Moorfields Eye Hospital NHS Foundation Trust

BCTU Birmingham Clinical Trials Unit

ATHENA

TRIAL PROTOCOL

ATHENA

OpticAl Coherence TomograpHy Angiography for the dEtection of Neovascular Age-related Macular Degeneration: a Comprehensive Diagnostic Accuracy Study – the ATHENA Study

This protocol has regard for the HRA guidance and is compliant with the SPIRIT guidelines (2013)

Version Number: V1.0

Version Date: 16th November 2021

PROTOCOL DEVELOPMENT

Protocol Amendments

The following amendments and/or administrative changes have been made to this protocol since the implementation of the first approved version.

Amendment number	Date of amendment	Protocol version number	Type of amendment	Summary of amendment

Funding and Support in Kind

Funder(s)/Supporting Organisations	Financial and non-financial support given:
National Institute for Health Research	Financial
Funding scheme (if applicable)	Health Technology Assessment Programme
Funder's reference number	NIHR131432
Department of Health disclaimer The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health	

PROTOCOL SIGN OFF

Chief Investigator (CI) Signature Page

I, the Chief Investigator, confirm that I have read and agree with the following protocol, and that I will conduct the trial in compliance with the version of this protocol approved by the REC and any other responsible organisations.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

I also confirm that I will make the findings of the trial publicly available through publication or other dissemination tools without any unnecessary delay and that an honest accurate and transparent account of the trial will be given; and that any discrepancies from the trial as stated in this and any subsequent approved protocol will be explained.

Trial name:	ATHENA - OpticAl Coherence TomograpHy Angiography for the dEtection of Neovascular Age-related Macular Degeneration: a Comprehensive Diagnostic Accuracy Study.
Protocol version number: Protocol version date:	Version: 1.0 16th November 2021
CI name:	Dr Konstantinos Balaskas
Signature and date:	_____ __ __ / __ __ / __ __ __ __

Sponsor Statement

By signing the IRAS form for this trial, **Moorfields Eye Hospital NHS Foundation Trust (MEH)**, acting as Sponsor, confirm approval of this protocol.

Compliance Statement

This protocol describes the ATHENA trial only. The protocol should not be used as a guide for the treatment of participants not taking part in the ATHENA trial.

The trial will be conducted in compliance with the approved protocol, UK Policy Framework for Health and Social Care Research 2017, the Data Protection Act 2018, and the Principles of Good Clinical Practice (GCP) as set out in the UK Statutory Instrument (2004/1031) and subsequent amendments thereof. Every care has been taken in the drafting of this protocol, but future amendments may be necessary, which will receive the required approvals prior to implementation.

Principal Investigator (PI) Signature Page

As Principal Investigator, I confirm that the following protocol has been agreed and accepted, and that I will conduct the trial in compliance with the approved protocol where this does not compromise participant safety.

I agree to ensure that the information contained in this document will not be used for any other purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of the Sponsor.

Trial name:	ATHENA - OpticAl Coherence TomograpHy Angiography for the dEtection of Neovascular Age-related Macular Degeneration: a Comprehensive Diagnostic Accuracy Study.
Protocol version number:	Version: 1.0
Protocol version date:	16th November 2021
PI name:	
Name of Site: Signature and date:	 _____ __ __ / __ __ / __ __ __ __

ADMINISTRATIVE INFORMATION

Reference Numbers	
Sponsor number	BALK1008
ISRCTN reference number	ISRCTN18313457
IRAS reference number	295260

Sponsor	
Moorfields Eye Hospital NHS Foundation Trust	
Moorfields Eye Hospital NHS Foundation Trust 162 City Road London EC1V 2PD	Email: moorfields.resadmin@nhs.net Tel: 0207 253 3411

Chief Investigator	
Dr Konstantinos Balaskas	Consultant Ophthalmologist
Moorfields Eye Hospital NHS Foundation Trust 162 City Road London EC1V 2PD	Email: k.balaskas@nhs.net Tel: 0744 696 1215

Trial Office Contact Details	
Birmingham Clinical Trials Unit (BCTU) Institute of Applied Health Research College of Medical and Dental Sciences Public Health Building University of Birmingham Birmingham B15 2TT	ATHENA@trials.bham.ac.uk
Randomisation website	https://bctu-redcap.bham.ac.uk
Trial website	www.birmingham.ac.uk/ATHENA

Trial Management Group	
Dr Konstantinos BALASKAS (CI)	Ophthalmologist
Professor Yemisi TAKWOINGI	Lead Statistician
Dr Ridhi AGARWAL	Statistician
Professor Jon DEEKS	Statistician
Professor Alastair DENNISTON	Ophthalmologist
Professor Richard GALE	Ophthalmologist
Professor Pearse KEANE	Ophthalmologist
Dr Ashleigh KERNOHAN	Health Economist
Mr Adam KHAN	Trial Manager
Professor John LAWRENSON	Ophthalmologist
Ms Savita MADHUSUDHAN	Ophthalmologist
Dr William MCKINNON	Trial Team Leader
Mr Praveen PATEL	Ophthalmologist
Professor Tunde PETO	Ophthalmologist
Professor Sobha SIVAPRASAD	Ophthalmologist

Co-Investigator Group	
Dr Konstantinos BALASKAS (CI)	Ophthalmologist
Professor Yemisi TAKWOINGI	Lead Statistician
Professor Jon DEEKS	Statistician
Professor Alastair DENNISTON	Ophthalmologist
Professor Richard GALE	Ophthalmologist
Professor Pearse KEANE	Ophthalmologist
Dr Ashleigh KERNOHAN	Health Economist
Professor John LAWRENSON	Ophthalmologist
Ms Savita MADHUSUDHAN	Ophthalmologist
Mr Praveen PATEL	Ophthalmologist
Professor Tunde PETO	Ophthalmologist
Professor Sobha SIVAPRASAD	Ophthalmologist

Trial Steering Committee	
Independent Members	
Professor Rupert BOURNE (Chair)	Ophthalmologist
Dr Catey BUNCE	Statistician
Mrs Geraldine HOAD	Patient & Public Involvement Representative
Non-Independent Members	
Dr Konstantinos BALASKAS	CI / Ophthalmologist

Data Monitoring Committee	
Professor Yit YANG (Chair)	Ophthalmologist
Mr Tomas Cudrnak	Ophthalmologist
Mrs Irene STRATTON	Statistician

ABBREVIATIONS

Abbreviation	Term
AMD	Age-related Macular Degeneration
BCTU	Birmingham Clinical Trials Unit
CD1	Clinical Diagnosis 1 – i.e. by clinicians at recruitment centre based on randomised test – informs Primary Outcome
CD2	Clinical Diagnosis 2 – i.e. by clinicians at recruitment centre based on all three tests
CE	Conformité Européenne (European Conformity)
CEA	Cost-effectiveness Analysis
CI	Chief Investigator
CRF	Case Report Form
CRN	Clinical Research Network
CSA	Clinical Study Agreement
DCF	Data Clarification Form
DMC	Data Monitoring Committee
DSA	Deterministic Sensitivity Analysis
eCRF	Electronic Case Report Form
FFA	Fundus Fluorescein Angiography
GCP	Good Clinical Practice
GDPR	General Data Protection Regulation
GP	General Practitioner
HRA	Health Research Authority
ICF	Informed Consent Form
ICGA	Indocyanine-Green Angiography
ICH	International Conference on Harmonisation
ISF	Investigator Site File
IVFA	Intravenous Fluorescein Angiography
MEH	Moorfields Eye Hospital NHS Foundation Trust
nAMD	Neovascular age-related macular degeneration

NHS	National Health Service
NIHR	National Institute for Health Research
NPV	Negative Predictive Value
OCT	Optical Coherence Tomography
OCTA	Optical Coherence Tomography-Angiography
OFA	Oral Fluorescein Angiography
PCV	Polypoidal Choroidal Vasculopathy
PI	Principal Investigator
PIS	Participant Information Sheet
PPV	Positive Predictive Value
PSA	Probabilistic Sensitivity Analysis
REC	Research Ethics Committee
RS1	Reference Standard 1 - Reading centre review based on all imaging modalities except OCTA
RS2	Reference Standard 2 - Reading centre review based on all imaging modalities including OCTA
TMG	Trial Management Group
TSC	Trial Steering Committee
UoB	University of Birmingham

TRIAL SUMMARY

Title

OpticAl Coherence TomograpHy Angiography for the dEtection of Neovascular Age-related Macular Degeneration: a Comprehensive Diagnostic Accuracy Study – the ATHENA Study

Objectives

Primary Objective

To assess whether the sensitivity and specificity of Optical Coherence Tomography-Angiography (OCTA) combined with Optical Coherence Tomography (OCT) is non-inferior to that of Fundus Fluorescein Angiography (FFA) combined with OCT, in patients with a positive or suspicious OCT, for the detection of Neovascular age-related macular degeneration (nAMD) as interpreted by clinicians (retinal experts) who provide direct care to patients with nAMD.

Secondary Objectives

1. To assess the diagnostic accuracy of OCTA alone and FFA alone as reviewed by Reading Centre expert graders for the detection of nAMD in patients with a positive or suspicious OCT.
2. To assess the positive predictive value (PPV) of OCT for the detection of nAMD in all patients presenting with suspicion of nAMD.
3. To compare the diagnostic accuracy of the combination of OCT+FFA versus OCT+FFA+OCTA as interpreted by retinal experts within the 'OCT+FFA' arm of the trial.
4. To compare the diagnostic accuracy of the combination of OCT+OCTA versus OCT+OCTA+FFA as interpreted by retinal experts for the detection of nAMD within the 'OCT+OCTA' arm of the trial.
5. For a subset of cases with OCT and clinical features suspicious of Polypoidal Choroidal Vasculopathy (PCV) that underwent Indocyanine-Green Angiography (ICGA), to assess diagnostic accuracy of OCTA, FFA, ICGA, alone and in combinations, for the detection of PCV.
6. To assess intra- and inter-rater agreement in the detection of nAMD on OCTA and FFA as assessed by Reading Centre graders.
7. To develop and validate criteria for the OCTA-based diagnosis of nAMD.
8. To estimate the incremental cost per true positive detected and incremental cost per correct diagnosis for nAMD through a within trial cost-effectiveness analysis.
9. To report nAMD cases by lesion type on FFA and OCTA (type 1-, type 2-, type 3-nAMD) as assessed by the reading centre graders.
10. To report limitations of OCTA use and adverse events.

Trial Design

Non-inferiority, prospective, randomised, multicentre diagnostic accuracy study with an internal pilot to confirm feasibility of the recruitment plan.

Participant Population, Sample Size and Setting

1067 people with a suspicion of nAMD in the first or second eye who have had an OCT and who present to a secondary care ophthalmology unit in the UK e.g.

- Patients referred by their community optometrist or General Practitioner (GP), or who self-refer to secondary care eye casualty departments with a suspicion of nAMD in the first or second eye (recent history of sudden vision worsening in the suspect eye in the form of sudden blur or distortion in central vision or development of a 'dark patch' in central vision).
- Patients already under the care of NHS eye units for treatment of nAMD in the first eye who develop symptoms of nAMD in the second eye.

Eligibility Criteria

Patients with suspicion of nAMD in the first or second eye who have had an OCT, who are able to provide informed consent, and who are able to tolerate the trial procedures.

Outcome Measures

The diagnostic accuracy of OCT, OCTA, FFA and ICGA alone and in combinations will be expressed as sensitivity, specificity, and predictive values. In particular for OCT alone, only PPV will be assessed. Intra- and inter-rater agreement of OCTA and FFA as assessed by Reading Centre graders will be estimated.

Other outcomes and outputs: Validation of criteria for the OCTA based diagnosis of nAMD; limitations of OCTA use; a simple economic evaluation of the tests and test combinations (e.g. cost per case identified).

TRIAL SCHEMA

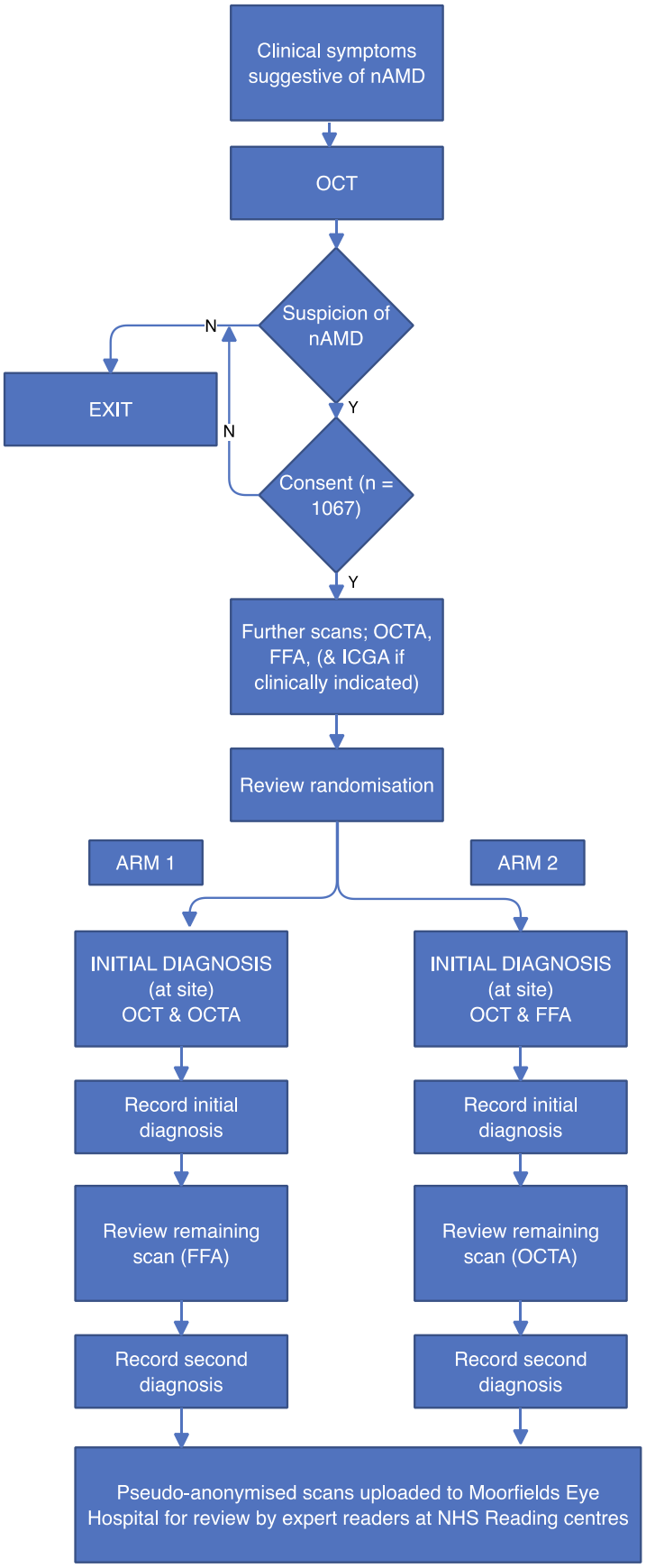

TABLE OF CONTENTS

1. BACKGROUND AND RATIONALE

1.1 Background

Age-related Macular Degeneration (AMD) is the most frequent cause of blindness in the UK[1]. Nearly 200 people aged 55 years or above in the UK lose sight daily from the severe form of this condition (neovascular AMD, nAMD)[2]. Early detection of nAMD is associated with improved visual outcomes and patient quality of life.

Diagnosis of nAMD is based on the interpretation of multiple imaging tests, including Fundus Fluorescein Angiography (FFA). This dye tracing technique uses a fluorescent dye (fluorescein) and a specialised camera to examine the circulation of the retina and choroid (parts of the fundus) at the back of the eye. The fluorescein can be administered orally in oral fluorescein angiography (OFA), but is more commonly given intravenously (intravenous fluorescein angiography (IVFA)) where it can cause discomfort to the patient[3] . Relying on a number of images taken over several minutes, FFA is labour-intensive, time-consuming and inconvenient for the patient. FFA is not always informative, thus a further dye test called Indocyanine-Green Angiography (ICGA) is occasionally required to confirm diagnosis of nAMD, especially when Polypoidal Choroidal Vasculopathy (PCV), a variant of nAMD, is suspected.

Newer non-invasive imaging techniques for the diagnosis of nAMD are now available. One such modality is Optical Coherence Tomography (OCT) that scans through the macula quickly. Together with clinical examination, OCT is now the preferred triaging imaging test for the diagnosis of nAMD. The findings of OCT, however, are not always specific for nAMD requiring further confirmation with other tests such as FFA/ICGA[4].

OCT-Angiography (OCTA) is a more recent technology that is able to identify features detected using both OCT and FFA. OCTA is a fast, non-invasive imaging technique that provides more detailed resolution of retinal structural and blood flow characteristics and has the potential to replace FFA[5-7]. Despite being available in many NHS Trusts, there is only a small body of moderate quality evidence to suggest OCTA alone is sufficiently accurate for the detection of nAMD[8].

1.2 Trial Rationale

There is an unmet need to evaluate the diagnostic performance of OCTA for the diagnosis of nAMD, and to compare it to other imaging tests currently used following a positive or suspicious OCT result.

OCTA is a relatively new technology for the assessment of retino-choroidal disease, including nAMD. It has significant benefits such as its non-invasive nature and combines attributes from both of the other standard diagnostic modalities currently used for nAMD detection; it provides information on retinal anatomy (similar to OCT), as well as on blood flow within retinal vessels (similar to FFA). Unlike FFA however it does not allow dynamic visualisation of vascular filling or leakage from blood vessels. Therefore, the exact role of OCTA in the detection of nAMD remains unclear, and a comprehensive diagnostic accuracy study of OCTA both alone and in combination with other imaging modalities is needed.

Early diagnosis and prompt treatment of nAMD is key to optimising the final visual outcome. As these patients are elderly, a reliable and accurate, but also quick, non-invasive diagnostic test would be more patient friendly.

A systematic review and meta-analysis of the performance of OCTA in retinal disease detection undertaken by our research group demonstrated the paucity of available evidence[8]. Over 1600

research articles involving OCTA have been published, but only 17 studies were diagnostic accuracy studies. None of the studies were prospective with a published study design and they provided only limited data on patient selection, data collection and analysis, masking, descriptions of the OCTA and the reference standard(s). Of the 17 studies, only 5 small studies evaluated detection of nAMD. These reported a wide range of sensitivity (0.50 to 1.00) and specificity (0.68 to 1.00), reinforcing the need for a well-designed diagnostic accuracy study to inform NHS decision-making on the role of OCTA. Since most of the studies on nAMD only included patients who already had a clinical diagnosis of nAMD, the diagnostic accuracy of OCTA in a mix of cases representative of all common nAMD phenotypes is currently unknown.

2. AIMS AND OBJECTIVES

2.1. Internal Pilot Objectives

The trial includes an internal pilot phase to assess recruitment and trial processes. The objectives of the internal pilot are:

1. Six first wave sites open to recruitment by the end of the pilot phase.
2. 100% of the expected monthly recruitment rate of the main trial is achieved by month six of recruitment commencing.
3. Adequate number (one grader per 100 patients recruited) of trained and accredited clinician graders and Reading Centre graders available by the end of the pilot phase.
4. Adherence to image acquisition protocol in ≥90% of cases.

2.2. Main Trial Objectives

Primary Objective

To assess whether the sensitivity and specificity of Optical Coherence Tomography-Angiography (OCTA) combined with Optical Coherence Tomography (OCT) is non-inferior to that of Fundus Fluorescein Angiography (FFA) combined with OCT, in patients with a positive or suspicious OCT, for the detection of Neovascular age-related macular degeneration (nAMD) as interpreted by clinicians (retinal experts) who provide direct care to patients with nAMD.

Secondary Objectives

1. To assess the diagnostic accuracy of OCTA alone and FFA alone as reviewed by Reading Centre expert graders for the detection of nAMD in patients with a positive or suspicious OCT.
2. To assess the positive predictive value (PPV) of OCT for the detection of nAMD in all patients presenting with suspicion of nAMD.
3. To compare the diagnostic accuracy of the combination of OCT+FFA versus OCT+FFA+OCTA as interpreted by retinal experts within the 'OCT+FFA' arm of the trial.
4. To compare the diagnostic accuracy of the combination of OCT+OCTA versus OCT+OCTA+FFA as interpreted by retinal experts for the detection of nAMD within the 'OCT+OCTA' arm of the trial.
5. For a subset of cases with OCT and clinical features suspicious of Polypoidal Choroidal Vasculopathy (PCV) that underwent Indocyanine-Green Angiography (ICGA), to assess diagnostic accuracy of OCTA, FFA, ICGA, alone and in combinations, for the detection of PCV.
6. To assess intra- and inter-rater agreement in the detection of nAMD on OCTA and FFA as assessed by Reading Centre graders.
7. To develop and validate criteria for the OCTA-based diagnosis of nAMD.
8. To estimate the incremental cost per true positive detected and incremental cost per correct diagnosis for nAMD through a within trial cost-effectiveness analysis.
9. To report nAMD cases by lesion type on FFA and OCTA (type 1-, type 2-, type 3-nAMD) as assessed by the reading centre graders.
10. To report limitations of OCTA use and adverse events.

3. TRIAL DESIGN AND SETTING

3.1. Trial Design

Non-inferiority, prospective, randomised, multicentre diagnostic accuracy study with an economic evaluation and an internal pilot to confirm feasibility of the recruitment plan.

3.2. Trial Setting

Patients with a suspicion of nAMD in the first or second eye who have had an OCT and who present to an NHS secondary care ophthalmology unit in the UK.

3.3. Assessment of Risk

As all the tests and imaging techniques used within ATHENA are CE marked and used within their licence, and are available as standard care within the NHS, this trial is categorised as:

Type A = No higher than the risk of standard medical care.

4. ELIGIBILITY

4.1. Inclusion Criteria

Patients who have had an OCT test with suspicion of nAMD in the first or second eye, will be included if they:

- Can provide informed consent;
- Can tolerate the trial specific procedures.

4.2. Exclusion Criteria

Patients who have the following will not be eligible to participate in ATHENA:

- Significant media opacities (cataract, vitreous opacities) that would not allow good quality fundus imaging;
- Diabetic retinopathy of severity worse than mild non-proliferative stage and with any degree of diabetic maculopathy;
- Other causes of choroidal neovascularisation (myopic, angioid streaks, inflammatory, retinal dystrophies, secondary to central serous chorioretinopathy, idiopathic);
- Inability to undergo dye-based imaging (FFA or ICGA) due to a history of allergy.

4.3. Co-enrolment

It is not anticipated that co-enrolment within other trials or studies will have an effect on potential recruits' participation in the ATHENA trial (assuming all of the ATHENA eligibility criteria are met), therefore co-enrolment is not prohibited for the ATHENA trial.

5. CONSENT

It will be the responsibility of the Investigator to obtain written informed consent for each participant prior to performing any trial related procedures. A research nurse or clinician is able to take consent providing that local practice allows this, and that this responsibility has been delegated by the Principal Investigator (PI) as captured on the Site Signature and Delegation Log.

A Participant Information Sheet (PIS) will be provided to facilitate this process at the time of initial consultation/hospital visit. Investigators or their delegate(s) will ensure that they adequately explain the aim, imaging modalities used in the trial, anticipated benefits and potential hazards of taking part in the ATHENA trial to the participant. They will also stress that participation is voluntary and that the participant is free to decline to take part and may withdraw from the trial at any time. The participant will be given sufficient time to read the PIS and to discuss their participation with others outside of the site research team. The participant will be given the opportunity to ask questions.

If the potential participant is willing to take part in the trial (and meets all of the eligibility criteria), they will be asked to sign and date the latest version of the ATHENA Trial Informed Consent Form (ICF). Where direct access to patient medical records is required, the participant will give explicit consent for members of the research team and/or representatives of the Sponsor to be given direct access to their medical records as required. This will be specified on the ICF.

The PI or delegate will then sign and date the ICF. A copy of the ICF will be given to the participant, a copy will be filed in the medical notes, and the original placed in the ATHENA Trial Investigator Site File (ISF). Once the participant is entered into the trial, the participant's trial number will be entered on the ICF maintained in the ISF and recorded in the participant's medical notes. A copy of the signed ICF will be sent to the Birmingham Clinical Trials Unit (BCTU) trial office for review, and the participant understands and acknowledges that a copy of the signed ICF will be transferred to the trial team at BCTU for review.

Details of the informed consent discussions will be recorded in the participant's medical notes. This will include date of discussion, the name of the trial, summary of discussion, version number of the PIS given to participant and version number of ICF signed and date consent received. Where consent is obtained on the same day that the trial related assessments are due to start, a note should be made in the medical notes as to what time the consent was obtained and what time the procedures started.

Electronic copies of the PIS and ICF will be available from the Trial Office and will be printed or photocopied onto the headed paper of the local institution. Details of all patients approached about the trial will be recorded on the Participant Screening/Enrolment Log and with the participant's prior consent, their General Practitioner (GP) will also be informed that they are taking part in the trial.

6. ENROLMENT, RANDOMISATION and BLINDING

6.1. Identification

Potential participants will be identified and approached by clinical staff in participating centres who are responsible for the potential participant's direct care. Clinical staff will have received appropriate training for the trial and will be delegated this task on the Site Signature and Delegation Log. Recruitment will take place in NHS ophthalmology clinics located across the United Kingdom and Northern Ireland. Research Ethics Committee (REC) approved posters making potential participants aware of the trial may be displayed in areas that will be accessed by them, such as waiting areas, clinics and consulting rooms.

6.2. Screening and Enrolment

The participant pathway through recruitment and randomisation is illustrated by the trial schema. Eligibility will be confirmed following discussions with the potential participant and a review of their medical notes by staff delegated this duty by the local PI.

Potential participants will be advised that taking part in the trial is entirely voluntary and they may withdraw from the trial at any stage without this affecting their usual care. Potential participants will be provided with a REC approved trial PIS and given sufficient time to consider their involvement.

People who give consent will proceed to randomisation if they are eligible to participate in the trial. Consent will be recorded on the approved ATHENA consent form, the original of which must be retained in the site file with, a copy filed in the medical notes, a copy given to the participant and a copy sent to the ATHENA Trial Office at BCTU.

We will train clinical staff at each site to facilitate recruitment. Recruitment will be supported by research nurses including those from the Clinical Research Network (CRN) in England. Local procedures at the participating hospitals are different, and the timing and mode of approach to potential participants and the consent process may vary in order to accommodate both the specific circumstances at each site and the needs of the potential participants.

The Investigator will also keep and maintain the ATHENA Participant Screening/Enrolment Log which will be kept in the ISF and should be available to be sent to the Trial Office upon request. The ATHENA Patient Recruitment and Identification Log and ATHENA Participant Screening/Enrolment Log should be held in strict confidence.

6.3. Randomisation

Randomisation will be provided by a secure online randomisation system at BCTU (available at https://bctu-redcap.bham.ac.uk). Unique log-in usernames and passwords will be provided to those who wish to use the online system and who have been delegated the role of randomising participants into the trial as detailed on the ATHENA Trial Site Signature and Delegation Log. These unique log-in details must not be shared with other staff and in no circumstances should staff at sites access either system using another person's login details.

The online randomisation system will be available 24 hours a day, 7 days a week, apart from short periods of scheduled maintenance. A telephone toll-free randomisation service (0800 953 0274) is available as a backup to the online randomisation system, Monday to Friday, 09:00 to 17:00 hrs UK time, except for bank holidays, government guided closures and University of Birmingham closed days.

After participant eligibility has been confirmed and informed consent has been received, the participant can be randomised into the trial. Randomisation Forms will be provided to investigators

and may be used to collate the necessary information prior to randomisation. All questions and data items on the Randomisation Form must be answered before the randomisation is completed via the online database.

Participants will be randomised at the level of the individual in a 1:1 ratio to which combination of tests is used first to diagnose the presence of nAMD. Thus, in approximately half the tests, the recruiting site clinician will review the OCT test and then the OCTA test and provide a clinical diagnosis (nAMD: yes/no). In the other half, the site clinician will review the OCT test and then the FFA test and will provide a clinical diagnosis (nAMD: yes/no), Clinical Diagnosis 1 (CD1).

Once they have completed the case report form (CRF) with CD1, the site clinician will review with the remaining third imaging test in each case (FFA or OCTA) and will provide again a clinical diagnosis (nAMD: yes/no), Clinical Diagnosis 2 (CD2) and will record it on the CRF.

A minimisation algorithm will be used within the online randomisation system to ensure balance in the randomisation allocations over the following variables. The minimisation algorithm will ensure that there is balance between:

- Recruiting centre
- Whether the affected eye is the first or second eye
- Whether the case is suspicious for PCV or not

To avoid the possibility of the randomisation allocation becoming predictable, a random element will be included in the algorithm. Full details of the randomisation specification will be stored in a confidential document at BCTU.

Following randomisation, a confirmatory e-mail will be sent to the randomiser, the local PI and the ATHENA trial inbox (ATHENA@trials.bham.ac.uk).

The local research team should add the participant to the ATHENA Participant Recruitment and Identification Log which links participants with their Trial Number. PIs must maintain this document securely and it must not be submitted to the Trial Office. The ATHENA Participant Recruitment and Identification Log should be held in strict confidence.

6.4. Blinding

Due to the nature of the index tests it is impossible to blind either the care providers, investigators or participants to their allocated group.

As it is impossible to blind the reviewing clinicians at site, it is not possible to obtain unbiased assessments of both OCTA and FFA for each patient as the knowledge from reviewing the first test will affect the assessment of the second.

Reading Centre graders will be blinded to all clinical, demographic and any other patient-specific information. Reading Centre graders will assess each imaging test in isolation.

We will therefore perform a prospective, randomised diagnostic accuracy study comparing the diagnostic accuracy of a first clinical diagnosis (CD1) (nAMD: yes or no) using either OCT+OCTA or OCT+FFA. All patients will receive OCT which will be reviewed first. Only patients with features suspicious of nAMD on OCT will be recruited into the trial and go on to have both OCTA and FFA (see details in Section 7.1).

6.5. Informing the Participant's GP and Other Parties

If the participant has agreed, the participant's GP will be notified that they are in the ATHENA trial by using the ATHENA GP Letter. If the participant does not want their GP to be aware of their participation in the ATHENA trial then they may opt out of this on the consent form.

7. TRIAL TESTS

7.1. Index Tests

An OCT test will be performed to confirm the clinical suspicion of nAMD (as part of standard care, prior to recruitment into the trial). If nAMD is clinically suspected following an OCT, the patient will have two more tests: OCTA and FFA.

Patients with clinical (orange nodule, large sub-retinal haemorrhage) and OCT features (high pigment epithelium detachment, double-layer sign, sub-retinal pigment epithelium notch) suggestive of PCV will also undergo ICGA at the same time as FFA.

In approximately half of the cases, chosen by chance via randomisation, the site clinician will review the OCT test and then the OCTA test and will provide a clinical diagnosis (nAMD: yes/no). In the other half of the cases the site clinician will review the OCT test and then the FFA test and will provide a clinical diagnosis (nAMD: yes/no) (CD1).

Once they have completed the CRF with CD1, the site clinician will also review the images from the remaining third test in each case (FFA or OCTA) and will either confirm or change their initial clinical diagnosis (nAMD: yes/no) and record it on the CRF (CD2). These responses will be recorded on the trial database (CD1 and CD2).

Comparison of the second clinical diagnosis (CD2) with the first clinical diagnosis (CD1) within each arm will provide additional evidence concerning the added value of using a combination of both OCTA and FFA in patients with a positive or suspicious OCT.

Following clinical review, sites will export a copy of the participant's tests with all the identifiable and metadata removed. The site will link the participant's trial number to the test and this will be uploaded onto the trial servers hosted by MEH alongside a short vignette of relevant clinical data.

These pseudo-anonymised tests will be presented via a secure portal to clinical staff at specialist NHS Reading Centres throughout the UK, who will make a clinical diagnosis based on the test and the clinical information presented. This clinical diagnosis will be recorded on the trial database but will not be made available to staff at the treating centre or the trial participants.

7.2. Reference Standards

The Reading Centres will also separately provide the reference standard using all available information from multi-modal imaging (OCT, OCTA, FFA and ICGA where available) enhanced with clinical vignette describing patient symptoms and follow-up clinical data. Two versions of the reference standard will be provided:

- RS1 based on all imaging modalities except OCTA;
- RS2 based on all imaging modalities including OCTA.

This will allow assessment of the potential effect of incorporation bias from inclusion of the primary index test (OCTA) in determining the reference standard. The primary analyses will be based on RS1.

The images will be interpreted by Reading Centre graders different to those involved in the masked assessment of the individual imaging tests, and they will review all imaging and clinical information for each patient.

Uncertain cases by primary grading will be reviewed by a senior adjudication panel (directors of the three Reading Centres) who will provide the reference standard in these cases.

7.3. Accountability Procedures

The results of the image interpretation will be recorded on an eCRF. The completed eCRFs will be monitored for compliance with the protocol. Should any concerns arise then investigations will be undertaken and the findings presented to the Trial Management Group (TMG) for their guidance. A summary of the compliance will be presented to the trial oversight groups.

7.4. Test Modification

Modification of the diagnostic pathways set out in this protocol are allowed if there are legitimate medical reasons for this, or at the participant's request.

Should any concerns arise then investigations will be undertaken to determine the reasons for modifying the diagnostic pathways. The findings will be presented to the TMG for their guidance. A summary of the compliance will be presented to the trial oversight groups.

The request to change diagnostic route, or the withdrawal of participants before all the imaging techniques have been performed should be an exception as people with suspected nAMD should be counselled as to the nature of the procedures before consenting to participate in the ATHENA trial.

8. OUTCOME MEASURES

8.1. Internal Pilot Outcomes

The following progression criteria using a red/amber/green traffic light system will be used to inform whether we progress to the main trial:

a. First wave recruitment sites are open to recruitment

Green: All 6 first wave sites are open to recruitment.

Amber: 4 or 5 first wave sites are open to recruitment.

Red: Less than 4 first wave sites are open to recruitment.

b. Recruitment rate

Green: ≥100% of the expected monthly recruitment rate of the main trial is achieved by month 6 of recruitment commencing.

Amber: ≥80% and <100% of the expected monthly recruitment rate is achieved by month 6 of recruitment commencing with at least 3 first wave sites at 100% of expected monthly recruitment rate.

Red: Less than 80% of the expected monthly recruitment rate is achieved by month 6 of recruitment commencing.

c. Availability of an adequate number of trained and accredited clinician graders and Reading Centre graders (one grader per 100 patients recruited) to allow for delivery of image grading within the trial timeline

Green: Adequate number of trained graders available by the end of the pilot phase. Minimum of 1 grader per Reading Centre by end of the pilot phase.

d. Fidelity check demonstrating adherence to image acquisition protocol

Green: Adherence to image acquisition protocol in ≥90% of cases.

Amber: Adherence to image acquisition protocol in ≥80% and <90% of cases.

Red: Adherence to image acquisition protocol in <80% of cases.

If at the end of the pilot phase any of the thresholds are at amber or red for any of the progression decision points, the ATHENA TMG will review and provide a recommendation to the ATHENA Trial Steering Committee (TSC). The TSC will then review and ratify this before providing any potential remedial actions that could be taken to allow progression to the main trial, to the Funder. If there are no obvious remedial actions that can be taken the TMG and TSC will discuss stopping the trial with the Funder.

8.2. Main Trial Outcomes

8.2.1. Primary Outcome

The primary outcome is the difference in sensitivity and difference in specificity of OCT+OCTA and OCT+FFA for the detection of nAMD in patients with a positive or suspicious OCT (test interpretation by retinal experts).

8.2.2. Secondary outcomes

1. Sensitivity, specificity, PPV and negative predictive value (NPV) of OCTA alone and FFA alone (based on assessment by Reading Centre expert graders) for the detection of nAMD in patients with a positive or suspicious OCT.
2. PPV of OCT for detection of nAMD in all patients presenting with suspicion of nAMD (test interpretation by retinal experts and Reading Centre graders).
3. Difference in sensitivity and difference in specificity of OCT+FFA and OCT+FFA+OCTA reviewed by retinal experts within the 'OCT+FFA' arm of the trial.
4. Difference in sensitivity and difference in specificity of OCT+OCTA and OCT+OCTA+FFA reviewed by retinal experts within the 'OCT+OCTA' arm of the trial.
5. Sensitivity, specificity, PPV and NPV of OCTA, FFA, ICGA, alone and in combinations, for detection of PCV in patients with OCT and clinical features suspicious of PCV.
6. Intra- and inter-rater variation in the assessment of OCTA and FFA by Reading Centre graders.
7. Validated criteria for OCTA-based diagnosis of nAMD.
8. Incremental cost per true positive detected and incremental cost per correct diagnosis for nAMD.
9. The number and percentage of nAMD cases of each lesion type (type 1-, type 2-, type 3-nAMD) on FFA and OCTA as assessed by the reading centre graders.
10. The number and percentage of participants unable to fully complete FFA test or ICGA due to adverse reactions as assessed in treating centre.

9. TRIAL PROCEDURES

The baseline visit should include the following:

- Confirmation of inclusion and exclusion criteria
- Informed consent
- OCTA and FFA test
- ICGA test, if clinical features and OCT are suggestive of PCV
- Randomisation of test review order and allocation of trial number
- Relevant medical history, including:
    - Presentation type (e.g. distortion, central dark patch, sudden vision worsening) and whether it is first or second presentation
    - Laterality (i.e. right eye or left eye)
    - Visual acuity per eye
    - Smoking history
    - Eye medication details
    - Ocular surgery history
    - History of: heart attack, stroke/transient ischaemic attack, asthma, diabetes, chronic obstructive pulmonary disease, hypertension, impaired mobility
    - Biological sex
- Review of all tests (OCT, OCTA, FFA and if applicable ICGA)

Following the baseline visit (within 14 working days), copies of the tests will be produced in which the identifiable and metadata will have been removed. These tests will be pseudo-anonymised with the participant's trial number and will be transferred from the recruiting centre to MEH servers alongside a short clinical vignette of relevant medical information. The tests and clinical vignette will be made available to blinded expert graders at the reading centres, and will be separately reviewed by expert graders at the reading centres to provide the reference standards.

9.1. Schedule of Assessments

Table 1: ATHENA Schedule of Assessments

Visit	***Pre-Baseline***	***Baseline***	***Baseline or + 7 - 14 working days***	***Reading Centre Review***
OCT test	X			
Eligibility check	X	X		
Valid informed consent		X		
Relevant medical history taken		X		
Additional tests (OCTA, FFA, and ICGA)*		X		
Randomisation		X		
All tests reviewed (NHS Trust):				
OCTA		X		
FFA		X		

OCT		X		
*ICGA**		X		
Tests transferred to MEH servers			X	
Index tests reviewed by Reading Centre Graders				X
Reference Standard provided by Reading Centre Graders				X

** ICGA tests performed in patients with clinical features and OCT suggestive of PCV only*

9.2. Withdrawal and Changes in Levels of Participation

Informed consent is defined as the process of learning the key facts about a clinical trial before deciding whether or not to participate. It is a continuous and dynamic process and participants should be asked about their ongoing willingness to continue participation.

Participants should be aware at the beginning that they can freely withdraw (discontinue participation) from the trial (or part of) at any time.

Types of withdrawal are as follows:

- The participant has provided consent but would like to withdraw permission for their tests or their interpretation being made available to the trial.
- The participant has provided consent but would like to withdraw permission for any further processing (analysis) of their data. Any data that has contributed to an analysis cannot be withdrawn, but will not be used in any new analysis.

The details of withdrawal (date, reason and type of withdrawal) will be clearly documented in the source data where this information is available.

10.ADVERSE EVENT REPORTING

10.1.Definitions

Table 2: Adverse event reporting definitions

Severity Definitions	Mild	Awareness of signs or symptoms that do not interfere with the participant's usual activity or are transient and resolved without treatment and with no sequelae.
	Moderate	A sign or symptom, which interferes with the participant's usual activity.
	Severe	Incapacity with inability to do work or perform usual activities.

Adverse Event	AE	Any untoward medical occurrence in a participant participating in the trial which does not necessarily have a causal relationship with the intervention received.
Related Event	RE	An event which resulted from the administration of any of the research procedures.
Serious Adverse Event	SAE	An untoward occurrence 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/ birth defect Or is otherwise considered medically significant by the Investigator**
Unexpected Event	UE	The type of event that is not listed in the protocol as an expected occurrence.
Related and Unexpected Serious Adverse Event	N/A	A SAE that meets both the definition of a Related and Unexpected Event.

* The term life-threatening is defined as diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.

** Medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the participant or may require intervention to prevent one of the other outcomes listed in the definitions above.

10.2.Adverse Event Recording – General

The recording and reporting of Adverse Events (AEs) will be in accordance with the UK Policy Framework for Health and Social Care Research, the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments) and the requirements of the Health Research Authority (HRA). Definitions for adverse event reporting are listed in *Table 2: Adverse event reporting definitions* in Section 10.1.

It is routine practice to record AEs in the participant's medical notes and it is also recommended that this includes the documentation of the assessment of severity and seriousness and also of causality (relatedness) in relation to the trial procedures in accordance with the protocol.

10.3.Adverse Event Reporting in ATHENA

The reporting period for AEs in ATHENA will last for the duration of the participant's baseline visit only. There is no follow-up for ATHENA after the baseline visit.

The safety profile for this trial population is well characterised and all index tests are currently carried out within the NHS as part of standard care, so a strategy of targeted reporting of AEs will not affect the safety of participants. Only specific AEs (as detailed below) will be collected for the trial, and these will be recorded on trial specific CRFs.

- Inability to tolerate bright light
- Allergic reaction to fluorescein dye
- Nausea/vomiting
- Anaphylactic reaction to indocyanine green

10.4.Serious Adverse Event (SAE) Reporting in ATHENA

As ATHENA is a diagnostic test accuracy study using already well established, well tolerated index tests that are part of standard care and are not being used in a novel way for the trial, there will be no additional reporting requirements for any SAEs beyond recording in the patient's medical notes. Targeted AEs will be recorded on the CRFs as specified in section 10.3.

If any SAEs do occur whilst the patient is at their baseline assessment, the PI or delegate must record this in the patient's medical notes. The PI or delegate does not need to report any SAEs to the trial office.

11. DATA HANDLING AND RECORD KEEPING

11.1.Source Data

Source data is defined as all information in original records and certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. In order to allow for the accurate reconstruction of the trial and clinical management of the subject, source data will be accessible and maintained.

Table 1: Source Data in ATHENA

Data	Source
Imaging	The source is the original imaging, usually as an electronic file. The clinical interpretation of the images will be summarised on an eCRF. This will be transferred to the clinical trials unit via Blueworks software hosted on servers based at MEH. Any images uploaded onto the Blueworks software will be stored in the Blueworks trial database and integrated onto the participant record. The Blueworks database will be stored on a secure server based at MEH. Where data is interpreted, the eCRF onto which it is transcribed becomes the source. eCRFs containing interpreted data will be held on the BCTU database located on secure servers at UoB as well as the Blueworks database, held on servers at MEH. The BCTU database will not contain copies of the images themselves.
Clinical event data	The original clinical notes are the source document. This may be found on clinical correspondence, or electronic or paper participant records. Clinical events reported by the participant, either in or out of clinic (e.g. phone calls), must be documented in the source documents. Information will be recorded on paper CRFs as well as being uploaded onto eCRFs on the Blueworks trial database hosted on secure servers at MEH servers. This will be securely transferred to UoB where it will be held on the BCTU trial database, on secure servers. Original paper CRFs will be kept at site, and any copies sent to BCTU will be stored in locked filing cabinets in a swipe-card accessed room.

Recruitment	The original record of the randomisation is the source. It is held on University of Birmingham servers as part of the randomisation and data entry system. The original record of consent is the ATHENA consent form. This should be kept in the ISF, and a copy sent to BCTU to be stored in locked filing cabinets in a swipe-card accessed room.
Drop out	Where a participant expresses a wish to withdraw, the conversation must be recorded in the source data.

Hospital source data will comprise of (but is not limited to) the hospital notes/electronic patient records, case report forms Hospital source data is kept as part of the participants' medical notes generated and maintained at site.

11.2.Case Report Form (CRF) Completion

A CRF is required and should be completed for each individual participant. Paper forms will be provided to aid the collection of trial data. Sites should retain records of the paper CRFs, and these should be transcribed onto the ATHENA trial database in the form of electronic CRFs. Sites and reading centres will be requested to submit 20% of completed paper CRFs to the BCTU trials team for quality control checks. The original should be filed in the Investigator Site File, and the copy will be filed securely at BCTU in locked filing cabinets.

Data reported on each form will be consistent with the source data and any discrepancies will be explained. All missing and ambiguous data will be queried. Staff delegated to complete CRFs will be trained to adhere to standard formats. Protocol and GCP non-compliances should be added to a Protocol Deviation Log, held by the site, and reported to the Trial Office on discovery. In all cases it remains the responsibility of the site's PI or their delegate to ensure that the CRF has been completed correctly and that the data are accurate. This will be evidenced by the signature of the site's PI or their delegate on the CRF.

11.3.Data Management

Blueworks, a professional ophthalmic imaging management solutions company, will provide a database to hold the patient's pseudonymised imaging tests, clinical vignette, trial number and test results. The Blueworks database will also provide random tests to the reading centres to allow expert graders to perform reviews of the tests. This database will be hosted on MEH's servers. A subset of data from the Blueworks database will be transferred to the BCTU database. This includes the participant's trial number, the results of recruiting sites' assessments of the tests, as well as the grading results from the reading centres, accompanied by the clinical vignette. All data transferred from the Blueworks database to the BCTU database will pseudonymised by the use of the participant's trial number. Blueworks staff will not have any access to this data without supervision from appropriate members of the research team at MEH.

Processes will be employed to facilitate the accuracy and completeness of the data included in the final report. These processes will be detailed in the trial specific Data Management Plan and include the processes of data entry and data queries on trial data. Coding and validation will be agreed between the trial manager, statistician and programmer and the BCTU trial database will be signed off once the implementation of these has been assured.

The bespoke BCTU database will hold the patient's clinical vignette, trial number, test results, date of birth and NHS number. The patient's name will be held on the paper ICF, which will be sent to the Trial Office at BCTU. The ICF will be stored in a locked filing cabinet, in a swipe-card access controlled room. Data will be entered onto the bespoke BCTU trial database by delegated staff at site. The data capture system will conduct automatic range checks for specific data values to ensure high levels of data quality. Queries on the trial data will be raised using the integrated data query system in the trial database, with the expectation that these queries will be completed by the site within 30 days of receipt. Overdue data queries will be requested on a monthly basis until receipt of the data or a file note to explain its absence.

11.4.Self-evident Corrections

No self-evident corrections will be permitted.

11.5.Data Security

Moorfields Eye Hospital NHS Foundation Trust

All data will be handled in accordance with the General Data Protection Regulations (GDPR) and Data Protection Act 2018.

All MEH clinical trial databases (for ATHENA this is the Blueworks database) are stored in secure, monitored servers. All MEH clinical trial databases are part of the MEH disaster recovery strategy and have a 5-day Recovery Time Objective.

Where data is transferred electronically to MEH this will be in accordance with the GDPR and UK Data Protection Act 2018, as well as MEH Information Security Policy and Trust Information Governance Policy. There will be a documented record of any data transfer regarding the trial management.

Access to trial data stored in MEH servers will be granted to authorised representatives from the Sponsor, host institution and other relevant bodies to permit trial-related monitoring, audits and inspections in line with participant consent.

University of Birmingham (UoB)

UoB has policies in place, which are designed to protect the security, accuracy, integrity and confidentiality of Personal Data. The trial will be registered with the Data Protection Officer at UoB and will hold data in accordance with the Data Protection Act (2018 and subsequent amendments). The Trial Office has arrangements in place for the secure storage and processing of the trial data which comply with UoB policies.

The Trial Database System incorporates the following security countermeasures:

Physical security measures: restricted access to the building, supervised onsite repairs and storages of back-up tapes/disks are stored in a fire-proof safe.

Logical measures for access control and privilege management: including restricted accessibility, access controlled servers, separate controls of non-identifiable data.

Network security measures: including site firewalls, antivirus software and separate secure network protected hosting.

System management: the system will be developed by the Programming Team at the Trial Office, and will be implemented and maintained by the Programming Team.

System design: the system will comprise of a database and a data entry application with firewalls, restricted access, encryption and role based security controls.

Operational processes: the data will be processed and stored within BCTU.

System audit: The system will benefit from the following internal/external audit arrangements:

- Internal audit of the system
- Periodic IT risk assessment

Data Protection Registration: UoB's Data Protection Registration number is Z6195856.

11.6.Archiving

It is the responsibility of the PI to ensure all essential trial documentation and source documents (e.g. signed ICFs, Investigator Site Files, participants' hospital notes, copies of CRFs etc.) at their site are securely retained for a minimum of 10 years.

As Sponsor, MEH will archive the Trial Master File for a minimum of 10 years.

Archiving will be authorised by MEH (Sponsor) following submission of the end of trial summary report.

To enable evaluations and/or audits from MEH (Sponsor), the investigator agrees to keep records, including the identity of all participants (sufficient information to link records, e.g., CRFs and hospital records), all original signed informed consent documents, copies of all CRFs, safety reporting forms, source documents, detailed records of tests performed and adequate documentation of relevant correspondence (e.g., letters, meeting minutes, telephone calls reports). The records should be retained by the investigator according to International Conference on Harmonisation (ICH), local regulations, or as specified in the Clinical Study Agreement (CSA), whichever is longer.

If the investigator becomes unable for any reason to continue to retain trial records for the required period (e.g., retirement, relocation), MEH (Sponsor) should be prospectively notified. The trial records must be transferred to a designee acceptable to MEH, such as another investigator, another institution, or to an independent third party arranged by MEH.

Investigator records must be kept for a minimum of 10 years after completion or discontinuation of the trial or for longer if required by applicable local regulations.

The investigator must obtain MEH written permission before disposing of any records, even if retention requirements have been met.

The Sponsor will be responsible for archiving the Trial Master File and databases, in line with the Sponsor SOP for archiving non-regulated studies. The sites will be responsible for archiving the site file in line with their local SOP for storage.

Destruction of essential documents will require authorisation from the Sponsor.

12.QUALITY CONTROL AND QUALITY ASSURANCE

12.1.Site Set-up and Initiation

The Chief Investigator (CI) is required to sign a Clinical Trials Task Delegation Log which documents the agreements between the CI and BCTU.

All local PIs will be asked to sign the necessary agreements including a Site Signature and Delegation log between the PI and the CTU and supply a current curriculum vitae and GCP certificate to BCTU. All members of the site research team are required to sign the Site Signature and Delegation Log, which details which tasks have been delegated to them by the PI. The Site Signature and Delegation Log should be kept up to date by the PI. It is the PI's responsibility to inform the Trial Office of any changes in the site research team.

Prior to commencing recruitment, each recruiting site will undergo a process of initiation, either a meeting or a teleconference, at which key members of the site research team are required to attend, covering aspects of the trial design, protocol procedures, adverse event reporting, collection and reporting of data and record keeping. Sites will be provided with an ISF containing essential documentation, instructions, and other documentation required for the conduct of the trial.

12.2.Monitoring

The monitoring requirements for this trial have been developed following a trial specific risk assessment by BCTU and as documented in the ATHENA monitoring plan.

12.2.1. On-site monitoring

For this trial we will monitor sites in accordance with the ATHENA trial risk assessment and monitoring plan. Any monitoring activities will be reported to the trials team and any issues noted will be followed up to resolution. Additional on-site monitoring visits may be triggered by, for example, poor CRF return, poor data quality, excessive number of participant withdrawals or deviations (also defined in the monitoring plan). Investigators will allow the ATHENA trial staff access to source documents as requested. The monitoring will be conducted by representatives of the Sponsor or BCTU.

12.2.2. Central monitoring

Trials staff will be in regular contact with the site research team to check on progress and address any queries that they may have. Sites will be requested to send in copies of signed ICFs and other documentation for central review for all participants providing consent. This will be detailed in the monitoring plan. Trials staff will check incoming ICFs and CRFs for compliance with the protocol, data consistency, missing data and timing. Sites will be sent queries requesting missing data or clarification of inconsistencies or discrepancies.

12.3.Audit and Inspection

The Investigator will permit trial-related monitoring, audits and ethical review at their site, providing direct access to source data/documents. The investigator will comply with these visits and any required follow up. Sites are also requested to notify BCTU of any relevant inspections.

12.4.Notification of Serious Breaches

The Sponsor is responsible for notifying the REC of any serious breach of the conditions and principles of GCP in connection with that trial or the protocol relating to that trial. Sites are therefore requested to notify the Trial Office of any suspected trial-related serious breach of GCP and/or the trial protocol. Where the Trial Office is investigating whether or not a serious breach has occurred,

sites are also requested to cooperate with the Trial Office in providing sufficient information to report the breach to the REC where required and in undertaking any corrective and/or preventive action.

Sites may be suspended from further recruitment in the event of serious and persistent non-compliance with the protocol and/or GCP, and/or poor recruitment. Any major problems identified during monitoring may be reported to the ATHENA management and oversight committees and the REC. This includes reporting serious breaches of GCP and/or the trial protocol.

A copy of the notification will be sent to the Sponsor's Research Compliance Team at the time of reporting to the REC.

13. END OF TRIAL DEFINITION

The end of trial will be 9 months after the last data capture. This will allow sufficient time for the completion of protocol procedures, data collection and data input and cleaning. The Trial Office will notify the REC and Sponsor that the trial has ended within 90 days of the end of trial. A copy of the end of trial notification will be sent by the Trial Office to the Sponsor at the Research & Innovation Office at MEH, and the REC. Where the trial has terminated early, the Trial Office will inform the REC within 15 days of the end of trial. The Sponsor, CI and Trial Office will provide the REC with a summary of the clinical trial report within 12 months of the end of trial.

14. STATISTICAL CONSIDERATIONS

14.1 Sample Size

Assuming that the combination of OCT+OCTA has a sensitivity of 92%[8-10] and that of OCT+FFA has a sensitivity of 90% for the detection of nAMD[4] , then 240 patients with nAMD are required to be 90% sure that the upper limit of a one-sided 97.5% confidence interval (or equivalently a 95% two-sided confidence interval) will exclude a difference in favour of OCT+FFA of more than 10 percentage points (non-inferiority margin). Given the significant expected advantages of OCTA in terms of patient experience of care and service delivery for busy AMD clinics, its role as a second-round test following OCT and the high estimates of accuracy already reported for all imaging modalities, a non-inferiority margin of 10 percentage points was deemed acceptable by the research team. Audit data from MEH indicate a prevalence of 75% of confirmed nAMD in patients with a positive or suspicious OCT and therefore 320 patients with suspected nAMD will be required. However, since we are also interested in comparing specificity and using the same estimates as for sensitivity, we require 960 patients. Allowing 10% for withdrawal of consent, missing data and inconclusive test results, we would aim to recruit a total of 1,067 patients with a positive or suspicious OCT.

14.2 Analysis of Outcomes

A separate Statistical Analysis Plan will be produced and will provide a more comprehensive description of the planned statistical analyses. A brief outline of these analyses is given below. No adjustment for multiple comparisons will be made.

14.2.1. Primary Outcome Measure

The diagnostic accuracy of OCTA and FFA in combination with OCT will be assessed on the basis of image review by clinicians in recruitment sites. The unit of analysis is the patient (one 'trial' eye per patient). The sensitivity, specificity, PPV and NPV of the tests will be calculated. A comparison of the diagnostic accuracy of OCT+OCTA and OCT+FFA will be performed to assess non-inferiority. We will estimate differences in sensitivity and specificity, and calculate two-sided 95% confidence intervals for the differences. If the lower boundary of the two-sided 95% confidence interval for the difference in sensitivity of OCT+OCTA relative to OCT+FFA is higher than −10 percentage points, then the sensitivity of OCT+OCTA will be considered non-inferior [11]. A similar analysis will be performed for the comparison of the specificity of OCT+OCTA and OCT+FFA.

14.2.2. Secondary Outcomes

Approaches for analyses of the secondary outcomes are outlined below. See section 15 for the methods for the cost-effectiveness analysis.

- Sensitivity, specificity, PPV and NPV of OCTA and FFA in isolation will be assessed on the basis of masked review by expert graders in the Reading Centres. For all of these proportions, 95% confidence intervals (CIs) will be calculated using the Wilson method.
- The PPV of OCT and its 95% CI will be estimated. Since only patients with a positive or suspicious OCT will have additional testing and the reference standard, the sensitivity, specificity and NPV of OCT cannot be assessed.
- For test comparisons including OCT+FFA versus OCT+FFA+OCTA and OCT+OCTA versus OCT+OCTA+FFA, we will estimate differences in sensitivity and specificity together with their 95% CIs and assess non-inferiority as stated above.
- For a subset of cases with OCT and clinical features suspicious of PCV, the diagnostic accuracy of OCTA, FFA and ICGA alone and in combination will be assessed by calculating their sensitivity, specificity, PPV and NPV (including their 95% CIs).

- For OCTA and FFA, intra- and inter-rater agreement will be determined using percentage agreement and Gwet's first-order agreement coefficient (Gwet's AC1)[12, 13].
- Cross-classification (number and percentage agreement) of FFA and OCTA for nAMD lesion type (type 1- type 2-, type 3-nAMD) as assessed by the reading centre graders.
- The number and percentage of participants unable to fully complete FFA test or ICGA due to adverse reactions as assessed in treating centre.

14.2.3. Missing Data and Sensitivity Analyses

Every attempt will be made to collect full follow-up data on all trial participants; it is thus anticipated that missing data will be minimal. Participants with indeterminate or missing index test and reference standard results will not be included in the primary analysis in the first instance. This presents a risk of bias, and sensitivity analyses will be undertaken to assess the possible impact of the risk. We will consider using multiple imputation to impute data on missing index test results. Full details will be included in the Statistical Analysis Plan. Further sensitivity analysis will include analysis of the primary outcome in the per-protocol population.

14.3.Planned Interim Analyses

Interim analyses of safety and efficacy for presentation to the independent DMC will take place during the trial. The committee will meet prior to trial commencement to agree the manner and timing of such analyses but this is likely to include the analysis of the primary and major secondary outcomes and full assessment of safety (SAEs) at least at annual intervals. Criteria for stopping or modifying the trial based on this information will be ratified by the DMC. Details of the agreed plan will be written into the SAP. Further details of DMC arrangements are given elsewhere in the protocol.

14.4.Planned Final Analyses

The primary analysis for the trial will occur once all participants have completed the index tests and judgements about the reference standards have been made, and the results have been entered onto the trial database and validated as being ready for analysis.

15. HEALTH ECONOMICS

A model-based cost-effectiveness analyses (CEA) will be conducted to estimate the incremental cost per true positive detected and incremental cost per correct diagnosis for nAMD. A separate Health Economics Analysis Plan will be produced and will provide a more comprehensive description of the planned analyses. A brief outline of these analyses is given below. The interventions to be analysed will be for the baseline analysis:

OCT+FFA,

OCT+OCTA

These correspond to the CD1 as defined in section 7.1. In further analysis, two further comparators will be added

OCT + FFA + OCTA

OCT + OCTA + FFA

These further comparators correspond to the CD2 as defined in section 7.1.

For the sub-group of participants with clinical features of PCV, we will consider the impact of the addition of ICGA conducted at the same time as the FFA.

Further sensitivity analysis will consider other plausible combinations of tests and the impact of including/excluding indeterminate test results into the results.

Estimating Resource Use

Costs will be estimated from the NHS perspective up to the end of the diagnostic phase. The costs of the different tests will be based upon the resources collected as part of the accompanying diagnostic accuracy study. The type and frequency of resources used to screen for nAMD will be estimated from the trial data. This will include costs on the frequency of procedures (e.g. injections of diagnostic dyes), pharmaceuticals used in diagnosis (Fluorescein, Lissamine green) and different ocular imaging techniques (e.g. OCT, OCTA, FFA and ICGA). Any drugs required in the process of diagnosis will also be included, these costs will be derived from the British National Formulary[14] . The incidence and type of any adverse effects will also be collected. Costs estimates for the resources will be derived from published sources such as NHS reference costs and Unit Costs of Social Care[15, 16]. If published costs are unavailable for any elements of the micro-costing then trial data, manufacturer costs or clinical expertise will inform these costs elements. Subsequent care costs beyond diagnosis will not be estimated as this is outside the scope of this trial.

Decision Model

A decision tree model will be designed in a suitable software such as Treeage[17]. For the base case analysis, only those with complete scan data will be included, with the consequences of indeterminate scans being examined as part of the sensitivity analyses. The structure of the model will be based on the diagnostic pathways specified in the trial (see section 7.1 and the definitions of CD1 and CD2). The time horizon for the model-based analysis will cover the diagnostic testing period only. The results of the model will be expressed an incremental cost effectiveness ratio. Specifically, this will be presented as a per true positive detected for each of the strategies. The decision model will require probabilities of events happening to the cohorts in the model (e.g. false positive, false negative). These probabilities will be derived from the sensitivity, specificity and PPV results from the trial and the reading centre analysis as described above. The decision model will also require information on the costs of tests (and adverse event management for a deterministic sensitivity analysis). If any additional parameters are required these will be sought by searching the existing literature. The decision tree will integrate these data to estimate the incremental cost per case detected.

Sensitivity Analysis

Sensitivity analysis will be carried out using both a Deterministic Sensitivity Analysis (DSA) and Probabilistic Sensitivity Analysis (PSA) approach. The sensitivity analysis will be used to assess parameter uncertainty, including any differences identified between the hospital based clinical trial and the diagnostic accuracy study based in the reading centre. DSA will used to explore plausible alternatives (for example, quantity of resources used or unit costs). One example of this kind of sensitivity analysis will be inclusion of the costs of the targeted AEs which may occur as a result of the procedures. The detail of any subsequent actions regarding targeted AEs will be taken from their reporting criteria and unit costs will be attributed where possible from published NHS reference costs[18]. These costs will be included in the economic decision model to assess whether these costs impact the overall conclusion of the cost effectiveness of the different strategies. A further DSA that will be carried out will include the costs of indeterminate tests, which could not be included in the base case analysis to assess the impact of these costs on the conclusions of the trial. The rate of indeterminate tests will also be varied to assess if the number of unusable scans can impact the cost effectiveness of an imaging strategy.

PSA will also be undertaken to characterise the joint imprecision surrounding model parameters and how this impacts the modelled estimates. This will take the form of a Monte Carlo PSA to address any uncertainty within the model. A distribution will be derived for each parameter, the choice of which will be governed by best practice with regards to economic decision modelling[19]. The results of the sensitivity analyses will be presented as cost and outcome plots as well as cost-effectiveness acceptability curves.

Subgroup Analysis

In addition to the base case analysis and the relevant sensitivity analysis. There will be a subgroup analysis for those with PCV compared to those who do not. The subgroup analysis will be performed with those who have a diagnosis of PCV. This will help understand the value of the additional imaging procedures for those with choroidal vasculopathy specifically. The results will be assessed to see if the cost effectiveness for this group differs from the larger group of macular disorders.

16.TRIAL ORGANISATIONAL STRUCTURE

16.1.Sponsor

The Sponsor for this trial is Moorfields Eye Hospital NHS Foundation Trust who are also the Lead Organisation (i.e. the contracting party with the Funder).

16.2.Coordinating Centre

The trial coordinating centre (Trial Office) is Birmingham Clinical Trials Unit (BCTU), based at the University of Birmingham.

16.3.Trial Management Group

The Trial Management Group will take responsibility for the day-to-day management of the trial, and will include (but is not limited to) the CI, co-applicants, statisticians, team leader and trial manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself.

16.4. Co-investigator group

The Co-investigator group, will comprise all members of the co-applicant group and will review progress, troubleshoot and plan strategically.

16.5. Trial Steering Committee

The role of the Trial Steering Committee (TSC) is to provide the oversight of the trial. The TSC will include members who are independent of the investigators, their employing organisations, Funder and Sponsor. The TSC will monitor trial progress and conduct and advise on scientific credibility.

A TSC will be created for the ATHENA trial and, unless in exceptional circumstances, will meet via video or teleconference as required depending on the needs of the trial.

Membership and duties/responsibilities are outlined in the TSC Charter. In summary, the TSC will provide overall oversight of the trial, including the practical aspects of the trial, as well as ensuring that the trial is run in a way which is both safe for the participants and provides appropriate feasibility data to the Sponsor and investigators.

16.6. Data Monitoring Committee

The role of the independent DMC is to monitor the trial data and make recommendations to the TSC on whether there are any ethical or safety reasons as to why the trial should not continue or whether it needs to be modified. To this end, data on safety outcomes and (where appropriate) primary and major secondary outcomes will be supplied to the DMC during the trial. Reports will be supplied in confidence.

The DMC will operate in accordance with a trial specific DMC Charter which will define the membership, roles and responsibilities of the DMC. The DMC will meet at least annually as a minimum. Additional meetings may be called if needed e.g., recruitment is faster than anticipated or a safety issue is identified.

Data analyses will be supplied in confidence to an independent DMC, which will be asked to give advice on whether the accumulated data from the trial, together with the results from other relevant research, justifies the continuing recruitment of further participants. The DMC will operate

in accordance with a trial specific charter based upon the template created by the Damocles Group[20]. The DMC will meet at least annually as agreed by the Committee and documented in the Charter, unless there is a specific reason (e.g. safety phase) to amend the schedule.

Additional meetings may be called if recruitment is much faster than anticipated and the DMC may, at their discretion, request to meet more frequently or continue to meet following completion of recruitment. An emergency meeting may also be convened if a safety issue is identified. The DMC will report directly to the TSC, who will convey the findings of the DMC to the Funder and Sponsor as relevant. The DMC may consider recommending the discontinuation of the trial if the recruitment rate or data quality are unacceptable or if any issues are identified which may compromise participant safety. The trial will stop early if any interim analyses shows differences between trial arms that were deemed to be convincing to the clinical community.

16.7. Finance

Funding for the ATHENA trial is provided by an award from the National Institute of Health Research (NIHR) Health Technology Assessment Programme Project reference NIHR131432. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care.

17. ETHICAL CONSIDERATIONS

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research and applicable UK Acts of Parliament and Statutory Instruments (and relevant subsequent amendments), which include Data Protection Act 2018 and the Principles of GCP as set out in the UK Statutory Instrument (2004/1031; and subsequent amendments). The protocol will be submitted to and approved by the REC prior to the start of the trial.

Before any participants are enrolled into the trial, the PI at each site is required to obtain the necessary local approval.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

The trial will be conducted in accordance with the UK Policy Framework for Health and Social Care Research, the applicable UK Statutory Instruments, (which include the Data Protection Act 2018) and the Principles of GCP, the Human Tissue Act (2008), the Medical Devices Regulations (2002) (SI 618) and Annex X of the Medical Devices Directive 93/42. The trial will be submitted to and approved by the main REC prior to circulation.

Before any participants are enrolled into the trial, the PI at each site will obtain local R&D approval/assurance. Sites will not be permitted to enrol participants until written confirmation of R&D approval/assurance is received by the trial team.

It is the responsibility of the PI to ensure that all subsequent amendments gain the necessary local approval. This does not affect the individual clinicians' responsibility to take immediate action if thought necessary to protect the health and interest of individual participants.

18. DATA PROTECTION AND CONFIDENTIALITY

The use of the data at MEH will meet the General Data Protection Regulation. All research using patient data must follow UK laws and rules.

The Sponsor maintains confidentiality standards by coding each patient enrolled in the trial through assignment of a unique patient identification number.

All patient medical information associated with the trial is confidential and may be used and disclosed only as permitted by the Informed Consent Form (or separate authorisation for use and disclosure of personal health information) signed by the patient.

MEH Data Protection Officer: Jo Downing, Head of Information Governance, Moorfields Eye Hospital. Email: Moorfields.ig@nhs.net

Birmingham Clinical Trials Unit at the University of Birmingham is the coordinating centre for the trial. Personal data recorded on all documents will be regarded as strictly confidential and will be handled and stored in accordance with the Data Protection Act 2018 (and subsequent amendments). The data collected will be processed by Moorfields Eye Hospital NHS Foundation Trust and the University of Birmingham. Moorfields Eye Hospital NHS Foundation Trust are the Data Controllers. Any data collection forms received at BCTU will be kept secure in locked cabinets in a swipe-card access controlled building. The data is also stored in the BCTU trial database on a secure server.

Participants will always be identified using their unique trial identification number, on the Case Report Form and on any correspondence between BCTU and local centres. Participants will give their explicit consent for the movement of their consent form, giving permission for BCTU to be sent a copy. This will be used to perform in-house monitoring of the consent process.

The Investigator must maintain documents not for submission to BCTU (e.g. Participant Identification Logs) in strict confidence. In the case of specific issues and/or queries resulting from audits/monitoring, it will be necessary to have access to the complete trial records, provided that participant confidentiality is protected.

BCTU will maintain the confidentiality of all participants' data and will not disclose information by which participants may be identified to any third party other than those directly involved in the clinical care of the participant and organisations for which the participant has given explicit consent for data transfer (e.g Sponsor). Representatives of the ATHENA trial team and Sponsor may be required to have access to participants' notes for quality assurance purposes, but participants should be reassured that their confidentiality will be respected at all times. The participants will provide consent for reading centre experts to be sent their tests accompanied with a short vignette of relevant clinical information and linked by their unique trial ID number. Written consent will also be obtained for the Health Economic experts based at the University of Newcastle to be provided with the results from their tests, their age in months and their unique trial ID number.

19. FINANCIAL AND OTHER COMPETING INTERESTS

There are no financial or other competing interests related to the results of this trial. Members of the TSC and DMC are required to provide declarations on potential competing interests as part of their membership of the committees. Authors are similarly required to provide declarations at the time of submission to publishers.

20. INSURANCE AND INDEMNITY

MEH has in place Clinical Trials indemnity coverage for this trial which provides cover to the contracting organisations for harm which comes about through their, their staff or their contractors' negligence in relation to the design or management of the trial and may alternatively, and at the Trust's discretion provide cover for non-negligent harm to participants.

With respect to the conduct of the trial at Site and other clinical care of the patient, responsibility for the care of the patients remains with the NHS organisation responsible for the Clinical Site and is therefore indemnified through the NHS Litigation Authority.

MEH and UoB are independent of any pharmaceutical company, and as such are not covered by the Association of the British Pharmaceutical Industry (ABPI) guidelines for participant compensation.

21.POST-TRIAL CARE

All participants will continue to receive standard medical care as provided by the NHS following participation in the clinical trial. There are no interventions that participants will be prevented from accessing after their participation in the trial has been completed.

22. ACCESS TO FINAL DATASET

During the period of the trial only the trial's statisticians will have access to the full trial dataset. The final dataset will be available to members of the Trial Management and co-applicant group who need access to the data to undertake the final analyses. All members of the oversight committees will ensure that the interim and overall results are not disclosed prior to the main publication, including by individual sites.

Following publication of the findings, the final trial dataset will be made available to external researchers upon approval from the trial management group, the BCTU data sharing committee, and the Sponsor in line with standard data sharing practices for clinical trial data sets.

23. PUBLICATION PLAN

Results of this trial will be submitted for publication in a peer reviewed journal. The manuscript will be prepared by the CI and authorship will be determined by the ATHENA trial publication policy.

Any secondary publications and presentations prepared by Investigators must be reviewed and approved by the TMG prior to wider circulation. Manuscripts must be submitted to the TMG in a timely fashion and well in advance of being submitted for publication to allow time for review and resolution of any outstanding issues.

Authors must acknowledge that the trial was performed with the support of the University of Birmingham and Birmingham Clinical Trials Unit, the University of Newcastle the Sponsor, and the

Funder. Intellectual property rights will be addressed in the Clinical Trial Site Agreement between Sponsor and site.

The trial question is important and has the potential to change clinical practice. This view has been validated by the health professionals and patient surveys that have been conducted by our research team and from research recommendations arising from systematic reviews and national, evidence-based guidelines. We have prioritised methods to ensure rapid, clinical impact once the results of the ATHENA trial are available. These include:

Guidelines: The information is expected to be rapidly incorporated into guidelines by the Royal College of Ophthalmologists, the National Institute of Health and Care Excellence (NICE) and international bodies before being disseminated nationally for implementation. This will be facilitated by the coinvestigator group who are, or who have links to, people who hold senior positions in many of these bodies.

All current systematic reviews and guidance have acknowledged the need for research and we therefore believe that authors will be receptive to these new findings.

Patient information resources: Production of lay information with links to appropriate patient organisations. With our Patient and Public Involvement co-applicants and contacts, we will produce effective, contemporary formats for dissemination e.g. the use of video podcasts and social media outlets.

Conferences: The findings will be presented and disseminated via national and international conferences.

Peer reviewed publications: We will aim to publish the findings in high impact peer reviewed journals. We will disseminate the completed paper to the Department of Health, the Scientific Advisory Committees of the relevant scientific bodies such as the Royal College of Ophthalmologists.

NIHR Journals Library: A monograph will be available through the NIHR Journals Library which will help with dissemination of findings and will provide an important, permanent and comprehensive record of the trial.

Media: In consultation with the investigators and appropriate journal, a press release will be issued to the media upon publication of the results.

Results of the trial will be shared with trial participants, staff members at research sites and investigators of other studies related to any of the imaging techniques investigated in ATHENA. A formal notification to the ethics committee, Department of Health, key partners and Sponsor will be made. Outreach to other key stakeholders (trial networks, health advocates) involved in related trials is planned. The trial team has key individuals to optimise the dissemination of results.

24. REFERENCE LIST

1. Wong WL, Su X, Li X, Cheung CM, Klein R, Cheng CY*, et al.* Global prevalence of age-related macular degeneration and disease burden projection for 2020 and 2040: a systematic review and meta-analysis. *Lancet Glob Health* 2014;**2**:e106-16. https://doi.org/10.1016/s2214-109x(13)70145-1

2. MacEwen C BJ. *The Way Forward. Management of Wet Age-Related Macular Degeneration*. Royal College Ophthalmologists (UK); 2015.

3. Kwiterovich KA, Maguire MG, Murphy RP, Schachat AP, Bressler NM, Bressler SB*, et al.* Frequency of adverse systemic reactions after fluorescein angiography. Results of a prospective study. *Ophthalmology* 1991;**98**:1139-42. https://doi.org/10.1016/s0161-6420(91)32165-1

4. Gualino V, Tadayoni R, Cohen SY, Erginay A, Fajnkuchen F, Haouchine B*, et al.* OPTICAL COHERENCE TOMOGRAPHY, FLUORESCEIN ANGIOGRAPHY, AND DIAGNOSIS OF CHOROIDAL NEOVASCULARIZATION IN AGE-RELATED MACULAR DEGENERATION. *Retina* 2019;**39**:1664-71. https://doi.org/10.1097/iae.0000000000002220

5. Coscas GJ, Lupidi M, Coscas F, Cagini C, Souied EH. OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY VERSUS TRADITIONAL MULTIMODAL IMAGING IN ASSESSING THE ACTIVITY OF EXUDATIVE AGE-RELATED MACULAR DEGENERATION: A New Diagnostic Challenge. *Retina* 2015;**35**:2219-28. https://doi.org/10.1097/iae.0000000000000766

6. Carnevali A, Cicinelli MV, Capuano V, Corvi F, Mazzaferro A, Querques L*, et al.* Optical Coherence Tomography Angiography: A Useful Tool for Diagnosis of Treatment-Naïve Quiescent Choroidal Neovascularization. *Am J Ophthalmol* 2016;**169**:189-98. https://doi.org/10.1016/j.ajo.2016.06.042

7. Spaide RF, Fujimoto JG, Waheed NK, Sadda SR, Staurenghi G. Optical coherence tomography angiography. *Prog Retin Eye Res* 2018;**64**:1-55. https://doi.org/10.1016/j.preteyeres.2017.11.003

8. Faes L, Bodmer NS, Locher S, Keane PA, Balaskas K, Bachmann LM*, et al.* Test performance of optical coherence tomography angiography in detecting retinal diseases: a systematic review and meta-analysis. *Eye (Lond)* 2019;**33**:1327-38. https://doi.org/10.1038/s41433-019-0421-3

9. Faridi A, Jia Y, Gao SS, Huang D, Bhavsar KV, Wilson DJ*, et al.* Sensitivity and Specificity of OCT Angiography to Detect Choroidal Neovascularization. *Ophthalmol Retina* 2017;**1**:294-303. https://doi.org/10.1016/j.oret.2017.02.007

10. Gong J, Yu S, Gong Y, Wang F, Sun X. The Diagnostic Accuracy of Optical Coherence Tomography Angiography for Neovascular Age-Related Macular Degeneration: A Comparison with Fundus Fluorescein Angiography. *J Ophthalmol* 2016;**2016**:7521478. https://doi.org/10.1155/2016/7521478

11. Castelloe J, Watts, D. Equivalence and Noninferiority Testing Using SAS/STAT® Software. Proceedings of the SAS Global Forum 2015 Conference; Cary, NC, abstract no. 860.

12. Gwet K. *Handbook of inter-rater reliability. The definiative guide to measuring the extent of agreement among raters*. 4 edn. Gaithersburg, MD 20886-2696, USA: Advanced Analytics, LLC; 2014.

13. De Raadt A, Warrens MJ, Bosker RJ, Kiers HAL. Kappa Coefficients for Missing Data. *Educ Psychol Meas* 2019;**79**:558-76. https://doi.org/10.1177/0013164418823249

14. NICE. *British National Formulary Medicines Complete 2019* National Institute of Health and Care Excellence; 2019. URL: https://improvement.nhs.uk/resources/reference-costs (accessed 2nd June, 2020).

15. Curtis L.A B, A. *Unit Costs of Health and Social Care 2017*. University of Kent; 2017. URL: https://kar.kent.ac.uk/65559/40/65559_rep_UCR-2017-v13finalKAR.pdf (accessed; https://doi.org/10.22024/UniKent/01.02/6555). https://doi.org/https://doi.org/10.22024/UniKent/01.02/6555

16. Curtis L, Burns, L. Community Based Health Care Stuff, in Unit Costs of Health and Social Care In: University of Kent 2018: 153 - 67.

17. Software T. TreeAge Pro. In. Williamstown MA; 2021.

18. DoH. *UK DoH. Reference costs 2017-2018. National Health Services (NHS)* 2018. URL: https://improvement.nhs.uk/resources/reference-costs/ (accessed 2nd June, 2020).

19. Briggs A CK, Sculpher M. *Decision Modelling for Health Economic Evaluation.*: Oxford University Press; 2011.

20. A proposed charter for clinical trial data monitoring committees: helping them to do their job well. *Lancet* 2005;**365**:711-22. https://doi.org/10.1016/s0140-6736(05)17965-3