related macular degeneration (nAMD), Lucentis (ranibizumab) and Avastin (bevacizumab) are compared at two different treatment regimes. The two regimes are 2 years of continuous treatment versus a reduced treatment regimen. The trial follows a factorial design, with each patient being randomised to one of four drug/treatment frequency combinations (Table 1).

Table 1IVAN treatment combinations

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

The objectives are to (a) compare the clinical efficacy of the two drugs; (b) compare the reduced treatment regimen versus two years of continuous treatment; (c) describe the cost effectiveness of different drugs and treatment regimens; (d) describe both eye-related and systemic side effects with different drugs and treatment regimens.

It is hypothesised that

a) Avastin is not inferior to Lucentis with respect to the benefits of VEGF inhibition in maintaining /improving visual acuity in eyes with nAMD.

b) Treatment with VEGF inhibition can be 'safely' withdrawn at 3 months with monthly review to detect reactivation, i.e. criteria for re-starting treatment can be pre-specified to prevent any difference in average visual acuity compared with continuing monthly treatment.

It is not expected that Avastin will be more effective than Lucentis with respect to visual acuity.

2.1 Treatment schedule

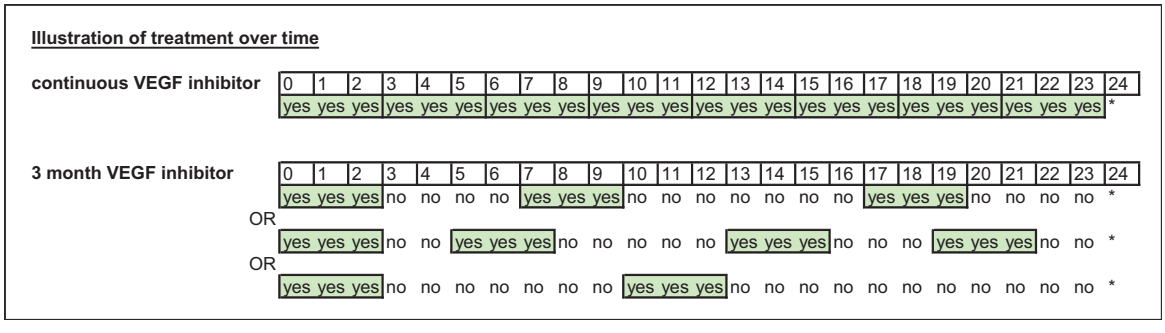
All patients receive a sequence of 3 injections at visits 0, 1, and 2. From visit 3 onwards the treatment schedule varies between patients randomised to continuous treatment and those randomised to stop treatment.

For patients randomised to continuous treatment, VEGF inhibitor is administered at each visit (from baseline, month 0, to month 23).

Patients randomised to stop treatment continue to attend on a monthly basis for assessment of their visual outcome, in exactly the same way as participants allocated to continue treatment. However, they do not receive treatment unless the clinician assessing lesion morphology (by clinical examination, OCT and FA) judges against pre-specified criteria (**see section 4.2**) that the lesion has reactivated and that treatment has failed.

Patients showing signs of reactivation in the discontinuous arm re-start treatment according to their original treatment allocation for a further 3 month cycle, and then stop treatment again (see Figure 1). The determination of treatment failure is also made for eyes within the continuous pathway in the same way.

Figure 1 Treatment over time in patients allocated to continue or stop treatment at 3 months



After 24 months, treatment will be stopped unless participants in a discontinuous arm are in the middle of a treatment cycle.

2.2 Follow-up schedule

Participants are followed monthly for 24 months from randomisation.

The minimum interval between visits is 28 days and the maximum is 35 days (excluding any unscheduled breaks in treatment).

2.3 *Primary outcome*

The primary outcome is the best corrected distance visual acuity (BCVA, ETRDS chart letters read [1]), measured 24 months after the start of treatment (visit 24). BCVA is also measured in the study eye at baseline before any treatment, and at every monthly visit.

2.4 *Secondary outcomes*

Secondary outcomes defined in the IVAN protocol are

a) Frequencies of adverse effects of treatment;
b) Generic health status and macular-disease specific quality of life;
c) Treatment satisfaction;
d) Cumulative resource use / cost, and cost-effectiveness;
e) Other clinical measures of vision;
f) Lesion morphology (from masked grading of FFAs and OCTs);
g) Survival free from treatment failure (i.e. satisfying one or more of the criteria for retreatment)

Clinical measures of vision comprise: contrast sensitivity (CS), near visual acuity and the reading index (words read per minute/size of print). Lesion morphology and metrics include lesion area, presence of fluid, total thickness at the fovea, and retinal plus subfoveal fluid thickness.

3. STUDY POPULATION

The study population is patients aged 50+ years, newly referred for the treatment of nAMD in the first or second eye, with BCVA ≥25 letters read on a standard ETDRS chart. Participants must have a component of the neovascular lesion involving the centre of the fovea.

Exclusion criteria include patients with long standing CNV (fibrosis >50% of the total lesion), a greatest linear diameter >6000μm, thick blood involving the centre of the fovea, 8 or more dioptres of myopia or other active ocular disease causing concurrent vision loss. Previous treatment (argon laser within 6 months, VPDT or a VEGF inhibitor to the study eye) was also an exclusion criterion.

This analysis will include all randomised patients who received at least one treatment injection. A flowchart of patient recruitment and progress through the trial will be presented (see **Figure F1**).

3.1 Randomisation

Randomisation is stratified by centre. Randomisation to both drug and treatment frequency occurs at recruitment, but the frequency (continuous or discontinuous) allocation is not revealed until the patient attends at 3 months.

3.2 Protocol breaches

We consider nine main protocol breaches:

- Patient received the alternative drug treatment to that allocated on at least one occasion
- Patient received alternative treatment regimen to that allocated
- Patient did not meet the trial eligibility criteria but was treated in the trial

- Patient was mid-way through a cycle of treatment (discontinuous group) or was in the continuous group, and attended the clinic but treatment was not given.
- The patient was allocated to the discontinuous arm: treatment was restarted but the criteria for retreatment were not met
- The patient was allocated to the discontinuous arm: treatment was not restarted but the criteria for retreatment were met
- The patient was allocated to the discontinuous arm: treatment was extended beyond the 3-months but the criteria for retreatment were either not assessed or not met at the visit(s) beyond the 3 months
- Time between two consecutive visits was < 28 days or >35 days
- Missed visits (prior to trial exit)

The frequency of each type of breach will be described by group (**Table T1**) and full details (along with reasons) of each protocol breach will also be described (**T2**). This will allow for the identification of any imbalances in protocol breach by group.

3.3 Flow of participants

The study population will be described via a flowchart, see **Figure F1**.

3.4 Withdrawals

A patient (or a clinician on the patient's behalf) can withdraw from the trial at any time. In some cases patients may be happy for some follow-up to continue. Data on all withdrawals is captured on a specific case report form (CRF), and will be presented in table form (grouped by reason and treatment allocation); see **Table T3**.

3.5 Analysis groups

The analysis population consists of all randomised patients excluding:

- Patients who were not treated
- Patients who withdrew (or were withdrawn) and who are unwilling for data collected to be used

This is illustrated in **Figure F1**. The analysis of the primary outcome will be performed on the basis of the treatment allocation, which is consistent with the analysis of the CATT trial [2, 3]. For the interim analysis we intended to include adjustment for the amount treatment received, as a sensitivity analysis, to reflect the CONSORT guidelines for the reporting of non-inferiority hypotheses which suggest that non-inferiority comparisons on the basis of treatment allocation can increase the type I error [4]. However, preliminary examination of the data indicated that including this additional covariate provided un-interpretable treatment estimates. We will therefore also exclude it from all analyses of the 2 year data.

3.6 Safety population

The safety population is the same as the analysis population for the IVAN trial. Reporting guidelines recommend that safety data is analysed by the treatment received [5]. As IVAN is a

masked trial with respect to drug allocation, the drug treatment received should equal the treatment allocated. If the drug received differs by visit (i.e. the wrong treatment was given on one or more occasions) the patient will be grouped according to the drug received with greatest frequency. Grouping patients according to the amount of treatment received is less straightforward. For consistency of reporting (see section 4.5), patients will be grouped according to the treatment frequency allocated.

4. IVAN DATA COLLECTION

Data for IVAN is collected at each planned visit from months 0 to 24, at any additional unplanned visit because of an adverse event, and if a patient exits the trial. Table 2 summarises the data collected at each visit. Quality of life data (EQ-5D and HUI3) are also collected when an SAE occurs.

4.1 Main study visits

The primary outcome BCVA in the study eye was recorded at all visits. For modelling purposes, visits 0, 3, 6, 9, 12, 15, 18, 21 and 24 will be used as 'main study visits' for BCVA and data from other visits will only be used if data from the previous main study visit is missing. All other visual outcomes are only collected at visits 0, 3, 6, 12, 18 and 24 so these are the 'main study visits' for these variables. As with BCVA, if main visits were missed and data was collected at the following visit, this data will be used instead.

4.2 Deferred visits

Deferred visits are those where visual outcome data is collected but the visit is not a 'main study visit'. This usually occurs when the previous main study visit was missed. If this is the case, data from a deferred visit may be used in place of a main study visit. See sections 5.1 and 5.2 for details of how deferred visit data will be used.

Table 2 Schedule of data collection

Treatment / Assessment	**Follow-up Month / Visit number**												
	0	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Demography	✓												
Height	✓												
Weight	✓			✓			✓			✓			✓
Past medical history	✓												
Cardiovascular symptoms (CCS, NYHA, ankle swelling/HF)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood pressure	✓			✓			✓			✓			✓
Binocular acuity	✓			✓			✓			✓			✓
Refraction (sphere, cylinder, axis)	✓	✓*	✓*	✓	✓*	✓*	✓	✓*	✓*	✓*	✓*	✓*	✓
Distance BCVA (letters read)[1]	✓ B	✓ S	✓ S	✓ B	✓ S	✓ S	✓ B	✓ S	✓ S	✓ S	✓ S	✓ S	✓ B
Near VA (logMAR) [1]	✓ B			✓ B			✓ B						✓ B
Reading index (words/minute/print size) [1]	✓ B			✓ B			✓ B						✓ B
Contrast sensitivity (letters) [1]	✓ B			✓ B			✓ B						✓ B
Imaging (OCT, photos)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Imaging (FFA)	✓			✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓
Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ocular history	✓												
Ocular exam (IOP, slit lamp, cataract grading, posterior segment abnormalities)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Ocular exam (anterior segment, lens)	✓												
Eligibility for IVAN	✓												

Serum sample	✓	✓										✓	✓
Blood sample (genetics)	✓												
Injection (date, see CF, IOP, antibiotics)	✓	✓	✓	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**
Adverse reaction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Stopping rules/re-treatment criteria				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
EQ-5D	✓			✓									✓
HUI-3	✓			✓									✓
MacDQoL				✓									✓
MacTSQ				✓									✓
Ocular symptoms		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Non-ocular symptoms		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Travel arrangements		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Masking				✓									✓
Reasons for withdrawal				✓									✓

Treatment / Assessment	**Follow-up Month / Visit number**												
	13	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**	**Exit**
Demography													
Height													
Weight			✓			✓			✓			✓	✓#
Past medical history													
Cardiovascular symptoms (CCS, NYHA, ankle swelling/HF)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓#

Blood pressure			✓			✓			✓			✓	✓#
Binocular acuity						✓						✓	✓#
Refraction (sphere, cylinder, axis)	✓*	✓*	✓*	✓*	✓*	✓	✓*	✓*	✓*	✓*	✓*	✓	✓#
Distance BCVA (letters read) [1]	✓ S	✓ S	✓ S	✓ S	✓ S	✓ B	✓ S	✓ S	✓ S	✓ S	✓ S	✓ B	✓# B
Near VA (logMAR) [1]						✓ B						✓ B	✓# B
Reading index (words/minute/print size) [1]						✓ B						✓ B	✓# B
Contrast sensitivity (letters) [1]						✓ B						✓ B	✓# B
Imaging (OCT, photos)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓#
Imaging (FFA)	✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓~	✓	✓#
Medications	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓#
Ocular history													
Ocular exam (IOP, slit lamp, cataract grading, posterior segment abnormalities)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓#
Ocular exam (anterior segment, lens)													
Eligibility for IVAN													
Serum sample											✓	✓	
Blood sample (genetics)													
Injection (date, see CF, IOP, antibiotics)	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**	✓**		
Adverse reaction	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Adverse events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓#
Stopping rules/re-treatment criteria	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓#
EQ-5D^												✓	
HUI-3^												✓	
MacDQoL												✓	

MacTSQ												✓	
Ocular symptoms – use if medical services	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓[#]
Non-ocular symptoms – use if medical services	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓[#]
Travel arrangements	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓[#]
Masking													
Reasons for withdrawal													

[1] If visit 3, 6, 9, 12, 18 or 24 is missed the full assessment is completed at the next visit attended

S=Study eye, B=Both eyes

***** Copied forward from visit 0, 3, 6, 12 or 18 unless tests needs to be re-performed

[~] Only done if required for treatment failure criteria

****** For patients in the discontinuous arm, only carried out if patient meets treatment failure criteria or is part of a cycle of three treatments

[#] Only carried out if patient physically attended the exit visit

^ Also completed when SAEs occur

5. DERIVATIONS

5.1 Primary outcome

The primary outcome is the distance BCVA (letters read) in the study eye.

If, at any assessment, no letters can be read the following scoring will be applied:

	Value assigned
Counting fingers (CF)	0
Hand movements (HM)	-15
Perception of light (PL)	-30

A value of zero equates to no letters read at 1 metre. The other values (which equate to a doubling of the visual angle) are chosen to allow the assignment of arbitrary points in deteriorating visual function to these categories.

For modelling purposes, if distance BCVA is not recorded at the intermediate main study visits (i.e. visits 3, 6, 9, 12, 15, 18, 21), but is measured at the following visit (i.e. visit 4, 7, 10 etc.), the main study visit missing value(s) will be imputed using the 'deferred visit' value(s). If distance BCVA is missing for both the main study visit and the following visit, the data will be considered missing. Patients with BCVA measured on at least one of the main study visits 0, 3, 6, 9, 12, 15, 18, 21 or 24, will be included in the analysis.

5.2 Secondary outcomes

For modelling purposes, if secondary outcome measures are not recorded at the intermediate main study visits (i.e. visits 3, 6, 12, 18), but are measured at the following visits, the main study visit missing value(s) will be imputed using the 'deferred visit' value(s). If both the main study visit data and the following visit data are missing, the data will be considered missing. Patients with outcome measures for at least one of the main study visits 0, 3, 6, 12, 18, or 24, will be included in the analysis.

5.2.1 Visual outcomes

The relationships between different measures of visual function will be examined and any apparent outliers identified. These will be discussed with the study clinician (maintaining the study blinding) to determine whether the values observed are plausible. Zero values for BCVA, contrast sensitivity, words read or Belfast reading index will also be investigated. Implausible values will be considered missing.

5.2.1.1 Belfast reading index

The Belfast chart used to assess reading ability depends on the patient's near vision (logMAR value). Any instances where the incorrect chart size has been used will be investigated. A chart of 1 size larger or smaller than the correct size will be accepted (see Table below). A chart two or more

sizes larger or smaller than the correct size will be treated as missing data, and the reading index will not be calculated.

LogMAR	Chart sizes used that will be treated as accurate data (N units)
0	2, 2.5, 3
0.1	2.5, 3, 4
0.2	3, 4, 5
0.3	4, 5, 6
0.4	5, 6, 8
0.5	6, 8, 10
0.6	8, 10, 12
0.7	10, 12, 16
0.8	12, 16, 20
0.9	16, 20, 25
1.0	20, 25, 32
1.1	25, 32, 40
1.2	32, 40, 50
1.3	40, 50, 63
1.4	50, 63, 80
1.5	63, 80
1.6	80

Patients with LogMAR of 1.6 may not have their reading ability measured as their vision is too poor. If there are any non-missing values of reading index for those with LogMAR of 1.6, the distribution of these will be investigated, and missing values will be imputed. The method of imputation will be guided by the observed distribution.

In order to calculate the Belfast reading index, the data collected on the IVAN CRF (in N units) needs to be mapped to a new measurement scale (M units). The mapping to be applied is shown in the table below.

Chart size (N units)	Chart size for calculation (M units)
2	0.25
2.5	0.32
3	0.40
4	0.50
5	0.63
6	0.80
8	1.00
10	1.25
12	1.60
16	2.00
20	2.50
25	3.20
32	4.00
40	5.00
50	6.30
63	8.00
80	10.00

5.2.2 Additional secondary outcomes

Details for deriving any secondary outcome variables are given below:

New variable	Rules
Dye leakage on angiogram	(Using FA variables) If CNV present=yes; then = Yes If CNV present=no; then = No If CNV present=cant grade; then = can't grade Else missing
Fluid on OCT	(Using OCT variables) If OHRB SRF present OR Intra retinal cycts present; then = Yes If OHRB SRF not present AND Intra retinal cycts not present; then = No Else if OHRB SRF = cant grade or Intra retinal cycts = cant grade; then = can't grade Otherwise – Data missing
Lesion area	(Using FA variables) = Classic CNV + occult FPED + occult LLIO + RAP + blocked fluorescence + SPED

New variable	Rules
Total thickness at fovea	(Using OCT variables) =(neuroretinal foveal thickness + OHRB thickness at fovea + PED thickness at fovea + SRF thickness at fovea) * 1000
Retinal thickness plus subfoveal fluid thickness	(Using OCT variables) = (neuroretinal foveal thickness + SRF thickness at fovea)* 1000
Any new GA	If DeNovo GA at final visit = yes OR (GA within lesion at final visit = yes AND EITHER 1) GA in study eye at baseline = no OR 2) GA in study eye at baseline = yes AND GA location at baseline IS NOT within lesion; then = Yes If DeNovo GA in study eye at final visit = no or n/a AND GA within lesion in study eye at final visit = no or n/a; then = No Else missing

5.3 Safety outcomes

Safety data is collected at each visit. In collating the safety data the following rules will be applied:

- Systemic serious adverse events (SAEs) will be grouped as per the CATT trial.
- Adverse events will be grouped using the MedDRA classification system. For non-ocular events the MedDRA general term will be reported. For ocular events the preferred term will be used.
- Traumatic cataract[1] and wound evisceration (in the eye), map to the MedDRA general term "Injury, poisoning and procedural complications", and endophthalmitis and herpes (in the eye) map to MedDRA general term "infection". For the purposes of IVAN (and to allow appropriate identification of ocular SAEs) these events will be re-mapped to the general term "Eye disorders"
- The MedDRA preferred term will be used to describe both ocular and non-ocular treatment-related serious adverse events.
- Non–serious adverse events will not be reported in the primary publication but will be included in the report to the funder.
- Dates of onset and resolution of events will be interrogated to minimise the chance of an event being counted more than once.
- If the onset date is missing or incomplete then the following rules will be applied

[1] defined in the IVAN protocol as an SAE

Occurrence	Rules
First (either not reported previously, or previous occurrence is resolved)	If 1) onset date = missing OR 2) onset day = missing AND onset month = missing AND onset year = year form completed OR 3) onset day = missing AND onset month = month form completed AND onset year =year form completed); then onset date = date form completed If onset day = missing AND onset month = missing AND onset year ≠ year form completed AND onset year = year form completed for previous visit attended; then onset day = 31 and onset month = 12 If onset day = missing AND onset month = month form completed -1 AND onset year = year form completed; then onset day = 31 If onset day = missing AND onset month = 12 AND month form completed = 1 AND onset year = year form completed -1; then onset day = 31 Otherwise = data query
Second or subsequent report of an on-going event	Onset date = date assigned for first report of the event as per rules outlined above

- All serious adverse events including those reported at an unplanned visit or exit visit will be included.
- A drop of 15+ letters in BCVA between 2 consecutive visits attended (i.e. current visit = previous visit + 1) with no associated cause, determined from the BCVA at each visit, will not be reported as an SAE. Any drop in VA reported explicitly as an SAE will be excluded**.**
- A change in 2+ CCS or NYHA categories between 2 consecutive visits attended (i.e. current visit = previous visit + 1) not resulting in hospitalisation will not be reported as an SAE. Worsening angina not resulting in hospitalisation reported explicitly as an SAE will be excluded.
- For the interim analysis, adverse event data was interrogated to determine if any ocular SAEs (as defined in the IVAN protocol) were recorded as adverse events. For the final 2 year analysis, identification of unreported SAEs will be determined through on-site monitoring visits prior to the database lock. Therefore, further interrogation of the adverse event data will not be required for the 2 year analysis.

Details for deriving serious adverse event variables are given below:

New variable	Rules
Time to death (days)	If death = yes and date of resolution ≠ missing; then = Date of resolution – randomisation date If death = yes and date of resolution = missing; then = Date of onset – randomisation date Otherwise = missing
Time to death event indicator variable	If death = yes; then = Yes Otherwise = No
Death from vascular causes	If death = yes and cause of death = MI, stroke or cardiac arrest; then = Yes Otherwise = No
Venous thrombotic event	If PE or DVT = yes OR (free text leading to MedDRA preferred term = pulmonary embolism OR deep vein thrombosis) then = Yes Otherwise = No
Primary safety endpoint (IVAN protocol)	If MI = yes OR stroke = yes OR death from vascular cause = yes OR heart failure = yes OR (free text leading to MedDRA preferred term = myocardial infarction OR stroke OR heart failure) then = Yes Otherwise = No
Systemic serious adverse event	If SAE is classified into one of the MedDRA system organ classes (excluding eye disorders); then = Yes Otherwise = No
Ocular serious adverse event	If SAE MedDRA system organ class = eye disorders; then = Yes Otherwise = No
Any serious adverse event	If systemic SAE = yes OR ocular SAE = yes; then = Yes Otherwise = No
SAE maximum intensity	Maximum of intensity variable on all reports of an ongoing event (spanning >1 visit) ever classified as an SAE (excluding a drop in BCVA without an associated cause or worsening angina not resulting in hospitalisation)
SAE relatedness	Maximum (worst case scenario) of relatedness variable on all reports of an ongoing event (spanning >1 visit) ever classified as an SAE (excluding a drop in BCVA without an associated cause or worsening angina not resulting in hospitalisation)

5.4 Treatment failure

A patient allocated to discontinuous treatment arm of the trial should be treated when they are eligible for treatment and the treatment failure criteria are met.

The treatment failure criteria are NOT assessed when the patient is part way through a cycle of three treatments (patients allocated to discontinuous treatment) or if the failure criteria were met at either of the last two visits attended (patient allocated to continuous treatment).

Component	Rules
Eligible for assessment of treatment failure	Met treatment failure criteria at the previous visit (i.e. current visit -1) = No AND Met treatment failure criteria at (current visit – 2) = No; then = Yes Otherwise = No
Treatment failure	If currently in a 3 month cycle of treatment (question A) = No AND [(OCT evidence of sub-retinal fluid in the study eye (question B1) = Yes **OR** OCT evidence of an increase in intra-retinal fluid in the study eye (question B2) = Yes **OR** Fresh blood in the lesion in the study eye (question B3) = Yes)]; then = Yes Else if question A = No AND question B1 = No or not sure AND question B2 = No or not sure AND question B3 = No or not sure AND OCT evidence of persistent intra-retinal fluid in the study eye (question C1) = Yes AND VA dropped by ≥10 letters over the last 3 months (question C2) = Yes; then = Yes Else if question A = No AND question B1 = No or not sure AND question B2 = No or not sure AND question B3 = No or not sure AND (question C1 = Not sure **OR** question C2 = Not sure) AND

Component	Rules
	[(evidence of extension of the CNV (question D1) = Yes **OR** leakage from >25% of the circumference of the CNV (question D2) = Yes)]; then = Yes Else if question A = No AND question B1 = No or not sure AND question B2 = No or not sure AND question B3 = No or not sure AND [(question C1 = No AND question C2 = No) **OR** (question C1 = Yes AND question C2 = No) **OR** (question C1 = No AND question C2 = Yes)]; then = No Else if question A = No AND question B1 = No or not sure AND question B2 = No or not sure AND question B3 = No or not sure AND (question C1 = Not sure **OR** question C2 = Not sure) AND question D1 = No AND question D2 = No; then = No If visit number = 0, 1 or 2 **OR** question A is Yes; then = N/A
Failure visit	= visit at which treatment failure = yes
Visit at which first failure occurs	= minimum(visit number) if treatment failure = yes = missing if patient never failed
Treatment failure date	= injection date if injection date ≠ missing & visit number = visit at which failure first occurs = injection form date if injection date = missing & visit number = visit at which failure first occurs = visual assessment form date if injection date = missing & injection form date = missing & visit number = visit at which failure first occurs = missing if patient never failed

Component	Rules
Time to treatment failure (days)	If visit at which first failure occurs ≠ missing; then = Treatment failure date – randomisation date Otherwise = Last attended visit date – randomisation date
Time to treatment failure event indicator variable	If treatment failure date ≠ missing; then = Yes Otherwise = No

5.5 Quality of life questionnaires

5.5.1 EQ-5D

A five digit 'state score' will be derived from the mobility, self-care, usual activities, pain/discomfort and anxiety/depression scores as follows:

State = 10000*mobility score + 1000*self-care score + 100*usual activities score + 10*pain/discomfort score + anxiety/depression score

Each five digit state will then be assigned a single summary index score according to standard scales. These index scores are numerical and range from -0.59 to 1.00, with a score of 1.00 denoting perfect health. If any of the five components of the state score is missing, the overall score will be missing.

Visual analogue scales are also collected. Such scores range from 0 to 100 (with higher scores denoting higher QoL).

5.5.2 MacDQoL

An average weighted impact score will be calculated as follows:

New variable	Rules
Weighted impact scores (for each question)	Impact rating (-3 to 1) * importance rating (0 to 3) Possible range from -9 (maximum negative impact of MD on QoL) to +3 (maximum positive impact of MD on QoL)
Average weighted impact (AWI) score (to be calculated from all domains except 'work)	(sum of weighted impact scores) / (number of applicable domains) Note AWI can be calculated providing at least 11 items have complete responses. If less than 11 items have been answered AWI is missing (based on Cronbach's alpha calculation).

5.5.3 MacTSQ

Three summary measures will be calculated as follows:

New variable	Rules
Subscale 1 (information provision and convenience)	Contains questions 1, 10b, 11, 13, 14, and 15. Each question is scored 0 (not satisfied) to 6 (very satisfied), and are summed to give a subscale score of 0 to 36 where higher scores

New variable	Rules
	reflect greater satisfaction. Note: If the answer to any of the six questions are missing, then subscale 1 = missing.
Subscale 2 (Impact of treatment)	Contains questions 2, 3, 4, 5, 6, and 9. Each question is scored 0 to 6, and are summed to give a subscale score of 0 to 36 where higher scores reflect greater satisfaction. Note: if the answer to one of the six questions is missing, we will use the summation of the other values. If answers to more than one question are missing then subscale 2 = missing (based on Cronbach's alpha calculation).
Single scale	The 12 items from subscales 1 and to can be added together to produce a single scale from 0 to 72. The higher the score, the greater the satisfaction. Note: if answers to three or less of the twelve questions are missing, we will still use the summation of the other values. If answers to more than three question are missing then single scale= missing (based on Cronbach's alpha calculation).

5.6 Other variables

Details for any other variables which will be derived for use in any other figures or tables are given below:

New variable	Rules
Injection given	If date of injection ≠ missing; then= Yes
Reason for exclusion from trial	If any eligibility criteria not met = Ineligible If all eligibility criteria met, but patient did not consent = Did not consent Otherwise = Other
Protocol breach type 1 – patient didn't receive allocated drug	If identified in a "note to file" outside the database; then = Yes Otherwise = No
Protocol breach type 2 – patient didn't receive allocated regimen	Identified by looking at patients in the discontinuous arm whose injection rate at attended visits >0.9, and continuous patients whose injection rate at attended visits <0.9. Retreatment criteria studied for these patients to identify genuine breaches.
Protocol breach type 3 – patient ineligible but treated	If either: 1) age <50 years OR 2) VA at visit 0 <25 letters AND injection given at visit 0 OR 3) exudative AMD not present ; then = Yes Otherwise = No

New variable	Rules
Protocol breach type 4 – attended the clinic but treatment was not given	If missed visit ≠ yes AND current visit < 3 AND date of injection = missing AND clinical assessment of risk>benefit ≠ yes; then = Yes If missed visit ≠ yes AND current visit ≥ 3 and allocation = continuous AND date of injection = missing AND clinical assessment of risk>benefit ≠ yes; then = Yes If missed visit ≠ yes AND current visit ≥ 3 and date of injection = missing AND allocation = discontinuous AND cycle number* ≠ missing AND clinical assessment of risk>benefit ≠ yes; then = Yes Otherwise = No Note: if a patient missed all 3 injections of a cycle, this is treated as a protocol breach type 6 and not type 4. * Cycle number is derived as follows: If allocation = discontinuous and current visit ≥ 3 AND missed visit ≠ yes AND treatment failure = yes AND date of injection ≠ missing; then = 1 If allocation = discontinuous and current visit ≥ 3 AND treatment failure at previous visit = yes AND [(failure visit = previous visit number AND missed visit ≠ yes) **OR** missed visit = yes]; then = 2 If allocation = discontinuous and current visit ≥ 3 AND treatment failure at current visit number – 2 = yes AND [(failure visit = current visit number - 2 AND missed visit ≠ yes) **OR** missed visit = yes]; then = 3
Protocol breach type 5 – Treatment was restarted but the criteria for retreatment were not met	If date of injection ≠ missing AND current visit ≥ 3 AND allocation = discontinuous AND eligible for assessment of treatment failure = yes AND treatment failure = no AND protocol deviation type 2 ≠ yes; then = Yes Otherwise = No Note: if treatment was restarted following a complete cycle of three but no further injections for that cycle were given, this will be treated as protocol breach type 7.
Protocol breach type 6 – Treatment was not restarted but the criteria for retreatment were met	If missed visit ≠ yes AND current visit ≥ 3 and date of injection = missing AND allocation = discontinuous and eligible for assessment of treatment failure = yes AND treatment failure = yes; then = Yes Otherwise = No

New variable	Rules
	Note: if the first injection of a cycle of 3 was missed but the following 2 injections were given, this will be treated as protocol breach type 4 and not type 6.
Protocol breach type 7 – treatment cycle extended beyond 3 months	If missed visit ≠ yes AND current visit ≥ 3 and date of injection ≠ missing AND allocation = discontinuous AND (treatment failure not assessed OR treatment failure= no) AND patient failed at current visit number - 3; then = Yes Otherwise = No Note: If the additional treatment was taken to be the first of a cycle at the following two visits, this will be treated as a protocol breach type 5 and not type 7.

Protocol breach type 8 – time between consecutive visits outside range	If (current visit injection date form completed (dfc) – previous visit injection dfc) < 28 days AND current visit = previous visit + 1; then = Yes
	If (current visit injection dfc – previous visit injection dfc) > 35 days AND current visit = previous visit + 1; then = Yes
	Otherwise = No

Protocol breach type 9 – missed visit	If missed visit = yes; then = Yes Otherwise = No
Last attended visit (LTV) date	For the interim 1 year analysis, exit dates were calculated and used to identify patients who exited the trial before the 12 month cut off. For the final 2 year analysis, the calculation will be revised and the exit date will be replaced by 'last attended visit date'. The reason for the change is that this will allow us to calculate a date for all patients, including those who have died and those who completed the study The exit date used in the interim analysis will not be calculated as all study data will be included so we will not need an exact date to determine whether withdrawals were prior to the 12 month time point. If a patient withdrew and attended an exit visit AND exit date form completed ≤105 days* after last attended study visit; then LTV date = exit date form completed If patient withdrew and did not attend exit visit OR patient withdrew and date form completed for exit visit >105 days after last attended study visit OR patient died OR patient did not withdraw from the study; then LTV date = date form completed of visual assessment

New variable	Rules
	form of last attended study visit * A cut-off of 105 days has been chosen to identify patients who have exit form for an attended visit completed instead of an exit form for absent patients.
Withdrawal indicator	If exit form completed OR exit form for absent patient completed; then = Yes Orherwise = No Note: if an exit was due to death then this will be reported as an SAE of death not as a withdrawal
Time of withdrawal (months)	= (Last attended visit date – randomisation date) * 12/365.25
Age	= (Randomisation date – DOB)/365.25
Non-white race	If race = white; then = No If race = missing; then = Missing Otherwise = Yes
Systolic BP	If 1 reading is done (contrary to protocol); then = SBP_1 If 2 readings are done; then = $(SBP_1 + SBP_2)/2$ If 3 readings done, take the mean of the two closest readings, i.e. order readings so that $SBP_1 \leq SBP_2 \leq SBP_3$. If $(SPB_2 - SPB_1) < (SPB_3 - SPB_2)$ then = $(SBP_1 + SBP_2)/2$ Otherwise $(SBP_2 + SBP_3)/2$
Diastolic BP	If 1 reading is done (contrary to protocol); then = DBP_1 If 2 readings are done; then $(DBP_1 + DBP_2)/2$ If 3 readings done, take the mean of the two closest readings, i.e. order readings so that $DBP_1 \leq DBP_2 \leq DBP_3$. If $(DPB_2 - DPB_1) < (DPB_3 - DPB_2)$ then = $(DBP_1 + DBP_2)/2$ Otherwise $(DBP_2 + DBP_3)/2$
Angina pain	If ever had angina = yes; then = Yes If ever had angina = no; then = No Otherwise = Missing
Dyspnoea	If NYHA = 0; then = No If NYHA =1, 2,3 or 4 = Yes
Number of treatments received	= number of injections given on visits 0 to 23
Drop of 15+ letters in BCVA	If (BCVA at previous visit – BCVA at current visit) ≥ 15 AND current visit number – previous visit number = 1; then = Yes Otherwise = No
Worsening angina	If (CCS class at previous visit – CCS class at current visit) ≥ 2 AND current visit number- previous visit number =1; then = Yes

New variable	Rules
	Otherwise = No
Deferred visit indicator	If data is from a deferred visit; then = Yes
	Otherwise = missing
Choroidal neovascularisation	(Using FA variables)
	If (classic CNV present AND classic CNV location = subfoveal) OR (occult FPED present AND occult FPED location = subfoveal) OR (occult LLIO present AND occult LLIO location = subfoveal) OR (RAP present AND RAP location = subfoveal); then = Yes
	Else if CNV present=yes/no AND FPED present=yes/no AND LLIO present=yes/no AND RAP present=yes/no; then = No
	Otherwise = missing
Haemorrhage	(Using Col variables)
	If (classic sub retinal blood present AND sub retinal blood location = (subfoveal or juxtafoveal)) OR (sub RPE blood present AND sub RPE location = (subfoveal or juxtafoveal)) OR (intra retinal blood present AND intra retinal blood location = (subfoveal or juxtafoveal)); then = Yes
	Else if sub retinal blood present=yes/no AND sub RPE blood present=yes/no AND intra retinal blood present=yes/no; then = No
	Otherwise = missing
Other foveal centre involvement	(Using FA variables)
	If (SPED present AND SPED location = subfoveal) OR (fibrosis present AND fibrosis location = subfoveal); then = Yes
	Else if SPED present=yes/no AND fibrosis present=yes/no; then= No
	Otherwise = missing
No choroidal neovascularisation or can't grade	(Using FA variables)
	If exudative AMD present = No OR exudative AMD = can't grade; then = Yes
	If exudative AMD present = Yes; then = No
	Otherwise = missing
Area of active neovascularisation	(Using FA variables)
	= area of classic CNV + area of occult FPED CNV + area of occult LLIO CNV + area of RAP
	= Missing if any of the above components are missing
Blood present	(Using COL variables)
	If intra-retinal blood = yes OR sub-retinal blood = yes OR sub-RPE = yes; then = Yes
	If intra-retinal blood = no AND sub-retinal blood = no AND sub-RPE

New variable	Rules
	blood = no; then = No
	Otherwise = missing
RPE tear	If RPE tear/Rip (from FA) = yes OR RPE tear (from Col) = yes OR OHRB discontinuous due to RPE tear (from OCT) = yes; then = Yes
	If RPE tear/Rip (from FA) = no AND RPE tear (from Col) = no AND OHRB discontinuous due to RPE tear (from OCT) = no; then = No
	Otherwise = missing
Fibrosis	If Fibrosis/atrophic scar (from Col) = yes OR Fibrosis (from FA) = yes; then = Yes
	If Fibrosis/atrophic scar (from Col) = no AND Fibrosis (from FA) = no; then = No
	Otherwise = missing
Area of fibrosis	= Fibrosis area from FA
Area of atrophy	= atrophic scar area (from FA)
	Note: = 0 if 'Atrophic scar' = No
Maximal retinal thickness	= maximal retinal thickness (from OCT)
Neuroretinal foveal thickness	= neuroretinal foveal thickness (from OCT)
Atrophy	If atrophic scar (from FA) = yes; then = Yes
	If atrophic scar (from FA) = no; then No
	Otherwise = missing
Height of PED	= PED thickness (from OCT)
GA present	If GA (from FA) = yes; then = Yes
	If GA (from FA) = no; then = No
	Otherwise = missing
Area of SRF	= Area of SRF (from FA)

6. STATISTICAL ANALYSES

6.1 Baseline characteristics and outcomes at 2 years

Baseline data (i.e. patient demography and past history), outcomes at 2 years and some change from baseline data will be described by treatment group (all Lucentis, all Avastin, all continuous and all discontinuous) for patients in the analysis population group.

Continuous variables will be summarised using the mean and SD (or median and inter quartile range (IQR) if the distribution is skewed), and categorical data will be summarised as a number and percentage. The summary statistic headings given in the tables are those we expect to use based on a-priori knowledge of the clinical measurements gained from the interim analysis and previous trials. However, if distributional assumptions are not valid, changes will be made.

Any imbalances in the characteristics of the patients at the start of the study will be described but statistical tests for baseline imbalance will not be carried out.

The results of statistical tests, comparing outcomes at 2 years, will not be included in the summary tables. Treatment effects will be reported graphically with 95% confidence intervals, and with the numerical details alongside (cf. Forest plot).

6.2 Quantification of treatment effects

6.2.1 Adjustment in models

The intention is to adjust all models for the factor included in randomisation, i.e. study centre. However, for some low frequency outcomes (e.g. safety) it is expected that this will not be feasible. Therefore, for consistency, analyses will be adjusted for centre size, fitted as a fixed effect rather than being adjusted for centre. Centres will be grouped into 7 bands as outlined in Table 3. If the frequency of the event is sparse and fewer bands are needed to ensure estimation then the bands will be examined to see where the estimation is not possible and adjacent bands will be combined. It is anticipated that bands 1 and 2 and/or 5 and 6 may need to be combined.

Adjustment for the deferred indicator will also be included in the models if it is significant at the 5% level.

For continuous outcomes that are measured pre-injection at baseline as well as subsequently (e.g. visual acuity, other measures of vision, quality of life scores); baseline and subsequent values will be modelled jointly in preference to the baseline value being modelled as a covariate. Joint modelling will avoid the necessity to either exclude cases with missing preoperative measures or to impute missing preoperative values.

Table 3 Centre banding according to size

Eligible patients recruited at centre	Number of centres	Total number of patients	Band
1-19	7	41	1
20-29	7	179	2
30-39	4	133	3
40-49	3	132	4
50-59	1	55	5
60-69	0	0	-
70-79	1	70	6
Total	23	610	

6.2.2 Drug by treatment frequency interactions

The interaction of VEGF inhibitor and treatment frequency will be tested, but differences between Lucentis and Avastin will only be reported separately for the continuous and discontinuous treatment arms if the interaction term reaches statistical significance (two-sided) at the 5% level for outcomes where the results from the CATT trial suggested possible interaction (i.e. OCT measures of thickness of the fovea and fluid and presence of fluid on OCT). For all other outcomes, where interactions are not anticipated, a statistical significance level of 1% (two-sided) will be used for the interaction term in order to reduce the type I error rate. If the interaction is not statistically significant then the main effects of Lucentis vs. Avastin and of continuous vs. discontinuous treatment after 2 years will be reported.

6.2.3 Analysis models

General methods of presentation and assessing treatment effects are outlined below. For all treatment comparisons, Lucentis and continuous treatment will be the reference groups. Details specific to each outcome are described as appropriate.

Binary outcomes will be compared between treatment groups using logistic regression with treatment estimates presented as odds ratios (OR) and 95% confidence intervals (95% CI). Formal statistical comparisons of treatment effects will only be performed if more than ten patients in total experience the outcome.

Categorical data measured at multiple time points (e.g. EQ-5D categories) will be presented at both the baseline and 2 year time points. For these category component scores no formal comparisons will be made between the treatment groups.

Continuous data measured at multiple times points (e.g. visual acuity, other measures of vision, EQ-5D single summary index) will be analysed using linear mixed effects methods. Multivariate normal models will be fitted incorporating separate parameter estimates for the mean baseline response and for each treatment at each follow-up time-point measured (i.e. saturated model with time fitted as a categorical variable). Many possible structures are available for the variance/covariance matrix and will be compared using information criteria such as AIC or DIC and likelihood ratio tests.

Time to event outcomes (e.g. time to first treatment failure) will be summarised by the median and IQR in each treatment group, estimated from survival modelling. Outcomes will be compared using Cox's proportional hazards models. Treatment comparisons will be presented as hazard ratios (HR) with 95% confidence intervals (CI). The validity of the assumption of proportional hazards will be tested and, if this assumption is violated, alternative modelling methods will be tried. Time to treatment failure will be censored using the censoring variable treatment failure yes/no.

Outcomes may also be presented graphically, if appropriate. For continuous primary or secondary outcomes this will consist of graphs depicting mean differences/ odds ratios and 95% confidence

intervals, and may also show estimated means and standard deviations over time for each treatment group.

6.2.4 Statistical significance

For hypothesis tests of superiority, two-sided p-values<0.05 are considered statistically significant. For tests of non-inferiority (primary outcome), Avastin will be considered inferior to Lucentis and discontinuous treatment inferior to continuous treatment if the lower limit of the 95% confidence interval is <-3.5 (inferiority margin set at 3-4 letters).

Likelihood ratio tests will be used in preference to Wald tests for hypothesis testing.

6.2.5 Model assumptions

For all methods outlined, underlying assumptions will be checked using standard methods, e.g. residual plots, etc. If assumptions are not valid then alternative methods of analysis will be sought. If outlying observations are found which mean models do not fit the data adequately, such observations will be excluded from the main analyses.

6.2.6 Subgroup analyses

Planned subgroup analyses for the report to the funder (listed in study protocol) are: (i) baseline visual acuity in study eye (<55 vs. ≥55 letters read), (ii) baseline CNV size (<6 vs ≥6 disc areas); (iii) proportion of classic CNV (<50% vs. ≥50%); (iv) presence of RAP; (v) fellow eye status (<75 vs. ≥75 letters read).

6.2.7 Sensitivity analyses

There are no planned sensitivity analyses defined in the study protocol. However, there are two sensitivity analyses on the primary outcome that will be considered:

- Carrying out the primary analysis including only the study visits at which all functional outcomes were assessed (visits 0, 3, 6, 12, 18 and 24).
- Carrying out the primary analysis including only data recorded at the study visit (i.e. not including data that was recorded at a deferred visit).

6.2.8 Missing data

For missing primary or secondary outcomes, see section 5.1 and 5.2 for explanations of how deferred visit data are used. It is anticipated that missing data will be low for the clinical outcomes, especially once deferred visit data is used. Missing data may be more common for some of the quality of life measures when some of the questions may not be directly applicable to the IVAN population, or the questionnaire may not have been completed.

In all tables missing data will be indicated by footnotes. The amount of missing data by group will be examined and if it differs substantially between groups potential reasons will be explored.

Missing data in any analysis models is now discussed:

- For continuous data measured at multiple time points, baseline values will be modelled jointly with those measured after treatment, as described previously, thereby allowing all cases with at least one observation to be included. If appropriate (i.e. the level of missingness is >20%) any variables that are predictive of missingness will be identified. If an assumption of missing at random (MAR) given these variables is reasonable (especially likely if the variable was measured at baseline), then such variables will be adjusted for. A model, which includes predictors of missingness, can be shown to provide unbiased estimates of the treatment effect and moreover multiple imputation approaches would not be expected to recover any additional information.
- By design, there will be no missing predictor data, other than already discussed in the points above.

6.2.9 Multiple testing

No formal adjustment will be made for multiple testing. The primary analysis (as specified here) will be clearly distinguished from secondary analyses. When interpreting the results, consideration will be given to the number of statistical tests performed.

6.3 Adverse events

All reported post-randomisation serious adverse events will be tabulated for all patients in the safety population. Events related to treatment will be described**.** For consistency, events will be presented grouped by the treatment allocated.

Formal comparisons (logistic regression) between treatment groups will be made for primary safety endpoints and for all MedDRA system organ class terms for which more than 10 events occurred.

6.4 Meta-analysis of CATT and IVAN trial results

Meta-analysis of the IVAN trial data with the CATT [2, 3] results is planned for the following outcomes: BCVA at 2 years, serious adverse events, geographic atrophy and total lesion thickness at the fovea. The following SAE outcomes will be analysed: all-cause mortality, arteriothrombotic event: (MI, stroke, death from a vascular cause), and ≥ 1 systemic serious adverse event (MedDRA classification). For the outcomes BCVA at 2 years and total lesion thickness at the fovea, change from baseline will be used, as this is the way the data has been presented in the CATT trial. The results from CATT and IVAN will be combined in a fixed effects meta-analysis and the results summarised as a forest plot for the main effects Avastin vs. Lucentis and continuous vs. discontinuous (prn in CATT) treatment. For comparisons of safety by treatment frequency we will contact the CATT team to see if we are able to obtain safety data to two years (not included in 2-year results paper [3]). If the team are unable to provide the information the 1- year results [2] will be used.

7. BIBLIOGRAPHY

1. Ferris FL, Kassoff A, Bresnick GH, Bailey I. New visual acuity charts for clinical research. Am J Ophthalmol. 1982; **94**: 91–96
2. The CATT Research Group. Ranibizumab and Bevacizumab for Neovascular Age-Related Macular Degeneration. *N. Engl. J. Med.* 2011; **364**: 1897–1908;
3. Martin DF, Maguire MG, Fine SL, et althe Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results.Ophthalmology 2012; 119: 1388-1398
4. Piaggio, G, Elbourne, Dr, Altman, DG, Pocock, SJ, Evans SLW for the CONSORT group. Reporting non-inferiority and equivalence randomised controlled trials. JAMA. 295; 1152-60
5. ICH Harmonised Tripartite Guideline Topic E9: Statistical Principles for clinical trials. www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E9/Step4/E9_Guideline.pdf (accessed 4 February 2013)

8. AMENDMENTS TO SAP

Previous version	Previous date	New version	New date	Brief summary of change
1.0	27/02/2013	2.0	2/12/2013	Section 2.4 – list of secondary outcomes excluded from the 2-year Lancet publication have been added
1.0	27/02/2013	2.0	2/12/2013	Section 5.2.2 – 'Any new GA' has been added to as an additional secondary outcome, and the imaging form used to capture morphology outcomes has been added for clarity
1.0	27/02/2013	2.0	2/12/2013	Section 5.3 – rules for imputing onset/resolution dates of adverse events, when missing, have been included
1.0	27/02/2013	2.0	2/12/2013	Section 5.6 – derivations for additional morphology variables identified for inclusion in summary tables have been added, and the imaging form and the imaging form used to capture morphology outcomes has been added for clarity

1.0	27/02/2013	2.0	2/12/2013	Section 6.2.3 – method for analysis of time to event outcomes has been added
1.0	27/02/2013	2.0	2/12/2013	Section 6.2.6 – sub-group analyses excluded from the 2-year Lancet publication have been added