

EDNA: **E**arly **D**etection of **N**eovascular **A**ge-related macular degeneration (AMD)

PROTOCOL

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Sponsor

Name :	Queen's University Belfast Research Governance Manager, Mrs Louise Dunlop Research and Enterprise
Address:	University Road Belfast BT7 1NN
Sponsor number	B14/49

Chief-Investigator

Name :	Prof Usha Chakravarthy
Address:	Queen's University Belfast Institute of Clinical Science Block A Grosvenor Road Belfast BT12 6BA
Telephone:	028 90635887
E-mail:	cem@qub.ac.uk

Study Office

Address:	EDNA Study Office Centre for Healthcare Randomised Trials (CHaRT) 3rd Floor, Health Sciences Building University of Aberdeen, Foresterhill Aberdeen AB25 2ZD
Telephone:	01224 438196
Fax:	01224 438165
E-mail:	edna@abdn.ac.uk
Website:	https://w3.abdn.ac.uk/hsru/EDNA/

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Usha Chakravarthy 

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VERSION HISTORY:

Amendment no.	Protocol version no.	Description of changes (incl. author(s) of changes)	Date Effective
	Version 1	New document	
	Version 1.1	Update of glossary Flow chart amended for consistency with inclusion/exclusion criteria Wording for Amsler positive test edited for clarity Correction of typographical errors	December 2014
	V2	• Correction of study end date to 31/3/2020 • Insertion of full EDNA contact details • Insertion of INFORMATION under section 3.6.6 on interpretation of any additional FFA's carried out by clinicians for the purpose of detecting changes in the non-EDNA study eye • Addition to section 7.3 detailing the internal pilot for EDNA • Addition of the names of the EDNA Steering Committee • Alteration of the study entry timeframe in flow diagram and section 3.5, 3.6 : Participants to be recruited between day of diagnosis and subsequent routine clinic visit (inclusively) • Clarification of withdrawal of consent procedures • Slight alteration to Flowchart and associated wording in section 3.6 to illustrate that if at any point the FFA result is ambiguous, it is the clinicians decision that should drive exit	April 2015
	V3	3 changes to help maximise eligible patients to approach about EDNA: • Change of inclusion criteria threshold of visual acuity to 68 letters (Section 3.5 and Figure 1) • Clarification of time-window for recruitment in inclusion criteria (section 3.5), recruitment	November 2015

		procedures (3.6.1) baseline measurements (3.6.4) and flowchart (figure 1) • Potentially eligible patients can be approached about EDNA by telephone (section 3.6.2) Clarification of baseline measurement protocol: • Table 1 footnotes and section 3.6.4 added to clarify that no additional FFA is required after consent and that any EDNA diagnostic tests already collected prior to consent can be used for the baseline EDNA measurement. • Schedule of data collection (section 6.2), baseline measurements to include reference standard results. Typographical changes: • Page 14: Flow chart caption Figure 1 • Changes to subsequent arrangement (section 3.6.9) – local research team to send out GP letters • Corrections to schedule of data collection table (table1) • Paragraph inserted (section 6.3) to clarify data processing by independent reading centre. • EDNA diagnostic tests under evaluation referred to as "index tests" throughout the protocol	
	V3.1	Changes to Independent Steering Committee Members list Page 10 • Removal of Carol Chambers • Addition of Felicity Hart, Michael Warren and Andrea Rogers. Change in follow up time period: Following the extension to the recruitment period some patients recruited later on into this recruitment period will not have opportunity to be followed up for three years fully. • To reflect this accurately throughout the protocol references to three years have been altered to say '***up until*** three years' • To reinforce further throughout the protocol references to the three year appointment are corrected to say the 'exit' appointment instead Clarification of time period allowed around 18 month appointment • Page 21: Wording changed to explicitly reflect that 2 months (8 weeks) either side of the	

		scheduled appointment date is permitted to perform the appointment within.	

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PROTOCOL SUMMARY

Question addressed:	What is the optimum non-invasive test strategy that will robustly detect nAMD in unaffected fellow eyes during follow-up in secondary care of persons with nAMD in the first affected eye.
Considered for entry	Patients with newly diagnosed nAMD (within previous 6 weeks) in one eye and an unaffected second eye (study eye) Setting: Secondary care, ophthalmology outpatient departments
Populations	All participants will receive all diagnostic tests under evaluation at each routine clinic visit.
Study entry	Eligible and consenting patients will be studied. Consent will be obtained after written and oral information has been provided.
Interventions	The following diagnostic tests (index tests) will be evaluated: 1. Fundus evaluation of signs of nAMD; 2. Patient's subjective assessment of vision 3. ETDRS visual acuity; 4. Amsler test; 5. Clinical assessment of images captured by OCT; The reference standard test is fundus fluorescein angiography;
Outcome assessment	**Primary diagnostic performance outcomes:** sensitivity and specificity of the index tests on detection of nAMD in the study eye in a monitoring setting. **Primary economic outcome:** incremental costs (to the health service) per quality adjusted life year (QALY) gained. **Secondary outcome measures** Secondary diagnostic performance outcomes: diagnostic odds ratio, likelihood ratio, proportion of

	indeterminate tests. The performance of combinations of tests will be evaluated. Other outcomes: time gain of early detection; visual acuity at diagnosis, performance of a risk predictor algorithm according to baseline characteristics, the establishment of a well characterised cohort of clinical and biological data for future research.
Co-ordination	**Local**: By local lead Ophthalmologist and Research nurse. **Central**: by Study Office in Aberdeen (Telephone 01224 438196). **Overall**: by the Project Management Group, and overseen by the Steering Committee

GLOSSARY OF ABBREVIATIONS	
AE	Adverse Event
AMD	Age-related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BNF	British National Formulary
CEAC	Cost-Effectiveness Acceptability Curve
CEAF	Cost-Effectiveness Acceptability Frontiers
CHaRT	Centre for Healthcare Randomised Trials
CI	Chief Investigator
CNV	Choroidal Neo-Vascularization
CRF	Case Report Form
CTU	Clinical Trial Unit
DMC	Data Monitoring Committee
ETDRS	Early Treatment Diabetic Retinopathy Study
FFA	Fundus Fluorescein Angiography
FPED	Fibrovascular Pigment Epithelial Detachment
GCP	Good Clinical Practice
GP	General Practitioner
HSRU	Health Services Research Unit
HTA	Health Technology Assessment
IPCV	Idiopathic Polypoidal Choroidal Vasculopathy
ISRCTN	International Standard Randomised Controlled Trial Number
LLIO	Late Leakage of Indeterminate Origin
nAMD	Neovascular Age-related Macular Degeneration
NHS	National Health Service
NIHR	National Institute Health Research
NOD	National Ophthalmology Dataset
NMB	Net Monetary Benefit
OCT	Optical Coherence Tomography
ORECNI	Office for Research Ethics Committees in Northern Ireland
PI	Principal Investigator
PIL	Patient Information Leaflet
PMG	Project Management Group
QALY	Quality Adjusted Life Year
RAP	Retinal Angiomatous Proliferation
RCT	Randomised Controlled Trial
R&D	Research and Development
REC	Research Ethics Committee
RNIB	Royal National Institute of Blind people
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SC	Steering Committee
UK	United Kingdom
VEGF	Vascular Endothelial Growth Factor

STUDY PERSONNEL

Chief Investigator

1 Usha Chakravarthy

Grant Holders

1 Craig Ramsay (Methodology)
2 Sobha Sivaprasad (Clinical)
3 Ruth Hogg (Clinical)
4 Graham Scotland (Health Economics)
5 Katie Banister (Trial management)
6 Jonathan Cook (Methodology)
7 Augusto Azuara-Blanco (Clinical)
8 Heinrich Heimann (Clinical)

Project Management Group (PMG)

This group is comprised of the grant holders along with representatives from the EDNA central study team:

1 Trial Manager(s)
2 Clinical Trial co-ordinator (Belfast)
3 Data co-ordinator
4 Senior Trial Manager
5 Senior IT Manager
6 Study statistician
7 Study health economist
8 Study programmer
9 Quality assurance manager

Steering Committee (SC) Members

The membership of this committee comprises of at least four independent members along with the Chief Investigator (Usha Chakravarthy) or a nominated delegate. The other EDNA study grant-holders and key members of the central office (e.g. the trial manager) may attend SC meetings.

Independent SC Members

1 (Chair) Rupert Bourne
2 Anat Loewenstein
3 Cathy Yelf
4 Yemisi Takwoingi
5 Michael Bowen
6 Mike Warren
7. Felicity Hart
8 Andrea Rogers

Study Office Team

This team comprises of the CI, Clinical trial co-ordinator (Belfast), and Aberdeen central office team members.

EDNA: Early Detection of Neovascular Age-related macular degeneration (AMD)

1. INTRODUCTION

1.1. Background

Neovascular age-related macular degeneration (nAMD) causes severe visual loss and is the most common cause of blindness in persons > 50 years old in the western world (Royal College of Ophthalmologists guidelines 2009). In recent years, there have been major advances in the clinical management of patients with nAMD, notably the introduction of biological therapies targeting vascular endothelial growth factor (VEGF), a protein implicated in the pathogenesis of this disease. Anti VEGF treatments have improved visual outcomes compared with laser therapies which were the mainstay in past decades (Rosenfeld 2006, Brown 2006). With anti VEGF treatments, although visual improvement occurs in some one-third and a further 40% of those treated will maintain visual acuity at their immediate pre-treatment level, there is a considerable residual burden of visual morbidity. This residual burden of visual disability is evident in the outcomes reported in the pivotal clinical trials as well as in subsequent trials and post licensing studies. For example 40% of patients will have acuities of 20/50 or worse after two years of intensive treatment and the proportion of those with 20/20 or better acuity (normal vision) is small (less than 5%) (Martin 2012). The reality is that normal vision is still a long way from being achieved. There are a multitude of reasons why the present treatments do not restore normal macular function. These include (a) the presence of a neovascular network with a large component of mature vessels which do not regress or permanently close with anti VEGF treatment (b) glial and fibrous tissue that distort the delicate cellular architecture of the retina, (c) neural and retinal pigment epithelium (RPE) cell loss. Thus permanent morphological damage of the macular tissues at the time of presentation and a degree of irreversible visual loss remain important barriers to visual recovery. Therefore there is a strong rationale to detect the onset of nAMD at a stage when the cellular constituents of the retina have the potential to recover, prior to the onset of fibrosis and when the neovascular complexes have not matured to the point where they are less likely to regress.

There is a body of evidence in the literature to indicate that when nAMD occurs in the first eye, it often remains undetected for long periods and patients are unaware of a visual deficit because the fellow eye usually has good function and masks the deficit (Age-related macular degeneration guidelines 2009 Royal College of Ophthalmologists). Patients are often more alert to alterations in visual function in the second eye. However evidence indicates the second eye too has suffered considerable losses of acuity by the time the patient has sought help. In one study which followed up patients enrolled in a laser prevention trial the average acuity at presentation when nAMD was detected in the better seeing eye was 20/100 which represents more than a quadrupling of the visual angle (Maguire 2008). Reasons for the delay in presentation included (a) development of the lesion at an extrafoveal location with no early impact on acuity (b) a sudden onset of a bleed or an acute increase in exudation with involvement of the fovea by these manifestations (c) adjustment to minor changes in visual function. Approximately 8-10% of patients with nAMD in one eye will develop the same condition in the fellow eye per year. Detection of nAMD at a stage when damage to the retina is not permanent with prompt initiation of treatment could result in much better preservation

of sight. Therefore there is a clear need for an easily and rapidly performed cost effective monitoring test that will detect the onset of nAMD with high diagnostic accuracy.

Scale of the problem in the UK and use of NHS resources
Neovascular AMD remains the most common cause of blindness and partial sight in the UK (Age-related macular degeneration guidelines 2009 Royal College of Ophthalmologists) despite improvements in treatments. The incidence of AMD increases with age, and therefore the burden is projected to rise steeply in future years as the population ages. Vision loss is associated with a profound impairment of quality of life, increased risk of falling, emotional distress, depression and inability to care for self and for others. Patients with bilateral vision loss suffer from visual hallucinations (Charles Bonnet syndrome), poor sleep patterns and loss of confidence. Managing neovascular AMD presents an enormous burden to the NHS. Ophthalmology accounts for 10% (five million per year) of all outpatient attendances to the NHS, and age-related macular degeneration accounts for 15% of all ophthalmology outpatient attendances. (Age-related macular degeneration guidelines 2009 Royal College of Ophthalmologists). This is because patients are typically seen every two months, after initiation of anti VEGF therapy, for up to two years and long term studies from the UK show that some 50% of those who are commenced on treatment are still on active treatment or being followed up even after 5 years (National ophthalmology dataset paper 1, submitted for publication, under review).

Evidence for monitoring intervals/diagnostic performance
When active nAMD is confirmed, treatment with anti VEGF therapy is initiated (Chakravarthy 2010, IVAN investigators 2012; Martin 2012). In the early phases of treatment (ie up to about one year), at each subsequent visit which is usually on an 8 week cycle, patients are re-assessed to evaluate disease activity. Visual acuity, clinical biomicroscopic examination and optical coherence tomography (OCT) are the most commonly employed tests in the follow up setting. OCT-guided re-treatment decisions is the standard of care in almost all NHS units, however the combination of VA, clinical examination and fluorescein angiography in selected cases is also used in the monitoring phase (Chakravarthy BMJ, Martin 2012). In the absence of disease activity on the tomogram, treatment is withheld and review arranged. Interrogation of the national ophthalmology dataset (NOD), which is an amalgamation of the electronic records of some 14,500 patients who have received anti VEGF treatments since 2009, (Chakravarthy is a contributing member) shows that the average number of visits is 10 in year 1 and around 8 in year 2. The average interval in year 1 between visits is 35 days (+/- 10). The interval between visits increases in years 2 to 5. However, even in year 5, more than half of all persons are on regular review and treatment. Thus there is an opportunity to obtain information on unaffected fellow eyes of patients with nAMD in one eye to determine the optimum method of early detection of incipient nAMD.

1.2. Rationale for the study

Scrutiny of the outcomes from the large clinical trials shows that if treatment is commenced when acuity is better than 73 letters (Snellen equivalent 6/12), over 90% maintain this level of vision or better (Martin 2012, IVAN 2012). Better acuity is associated with smaller nAMD lesions and thus early detection of nAMD and prompt initiation of treatment will result in final visual outcomes that are consistent with good visual function. The proposed research is

particularly important because (1) there is a large patient pool whose care pathway requires regular visits and monitoring (every 8 weeks) offering the ideal situation for a study of early detection of nAMD in fellow eyes of patients with nAMD in one eye (2) these patients are subjected to tests of function (acuity) and tomography and it is current clinical practice to acquire information on both eyes at every visit (3) the tomographic examination is quick (performed without the need for pupillary dilation and the quality of the tomograms are high as all the NHS units offering anti VEGF therapies have invested in high resolution fourier domain OCT technology (4) the patients are motivated and the NOD has shown that attendance is high with dropout less than 10% per annum.

2. STUDY AIM AND OBJECTIVES

Aim: To identify the optimum non-invasive test strategy that will robustly detect nAMD in fellow eyes during follow-up in secondary care of persons with nAMD in the first affected eye.

Objectives

Primary objective: determine the diagnostic monitoring performance of the interventions (ETDRS visual acuity; fundus evaluation of signs of nAMD; the Amsler test; clinical assessment of images captured by OCT; patient's subjective assessment of vision against the reference standard of fundus fluorescein angiography);

Secondary objectives:

1. develop an economic model to identify an optimal monitoring regime;
2. develop a risk prediction model using baseline characteristics to predict the development of nAMD in the study eye;
3. create a cohort (including a Biobank) which can be used for future prognostic and diagnostic studies.

3. STUDY DESIGN

The study design is a multi-centre prospective cohort diagnostic accuracy study with up to 3 year follow-up. Once enrolled into the study, the participants will be monitored following standard clinical practice in the diseased eye. The standard of care in the NHS for patients newly diagnosed with nAMD is regular (approximately every 8 weeks) assessment and treatment if required. At each monitoring visit, patients will be examined using all index tests in the study eye (unaffected) and a reference standard measurement triggered if any of the index tests are positive (see flow chart). All patients will be followed-up according to standard clinical practice until confirmed treatment for nAMD in the study eye or up to 3 years from enrolment, whichever is sooner. Patients who do not have confirmed nAMD in the study eye during the follow-up period will have a FFA at 18 months and at exit. The study has been designed to have minimum impact on the current patient care pathway. A schematic of the study design is shown below.

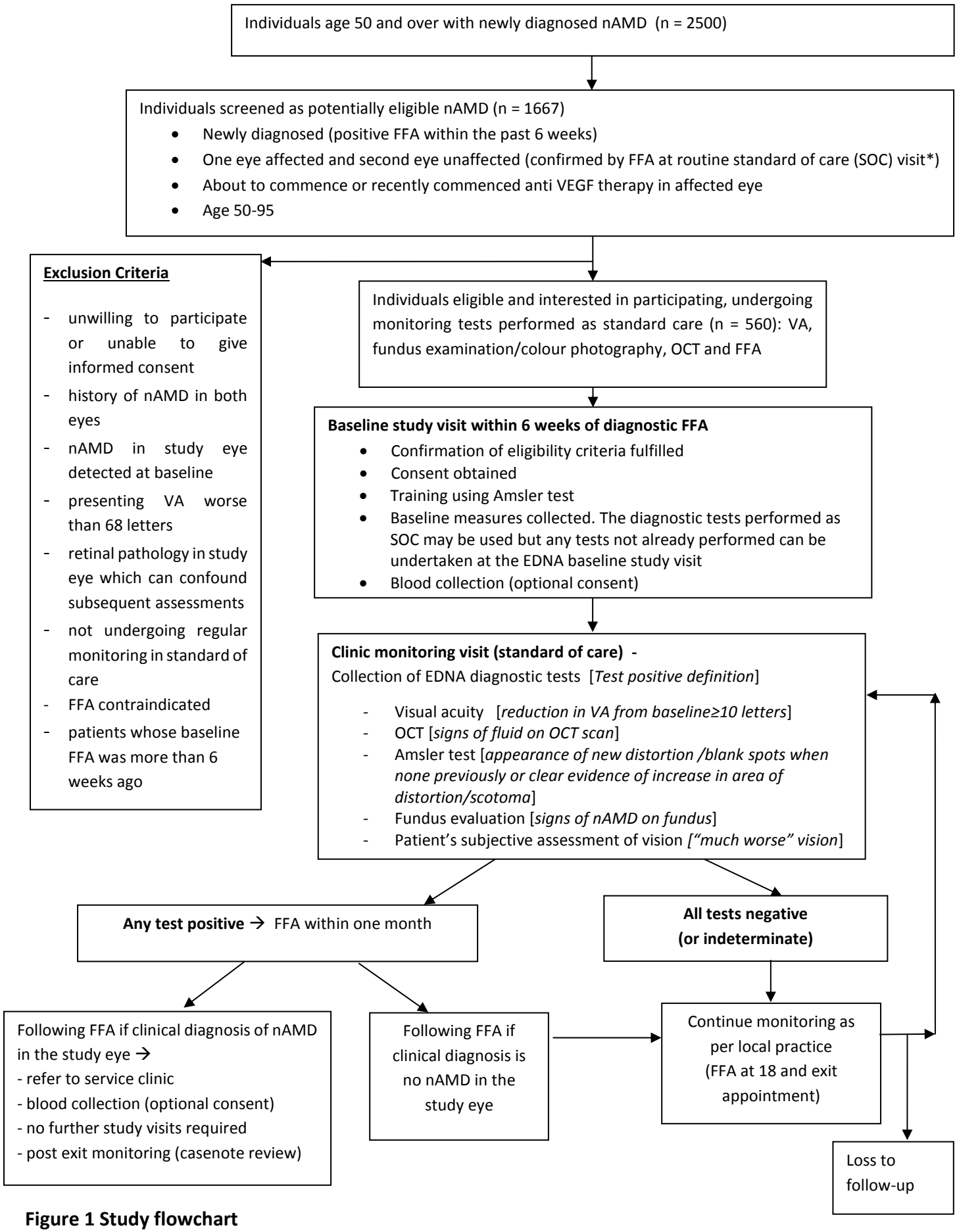

Figure 1 Study flowchart

*** Referred to as "diagnostic FFA" from now on**

3.1. Definition of the study eye

The “study eye” is the eye without nAMD at the baseline visit.

3.2. Interventions to be evaluated (Index tests)

As part of routine care for the fellow eye (with nAMD) it is expected that patients will attend regular monitoring visits. The frequency of visits is likely to be between 4 and 8 weekly in year 1 and extended to between 8 and 12 weekly in year two but is contingent on local AMD treatment pathways. The candidate tests which are part of routine clinical practice are performed on both eyes at every visit and therefore the data acquired at these visits on the EDNA study eye will be collected and evaluated:

3.2.1. Fundus evaluation

Examination of the macula can reveal fluid and/or lipid (yellow deposition) and/or blood. Other features of AMD such as drusen and pigmentary irregularities may be observed. Sometimes these latter features are obscured by the exudative manifestations or may be absent in specific AMD phenotypes such as idiopathic polypoidal choroidopathy. This can be assessed using slit lamp biomicroscopy or fundus photography

Signs suggestive of nAMD include the following:

- Subretinal or sub-RPE neovascularisation which may be visible as a dark grey lesion. Occasionally the lesion will have a dark pigmented edge which is thought to be due to proliferation of the RPE at the edge of the membrane.
- Serous detachment of the neurosensory retina.
- RPE detachment.
- Haemorrhages- subretinal pigment epithelial, subretinal, intraretinal or preretinal. Breakthrough bleeding into the vitreous may also occur, indicating most often the presence of idiopathic polypoidal choroidal vasculopathy (IPCV).
- Hard exudates (lipids) within the macular area related to any of the above, and not related to other retinal vascular disease.
- Epiretinal, intraretinal, subretinal or sub-pigment epithelial scar/glial tissue or fibrin-like deposits.
- Retinal angiomatous proliferations: microvascular proliferative lesions located within the retina
- Choroidal polyps: spherical lesions associated with choroidal vessels which cause the RPE to be focally elevated.

Definition of test positive:
A positive fundus evaluation test is one as determined by an expert showing signs of nAMD on the fundus, and will trigger a reference standard test (FFA).

3.2.2. Patient’s subjective assessment of vision

The onset of exudative AMD may be heralded by the appearance of central visual blurring and distortion. Patients may complain that straight lines appear crooked or wavy when the lesion involves the central macula. At each follow-up visit patients will be given standard instructions to answer the following question: “how is your vision in the (unaffected) eye?” The patient will be prompted to answer one of the following four possibilities: “about the same or better”, “a bit worse”, “worse”, or “much worse”.

Definition of test positive:
A positive subjective report test is one where the patient reports “much worse” deterioration and it will trigger a reference standard test (FFA).

3.2.3. Visual acuity

Patients with new onset nAMD will usually have a decrease in best corrected visual acuity (BCVA). Visual acuity is a measure of the spatial resolution of the visual processing system. It is a psychophysical test requiring a response from the person to be tested. Usually high contrast letters of diminishing size are displayed on a chart at a set distance. The most commonly used chart is the early treatment diabetic retinopathy study chart (ETDRS) which is based on a geometric progression of letter sizes with 5 letters in each row. A 3 line difference in either direction from any given line represents a halving or a doubling of the visual angle. BCVA provides a measure of resolution at the fovea. A change of $\leq$ 5 letters (one full line) on the ETDRS chart is considered to be within the limits of the reliability and reproducibility of the measurement. Therefore a change of 10 letters or more will be considered to be a true reduction in BCVA.

Definition of test positive:
A positive visual acuity test is one where there is a reduction of 10 or more letters in BCVA from baseline and this will trigger a reference standard test (FFA). In the event that the triggered FFA is negative, and at subsequent visits there is additional vision loss, an FFA can be triggered at the discretion of the clinician.

3.2.4. Amsler test

The Amsler chart or grid is a grid of horizontal and vertical lines used to monitor a person's central visual field. It is a simple, inexpensive, diagnostic tool that aids the detection of visual disturbances caused by changes in the retina, particularly the macula (e.g. macular degeneration). In the test, after covering one eye the person looks with the eye to be tested fixating at the small dot in the centre of the grid printed on the Amsler test sheet. Patients with macular fluid may see distortion of the straight lines or areas of the pattern may be missing. Patients should have a normal Amsler test in the study eye at baseline. In patients who have distortion on Amsler at baseline, Amsler tests will not be collected in the subsequent assessments or trigger any FFA.

Definition of test positive:
For the purpose of this study a positive Amsler test is, as assessed by the clinician, appearance of a new area of distortion or blank spots when previously there was none or clear evidence of increase in the area of distortion or scotoma. This will trigger a reference standard test (FFA).

3.2.5. Optical Coherence Tomography (OCT)

Optical coherence tomography is a light-wave based technology producing cross sectional images of the retina with scan rates and resolution parameters that have greatly improved over the last 10 years. It is a non-invasive, non-contact visual test, rapidly and easily performed requiring less than 5 minutes to assess both eyes. (Medical Advisory Secretariat 2009) Tomograms are acquired by trained medical photographers. The tomogram is a sequential collection of some 25,000 A scans (reflectivity profile in depth) which are sequentially incorporated into a cross sectional image of the retina which is a B scan. A series of B scans

are constructed across the macular region of the eye and depending on the orientation of the scan can be a rectangular raster or a star pattern. The density of the scan lines can be modified from widely to tightly spaced with the latter providing more detailed information. The scans can be displayed in 3 dimensional mode providing information on the various retinal layers. Automated segmentation algorithms provided by the manufacturer generate averaged retinal thickness and volume measurements for regions (sectors) of retina. These algorithms have been shown to provide consistent and reliable estimates in normal eyes. However in the presence of disease with alterations in the retinal layer anatomy the algorithms frequently fail leading to considerable error and variability in the segmentations and thus the thickness and volume measurements are generally unreliable. Presently many groups including that of one of the applicants are exploring the use of automated segmentation algorithms on the imaging outputs. Promising results indicate that automated segmentation is a reality and that subjectivity of interpretation may be replaced in the future by objective computerised assessments.

A scan passing through a normal retina is shown. The separation of the various retinal layers can be seen and there may be deviation in the interfaces between the layers and or alterations in reflectivity. In nAMD, abnormal dilations and growth of blood vessels in the retina and choroid can result in fluid and or blood seeping into the various tissue spaces changing the normal retinal architecture and or altering the normal reflectivity. These characteristics are noted and reported by clinicians experienced in the interpretation of OCT.

When abnormalities as a consequence of AMD develop in the retinal and choroidal circulations (such as dilation of existing vessels or growth of new vessels), there is accumulation of fluid within the macular tissue compartments with separation of the normal tissue interfaces. In addition seepage of haemoglobin, other cellular and proteinaceous or lipid constituents of blood into the retina can cause alterations in the internal reflectivity and homogeneity of the retinal layers and these can take the form of areas of dense hyperreflective material or foci. The appearance of abnormalities when previously there was none as well as their spatial localisation and distribution can alert the clinician to the onset of nAMD even when the signs are subtle and only just discernible.

For the purpose of this study any OCT machine can be used for data collection.

Definition of test positive:

Any of the above positive findings in the OCT exam as interpreted by an experienced ophthalmologist, will trigger a reference standard test (FFA)

3.3. Comparator intervention: Reference standard: fluorescein angiography (FFA)

Fluorescein angiography is currently the reference standard for diagnosing choroidal neovascularization (CNV) in AMD (i.e, nAMD). A fluorescein angiogram is a sequence of images of the fundus captured over a 10 minute period after injection of the non-toxic dye fluorescein isothiocyanate into a suitable peripheral vein. The diagnosis of neovascular AMD is by FFA. A technician or photographer performs the test, which is interpreted by an ophthalmologist. Pupils need to be dilated prior to the test. Neovascular AMD can be classified on the basis of the temporal and spatial features of the patterns of fluorescence as observed on the FFA:

Classic CNV is said to be present when an area of well delineated hyperfluorescence appears in the early phases of the FFA. Most commonly, classic CNV represents new vessels that have breached the RPE and lie in the subretinal space. Sometimes a typical lacy pattern of hyperfluorescence is observed in the very early phase of the angiogram which corresponds to the vascular profiles before the fluorescein has leaked out of these vessels and obscured the margins. Classic CNV also leak aggressively and hence there is considerable pooling of fluorescein dye in the sub-retinal space in late frames of the angiogram. Multimodal imaging shows that these neovascular complexes lie between the RPE and the neurosensory retina and have a feeder vessel arising from the choroidal circulation.

Occult CNV, as its name suggests, refers to the presence of leakage without clear evidence of neovascular profiles in the early angiographic images. Two types of occult leakage are recognised. The first is a characteristic stippled hyperfluorescence which occurs early and is located at the level of the RPE. The RPE layer is elevated and in the later phases of the angiogram there is increasing hyperfluorescence and pooling of dye in the subretinal pigment epithelial space. The pattern of leakage suggests new vessels between Bruch's membrane and the RPE and it is therefore considered to be a fibrovascular pigment epithelial detachment (FPED). The second pattern of occult leakage is a more diffuse hyperfluorescence with poorly demarcated boundaries which occurs late in the angiographic phase generally after 2 minutes have elapsed since injection of dye. There is no corresponding hyperfluorescence in the early frames and there is shallow elevation of the RPE. This type of leakage is referred to as late leakage of indeterminate origin (LLIO). OCT has shed further light on these patterns of leakage and has revealed that the neovascular complexes of FPED and LLIO patterns are present in the sub-retinal pigment epithelial space causing irregular elevation of the RPE.

Retinal angiomatous proliferation (RAP). This type of neovascularisation consists of intraretinal telangiectatic blood vessels that are strongly associated with serous pigment epithelial detachments and a form of drusen known as reticular drusen.

Idiopathic polypoidal choroidal vasculopathy (IPCV). Polyps are seen as focal, round areas of abnormal dilated choroidal vessels, often associated with large areas of lipid deposition and haemorrhage. The presence of haemorrhagic PED is highly suggestive of the presence of this phenotype. These polyps are best visualised by indocyanine green angiography which is recommended if the combination of FFA and OCT features suggest presence of this variant of nAMD (Age-related macular degeneration guidelines 2009 Royal College of Ophthalmologists).

Definition of test positive:

A positive reference standard (FFA) test is one showing typical changes of nAMD as described above and as determined by an experienced ophthalmologist,

3.4. Study population

Patients with newly diagnosed nAMD in one eye and an unaffected second eye (study eye)

Setting: Secondary care, ophthalmology outpatient departments

3.5. Planned inclusion and exclusion criteria

Inclusion criteria:

- Newly diagnosed nAMD in one eye and an unaffected second eye (diagnostic FFA to be within 6 weeks prior to consent)
- About to commence or recently commenced anti VEGF therapy in the first eye
- Age 50 -95

Exclusion criteria:

- patients with a history of nAMD in both eyes;
- nAMD in study eye detected at baseline;
- presenting visual acuity worse than 68 letters;
- retinal pathology in the study eye which can confound subsequent assessments (e.g diabetic retinopathy, macular hole);
- not undergoing regular monitoring in standard of care;
- patients who cannot give informed consent;
- unable to undergo a fundus fluorescein angiography (FFA) test;
- patients whose diagnostic FFA was more than 6 weeks ago

3.6. Recruitment and Study Procedures

3.6.1. Identifying participants

Definition of 'newly diagnosed'

For the purpose of EDNA, a patient is defined as 'newly diagnosed' if they are newly referred to secondary care and have had a diagnosis of neovascular AMD in one eye only and begin treatment with an anti VEGF. At the point of enrolment into EDNA (i.e. consent) this must be within 6 weeks of diagnosis by an FFA (the diagnostic FFA). Although a time interval of 6 weeks is permitted, it is recommended that enrolment into EDNA with appropriate data extraction occurs sooner than the maximum permitted 6 week window.

Patient approach

Patients newly diagnosed with nAMD will be identified by the clinician or research nurse in each centre. Patients will be approached by the clinician or research nurse at the time of diagnosis. Information about this study will be given to potentially eligible patients. A log of potentially eligible patients will be taken in order to document reasons for non-inclusion in the study to inform the study flow diagram. Patients who agree to participate will be invited to attend a study clinic. This may take place any time from the date of initial diagnosis (by diagnostic FFA) until 6 weeks later. A full baseline eligibility assessment (according to inclusion and exclusion criteria listed in section 3.5) will be undertaken at the first study visit (See flow chart). Once a patient has been confirmed as eligible, informed consent will be obtained by an appropriately trained individual.

3.6.2. Informed consent

Informed consent to participate in the study will be sought and obtained according to the principles of Good Clinical Practice (GCP). Informed signed consent will be obtained from the

participants in all centres, by an appropriately trained individual. Participants will be given sufficient time to accept or decline involvement and will be free to withdraw from the study at any time. Participants who cannot give informed consent (e.g. due to their mental state) will be not be eligible. The participants will be asked to consent to participation with an option to consent for the following: follow up; contact in the future about this and other research; electronic tracing using NHS data; and data linkage with routine NHS data sources; consent to the taking and storage of blood.

In order to facilitate recruitment, potentially eligible patients who have been diagnosed in clinic may also be approached about EDNA participation via telephone during this 6 week window.

3.6.3. Ineligible and non-recruited participants

Brief details of all screened patients will be recorded (including – where known – age and sex). Reasons for ineligibility or if eligible but declined to take part, reasons for declining will be logged whenever possible.

3.6.4. Baseline measurements

The list of procedures by visit is shown in Table 1.
The diagnostic FFA is collected as part of routine care and used to assess eligibility prior to consent. This FFA measurement is used as the baseline FFA for EDNA and therefore does not need to be repeated after consent. Any EDNA diagnostic tests (described in section 3.2 above) which have already been collected as part of routine care within 6 weeks prior to consent may be included in the case report form for the baseline measurement.
The following assessments may be performed at the baseline study visit if data from the routine visit is not available in order to establish a baseline for all the index tests at study entry. VA in the EDNA study eye. Recording of findings arising from slit lamp biomicroscopy with particular emphasis on the status of the macula and the vitreo retinal interface. Colour fundus photography central macular fields 1 and 2 and a single wide field image if appropriate equipment is available. Fundus autofluorescence with blue or green (optional). Macular raster OCT without and with enhanced depth imaging of the choroid. Amsler chart completion.

Patients who consent to have blood collection and storage will have blood collected at baseline and at study exit.

A participant will enter the EDNA cohort if measurements on the baseline case report form have fulfilled the eligibility criteria, and informed consent and all baseline measurements have been obtained within 6 weeks of diagnostic FFA.

3.6.5. Blood collection and storage

Patients who agree to the collection of blood will have approximately 20ml of blood collected at their study visit. Blood will be labelled with a code and any personal details will be removed. The coding will maintain confidentiality whilst allowing biological details to be analysed. The samples collected in this study will be sent to Queen's University Belfast for storage and will be stored indefinitely. Research using the samples will be conducted only after approval by a Research Ethics Committee. Participants may grant advance authorisation for possible future research, with the understanding that confidentiality will be fully protected or can consent just for the analysis for the needs of the EDNA study.

3.6.6. Follow-up procedures

Once enrolled into the study, the participants will be clinically monitored following standard clinical practice in the eye with nAMD. The standard of care in the NHS for patients newly diagnosed with nAMD is regular (approximately every 8 weeks) assessment and treatment as required. At each follow up clinic visit VA, clinical signs on fundus, comments on the OCT appearance, self reported function and Amsler [index tests that are performed in the EDNA study eye] will be extracted. A FFA (reference standard assessment) will be triggered if any of the index tests are positive (see flow chart). Following this a clinical diagnosis of the presence of nAMD in the study eye will be made. If nAMD is diagnosed the patient will be clinically monitored and treated as per local clinical practice.

At M 18 a study visit which will occur if the participant remains in the study by virtue of not having experienced a neovascular event in the EDNA study eye, all tests undertaken at baseline along with an FFA will be performed with subsequent clinical diagnosis of the presence of nAMD in the study eye. Similarly, at M 36 a study exit visit which will occur if the participant remains in the study by virtue of not having experienced a neovascular event in the EDNA study eye during the entire period of follow up, all the tests recorded at baseline along with an FFA will be performed. These study visits can take place within a 2 month time window either side of the exact due date.

If, as part of routine clinical management, an additional FFA is performed in the non study eye and results in the detection of nAMD in the EDNA study eye then these results should be recorded in the EDNA CRF and study monitoring follow-up will cease.

3.6.7. End of participant follow-up

All patients will be followed-up according to standard clinical practice up to 3 years from enrolment. Study monitoring follow-up will end prior to 3 years upon a clinical diagnosis of nAMD in the study eye or if a patient withdraws consent to continue this follow-up (see section 3.6.8 for information on the withdrawal procedures). If the participant does not attend for their last study visit this can be rearranged within the following 2 months.

3.6.8. Change of Status/Withdrawal procedures

Participants will remain in the study unless they choose to withdraw consent or if they are unable to continue for a clinical reason. All changes in status with the exception of complete withdrawal of consent will mean the participant is still followed up for all study outcomes wherever possible. All data collected up to the point of complete withdrawal will be retained and used in the analysis unless the participant requests this to be destroyed and excluded. If the participant had previously consented to and donated blood for storage, and the participant later withdraws consent, they may also request for their donated blood to be destroyed.

3.6.9. Subsequent arrangements

Informing key people

Following formal study entry the local research officer will:

1) Inform the participant's General Practitioner (by letter enclosing information about the EDNA study and Study office contact details).

2) File the hospital copy of the consent form in the hospital notes along with information about the EDNA study.
3) Use the EDNA study database to enter data regarding the participant
4) File study documentation according to local regulations.

Notification of/by GPs
GPs are asked to contact the study office if one of the participants moves, becomes too ill to continue or dies, or any other notifiable event or possible serious adverse event occurs. Alternatively, staff at the study office may contact the GP.

4. SAFETY

4.1. Definitions

Within the EDNA study we will record only any AE/SAE relating to collection of blood or FFA requested during involvement in the study. AEs relating to FFAs conducted prior to recruitment to the study will not be reported.

Any AE/SAE resulting from treatment to the nAMD eye during the study will not be recorded as an AE/SAE. Once an EDNA participant has nAMD in the study eye, or the end of follow-up, any subsequent AE or SAE will not be recorded.

An **adverse event** (AE) is any untoward medical event affecting a clinical study participant. Each initial AE will be considered for severity, causality or expectedness and may be reclassified as a serious event or reaction based on prevailing circumstances.
A **serious adverse event** (SAE), is any AE, that:

- results in death;
- is life threatening (i.e. the subject 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);
- requires hospitalisation or prolongation of existing hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect,
- is otherwise considered medically significant by the investigator

EDNA Expected adverse events:
In this study the only AE and SAE that are expected relate to the collection of blood and the FFA.

FFA related expected adverse events: These may be local skin irritation, development of erythematous lesions on the skin immediately after FFA and more generalised reaction to the FFA with pulmonary and or other systemic manifestations (anaphylaxis)

Blood collection expected adverse events: bruising and discomfort at the site of any puncture

Reporting of deaths during the study:
Most participants in the study will be elderly, and we anticipate that 50% will be >75 years at the time of recruitment. Therefore it is expected that a proportion of the cohort will die from

causes unrelated to the study over the period of follow up. Deaths unrelated to the study procedures will not be recorded as SAEs but will be recorded within the CRF.

4.2. Procedures for detecting, recording, evaluating & reporting AEs, SAEs

4.2.1. Detecting AEs and SAEs

All AEs and SAEs as defined in section 4.1 above must be recorded from the time a participant consents to join the study until the last study visit.
The Investigator should ask about the occurrence of AEs/SAEs at the next study visit after any study FFA or blood collection. If there is any doubt as to whether a clinical observation is an AE, the event should be recorded.

4.2.2. Recording AEs and SAEs

Depending on severity, when an AE/SAE occurs after blood collection or FFA, it is the responsibility of the Investigator (or delegate) to review appropriate documentation (e.g. hospital notes, laboratory and diagnostic reports) related to the event. The Investigator (or delegate) should then record all relevant information in the CRF and on the SAE form if it is an SAE.
Information to be collected includes type of event, onset date, Investigator assessment of severity and causality, date of resolution as well as treatment required, investigations needed and outcome.

4.2.3. Evaluating AEs and SAEs

Seriousness, causality, and expectedness should be evaluated.

Assessment of Seriousness

The Investigator should make an assessment of seriousness as defined in Section 4.1.

Assessment of Causality

The Investigator must make an assessment of whether the AE/SAE is likely to be related to treatment according to the following definitions:

- **Related**: resulted from administration of any of the research procedures
- **Unrelated**: where an event is not considered to any of the research procedures.

Alternative causes such as natural history of the underlying disease, concomitant therapy, other risk factors and the temporal relationship of the event to the intervention should be considered.

Assessment of Expectedness

When assessing expectedness refer to the expected events (Section 4.1).

4.2.4. Reporting AEs and SAEs

Reporting responsibilities of the CI

When an SAE form is uploaded onto the study website, the Trial Manager will be automatically notified. If, in the opinion of the local PI and the CI, the event is confirmed as being *serious* and *related* and *unexpected*, the CI or Trial Manager will notify the sponsor within 24 hours of receiving the signed SAE notification. The sponsor will provide an assessment of the SAE. A Sponsor cannot downgrade an assessment from the PI or CI. Any disparity will be resolved by further discussion between these parties.
The CI or delegate will report any related and unexpected SAEs to the REC within 15 days of the CI becoming aware of it. All related SAEs will be summarised and reported to the Ethics Committee, the Funder and the Steering Committee in their regular progress reports.

If all the required information is not available at the time of reporting, the Investigator must ensure that any missing information is provided as soon as this becomes available. It should be indicated on the report that this information is follow-up information of a previously reported event.

4.2.5. Regulatory reporting requirements

The Chief Investigator is responsible for submitting annual reports to the REC on the anniversary of the approval.

All adverse events will be assessed in respect of seriousness, relationship to study intervention, whether expected or unexpected, and therefore, whether constituting a Serious Adverse Event (SAE) by the local PI, CI or their deputies.

5. OUTCOME MEASURES

5.1. Primary outcome measure

The **primary diagnostic performance outcomes** will be the sensitivity and specificity of the index tests on detection of nAMD in the study eye in a monitoring setting.
The **primary economic outcome** will be the incremental costs (to the health service) per quality adjusted life year (QALY) gained.

5.2. Secondary outcome measures

Secondary diagnostic performance outcomes will include diagnostic odds ratio, likelihood ratio, proportion of indeterminate tests. The performance of combinations of tests will be evaluated. Other outcomes: time gain of early detection; visual acuity at diagnosis, performance of a risk predictor algorithm according to baseline characteristics, the establishment of a well characterised cohort of clinical and biological data for future research.

6. DATA COLLECTION AND PROCESSING

6.1 Measuring outcomes

In order to assess the sensitivity and specificity of the diagnostic tests under evaluation, each of the diagnostic tests being assessed will be performed on the study eye at each routine clinic visit during the period of follow up.
Results from the diagnostic tests according to the definitions described in 3.1 above will be recorded on a standardised case report form. If any diagnostic tests are positive this will trigger the request for an FFA and the absence/presence of nAMD (and classification) will be recorded. These data will be uploaded to the study website by study staff.

Economic outcomes will be modelled based on diagnostic performance data collected above.

6.2 Schedule of data collection

Assessment	Recruitment	Routine visits (approx. every 8 weeks)	If any diagnostic test positive	If FFA positive	18 months	Exit
Assessment of eligibility criteria	✓					
Written informed consent	✓					
Baseline vision and risk factors	✓					
Blood collection	✓			✓		✓
Diagnostic (index) tests: • Subjective patient vision • AMSLER • Visual acuity • OCT • Fundus examination • Autofluorescence (only if available)	✓*	✓			✓	✓
Reference standard: FFA	✓**		✓		✓	✓
Post conversion case note review						✓
Upload of required imaging to reading centre for analysis	✓		✓		✓	✓

*Any EDNA diagnostic tests which have already been collected as part of routine care within 6 weeks prior to consent do not need to be repeated after consent for the baseline measurement.

**The diagnostic FFA which is collected as part of routine care and used to assess eligibility prior to consent is used as the EDNA baseline FFA measurement and does not need to be repeated after consent. The FFA must have been undertaken within 6 weeks prior to consent.

Table 1: Schedule of data collection

Baseline measurements
At baseline, data collection will include: participant demographics, risk factors, whole blood (separated into white cells, serum and plasma), index test results, and reference standard results. Where baseline measures have already been documented in the clinical casenotes within 6 weeks prior to consent, these measures will be used for the baseline data collection form and they do not need to be repeated.

Follow-up measurements
Data collected at each routine clinic visit during follow-up will be extracted from the medical records. This will include, index test results, indication for FFA, FFA results if requested.

Post Conversion Case Note Review
Following conversion to nAMD, any routinely collected data on anti VEGF treatments, functional and morphological outcomes and medical assessments for up to 3 years post study recruitment will be extracted from the patient's medical records.

6.3 Data processing
Research nurses will enter locally collected data in the centres. Staff in the Study office will work closely with local Research Nurses to ensure the data are as complete and accurate as possible. Extensive range and consistency checks will be undertaken to further enhance the quality of the data.

Reading centre
An ophthalmic reading centre (Central Angiographic Resource Facility**)** located at Queen's University Belfast will independently undertake grading of anonymised images (FFA, OCT, fundus photography, autofluorescence- optional) acquired at all the timepoints highlighted in table 1.

7. SAMPLE SIZE, PROPOSED RECRUITMENT RATE, MILESTONES & INTERNAL PILOT

7.1 Sample size

The sample size is based upon comparative diagnostic accuracy to ensure the ability to detect differences in sensitivity and specificity between candidate tests. The calculation is based upon McNemar's test. (Obuchowski 1998) Under the primary analysis, a positive candidate test result will be defined as any positive result during the monitoring period on the respective test. At 2-sided 5% significance level and 90% power, a paired difference of 15% (80% to 65%) in sensitivity will require 491 participants (560 allowing for indeterminate/missing data results - including patients lost to follow-up cumulatively of up to 12%) given a cumulative incidence of 28% at 3 years.(Karnon 2008) This calculation assumes a disagreement between tests of 0.30 which was based upon data from a diagnostic study involving OCT for diagnosis glaucoma (HTA reference 09/22/111). A smaller difference in specificity will be identifiable (7%; 94% to 87% with power and significance levels as before) given most participants will not convert during the 3-year follow-up period even if the maximum level of disagreement occurs. The reference sensitivity and specificity values used in this calculation are the values observed for OCT in a pilot study with a similar study design.(Parnick-Silver 2012) Differences in sensitivity and specificity of at least 20% will also be detected at the same power and significance levels even if the

sensitivities/specificity are substantially lower (e.g. 60 to 40%) or the level of missing data is higher (e.g. 20%). These calculations conservatively assume maximum possible disagreement between tests. A sample of this size would be of sufficient size for other measures of diagnostic performance (e.g. the sensitivity and specificity of individual technologies will be estimated to 95% confidence interval of width 16% and 10% respectively given a sensitivity/specificity of 65% or higher). Such a sample will also provide a sufficient sample for the GEE analysis given the anticipated gain in precision due to use of multiple repeated measures over time.(Rochon 1998) Similarly, this sample will be more than sufficient for the development of a risk prediction model with over 130 events (conversions to AMD) anticipated and given 10 events per predictor variable/contract are typically recommended.(Peducci 1995)

7.2 Recruitment rates & Milestones

The study will recruit 560 participants. We aim to recruit from at least 16 centres, each centre recruiting around 4 patients a month.

In 2012, over 2000 newly diagnosed patients with nAMD were seen in 16 of our potential study sites. We anticipate that some 2/3 of these patients will be eligible for the study. Assuming that of these eligible patients 50% will be willing to participate, recruitment to target sample size should be achievable in a 16-month period. Site start-up will be in a staggered fashion from month 4 - 14. Recruitment by site will vary depending on length of recruitment phase and the size of the local patient pool. It is expected that each site will recruit between around 20 and 60 participants.

Recruitment and study milestones are shown below

Month	Milestone
Pre –funding	Ethical approval
1	First steering group
1-6	Study set-up, authorisations and protocol finalised
4-14	Centre set-up; recruit local staff
15	Report on internal pilot
4 – 28	Recruit patients (staggering centre start-up)
55	Final patient follow-up (up to 3 years)
55-59	Data cleaning and preliminary analyses
59-63	Final analyses and reporting

7.3 Internal Pilot

We propose to run an internal pilot in this study designed primarily to verify that recruitment to target is possible. In addition, we will assess the quality and completeness of data collection at routine follow-up appointments. We will make a decision about feasibility at around month 14 when 86 centre months have been accrued and approximately 280 participants have been recruited. At this timepoint we anticipate that the initial 3 centres will have reached steady state and have up to 6 months of follow-up data to assess data collection; initial data from up to 6 sites more recently set-up will be included. Our stop-go criteria at this point in time are categorised into three: if recruitment was <50% of the anticipated recruitment rate at this time

we would consider this effort futile and stop the study; if between 50% and 75% we would make major changes (additional centres, review of inclusion/criteria etc); and if >75% we would proceed with minor changes, as we would be confident of attaining our recruitment target. We have based our calculations on an estimated recruitment of between 3 to 4 participants per centre per month. In addition to recruitment, the other important measure is the application of the study protocol interventions. In particular, that if any of the tests are positive, a FFA will be requested. After 86 centre months, we will also report the proportion of FFA requested after a positive test. If the proportion <50%, we would consider this futile and stop. The thresholds for the actions - <50% for futility, 50-75% for major change, and >75% for continuation with at most minor modification, are of course for guidance. They are intended to provide indicative thresholds to concentrate the discussions around the three options. Potential modifications of the design could include more centres and/or a longer recruitment window, and would be discussed carefully with the HTA's full input. If the trial progressed as planned we would anticipate having162 participants by month 12, and 560 by month 19.

8. STATISTICAL ANALYSIS

Participants are categorised as AMD or not AMD according to the presence of a positive FFA result during the follow-up period. Two main statistical analyses of diagnostic accuracy are planned, a) the primary single test result diagnostic accuracy analysis and b) a more secondary complex analysis which utilises repeated test results.

Under the first approach, repeated monitoring test assessments are collapsed over time to give a single candidate test result (positive or negative). The presence of a positive candidate test result within a fixed time period (e.g. within 6 months of diagnosis/study completion) of the positive reference standard value is treated as a true positive, positives outwith this period are false positives, participants who tested negative through the period are either true negative (if there is no positive reference standard test within the follow-up period) or false negative (if not). Under the primary analysis, monitoring sensitivity and specificity of the tests will be compared using McNemar's statistical test (with 95% confidence intervals produced using Newcombe's method).(Newcombe 1998) Sensitivity analyses will include assessment of alternative definitions of a positive test result in a monitoring setting (e.g. using only the test result at diagnosis/study completion), and consider combinations of tests. Sensitivity, specificity, positive and negative likelihood ratios and (when possible) the area under the receiver operating characteristics curve will be calculated (with 95% confidence intervals) for each test using FFA test results as assessed by the responsible ophthalmologist as the reference standard (Zhou 2002, Altman 2000). A secondary analysis will use an alternative reference standard of FFA test results as assessed by the reading centre. A ROC curve for each imaging test will be produced and the area under the ROC curve will also be formally compared between technologies.(DeLong 1988) All analyses will be conducted at 5% (2 sided) significance level with 95% confidence intervals produced where appropriate.
A GEE modelling approach will be used to allow the simultaneous modelling of sensitivity and specificity in a regression framework and use of multiple test results per participants over time. The score test from the GEE model can be viewed as a generalisation of McNemars test and will be used to formally compare sensitivity and specificity between tests.(Leisenring 1998) A GEE modelling has the advantage of allow a flexible regression framework (with easy comparison

between tests), allowing for clustering of observations by participants and incomplete data without only requiring extensive distributional assumptions.

Sensitivity analyses will be conducted to assess the impact of severity of nAMD at the time of conversion. Further sensitivity analyses will look at the impact of varying the test cut-off for relevant tests (varying positive test definition of the patient's subjective assessment to "worse" and of the visual acuity test to 4/6 letters) to explore possible threshold effects. Additionally, using a combination of tests under simple approaches (e.g. both positive or either positive) or by generating a prognostic rule using multivariable logistic regression model, instead of a single test under the diagnosis analysis approach.(Miettinen 1998) Specifically, the impact of combining OCT with fundus evaluation, Amsler test, patient's subjective assessment of vision, or visual acuity tests will be considered.

The survival distribution of conversion to nAMD over the follow-up period will also be estimated. A Kaplan-Meier curve will be fitted to estimate the underlying nAMD conversion distribution. Time of conversion will be estimated based upon the date of conversion confirmation, previous visits and the last FFA. The impact of varying this assumption will be assessed along with modifying the definition of conversion to nAMD. Furthermore, a risk prediction model using Cox regression will be developed to predict conversion to nAMD in the fellow (normal) eye using baseline risk factors. The following risk factors have been shown to determine the development of nAMD: age, raised blood pressure, smoking, obesity, ethnicity, and ocular risk factors (including type, size and number of drusen in the fundus of the study eye, presence of pigmentary abnormalities in the fundus of the study eye, and type and severity of nAMD in the diseased eye) and will be collected at the baseline visit. The model's predictive performance will be assessed in terms of discriminative and calibrative ability. Discriminative ability will be assessed using Harrell's *c*-index. Calibration will be assessed by plotting the average predicted risk will be compared with the corresponding Kaplan-Meier estimate of the observed risk by tenth of predicted risk. Recalibration of the model will be undertaken via adding/removing predictors if necessary. Internal validation will be undertaken using a bootstrapping approach.(Moons 2012) The impact of missing data will be assessed and multiple imputation used if appropriate (implemented in STATA software through the ICE command).(StataCorp 2011)

Planned subgroup analyses

We will undertake pre-planned subgroups evaluation according to type of AMD (Classic CNV, Occult CNV, RAP and IPCV). These subgroup analyses will be classified as exploratory and evaluated at the 2-sided 5 significance level.

All study analyses will be according to a statistical analysis plan that will be agreed in advance by the Study Steering Committee. Should the analysis plan deviate from the approved protocol, the analysis plan shall take precedence.

Proposed frequency of analyses

No formal interim analyses are planned. The TSC will monitor blinded event (nAMD conversion) data to evaluate the key assumption in the sample size calculation. A single final set of analyses is planned once the study has recruited and data has matured.

9. ECONOMIC EVALUATION

An economic decision analytic model will be developed to determine the optimal monitoring strategy for patients with nAMD in one eye. It is anticipated that the modelling will utilise a micro-simulation approach, whereby individual patients (with characteristics matching those of patients in the prospective cohort) will be simulated to pass through the model one at a time. Time to event analysis (from the prospective cohort data) will be used to derive the probability of conversion of the second eye (to active nAMD of varying states of severity) based on patient characteristics. This survival analysis will inform estimates of the rate of conversion to early nAMD and the rate of progression through to more severe nAMD requiring treatment. Focused reviews of existing literature will provide another source of information on the rate of progression of eyes post conversion. Following conversion to nAMD, eyes will be modelled to lose vision at the rates observed for untreated eyes in existing RCTs (e.g. Mitchell *et al*. 2010). Based on their modelled visual acuity, patients will be assigned to one of several discrete health states based on the acuity in their best seeing eye, and assigned the appropriate quality of life weight and costs for that state. The quality of life weights will reflect the desirability of the alternative visual acuity states on a scale where 0 is equal to death and 1 is equal to full health, such that time spent in alternative states can be multiplied by the appropriate weight to generate quality adjusted life years. The natural history model will capture conversion and onward progression of the second eye, visual acuity change, and quality adjusted life years in the absence of monitoring and treatment. It will also capture visual changes in the first eye of patients, as well as correlations between eyes in terms of deterioration/improvement (based on analysis of the study cohort).

Alternative monitoring/diagnostic strategies for the second eye will then be superimposed on top of this natural history model, applying the sensitivity/specificity estimates (by severity of AMD at time of detection) obtained for the alternative tests (from analysis of the prospective cohort data). By superimposing alternative diagnostic strategies on top of the natural history model, we will be able to estimate the time gain from conversion to detection associated with more sensitive tests which are capable of picking up disease earlier. As well as allowing alternative monitoring tests to be evaluated, the model will allow the cost-effectiveness of alternative monitoring intervals to be explored. Patients' whose second eye converts to nAMD will be modelled to receive anti VEGF injections upon deterioration of vision, and their vision will be modelled to deteriorate/improve at the rates observed for treated eyes in published RCTs. Those modelled to remain unidentified by any specific strategy (post conversion) will continue to progress at rates observed for untreated eyes. As such, the model will capture the visual acuity and health related quality of life benefits associated with early detection and treatment post conversion.

To inform model parameters we will use a combination of primary analysis of the observed cohort data (utilising results from the risk prediction models analyses described in section 7.9) as well as structured reviews of published literature (e.g. for appropriate health state utilities and relative treatment effects). Mortality will be modelled using age/sex specific UK life tables, and costs will be obtained where possible from standard UK sources (e.g. BNF; Department of Health, 2012; PSSRU, 2012). In order to obtain more accurate costs for performing the different types of monitoring tests, it is likely that a cost survey of participating centres will be required.

This will focus on the staff time, equipment and consumables required to undertake the different procedures.

The analysis will capture cumulative health and social care costs and QALYs accruing to patients under alternative monitoring strategies over their lifetimes. Future costs and QALYs will be discounted a rate of 3.5% per annum, in line with NICE guidelines (http://www.nice.org.uk/aboutnice/howwework/devnicetech/guidetothemethodsoftechnologyappraisal.jsp). Incremental cost-effectiveness ratios will be estimated by comparing each strategy to its next less effective strategy (excluding those strategies that are more costly and less effective than an alternative option). The net monetary benefit (NMB) approach will be used to help interpret the cost-effectiveness findings. The NMB approach transforms the cost-effectiveness ratio for each strategy into a linear combination of the two components, using a ceiling willingness to pay threshold (Rc) per unit of effect: NMB = (Effects*Rc)-Costs. By imputing the NMB for each strategy, using a range of plausible values for Rc, the strategy with the greatest net monetary benefit can be identified at each value.

To account for the joint uncertainty surrounding the estimated costs and effects for each strategy (and the incremental differences between strategies), the model will be made probabilistic by assigning an appropriate probability distribution to each input parameter (reflecting the uncertainty surrounding the estimate for each input). Monte Carlo simulation techniques will then be used to analyse the model a large number of times, with a value for each parameter drawn at random from its assigned probability distribution for each iteration. The output from this probabilistic analysis will be presented as cost-effectiveness acceptability curves (CEACs) and acceptability frontiers (CEAFs) (Briggs et al., 2006). CEACs present the probability of alternative strategies generating the greatest net monetary benefit for different values of willingness to pay per QALY gained, while acceptability frontiers present the probability of the strategy with the highest expected net monetary benefit (at different values of Rc) being cost-effective. Further deterministic sensitivity analyses will be undertaken to assess the impact on findings of uncertainty surrounding key model parameters and structural assumptions.
All study analyses will be according to an economic analysis plan that will be agreed in advance by the Study Steering Committee. Should the analysis plan deviate from the approved protocol, the analysis plan shall take precedence.

10. METHODOLOGICAL RESEARCH

Validated risk calculators have become useful tools in risk assessment for coronary heart disease and other health areas; nAMD like coronary heart disease is a chronic disease with known risk factors, and several risk algorithms for the development of nAMD in patients without the disease have been proposed. In this study, in addition to estimating the nAMD conversion distribution, a risk predictor model for the conversion of the fellow eye in patients with unilateral disease will be developed; together they will allow objective risk assessment in the management of patients at high risk of developing nAMD in the fellow eye and inform the optimal monitoring interval for patients and the corresponding impact upon resources. The following (baseline) risk factors have been shown to determine the development of nAMD: age, raised blood pressure, smoking, obesity, ethnicity, and ocular (fundus) characteristics, including number, type, and size of drusen in the fundus, and presence of pigmentary abnormalities in the fundus. Baseline characteristics, and type and severity of nAMD in the diseased eye, will be assessed at the first visit. Fundus pictures to quantify ocular risk factors will be assessed in a

certified reading centre (at Queen's University Belfast). The model will be assessed in terms of predictive ability, both discriminative performance and calibration

11. ORGANISATION: STUDY MANAGEMENT AND OVERSIGHT ARRANGEMENTS

11.1. Study management

Overall management of the study will be the responsibility of the joint chief investigators, Professor Usha Chakravarthy, based at Queen's University Belfast and Professor Craig Ramsay, University of Aberdeen.
A clinical trials co-ordinator at the Centre for Experimental Medicine at Queen's University Belfast will lead the governance support for the project.
The main study office is in the Centre for Healthcare Randomised Trials (CHaRT) based within the Health Services Research Unit, University of Aberdeen and provides day to day support for the clinical centres. The study manager in CHaRT at Aberdeen will take responsibility for the day to day transaction of study activities. The data co-ordinator will provide clerical and support for data queries to the study.

The EDNA Study Office Team will meet formally at least monthly during the course of the study to ensure smooth running and trouble-shooting. Finally, we intend to produce a yearly EDNA Study Newsletter for participants and collaborators to inform everyone of progress and maintain enthusiasm.

11.2. Local organisation in sites

The local principal investigator (PI) and research nurse will be responsible for all aspects of local organisation including identifying and consenting participants along with facilitating the delivery of the study and notification of any problem or unexpected developments for the duration of the study. The research nurse will be responsible for ensuring that study data is collected for baseline assessments, collecting and recording participant study data on study specific case report forms and will log details onto the remote web-based data capture system.

11.3. Project Management Group (PMG)

The study is supervised by a Project management Group (PMG). This consists of the grant holders and representatives from the Study Team. Observers may be invited to attend at the discretion of the PMG. The PMG will meet/teleconference monthly on average.

The research team has the expertise to cover the clinical and surgical aspects of the research.

11.4. Steering Committee (SC)

The study is overseen by a Steering Committee (SC). The membership of this Committee is comprised of at least four independent members along with the Chief Investigator (Usha Chakravarthy) or a nominated delegate. The study sponsor, other EDNA grant-holders and key members of the central office (e.g. the study manager) can participate in SC meetings but are not members. The funders will be notified in advance of meetings and a representative invited to attend. Other relevant experts may be invited to attend as appropriate. Details of the membership of the SC can be found at the start of this protocol. CHaRT recommends to

steering committees that they adopt the MRC CTU template to form the basis for each individual study charter. The SC will meet approximately yearly throughout the study.

11.5. Data Monitoring Committee (DMC)

There will be no DMC for this study as there is no blinding or interventional aspect to the study.

11.6. Patient and public involvement

We have collaborated with the Macular Society and the Royal National Institute of Blind People (RNIB). They assisted with the development of the protocol, patient information leaflets, consent forms and will help monitor study progress including accrual and engagement at the local level. At least one representative of the Macular Society will be a member of the steering committee.

12. RESEARCH GOVERNANCE, DATA PROTECTION AND SPONSORSHIP

12.1. Sponsorship and Research Governance

Queen's University Belfast is the sponsor for the study.
The study will be co-ordinated under the auspices of CHaRT based at HSRU, University of Aberdeen, with support from University of Oxford, Moorfields Eye Hospital NHS Foundation Trust and Royal Liverpool and Broadgreen University Hospitals NHS Trust. This will ensure compliance with Research Governance, and provide centralised study administration, database support and economic and statistical analyses. CHaRT is a registered Clinical Trials Unit with particular expertise in running multicentre RCTs of complex and surgical interventions.

The CI will ensure, through the steering committee, that adequate systems are in place for monitoring the quality of the study (compliance with appropriate governance) and appropriate expedited and routine reports, to a level appropriate to the risk assessment of the study.

12.2. Data protection

Data collected during the course of the research will be kept strictly confidential and accessed only by members of the study team. Participant's details will be stored on a secure database under the guidelines of the 1998 Data Protection Act and regular checks and monitoring are in place to ensure compliance. Data are stored securely in accordance with the Act and archived to a secure data storage facility. The CHaRT senior IT manager (in collaboration with the Chief Investigator) will manage access rights to the data set. Participants will be allocated an individual specific study number and their details will be anonymised on the secure database. We anticipate that anonymised study data may be shared with other researchers to enable international prospective meta-analyses. To comply with the 5th Principle of the Data Protection Act 1998, personal data will not be kept for longer than is required for the purpose for which it has been acquired.

13. ETHICS AND REGULATORY APPROVALS

The Office for Research Ethics Committees in Northern Ireland (ORECNI) has reviewed this study. The study will be conducted according to the principles of good clinical practice provided by Research Governance Guidelines. Annual progress reports and a final report at the conclusion of the study will be submitted to ORECNI REC within the timelines defined in the regulations.

14. QUALITY ASSURANCE

The study will be monitored to ensure that the study is being conducted as per protocol, adhering to Research Governance, and the appropriate regulations.

14.1. Risk assessment

An independent risk assessment has been carried out by the sponsor. The approach to, and extent of, monitoring is specified in the study monitoring plan and is appropriate to the risk assessment of the study.

15. FINANCE AND INSURANCE

The study is funded by a grant awarded by the NIHR Health Technology Assessment programme.

The necessary study insurance is provided by Queen's University Belfast.

16. END OF STUDY

The end of follow-up for each participant is defined as the final data capture to answer the research question. The end of the study is defined as the end of funding.

The end of the study will be reported to the REC within 90 days, or 15 days if the study is terminated prematurely. The Investigators will inform participants and ensure that the appropriate follow up is arranged for all involved.

A summary report of the study will be provided to the REC within one year of the end of the study. An end of study report will also be issued to the funders at the end of funding.

17. DATA HANDLING, RECORD KEEPING AND ARCHIVING

Clinical data will be entered into the database by the local investigator and/or research nurse working in each hospital site, together with data from questionnaires completed at clinic. Staff in the study office will work closely with local research nurses to ensure that the data are as complete and accurate as possible. Extensive range and consistency checks will further enhance the quality of the data.

The sponsor is responsible for ensuring that study data is archived appropriately. Essential data shall be retained for a period of at least 10 years following close of the study.

18. SATELLITE STUDIES

It is recognised, that the value of the study may be enhanced by smaller ancillary studies of specific aspects. Plans for these will be discussed in advanced with the Project Management Group. REC approval will be sought for any new proposal, if appropriate.

19. AUTHORSHIP PUBLICATION

We have a commitment to publish the findings of the research. At a minimum this study will have a results paper published in a peer- reviewed medical/scientific journal. If all grant-holders and researcher staff fulfil authorship rules, group authorship will be used under the

collective title of 'the EDNA study Group'. If one or more individuals have made a significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to the named individual(s) and the EDNA Study Group.

For reports which specifically arise from the study but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to the named individual(s) for the EDNA Study Group.

To safeguard the integrity of the main study, reports of explanatory or satellite studies will not be submitted for publication without prior arrangement from the Project Management Group.

We intend to maintain interest in the study by publication of EDNA newsletters at intervals for staff and collaborators. Once the main report has been published, a lay summary of the findings will be sent in a final EDNA Newsletter to all involved in the study. Further details on the publication policy can be found in Appendix A.

20. REFERENCE LIST

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Appendix A: Authorship Policy

1. PRINCIPLES OF AUTHORSHIP

The following principles of authorship have been derived from editorial publications from leading journals (see references) and are in accordance with the rules of the international Committee of Medical Journal Editors.

a. Group authorship

Group authorship will be appropriate for some publications, such as main reports. This will apply when the intellectual work underpinning a publication 'has been carried out by a group, and no one person can be identified as having substantially greater responsibility for its contents than others'.[1] In such cases the authorship will be presented by the collective title - The EDNA Study Group - and the article should carry a footnote of the names of the people (and their institutions) represented by the corporate title. In some situations one or more authors may take responsibility for drafting the paper but all group members qualify as members; in this case, this should be recognised using the by-line 'Jane Doe *and* the Study Group'.[2] Group authorship may also be appropriate for publications where one or more authors take responsibility for a group, in which case the other group members are not authors but may be listed in the acknowledgement (the by-line would read 'Jane Doe *for* the Study Group').[2]

b. Individual authorship

Other papers, such as describing satellite studies, will have individual authorship. In order to qualify for authorship an individual must fulfil the following criteria[1]:

i. each author should have participated sufficiently in the work represented by the article to take public responsibility for the content.

ii. participation must include three steps:

- conception or design of the work represented by the article OR analysis and interpretation of the data OR both; AND
- drafting the article or revising it for critically important content; AND
- final approval of the version to be published.

Participation solely in the collection of data is insufficient by itself. Those contributors who do not justify authorship may be acknowledged and their contribution described.[1]

c. Determining authorship

Tentative decisions on authorship should be made as soon as possible[1]. These should be justified to, and agreed by, the Project Management Group. Any difficulties or disagreements will be resolved by the Steering Committee.

2. AUTHORSHIP FOR PUBLICATION ARISING FROM EDNA

a. Operationalising authorship rules

We envisage two types of report (including conference presentations) arising from the EDNA study and its associated projects:

i. Reports of work arising from the main EDNA study

If all grant-holders and research staff fulfil authorship rules, group authorship should be used under the collective title of 'The EDNA Study Group'; if one or more individuals have made a

significant contribution above and beyond other group members but where all group members fulfil authorship rules, authorship will be attributed to 'Jane Doe and the EDNA Study Group'.

ii. Reports of satellite studies and subsidiary projects

Authorship should be guided by the authorship rules outlined in Section 1 above. Grant-holders and research staff not directly associated with the specific project should only be included as authors if they fulfil the authorship rules. Grant-holders and research staff who have made a contribution to the project but do not fulfil authorship rules should be recognised in the Acknowledgement section. The role of the EDNA Study Group in the development and support of the project should be recognised in the Acknowledgement section. The lead researcher should be responsible for ratifying authorship with the Project Management Group.

For reports which specifically arise from the EDNA study but where all members do not fulfil authorship rules (for example, specialist sub-study publications), authorship should be attributed to 'Jane Doe for the EDNA Study Group'. If individual members of the group are dissatisfied by a decision, they can appeal to the Management Group for reconciliation. If this cannot be achieved, the matter should be referred to the Steering Group.

b. Quality assurance

Ensuring quality assurance is essential to the good name of the study group. For reports of individual projects, internal peer review among members of the Project Management Group is a requirement prior to submission of papers. All reports of work arising from the EDNA study including conference abstracts should be peer reviewed by the Project Management Group.

The internal peer review for reports of work arising from the EDNA project is mandatory and submission may be delayed or vetoed if there are serious concerns about the scientific quality of the report. The Project Management Group will be responsible for decisions about submission following internal peer review. If individual members of the group are dissatisfied by decisions, the matter may be referred to the Steering Group.

The Project Management Group undertakes to respond to submission of articles for peer review at the Project Management Group Meeting following submission (assuming the report is submitted to the study secretariat in Aberdeen at least two weeks prior to the meeting).

3. REFERENCES

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