Five year observational follow-up of the IVAN trial cohort: a study of function and morphology

IVAN Follow-Up

REC No
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Glossary / abbreviations

AMD	Age-related macular degeneration
ANCHOR	Anti-VEGF Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration
Anti-VEGF drug	Drug that inhibits the action of vascular endothelial growth factor, e.g. ranibizumab, bevacizumab or aflibercept
BCVA	Best corrected visual acuity
CATT	Comparison of Age-related macular degeneration Treatment Trials
CF	Colour Fundus
CRF	Case report form
CTEU	Clinical Trials and Evaluation Unit
EQ-5D-5L	Euroqol EQ-5D health status questionnaire, with five response levels
ETDRS	Early Treatment Diabetic Retinopathy Study
EXCITE	Efficacy and safety of monthly versus quarterly ranibizumab treatment in neovascular age-related macular degeneration study
FOCUS	A phase I/II study designed to evaluate the safety, tolerability, and efficacy of ranibizumab treatment in conjunction with verteporfin PDT compared with verteporfin PDT alone in patients with subfoveal, predominantly classic CNV secondary to AMD.
GA	Geographic atrophy
HES	Hospital eye service
HORIZON	An open-label, multicenter, extension study of intravitreally administered ranibizumab in patients with primary or recurrent choroidal neovascularization secondary to AMD.
ICH-GCP	International conference for harmonisation of good clinical practice
IVAN	Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation
MARINA	Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration
MRC	Medical Research Council
nAMD	Wet or neovascular age-related macular degeneration
NetwORC	Network of Ophthalmic Reading Centres, UK
NHS	National Health Service
NVA	Near visual acuity using Bailey-Lovie near vision charts
OCT	Optical coherence tomography
PI	Principal investigator
PIL	Patient information leaflet
REC	Research ethics committee
SSC	Study Steering Committee
SECURE	A phase IV, 2-year extension study in nAMD patients who had completed 1 year of treatment with ranibizumab in the EXCITE or SUSTAIN studies.
SOP	Standard operating procedure
SUSTAIN	Study of Ranibizumab in Patients With Subfoveal Choroidal Neovascularization Secondary to Age-related Macular Degeneration trial
UK	United Kingdom
VEGF	Vascular endothelial growth factor

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1. Study summary

This study (IVAN Follow-Up) aims to follow up participants in the Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial to answer additional research questions of major importance to the UK National Health Service (NHS) about the management of wet age-related macular degeneration (AMD) in the longer term. The IVAN trial recruited 610 participants with wet AMD. They were allocated to one of two drugs (ranibizumab or bevacizumab; 'anti-VEGF' drugs) and one of two re-treatment regimens (monthly or discontinuous) and were followed monthly over two years. The two drugs and two treatment regimens were found to have very similar benefits with respect to visual acuity.

Emerging information suggests that many patients will lose vision, despite treatment with anti-VEGF agents for longer than two years after starting treatment. It appears that anti-VEGF drugs do not preventing scarring and, if used for many years, may actually promote thinning of the retina. However, few studies have investigated these effects over many years of treatment.

At the end of the IVAN trial, participants continued to access treatment in the NHS. The original IVAN investigators now propose to invite participants to a one-off research visit to have pictures taken of their eyes and to have their vision measured. Participants will have travel expenses for these visits paid by the study. IVAN Follow-Up will not alter patient's ongoing care in the NHS and seeks only to collect data about the care that has been given since participants completed the trial.

These patients will also be asked to complete a questionnaire about their daily abilities

Thinning of the retina and the other tissues such as the retinal pigment epithelium in the macular fundus assessed using ocular imaging outputs, is the primary focus of the study. However, the study will also collect information about how well participants are seeing, whether they are still being reviewed and treated in the NHS, whether the second eye has needed treatment, and how their current level of vision affects their quality of life.

The study is not expected to benefit participants although any information obtained from the research visit that is relevant to a participant's ongoing care will be fed back quickly to the participant's consultant. Similarly, participants will not run any risk from taking part, since the study will not alter their treatment or carry out any invasive test for the research. (The IVAN Follow-Up study visit will measure function and assess the retinal fundus using only non-invasive tests.)

Whilst our primary objective is best answered from active involvement in this follow up study, many of the patients, most of whom will have continued to have NHS treatment for their eye condition, will now be deceased or too ill to participate in the active part of this study or be 'lost to contact'. Data and images collected during their routine appointments would be extremely valuable in modelling and estimating the benefit of the anti VEGF therapies in the longer term. The IVAN trial participants consented to their data to be used for long term follow up and we propose collecting the data from these patients' notes to assist in answering the secondary outcomes of this study. This data will not be collected for any patient who withdrew their consent at any point.

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2. Background

2.1 Rationale for long term observational follow up of the IVAN trial cohort

This follow-up study of the participants randomised in the Inhibition of VEGF in Age-related choroidal Neovascularisation (IVAN) trial**[1-3]** is designed to answer additional research questions of major importance to the UK National Health Service (NHS) about the management of neovascular age-related macular degeneration (nAMD) in the longer term.

The IVAN trial recruited 610 participants with neovascular (nAMD) age-related macular degeneration. Participants were randomly allocated to one of two drugs (ranibizumab or bevacizumab; anti-VEGF drugs) and one of two re-treatment regimens (monthly or discontinuous) and followed monthly over two years. The last follow-up visit took place in November 2012. The study has reported its main findings[**1-3**]. The two drugs and two treatment regimens had similar efficacy for the primary outcome of best corrected distance visual acuity (BCVA) after two years of follow up.

nAMD is a chronic disease and, despite two years of therapy during the trial, it was anticipated that almost all would require regular assessments after exiting the trial in order to ensure that any continuing need for re-treatment was met. Therefore, after the 24 month visit, the IVAN study teams at each site transferred participants to the NHS macular services at each site for continuing assessment and re-treatment as required.

Emerging clinical information (see below for details) indicates that many patients will develop additional functional deficits with losses of acuity, despite treatment with anti-VEGF agents, beyond year 2. Studies of structure and function of the retina in nAMD eyes receiving anti-VEGF therapy indicate that fibrosis and atrophy are key determinants of worsening vision. Anti-VEGF agents would therefore appear to be incapable of preventing fibrosis. In addition, the chronic inhibition of VEGF in the environment of the posterior fundus is thought to have the potential to switch off the growth promoting and maintenance roles of the VEGF protein, a consequence of which may be progression to geographic atrophy (GA).

None of the clinical trials comparing ranibizumab and bevacizumab undertaken up to now have extended beyond two years. Despite several comparative effectiveness clinical trials having completed[**4**], none apart from the IVAN and CATT trials have plans to investigate long term outcomes. Two open-label industry-sponsored studies following up participants in trials carried out to support marketing authorisations for ranibizumab have reported findings, namely HORIZON (following up participants in the ANCHOR, MARINA and FOCUS trials[**5-7**])[**8**] and SECURE (following up participants in the SUSTAIN and EXCITE trials[**9,10**])[**11**]. They observed a decrease in the visual acuity benefit of ranibizumab in the long term but did not identify the cause. We hypothesize that atrophy of the macular tissues, which is a component of the disease process itself, could be accentuated and accelerated by anti-VEGF treatment.

Furthermore, the findings of HORIZON and SECURE are of limited value as they do not address objectives of importance in the UK setting: (i) treatment during follow-up was not consistent with current treatment provision in the NHS, i.e. regular review and retreatment based on ocular coherence tomograms (OCTs),; (ii) treatment in the initial trials was all 'continuous' (monthly); (iii) there was either low recruitment to the follow-up studies (<40% in

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SECURE) or high attrition during follow up (>30% amongst recruits to the follow-up studies in HORIZON); (iv) the primary objective of both studies was to document long term safety[**8,11**]. Nevertheless, their findings that visual acuity gains during the initial trials were largely lost over the longer term highlight the importance of extending follow-up for IVAN trial participants.

In the UK, dedicated macular service clinics to provide treatment with anti-VEGF agents to patients with nAMD have been implemented widely throughout the NHS. At the end of the IVAN trial, participants were subsumed into the local clinical services and have continued to access treatment in the NHS. Therefore, the IVAN investigators propose an observational study to follow-up participants, extracting the accrued clinical information on IVAN participants and also performing a single study visit assessment at which a structured clinical and morphologically evaluation of the posterior retina would be performed (IVAN Follow-Up). IVAN Follow-Up will obtain data to allow the analysis of structure and functional relationships in the context of the history of treated nAMD and provide insights into the causes of continuing vision loss in years 3 to 5 (on average) after the initiation of treatment.

2.2 Importance of the study to the NHS

Health care planners need to know how often patients are reviewed and treated in the long term, and whether these frequencies and visual outcomes depend on the number of earlier injections. They also need summaries of the patterns of treatment over time and how the workload is managed. Although the impact of different management practices would be better evaluated in trials, nAMD care in the NHS over the last 5 years represents a natural experiment because the Hospital Eye Service (HES) has sometimes struggled to provide monthly review. Some hospitals have also experimented with treat-and-extend regimens to manage their workloads.

The 2 year findings of the IVAN trial observed that the GA was detected more frequently among participants who received continuous treatment compared to those who received discontinuous treatment; this observation was also reported by the Comparison of Age-Related Macular Degeneration Treatments (CATT) trial[**12**] and, when data from both trials were pooled, the finding was highly statistically significant.[**2,3**] Although the development of GA is a component of the natural history of nAMD, our findings may represent a dose response effect. GA is itself sight threatening and it is important to assess the long term impact of GA on visual function. The average loss of 10 letters among participants in the HORIZON study (over 3-5 years following monthly ranibizumab in years 1 and 2) is consistent with increasing GA; unfortunately, the development of new GA was not assessed in the HORIZON study.[**8**]

3. Aims and objectives

The aim of the study is to describe treatment, function and morphology in surviving participants in the IVAN trial cohort and to investigate factors influencing the development of new GA.

The trial has five specific objectives:

I. To describe the management, clinical outcomes and health status of IVAN participants in usual NHS nAMD clinics from completion of the trial to present (e.g. number of visits, number of treatments, development of nAMD in the fellow eye, visual acuity in study and fellow eyes)
II. To describe the rate of development of new GA among IVAN participants.

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III. To estimate the effects of trial allocations, and numbers of treatments administered during the trial, on patients' management and clinical outcomes and health status (EQ-5D-5L).
IV. To estimate the effects of original trial allocations on the rate of development of new GA.
V. To investigate whether new GA impacts on visual function and health status (EQ-5D-5L) in the longer term, potentially offsetting the benefit of treatment.

Objectives 1 and 2 are descriptive only. For objective 3, we do not hypothesise any differences on the basis of the experimental allocations. For objective 4, we hypothesise that the risk of new GA will be higher among patients allocated to continuous (monthly) treatment and those who have had more, as opposed to less, treatment (based on findings after 2 years' follow-up in the CATT and IVAN trials [**2,3,12**]). For objective 5, we hypothesise that the risk of new GA will be higher among patients allocated to continuous (monthly) treatment and those who have had more, as opposed to less, treatment (number of injections analysed as a continuous or ordered categorical exposure).

4. Plan of Investigation

4.1 Study design

The design is a multi-centre, longitudinal cohort study, based on the cohort of participants in the IVAN trial. Different aspects of the study will be prospective (e.g. determining whether new GA has developed) and retrospective (e.g. historical record of clinical management and treatment since exiting the IVAN trial).

4.2 Study population

4.2.1 Inclusion criteria

Any participant in the IVAN trial analysis population will be eligible.
For the patients attending the visit: Ability to consent

4.2.2 Exclusion criteria

There will be no exclusion criteria, although not all participants may want to take part.

4.3 Exposures (predictors of outcome) to be studied

The primary exposures of interest will be the experimental allocations in the IVAN trial, namely (a) ranibizumab vs. bevacizumab and (b) continuous (monthly) vs. discontinuous (protocol-defined treatment-as-needed) treatment regimens.

Secondary exposures of interest will be:

a. Number of intravitreal injections since starting treatment (sum of injections received in the IVAN trial plus injections received since)
b. For objective 4 (analysing predictors of visual acuity), presence or absence of new GA

4.4 Primary and secondary outcomes

4.4.1 Primary outcome

The primary outcome will be the development of new GA. This outcome will be determined from colour fundus (CF), OCT and autofluorescence images (where available) of the study eye, submitted to the Network of Ophthalmic Reading Centres (NetwORC). NetwORC will grade all

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images that are submitted without knowledge of experimental allocations or other exposures of interest and classify study eyes as having developed new GA or not.

4.4.2 Secondary outcomes

Secondary outcomes will be:

- Best corrected distance visual acuity (BCVA; VAlogMAR), with standard and low luminance, measured as the number of letters read on a standard ETDRS Early Treatment Diabetic Retinopathy Study (ETDRS) letter charts**[13]** chart at 1 metre (testing at 4 metres initially and then at 1 metre if <20 letters are read at 4 metres; total letters read are scored 'as if' viewing at 1 metre). This will be recorded for each visit from a participant's medical record for both study and fellow eyes.
- Duration of monitoring for reactivation: This will be derived from the date of first treatment in the IVAN trial and the date of the last / most recent clinical review (with or without injection) documented in the medical records. If a participant has been discharged at some point since exiting the IVAN trial, then restarted treatment, the date of restarting treatment (and subsequent cessation of clinical reviews) will be recorded. If a fellow eye has developed nAMD requiring treatment during or after exiting the IVAN trial, the same information will be recorded for the fellow eye.
- Number of visits: In addition, the eye(s) being reviewed at each visit will be recorded, i.e. study, fellow or both.
- Number of injections: This outcome will be recorded separately for study and fellow eyes. The drug used for each treatment will also be recorded
- nAMD status of fellow eye
- EuroQol EQ-5D-5L [**14**]
- Near visual acuity (NVA; Bailey-Lovie) scores (where available).

4.5 Measures taken to avoid bias

4.5.1 Confounding / allocation bias

Objectives 1 and 2 are descriptive only. Objectives 3 and 4 will estimate effects attributable to the original experimental allocations. Confounding may arise from loss to follow-up that is differential but this was not observed during the trial and is not expected. Analyses for objective 5, investigating the extent to which new GA is associated with BCVA and EQ-5D-5L utility, will adjust for potential confounding by factors characterised during the IVAN.

4.5.2 Detection bias

It is very unlikely that measurement of BCVA or secondary outcomes will be differentially biased because the objectives of this follow-up study (established only recently) were not known by the participants or personnel when they were recorded (5.3).

4.5.3 Performance bias

Performance bias will be unlikely for the reasons stated above, i.e. the objectives of this study were not known during follow-up (4.5.2).

4.5.4 Attrition bias

There is a risk of attrition bias because, given that the trial population was elderly at the time of recruitment, additional participants will have died since they exited the trial and others may be unwell and unable to take part. We hope to minimise the risk by including all participants in the

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passive follow-up (e.g. extraction of data from medical notes and completion of a questionnaire) unless they have withdrawn consent at any time. We will also compare the characteristics of participants not followed up with those who are followed up.

4.5.5 Reporting bias

Reporting bias will be minimised by analysing and reporting all outcomes defined in the protocol stage in accordance with a statistical analysis plan finalised before starting data analyses.

4.6 Justification of target sample size

The maximum sample size for this study is set by the number of participants available for continuing follow-up at the end of the IVAN trial (525/610 completed 2 years follow-up; 30 of the remaining 85 had died). We expect that the majority of participants will consent to attend for a single follow up. We also anticipate obtaining data passively from all IVAN trial participants unless they have withdrawn consent. We have assumed that the incidence of new GA will have increased from 30% (at 2 years) to 45% with additional follow-up and that the relative risk observed at 2 years (odds ratio≈1.45) has been maintained. For these assumptions, the trial will have 80% power to detect a difference of ≥14% (38% vs. 52%) between continuous and discontinuous treatment regimens.

5. Study methods

5.1 Selection of exposed and unexposed groups

All members of the original IVAN trial cohort who have not withdrawn consent will be included. Therefore, there will not be any selection / sampling.

5.2 Selection of confounders

Characteristics of participants collected for the IVAN trial, chosen to include key prognostic factors for nAMD, will be available for this study. The extent to which these factors are potential confounders for the development of new GA is not known.

5.3 Masking

In the original IVAN trial, participants and clinical and trial personnel were masked. After the end of the trial, the ongoing care of participants was transferred back to the HES (i.e. usual nAMD clinics). Since that time, participants will almost certainly have been treated with ranibizumab, if treatment has been needed, because ranibizumab is the current standard of care and BCVA will have been measured using the local protocol at each site. Therefore, although health professionals and participants have not been masked to ongoing care, the available treatment has been the same; ophthalmologists managing participants are extremely unlikely to know the original experimental allocations. Even if they were known, there is no reason for suspecting that they would have differentially influenced the measurement of visual acuity or decisions about ongoing care during the follow-up period because the objectives of this follow-up study (established only recently) were not known by the participants or personnel at the time.

5.4 Research procedures

Participants will be invited to participate in the follow up study by either:

a) Attending a single research visit in person, for eye examinations and a questionnaire.

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or

b) Completing a questionnaire by post

They will also be offered the option of withdrawing from the study.

The coordinating centre (Clinical Trials and Evaluation Unit (CTEU) Bristol) will send a letter to surviving and non-withdrawn IVAN trial participants, enclosing information about the study and a reply slip. The letter will be on the headed paper of the hospital where the patient's last IVAN appointment took place, and bear the signature of the PI at that site. The reply slip will allow patients to indicate if they wish to attend for a research visit or complete a questionnaire. It will also give them the opportunity to withdraw from the study.
The CTEU will facilitate data collection and share responses with the sites, by use of a secure password protected database hosted on the NHS network. Scheduling of face-to-face follow up visits will be carried out by sites. "Queuing" of participants by date of original recruitment into the trial will be encouraged in order to maximise the duration of follow-up.

Research procedures carried out specifically for the study will, therefore, include all activities carried out at the single research visit (if attended):

- BCVA (letters read; assessed by a research optometrist) in each eye at this visit;
- Near Visual Acuity (Bailey- Lovie) if facilities are available.
- Face-to-face administration of the EQ-5D-5L Questionnaire;
- Colour Fundus images of the study and fellow eyes;
- OCT images of the study and fellow eyes;
- Where available (estimated to be half of sites), autofluorescence images of the study and fellow eyes.

All CF, OCT and autofluorescence images will be submitted to the NetwORC for independent grading.

Assessment by a doctor will not be required routinely at these visits. The photographer will refer a participant to an ophthalmologist if anything is detected on the visit that he/she considers to require a medical opinion. Additionally, the visual acuity results and information provided by the patient will be reviewed after the visit, by a research nurse, to check for any incidental finding. Any causes for concern will be raised clinically.

5.5 Definition of end of study

The end of this study for the patients is when they have either completed all requirements of the attended visit or when they have returned the questionnaire by post.
The end of the study for trial purposes is when the database has been locked and all queries have been answered..

5.6 Data collection

Data collected at the research visit:

- Date of visit
- Consent for this visit.

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- Medical History
- Any registration or certification of visual impairment.
- Diagnosis of nAMD in Fellow Eye
- Near Visual Acuity (Bailey-Lovie) scores (if available)
- Completion of EQ-5D-5L questionnaire
- Imaging of colour fundus
- Imaging by autoflourescence (if available)
- Imaging by OCT
- Best Corrected Visual Acuity in each eye.

We propose to collect the following data passively (i.e. from medical notes):

- For each ophthalmology appointment since their last IVAN appointment:
    - Date of appointment
    - Distance visual acuity (letters read) in each eye
    - Were any imaging tests performed at this visit, if yes, which types.
    - Was an anti-VEGF injection given in IVAN eye?
    - Was an anti-VEGF injection given in Fellow eye?
    - If injections were given which drug was prescribed?
    - Next step e.g. discharged, reasons for discharge, further appointment, transferred etc.
    - If the appointment is due to a re-referral, the reason for that re-referral.

This data will provide:

- Frequency of follow up
- Number on anti- VEGF injections given.
- Type of anti-VEGF injections given.
- History of Visual acuity.
- Confirmation that the participant is still receiving active NHS follow-up

Data collection will be completed using a paper CRF system and the site staff will enter the data onto the IVAN Follow-Up database which will be hosted on a secure NHS server and access will only be granted to authorised staff.

5.7 Source data

Source data will differ according to the data items being collected:

- For research visits attended by participants, custom data collection forms (CRFs), which including administration of the EQ-5D-5L questionnaire, and are completed during the visit, will provide the source data.
- The images collected during the ophthalmology tests are source data.
- For patients declining the visit, the completed EQ-5D-5L questionnaire that they send to CTEU will be the source data.

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- For passive data collection the paper and electronic medical records and NHS databases containing data collected in the course of usual care will provide the source data.

- The original IVAN trial database will provide source data for the original experimental treatment allocations and other data up to completion of the trial that may be required for the follow-up study.

5.8 Planned recruitment rate

There will be no new recruitment for this study. The rate limiting step in contacting surviving participants will be 're-awakening' IVAN sites and obtaining local research governance approvals for this study. We have allowed 12 months for all data collection activities including contacting surviving participants and completing the attended visits. We will prioritise research approvals and data collection at sites that recruited the largest number of patients and request, where possible, that visits are scheduled in order of the date of original randomisation.

5.9 Participant recruitment

Once a site has research approvals in place, a letter signed by the local principal investigator will be sent to each surviving participant enclosing the patient information leaflet (PIL) for the study, a reply slip and a reply-paid envelope addressed to the CTEU. (The CTEU will coordinate posting of these letters and enclosures.)

Establishing contact with IVAN participants, who have moved or who do not reply to the initial invitation will be addressed by either the appropriate site personnel or CTEU personnel liaising on a case by case basis. A follow up letter may be sent. This may be to the same or to a different address.

5.10 Discontinuation/withdrawal of participants

Participants will not have their treatment altered by participating in the study and will not be followed actively in the study. The PIL will explain that a participant can withdraw their consent for their data to be used for the study at any time. New data will not be collected for any patients who withdrew from the IVAN trial or expresses that they do not wish their data to be used as part of the follow-up study.

5.11 Frequency and duration of follow up

Data collection requiring the active participation of the patient will take place during a single research visit or require the participant to complete a questionnaire in their own time. The majority of the data collection is passive and will not require the patient's involvement.

5.12 Likely rate of loss to follow-up

Participants will not be followed up in this specific study. They have consented for the information to be used in long term follow up and this is not time limited.

5.13 Expenses

The study will pay travel expenses to participants and their carers who choose to attend for research visits. This information will be stated in the PIL.

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5.14 Relocation

If the participants have moved away from their original hospital area it may be possible for them to attend at another IVAN centre. This will be addressed on a case by case basis.
Data collection will be limited to NHS care received at IVAN centres.

6. Statistical analyses

6.1 Plan of analysis

Outcomes of interest are the same as in the IVAN trial, notably including the development of GA (not specified in the trial protocol at the outset but defined in the 2-year analysis plan for the trial).

Objectives 1 and 2 are descriptive and will be reported without adjustment, other than is required to take into account the hierarchical structure of the data (e.g. adjusting for centre).

Objectives 3 and 4 will be addressed through intention-to-treat analyses similar in principle to those reported in publications of the IVAN trial and in the report about the trial to the NIHR. We will not attempt to 'adjust' for dilution because of crossover (expected to be almost entirely from bevacizumab to ranibizumab, and from continuous to discontinuous), since ranibizumab has been the standard of care in the NHS since October 2008.

Objective 5 will be addressed through observational analyses of the impact of treatment frequency on outcomes. These analyses may be at risk of confounding, in particular by age or baseline visual acuity. One solution may be to fit random allocation to treatment regimen as an instrumental variable (allocation should be predictive of the total number of treatments, even after 5 years, but only to outcomes of interest through its association with number of treatments). We will investigate this method of analysis but, ultimately, its feasibility will only become apparent once the data about treatment frequency (and the association between treatment frequency and random allocation to treatment regimen) are available.

Final analyses may differ from this plan if unexpected features of the data collected during this study suggest that the planned analyses are not feasible. As for the main trial, a full analysis plan will be written prior to locking the database (i.e. with knowledge of the accruing data but without 'un-masking' key predictor variables. This document will explain and justify any deviations from the above summary plan.

6.2 Subgroup analyses

No subgroup analyses are planned.

6.3 Frequency of analyses

The primary analysis will take place when follow-up is complete for all participants. There will be no formal interim analysis.

6.4 Criteria for the termination of the study

The study does not involve any intervention and, therefore, there can be no reason for terminating the study on safety grounds. We also cannot envisage the study being terminated on grounds of futility, given that most participants agreed to long term follow up of their data.

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6.5 Economic issues

No planned analysis relating to the health economic evaluation has been specified although data from the study will permit further evaluation of the cost-effectiveness of anti-VEGF treatments over a longer time horizon, should this become a priority for the NHS.

7. Study management

7.1 Day-to-day management

The study will be managed by CTEU Bristol, a fully registered UK Clinical Research Collaboration Trials Unit.

CTEU Bristol will liaise with each site to create appropriate local invitation letters, confirm the status and address of surviving IVAN participants and collect data. Data queries and day to day logistics will be addressed as necessary.

Management and validation of data will use the infrastructure that was used successfully during the trial (NHS server in Bristol, with password-protected web access to authorised users at sites). Images collected by sites during face-to-face follow up visits will be submitted to the UK Network of Ophthalmic Reading Centres (NetwORC) using the same principles as in the trial. The NetwORC has given assurance that it has the capacity to grade the images, including autofluorescence images (not included as part of the original trial), in a timely manner.

7.2 Monitoring of sites

Central monitoring by CTEU Bristol will be completed but on site monitoring will not be carried out unless deemed necessary. Site visits may be carried out by CTEU staff to facilitate data collection or training using the study database.

7.3 Trial oversight

A study steering committee (SSC) is being established to oversee this study. It will include as many of the independent members of the original IVAN Trial Steering Committee as are available and willing.

There will be no Data Monitoring and Safety Committee because this is an observational study.

8. Safety reporting

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Table 1: Terms and Definitions for Adverse Events

Term	Definition
Adverse Event (AE)	Any untoward medical occurrence in a participant to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product.
Adverse Reaction (AR)	Any untoward and unintended response in a participant to an investigational medicinal product, **which is related** to any dose administered to that participant.
Unexpected adverse reaction (UAR)	An adverse reaction the nature and severity of which is not consistent with the information about the medicinal product in question as set out in the protocol.
Serious Adverse Event (SAE)	Any adverse event that: 1. results in death: Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring **within 28 days of randomisation must be treated as an SAE and reported as such.** 2. is life-threatening: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. 3. requires hospitalisation or prolongation of existing hospitalisation: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore patients do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation (including for an elective procedure) for a pre-existing condition (prior to study) entry which has not worsened does not constitute a serious experience. 4. results in persistent or significant disability or incapacity: (substantial disruption of one's ability to conduct normal life functions) 5. consists of a congenital anomaly or birth defect: (in offspring of subjects or their partners) taking the IMP regardless of time of diagnosis 'Important medical events' may also be considered

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	serious if they jeopardise the subject or required an intervention to prevent one of the above consequences. They also include; Overdoses (accidental or intentional) Pregnancy outcome (of subject or partner) An alarming adverse experience Non-serious AEs and/or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and requiring reporting.
Serious Adverse Reaction (SAR)	Any adverse reaction that: 1. results in death: Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring **within 28 days of randomisation must be treated as an SAE and reported as such.** All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAR and reported as such. 2. is life-threatening: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. 3. requires hospitalisation or prolongation of existing hospitalisation: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore patients do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation (including for an elective procedure) for a pre-existing condition (prior to study) entry which has not worsened does not constitute a serious experience. 4. results in persistent or significant disability or incapacity: (substantial disruption of one's ability to conduct normal life functions) 5. consists of a congenital anomaly or birth defect: (in offspring of subjects or their partners) taking the IMP regardless of time of diagnosis 'Important medical events' may also be considered serious if they jeopardise the subject or required an intervention to prevent one of the above consequences. They also include; Overdoses (accidental or intentional) Pregnancy outcome (of subject or partner) An alarming adverse experience Non-serious AEs and/or laboratory abnormalities which

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	are listed in the trial protocol as critical to safety evaluations and requiring reporting.
Unexpected Serious Adverse Reaction (UAR)	Any unexpected adverse reaction that: 1. results in death: Death may occur as a result of the basic disease process. Nevertheless, all deaths occurring **within 28 days of randomisation must be treated as an SAE and reported as such.** All deaths which may be considered as related to the trial agent, regardless of the interval, must be treated as a SAR and reported as such. 2. is life-threatening: The term 'life-threatening' in the definition of 'serious' refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. 3. requires hospitalisation or prolongation of existing hospitalisation: hospitalisation is defined as an inpatient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Therefore patients do not need to be hospitalised overnight to meet the hospitalisation criteria. Hospitalisation (including for an elective procedure) for a pre-existing condition (prior to study) entry which has not worsened does not constitute a serious experience. 4. results in persistent or significant disability or incapacity: (substantial disruption of one's ability to conduct normal life functions) 5. consists of a congenital anomaly or birth defect: (in offspring of subjects or their partners) taking the IMP regardless of time of diagnosis 'Important medical events' may also be considered serious if they jeopardise the subject or required an intervention to prevent one of the above consequences. They also include; Overdoses (accidental or intentional) Pregnancy outcome (of subject or partner) An alarming adverse experience Non-serious AEs and/or laboratory abnormalities which are listed in the trial protocol as critical to safety evaluations and requiring reporting.

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Suspected Serious Adverse Reaction (SSAR)	Any adverse reaction that is classed in nature as serious and is consistent with the information about the medicinal product in question as set out in the protocol.
Suspected Unexpected Serious Adverse Reaction (SUSAR)	Any adverse reaction that is classed in nature as serious and is not consistent with the information about the medicinal product in question as set out in the protocol.

8.1 Identifying Adverse Events

We will collect adverse event (AE) data for participants once they have consented to the IVAN follow-up visit. Consent will take place at the follow-up clinic. Any adverse events that occurred between the end of the IVAN trial and consent to the follow-up will be considered medical history.

8.2 Assessment of Seriousness

The PI or designee should make an assessment of seriousness. A serious adverse event is an adverse event, adverse reaction or suspected unexpected adverse reaction that:

- Results in death
- Is life-threatening
- Requires hospitalisation or prolongation of existing hospitalisation
- Results in persistent or significant disability or incapacity
- Consists of a congenital anomaly or birth defect
- Is any other important medical event(s) that carries a real, not hypothetical, risk of one of the outcomes above

8.3 Assessment of Causality

The PI or designee should make an assessment of causality, i.e. the extent to which it is believed that the event may be related to the study drug:

- **Not Related**: Temporal relationship of the onset of the event, relative to administration of the product, is not reasonable or another cause can by itself explain the occurrence of the event.
- **Unlikely**: Temporal relationship of the onset of the event, relative to administration of the product, is likely to have another cause which can by itself explain the occurrence of the event.
- **Possibly***: Temporal relationship of the onset of the event, relative to administration of the product, is reasonable but the event could have been due to another, equally likely cause.
- **Probably***: Temporal relationship of the onset of the event, relative to the administration of the product, is reasonable and the event is more likely explained by the product than any other cause.
- **Definitely***: Temporal relationship of the onset, relative to administration of the product, is reasonable and there is no other cause to explain the event, or a re-challenge (if feasible) is positive.

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* Where an event is assessed as possibly, probably or definitely related, the event is an adverse reaction (AR).

8.4 Assessment of Severity

The PI or designee should make an assessment of severity for each AE according to the following categories:

- **Mild:** A reaction that is easily tolerated by the trial participant, causing minimal discomfort and not interfering with every day activities
- **Moderate:** A reaction that is sufficiently discomforting to interfere with normal everyday activities
- **Severe:** A reaction that prevents normal everyday activities

Severity is used to describe the intensity of a specific event. This is not the same as 'seriousness'.

8.5 Assessment of Expectedness

The Sponsor is required to make an assessment of expectedness of any AEs which are possibly, probably or definitely related to the IMP based on the protocol. Adverse reactions may be classed as either;

- Expected: The AR is listed in the protocol as expected.
- Unexpected: The AR is not listed in the protocol as expected.

NB An AR may also be described as 'unexpected' if it has occurred with greater frequency or severity that might otherwise have been expected.
The Sponsor delegates this responsibility to PIs and co-investigators.

8.6 Follow-up of Adverse Events

The AE reporting period for the study begins upon completion of the consent form for the clinic appointment until the patient leaves the clinic appointment.

8.7 Expected Adverse Events

There are no expected adverse events in this study as there is not intervention being administered to patients as part of this study. The following adverse events are 'anticipated' as they may be experienced as part of the natural history of the disease, or due to any current treatment by intravitreal injection the participants may be receiving for their condition. These anticipated events will not be subject to expedited reporting as agreed with the Sponsor and the MHRA.

8.7.1 Ocular events:
Amaurosis fugax
Blindness
Diplopia
Keratitis
Retinal vein occlusion
Vitreous haemorrhage
Serious visual loss

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Retinal haemorrhage
Lesion progression
Retinal atrophy
Endophthalmitis (confirmed by culture positive vitreous tap)
Severe uveitis (vitreous flare and cells (culture negative or no vitreous tap obtained) using the international uveitis severity classification)
Traumatic cataract (cataract caused by needle trauma)
Retinal detachment (rhegmatogenous detachment following intravitreal injection, location associated with the site of needle penetration)
Retinal pigment epithelial (RPE) tears.
Conjunctival haemorrhage
Increased visual disturbance ≤48 hrs of injection
Other retinal detachment
Ocular pain/irritation
Increased lacrimation
Vitreous floaters
Vitreous detachment
Intraocular inflammation
Visual hallucinations
Elevated intraocular pressure
Immediate post-injection vascular occlusion
Progressive cataract

8.7.2 Systemic events:
Stroke
Myocardial infarction
Incident, or worsening of, angina
Deep vein thrombosis of pulmonary embolism
Non-ocular haemorrhage
Heart failure
Hypertension
Urinary tract infection
Nasopharyngitis
Headache
Arthralgia
Bronchitis
Cough
Sinusitis
Nausea
Transient ischaemic attack/non-permanent stroke
Upper respiratory tract infection
Influenza

8.8 Recording and Reporting of Adverse Events (AEs)

All AEs should be recorded in the patient medical notes and on the AE form within the CRF.

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8.9 Recording and Reporting of Serious Adverse Events (SAEs)

SAEs will be reported using the SAE Form and recorded in the patient medical notes. All SAEs will be reported to CTEU Bristol within 24 hours of becoming aware of the event. All SAE reports will be forwarded to the Sponsor by CTEU Bristol, and the Sponsor will be responsible for reporting Suspected Unexpected Serious Adverse Reactions (SUSARs) to the MHRA and REC within the required timelines as per the regulatory requirements. A copy of the SUSAR report will be forwarded to CTEU Bristol for information.

8.10 Recording and Reporting of Urgent Safety Measures

If the Sponsor becomes aware of information that necessitates an immediate change in study procedure to protect clinical trial participants from any immediate hazard, they may act to eliminate an immediate hazard without prior approval from the REC or MHRA. They should phone the Clinical Trial Unit at the MHRA and discuss the issue with a safety scientist immediately once an urgent safety measure was taken at a site. The Sponsor delegates this responsibility to PIs and co-investigators.
The PI or designee should report the urgent safety measure immediately to the Sponsor, via the CTEU Bristol. The Sponsor will notify the MHRA and the main REC in writing providing full details of the information they have received and the decision making process leading to the implementation of the urgent safety measure within 3 days of the measure being taken.

9. Ethical considerations

9.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the study and other study related essential documents (e.g. PIL and consent form) will be carried out by a UK Research Ethics Committee (REC).

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

9.2 Risks and anticipated benefits

There are no anticipated benefits to participants from taking part although any information obtained from the research visit relevant to a participant's ongoing care will be fed back to the participant's consultant.

There are also no anticipated harms to participants from taking part, since the study will not alter their treatment or carry out any invasive test for the research. With respect to the latter point, the imaging tests that will be carried out at research visits are not invasive, other than requiring dilatation of the pupils. Autofluorescence images are obtained with a confocal scanning laser ophthalmoscope. Fluorescein angiography (an invasive test involving intravenous injection of fluorescein which was part of the IVAN study) will **not** be carried out.

9.3 Informing potential study participants of possible benefits and known risks

The above information (9.2) will be described in the PIL.

9.4 Obtaining informed consent from participants

All participants gave consent to long term follow-up when they enrolled into the IVAN trial.

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Participants who agree to attend for the visit will be required to give written informed consent at the start of the visit for the tests involved. This process will be described in the PIL which will be posted with the invitation letter and reply slip.

Participants who choose to just complete the questionnaire by post will indicate their continued interest twice by returning the reply slip and returning the questionnaire.

Passive data collection will go ahead for all patients who have not previously withdrawn consent unless they respond to the reply slip indicating they are withdrawing consent.

10. 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

10.1 Sponsor approval

Any amendment to the study documents must be approved by the sponsor prior to submission to the REC.

10.2 NHS approval

Approval from the local NHS Trust is required prior to the start of the study. Any amendments to the study documents approved by the REC will be submitted to the Trust for information or approval as required.

10.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting any participant. Investigators will be required to ensure compliance to the protocol and study manual and with 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 or CTEU Bristol or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved the REC that they receive and ensure that the changes are complied with.

10.4 Monitoring by sponsor

No on site monitoring will be carried out for this study unless deemed necessary. CTEU Bristol will conduct central monitoring and the details will be arranged with the Sponsor. The Sponsor may monitor CTEU Bristol.

10.5 Indemnity

This study will be sponsored by Belfast Health and Social Care Trust which has appropriate indemnity insurance. No risks from participating in the trial are anticipated (section 9.2).

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11. Data protection and participant confidentiality

11.1 Data protection

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

11.2 Data handling, storage and sharing

11.2.1 Data handling

Data will be submitted to the CTEU Bristol directly into the database which will be accessed by sites via the NHS portal. Data will be entered onto a purpose designed database developed and maintained by the CTEU. Data validation and cleaning will be carried out throughout the study. Standard operating procedures (SOPs) for database use, data validation and data cleaning are available and will be regularly maintained.

11.2.2 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where study related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the study. In compliance with the Medical Research Council (MRC) Policy on Data Preservation, relevant 'meta'-data about the study and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier, and key personal identifiers (e.g. name, date of birth and NHS number) will also be held indefinitely, but in a separate file and in a physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

11.2.3 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body.

12. 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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13. References

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14. Amendments to protocol

Amendment number (i.e. REC number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)
	1.0		2.0			NB Version 1 was never approved or in use.
	2.0		3.0			
	3.0		4.0			
	4.0	07/09/2015	5.0	20/11/2015	Safety section updated in line with Sponsor's policy Addition of "standard and low luminance" to Secondary outcome.	
	5.0	20/11/2015	6.0	15/02/2016	Safety section updated in line with MHRA assessment	

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