Study Title: Quality-Assured Follow-up of quiEscent Neovascular agE-relaTed maculaR dEgeneration by non-medical practitioners: a randomised controlled trial
The FENETRE study

1. Summary of Research (abstract)

Research Question: Can non-medical practitioners follow-up patients with Quiescent neovascular Age-related Macular Degeneration (QnAMD) in the community in a safe and clinically and cost effective way?

Background: Age-related Macular Degeneration (AMD) is the most frequent cause of blindness and accounts for 50% of all certifications of visual impairment in the UK. (Wong et al, Quartilho et al). Capacity within hospital-based ophthalmology services for management of neovascular AMD (nAMD) is severely constrained. (RCOpth Way forward) For many patients with nAMD, the disease will become inactive at some point in the course of their treatment. The 2016 HTA funded ECHOES study showed that there is potential to follow-up patients with Quiescent nAMD (QnAMD) safely and effectively by suitably trained non-medical practitioners (Reeves et al). If safe, integrated and quality assured community care can be developed, this should provide opportunities to make services more accessible and convenient for patients while also easing pressure on hospital eye departments and potentially lowering costs.

Primary Objective: To assess the non-inferiority of non-medical practitioner follow-up of QnAMD in the community against secondary care eye-clinics in correctly classifying re-activation due to nAMD.

Methods: A prospective randomised multi-site clinical trial will be conducted recruiting 742 patients with QnAMD from secondary care sites. Patients will be randomised to be followed-up monthly for 12 months either in secondary care or in community-based optometry practices. The study will involve a development phase for community optometrist training and a pilot phase with process evaluation to assess feasibility of the recruitment plan and quality assurance on the training programme. The full trial will involve an economic evaluation and process evaluation.

Timelines:

1) Training development and delivery, set-up of pathways: 6 months
2) Internal Pilot: 6 months
3) Patient recruitment from secondary care (18 months) and follow-up in the two pathways (12 months): 30 months
4) Reading Centre analysis, statistical analysis, economic evaluation, process evaluation, report of results: 6 months

Anticipated impact and dissemination: This research project will potentially validate in terms of safety, clinical- and cost-effectiveness a model of care for patients with QnAMD by non-medical practitioners in the community. This will be in line with the strategic priorities of the NHS and priority research areas defined by NICE (NICE AMD 2018) for facilitating access to care for vulnerable patients and bringing care closer to home, while reducing capacity pressures within secondary care. Dissemination will take place through scientific publications, the ophthalmic charities, NHS commissioning bodies and NHS England.

2. What is the problem being addressed

The annual incidence in the UK of the aggressive neovascular form of AMD (nAMD) has been estimated as 39,700 new cases per year, a figure projected to rise by a third by 2020 (National

AMD Audit 2017). nAMD requires repeated eye injections on regular intervals for long periods of time to preserve vision. Capacity within hospital-based ophthalmology services for management of neovascular AMD (nAMD) is severely constrained (RCOphth Way Forward). For many patients with nAMD, the disease will become inactive at some point in the course of their treatment, meaning that injections are no longer needed to maintain disease control. There is no definitive cure for nAMD and patients that have reached quiescence require regular follow-up to pick-up signs of re-activation that may warrant resuming treatment. The 2016 HTA funded ECHOES virtual study showed that there is potential to follow-up patients with QnAMD safely and effectively by suitably trained non-medical practitioners (Reeves et al). If safe, integrated and quality assured community care can be developed and validated through a prospective clinical trial, then services could be made more accessible and convenient for patients while also easing pressure on hospital eye departments and potentially making the management of this condition more efficient while improving patient experience of care.

3. Why is this research important in terms of improving the health and/or wellbeing of the public and/or to patients and health and care services?

Public and Patient Involvement work in preparation for this proposal highlighted that people with QnAMD place great importance on receiving care closer to home, in a timely and convenient way and that repeated visits and long waits in crowded hospital-based clinics adversely affect their experience of care. Our proposal brings together outstanding expertise to ensure delivery of all aspects of the commissioning brief with a carefully designed, realistic and comprehensive research plan.

3a. Review of existing evidence - How does the existing literature support this proposal?

Recommendations for the development of community based eye-care services have been proposed in the Royal College of Ophthalmologist's 'Way Forward' report. Recent work has highlighted inequalities in access to treatment strengthening the case for facilitating access to care closer to home. (Hollingworth et al) The evolving area of tele-ophthalmology offers new possibilities for integrated care by linking community practice with hospital-based services (Kawaguchi A). The recent revision of NICE guidance on the management of AMD makes specific reference to the need for further research on service delivery models with emphasis on allied-health professional extended roles and community-based care. (NICE AMD 2018)

The current proposal brings together a clinical and methodological interdisciplinary team, who with assistance from patients and the public, produced a trial design that fully addresses all the elements of the commissioning brief while incorporating improvements in response to all the suggestions made by the HTA review panel during the first stage of the application process.

4. Aims and Objectives

Aim: To assess the clinical and cost effectiveness of non-medical practitioner follow-up of patients with quiescent neovascular age-related macular degeneration (nAMD) in the community

Primary Objective: To assess safety of non-medical practitioner follow-up of Quiescent neovascular AMD (QnAMD) in the community compared to secondary care eye-clinics in correctly classifying re-activation due to neovascular age-related degeneration (nAMD).

Secondary objectives:

1. To assess efficiency (rate of over-referral) of community-based and secondary care QnAMD pathways against a reference standard (expert Reading Centre).

2. To assess non-inferiority of non-medical practitioner follow-up of QnAMD in the community versus secondary care eye-clinics in correctly classifying re-activation due to nAMD.
3. To estimate the cost-effectiveness and budget impact of community-based optometry QnAMD pathways against secondary care pathways.
4. To assess patient and practitioner acceptability of community based QnAMD pathways
5. To develop a transferable training program for community delivered QnAMD care by non-medical healthcare practitioners.
6. To assess the impact on secondary care services (e.g. utilisation of services, waiting lists, etc) of community based QnAMD pathways.
7. To develop and assess quality standards (co-developed with patients) for system and individual performance in community based QnAMD pathways.

5. Project Plan

Health Technologies being assessed: Follow-up of patients with QnAMD by trained community-based optometrists

Design and theoretical/conceptual framework: This is a prospective, randomised, multi-site clinical trial testing the non-inferiority of community optometry follow-up of patients with QnAMD over 12 months. It involves the delivery of a training package for community optometrists, a pilot trial to assess feasibility of the recruitment plan, perform quality assurance of the training package and a process evaluation with criteria for progression to a full trial. The full trial includes economic and process evaluation. The trial design has been developed with the accredited CTU unit at King's College London (KCTU), the Moorfields Clinical Research Facility, a trial statistician, methodologists, a qualitative expert, patients affected by nAMD and an experienced research team of optometrists and retinal specialists.

A. Development Stage (6 months)

The Development and delivery of a competency-based training package for community optometrists: The research team has extensive expertise in developing and implementing sub-specialist competency-based training programmes linked to extended roles for non-medical allied health professionals (Harper et al, Mason et al), including the College of Optometrists higher professional qualifications in Medical Retina (Prof John Lawrenson). The College of Optometrists strongly supports this project and has agreed to contribute to and advise on the development of a bespoke training package (see attached letter of support) for the management of QnAMD based on its nationally recognised qualifications. (College of Optometrists, Medical Retina Qualifications)

Qualitative findings from our work have suggested that community optometrists prefer distance/online learning (Baker H et al, Creer R et al, Konstantakopoulou et al) in supporting extended roles. Taking on board suggestions by PPI contributors, training will adopt a blended learning approach, combining distance learning and face to face clinic-based teaching provided by local ophthalmologists. City University will host the online training under the supervision of Prof Lawrenson, who with Dr Harper will provide oversight of locally delivered training. Distance learning will use a flexible virtual learning platform incorporating synchronous and asynchronous learning tools e.g. online lectures, webinars and a discussion forum.

The content of the training package will be developed by retinal specialists within the research team and will consist of: 1. Online lectures covering all aspects of Neovascular AMD diagnosis

and differential diagnoses and its management with an emphasis on detecting signs of re-activation in those with previously established disease and signs of recent onset nAMD that can potentially develop in the fellow unaffected eye in the course of follow-up. 2. Interactive webinars incorporating case-based discussions 3. Clinical sessions (minimum of four sessions in AMD treatment clinics) delivered by local secondary care teams providing enhanced understanding of the pathways involved in management of patients with Wet AMD. 4. Formative assessment to provide ongoing feedback, monitor progress and identify learning needs

On completion of training, optometrists will undertake a formal accreditation assessment in the form of an online test comprising a series of case vignettes containing fundus images, OCT scans and clinical data with a task assignment for classification as active or inactive. Accreditation threshold will be 75% correct classifications (with further training and re-sit opportunity offered for those scoring less than 75%).

A formative assessment for self-evaluation will take place during training and after 6 months. Refresher courses and repeat accreditation testing will take place after 12 months. This mirrors the model for training and accreditation adopted by the Diabetic Retinopathy Screening Program. An on-line discussion forum will be developed to provide networking opportunities for study participants. The forum will be regularly updated with cases for discussion contributed by local eye unit co-applicants.

Sampling:

Selection of sites- Secondary Care sites: A 'first wave' of secondary care sites will recruit during the pilot phase of the study. These sites are: Moorfields Eye Hospital (central site and three satellite sites) and 5 regional centres (Bristol, Bradford, Manchester, Leeds, York). The corresponding Principal Investigators from these sites will have enhanced responsibility in terms of engagement with local community optometry practices, contribution to educational material for the training programme, delivery of webinars and patient recruitment and involvement in qualitative research during the pilot phase of the study (see section on process evaluation during the pilot phase).

A 'second wave' of recruitment sites has been identified and agreed to participate in the full trial. In the second wave will be eye units corresponding to the North Thames Clinical Research Network area engaged through the North Thames Clinical Research Network Lead Mr Praveen Patel. We will also include eye units in the wider geographical area corresponding to the 5 'first wave' sites noted above. Local 'first wave' co-applicants will facilitate study induction and set-up for 'second wave' sites. Work during the pilot phase of the trial will set up these sites with a view to commencing recruitment once progression to the main study has been decided.

A 'third wave' of recruitment sites have been approached with study-related material communicated by the National Clinical Research Network Ophthalmology sub-specialty group under its co-lead Prof Faruque Ghanchi. Requests for information and interest in the study have been expressed and additional sites will join the study if needed to mitigate against any recruitment delays in the first and second wave sites. Ongoing monitoring of site start-up and recruitment will be performed by the trial manager, Chief Investigator and the Trial Steering Committee (TSC).

Selection of sites- community optometry practices: We have identified and engaged with community based optometry practices (independents, small groups, multiples) with availability of imaging equipment (Optical Coherence Tomography, OCT). A number of independent and

small group practices as well as Specsavers and Vision Express have agreed to participate in this programme.

The recruitment strategy for community optometry practices includes:

- Engagement with major employers (e.g. Specsavers and Vision Express) who are enthusiastic about the trial and have agreed to promote the study and facilitate recruitment of practices.
- Engagement with the Local Optical Committee Support Unit (LOCSU), whose role is to develop, negotiate and implement local primary ophthalmic services. LOCSU is very supportive and will promote the project to independent and small group practices via the Local Optical Committees within the catchment area of each secondary care centre.
- Engagement on a local level with independent and small group practices leveraging existing relationships with optometry and retinal specialist co-applicants.

. Community Optometry practices will follow-up between 1 and 3 patients per week (depending on recruitment target of associated secondary care site).

Inclusion criteria for healthcare professionals:

- Ophthalmologists are required to have ≥3 years post-registration experience in ophthalmology, have passed part 1 of the Royal College of Ophthalmologists or the Diploma in Ophthalmology or an equivalent, and have experience within the AMD service.
- Specialist Optometrists and nurses involved in secondary care are required to have undertaken site-specific training and have experience within the AMD service as per local arrangements in each secondary care site. (control arm)
- Community Optometrists are required to be fully qualified, registered with the General Optical Council (GOC) for ≥3 years. (intervention arm)

Sample size: The ECHOES study has shown that the rate of false negatives per lesion assessment when conducted by an ophthalmologist was 62/994 i.e. 6.2 % with a confidence interval of (4.8 % to 7.9 %). Over the course of one year, a patient will typically have lesions assessed on twelve occasions. The overall chance of being a false negative at any point during the 12 months of follow up is estimated at 20% (determined by the summation of the probability of reactivating and the probability of being a false negative and deducting the chance of being a false negative on repeat occasions with figures estimated from Madhusudhana et al). This estimate requires adjustment for the fact that ECHOES figures were based upon scenarios and vignettes and did not factor in additional information that will be provided by patient input, thus the false negative rate is expected to be lower than 20% in reality. The test of non-inferiority will be one-sided at the 2.5% level. This approach is the conservative approach which is the standard for regulatory approval of new pharmaceuticals and many devices (Pocock SJ et al). Whilst approval has been made on the basis of a non-inferiority design with a 1-sided alpha of 5 % this is generally frowned upon and thus we have adopted the more conservative approach. One of the major challenges in the design of a non-inferiority trial is the determination of the non-inferiority margin. This is the smallest difference between patient management approaches which, if true, would mean that management by non-medical professionals is declared inferior. We adopted a non-inferiority margin of 10%. This was the non-inferiority margin adopted by the ECHOES study and appraised by five peer reviewers, none of whom suggested it was too large. It has subsequently been published within the BMJ-Open paper (Reeves et al 2016) and attracted no criticism or referee comment about it being too high. It should be noted that whilst

not detecting reactivation in a patient is a concern, patients will be reassessed within one month which can be shorter than the time between real world visits in standard care.
With an overall sample size in each group of 337, a two-group large-sample normal approximation test of proportions with a one-sided 0.025 significance level will have 90% power to reject the null hypothesis that the test and the standard are not equivalent (the difference in proportions, $\pi_1 - \pi_0$, is 0.1 or farther from zero in the same direction) in favour of the alternative hypothesis that the proportions in the two groups are equivalent, assuming that the expected difference in proportions is 0 and the proportion in the standard group is 0.2.
Thus, data of the primary outcome would be required from 674 participants in total. 7% loss to follow-up was observed in the 1st year of the NIHR HTA IVAN study (Chakravarthy et al) on a patient population with nAMD. We adopted a more conservative estimate of 10% loss to follow-up, leading to an overall sample size of 742 patients. Of these 72 are expected to be recruited in the pilot trial, with the remainder recruited from the full trial. Sample size calculation was conducted using nQuery Advanced software version 8.1.2.0.
Set up of pathways: Key features for the community-based QnAMD clinics have been defined prior to the trial through consultation with the College of Optometrists, the optometry practices that will be involved (which include representatives from independents, small groups and multiples), the Local Optical Committee Support Unit and through feedback from PPI event. These include:

- Availability of imaging equipment (OCT device);
- Presence of at least one optometrist per practice who has successfully completed the bespoke training package;
- Possibility for real-time communication of results to the patients during consultation;
- IT environment that will allow secure transfer of clinical data to the Reading Centre for quality assurance.

Care pathway in Community QnAMD clinics will include Visual Acuity check, Optical Coherence Tomography, Clinical history taking on bespoke clinical pro-formas, and direct clinical examination by a trained Optometrist.
The control arm will pragmatically involve representative existing models of secondary care-based QnAMD clinics. This will reflect current care in hospital-based QnAMD follow-up clinics. The findings of an on-line survey of retinal experts identified that current secondary care largely conforms to a consultant-led model with variation as regards to profession mix in the delivery of care by ophthalmologists, optometrists or nurses. Care for QnAMD in secondary care is homogenous irrespective of delivery model, reflecting acceptance of common standards and involvement of highly experienced Ophthalmologists either in direct delivery or supervision/arbitration for QnAMD care. Nevertheless, to minimise variation, the control arm will involve all existing models of secondary care-based QnAMD clinics, provided that they are Ophthalmologist-led (specifically there is at least access to advice by a Consultant or experienced ophthalmologist in AMD management).

B. Internal Pilot (6 months)

Objectives

1) To ascertain recruitment rates and retention at 6 months follow up;
2) To verify number of eligible cases in recruitment centres;

3) To assess adherence to study protocol (fidelity check);
4) To perform qualitative research to inform the full trial;
5) To perform quality checks to community optometry training.
All 'first wave' secondary care and community-based sites will participate in the pilot study. Progression to the main study will be decided on the basis of pre-specified progression criteria outlined below.
Patient Recruitment: The internal pilot will serve to confirm the feasibility of the recruitment plan as detailed in the main study section. Evidence of recruitment and retention rates will be assessed. The 6 month development period will be used to ensure that all first wave sites are ready to start recruiting on month 6.
Patient population, setting, pathways, randomisation and inclusion/exclusion criteria will mirror those of the main study (detailed below). A fidelity check will be conducted to assess adherence to the pathways and lost to follow up rates will be recorded.
The data collection framework presented in detail below in the main study section will be activated during the pilot phase. Data on paper-based and electronic Clinical Research Forms (eCRFs) will be recorded and collected, including Visual Acuity and clinical information as required on the study-specific clinical pro-formas. eCRFs will be completed and images obtained (OCT scans) will be uploaded onto the web-based trial database on a monthly basis. The task will be performed by the trial co-ordinator in secondary care sites and by the optometrist in primary care sites.
Data analysis to be conducted during the pilot phase will include summary statistics on recruitment progression and the completeness of data collection as per the trial protocol.
At the end of the pilot we will assess the number of eligible participants and compare this to those originally supplied for planning purpose by the centres. We will calculate the recruitment rate by centre.
Process Evaluation - Internal pilot: The process evaluation in the internal pilot will determine how the implementation of the community based QnAMD clinics can be improved for the main study and identify corresponding contextual factors that underpin how and why the clinics work. (Moore et al) The purpose is to increase the likelihood of a successful outcome of the main clinical trial. To this effect, a minimum of four secondary care and four community-based optometry practices will be invited to participate in a triad of data collection which will involve interviewing patients, staff in secondary care and optometry practices, and observing the pilot clinics in operation. Practices and hospitals will be selected to provide a range of practice/hospital sizes and geographical locations.
A researcher independent of the NHS Trusts will be immersed for four days at each of four practices between months 2-4 of the pilot study. This approach to sampling and data collection has been selected because it can be easily conducted providing timely information on refinements to or new aspects on the implementation of the QnAMD clinics for the main trial. Qualitative interviews will be conducted with a total sample of 9-12 patients (about 3-4 per practice) depending on how quickly data saturation is reached. (Charmaz et al) The interview questions will be open ended and focus upon what works and why in the QnAMD clinic and what they would improve to make it more acceptable to patients. The interviews will explore, for example, how patients access the clinic and their views on being seen nearer home, what changes if any they would make to the organisation of the clinic, whether staffing is appropriate

and frequency of appointments, and their views of the care they received. The interviews will also explore unexpected consequences of the new arrangements. Inclusion criteria will be: adult patients aged ≥ 55 years, who have attended one of the pilot QnAMD clinics and have agreed to participate in the study.

A further set of qualitative interviews will be carried out with a total sample of 6-9 (about 1-2 per practice) ophthalmologists and optometrists associated with QnAMD clinics. Open ended questions will focus on whether the optometrist training programme was adequate and why. If it were stated that it were not adequate, the interviewees will be asked what would they change? Interviewees will also be asked if/how they have had to reorganise their practice and the impact this had on the delivery of services to general patients. Finally, the interviews will elicit views as to whether and why the pathway has achieved its aim of managing QnAMD in the community considering patient safety, outcomes, patient experience and access to care.

To supplement the data on the patient and staff interviews, we will also carry out semi-structured qualitative observation of the pilot QnAMD clinics in situ. The purpose of collecting observational data is to identify other practical, organisational, professional or behavioural issues in the implementation that would not typically arise during an interview and to observe any variations in practice. The observer will shadow up to 2 patients per practice as they pass through the clinics making a maximum 12 hours of observation.

The data from the interviews and the observations will be analysed qualitatively according to framework analysis (FA). (Ritchie et al 1994&2005) FA comprises five linked steps that aim to map connections or relationships between different themes and interpret the charts to identify why and how the pathway works and how to improve the education programme, and the implementation, structures, processes and outcomes of the pathway. This information will be used to enhance the QnAMD clinics in the main study. The data will shed light on, for example, how and what messages to include to communicate the new scheme to patients, how best to manage practically the new arrangements within a busy optometry practice and how professional communication between the hospital and optometry practice could work.

Quality assurance on training: Quality assurance of all aspects of the training program will take place during the pilot study. This will consist of:

A. External Quality Assurance:

- External peer review of training and assessment (optometry and ophthalmology colleagues outside of the research team will be invited to review the content and delivery of the training material and review assessment processes and trainee performance)

B. Internal Quality Assurance:

a. Trainees' perception of training

- Trainee Feedback (formal evaluation via ongoing and post-training surveys)

b. Student engagement and achievement of learning outcomes

- Completion records of participation in online/face-to-face training/ monitoring of failure rates/drop-outs
- Engagement with online discussion forum
- Performance in formative and accreditation assessments

c. Trainees' change in behaviour

- Performance in confidence-based formative assessments (an assessment method which asks the student not only to provide the answer to a question, but also to report their level of confidence (or certainty) in the correctness of their answer).
- Assessment of community optometry confidence and independence in QnAMD patient review as part of the qualitative interviews

d. Resilience of training outcomes

- Performance in re-accreditation assessment
- Minimum number of cases reviewed per month per optometrist to maintain skills

Progression Criteria: Progression to the main study will be decided on the basis of the criteria below (Avery KNL et al):

1. All 6 secondary care recruitment centres open to recruitment;
2. At least one optometry practice with a trained and accredited specialist optometrist per associated secondary care site delivering the intervention arm (2 for Moorfields);
3. Recruitment rate of at least 80% (6 patients per month for Moorfields, 2 patients per site per month for the other 5 first wave sites) of the expected main trial recruitment rate, allowing for recruitment acceleration; and
4. Adherence to 4-weekly review intervals for secondary and primary care sites

A Red/Amber/Green 'traffic lights' system for assessing progression criteria will be used (Avery KNL et al). Progression to the main study will not be recommended if none of the progression criteria are met (Red). Progression will be recommended if all four progression criteria are met (Green). If performance in terms of set-up and recruitment activity does not meet the prescribed thresholds, progression to the main study will be considered by the Independent TSC that can take into account any mitigating circumstances and potential for improved performance during the main study. This will include the potential for improved performance of 'first wave' sites during the main study, the recruitment potential of 'second wave' sites and the availability of 'third wave' sites. The TSC will make a recommendation to the HTA on progression to the main study.

C. Main study (Full Trial)

Patient Population: Patients with QnAMD (treated in secondary care) after a Treatment-Free Interval of 3 months (for Pro ReNata regimens) or once extended and maintained at 12 weekly intervals on two consecutive occasions (for Treat and Extend regimens).

Definition of Quiescence: Patients with nAMD undergoing treatment with anti-Vascular Endothelium Growth Factor injections and who have reached disease quiescence will be approached for recruitment into this study. For the purposes of this study, disease quiescence for nAMD will be defined as:

- For patients on monthly Pro Renata (PRN) regimens a period of at least 3 months during which treatment has not been required
- For patients on Treat and Extend regimens, successful extension of re-treatment interval to 12 weeks and maintenance of this interval for two consecutive occasions.

Setting: Recruitment will take place in 6 'first wave' hospital-based eye units (Moorfields, Manchester, Bristol, Bradford, Leeds, York), where also the secondary care arm of the trial will be delivered. These will continue recruitment already initiated during the pilot phase. A 'second wave' of 10 recruitment sites will be set-up for the main study.. Patients randomised into the

community care arm will have follow-up in community-based optometry practices (independents, small groups and multiples). Expecting an average of 1-3 appointments per week per optometry practice (up to 144 per year), 35 community optometry practices will be recruited. Practices will be selected to provide a range of practice sizes and type (independent, small group, multiples) and geographical locations to allow judgements to be made about applicability of findings to the wider UK population.

Inclusion Criteria: Patients receiving treatment in nAMD injection clinics, who have reached the agreed definition of disease quiescence and provided informed consent, were aged $\geq$ 55 years and had the ability to perform study specific procedures

Exclusion Criteria: Patients will be excluded if they had significant media opacities (cataract, vitreous opacities) that would not allow good quality fundus imaging. They will also be excluded if they have diabetic retinopathy of severity worse than mild non-proliferative stage and with any degree of diabetic maculopathy; or a history of other causes of Choroidal Neovascularisation (myopic, angioid streaks, inflammatory, retinal dystrophies, secondary to Central Serous Chorioretinopathy, idiopathic).

Allocation to trial groups: Randomisation will be performed by site staff using the web based randomisation tool Sealed Envelope, (http://www.sealedenvelope.com) Sealed Envelope provides a proven reliable and centralised randomisation system. The system will be custom designed to the trial requirements. This will use randomized permuted blocks of varying sizes with stratification by centre, treatment regimen and number of eyes eligible at baseline (unilateral or bilateral).

Control Arm: Monthly review in secondary care as per local arrangements in participating sites. For each case (eye), a classification into 'active' or 'inactive' disease will be made. The control arm will involve any of the following pathways (including virtual pathways):

- Consultant-led and delivered QnAMD clinics
- Consultant-led and ophthalmologist-delivered QnAMD clinics
- Consultant-led and optometrist-delivered QnAMD clinics
- Consultant-led and nurse-delivered QnAMD clinics

'Active' cases will be referred for treatment and will discontinue study visits but remain in the study.

Study Arm: Monthly review in community setting by non-medical healthcare practitioners (community optometrists). Classification into 'active', 'inactive' or 'suspicious' will be performed at each visit. 'Active' and 'suspicious' cases will be referred to secondary care for review/treatment and will discontinue study visits but remain in the study.

Reference Standard: Data (images and case report forms) from all participants will be sent via secure tele-ophthalmology link on an electronic database hosted in the Reading Centre at Moorfields/UCL Institute of Ophthalmology BRC. Classification as active or inactive nAMD by the Reading Centre on the basis of OCT and clinical vignette (standardised pro-forma with visual acuity, systemic and ocular history and patient symptoms completed for each case) will be performed to provide the reference standard. Quality-assured processes of grading will be used in the Reading Centre based on double reading with adjudication by Reading Centre lead. Reading Centre grading will be masked to patient identifiers and site of origin of data.

Quality Assurance/Safety control: A random sample of 20% pseudo-anonymised cases (sent with study ID with a key to link them back to original patient data if needed) per community

optometrist will be reviewed every month at the Reading Centre with feedback to respective clinical teams. Patterns in rates of vision threatening errors will be evaluated by a Quality Assurance Panel (consisting of the CI, two clinician co-applicants and a professor of optometry) to introduce remedial measures if required (e.g. enhanced training, pausing recruitment). If discrepancy in classification between the Reading Centre and community optometrist is identified, patient will be withdrawn from follow-up and transferred to secondary care.

Recruitment plan:

Recruitment will commence during the pilot phase in the first wave sites. With an expectation of at least 80% of full trial recruitment rate to allow for recruitment acceleration, this will lead to 72 patients recruited during the pilot phase. As this is an internal pilot, this recruitment will count towards the overall recruitment target, leading to a target of 670 for the main study. With a conservative expectation of 8 recruitments per month for Moorfields and its satellites and 3 for each of the other 5 'first wave' sites, 414 patients will be recruited from the 'first wave' sites over the 18 months of recruitment. 256 patients will be recruited by 10 'second wave' sites with an expected recruitment rate of 1-2 patients per site per month

With a recruitment potential of 800 patients from the above sites, reserve capacity is embedded in the recruitment plan to mitigate against potential recruitment under-performance.

Follow-up period and review frequency: Research conducted by our team demonstrated a high rate (77%) of reactivation of QnAMD in a period of 12 months (Madhusudhana et al). The follow-up period was determined at 12 months with an expectation of 2 cases of reactivation per optometry practice/secondary care site per week. Review frequency was determined at 4-weekly intervals as per routine clinical practice in QnAMD clinics.

Primary Outcome: The proportion of patients who reactivate within 12 months of randomisation but are not identified as having re-activated (false negatives).

Primary economic outcome: Incremental cost per quality adjusted life year (QALY) gained over the estimated patient lifetime estimated from an economic model informed by trial data.

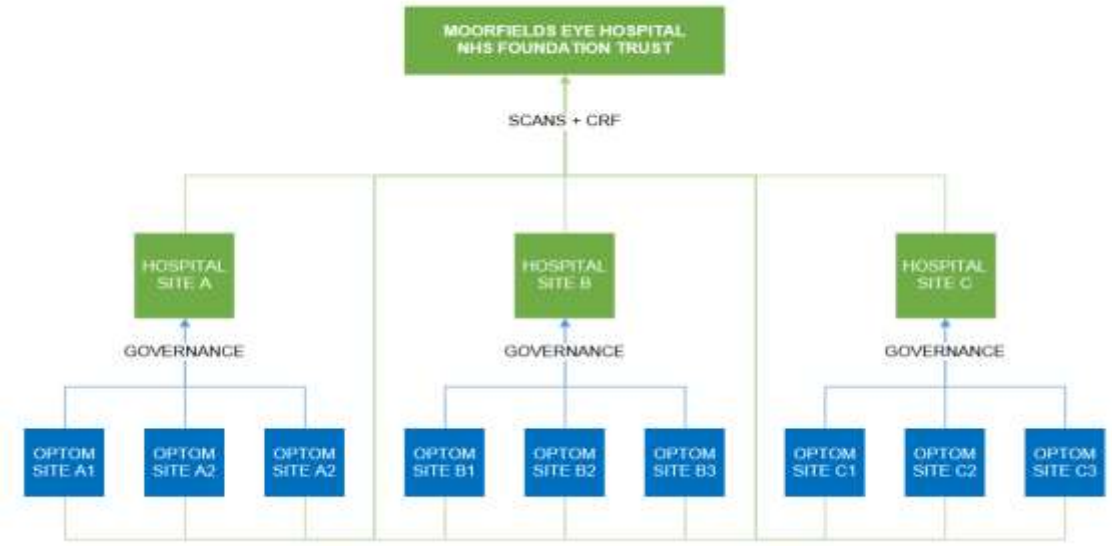
Secondary outcomes

1) Diagnostic accuracy of the intervention (community optometry follow up of QnAMD) against the reference standard (rate of false negatives and false positives)
2) Rate of over-referral (i.e. Reference Standard is quiescent but classification is 'reactivated' or 'suspicious')
3) Mean change in visual acuity (measured with habitual correction and pinhole) for patients in the intervention and control groups
4) Rate of 'suspicious' lesion classification in community care
5) Rate of patient non-attendance and loss to follow up in secondary and primary care
6) Use of health services and patient costs collected via eCRF and participant completed questionnaires
7) Costs of interventions and subsequent care to the NHS modelled over the estimated lifetime
8) Modelled estimates of visual impairment and QALYs based on responses to the EQ-5D-5L

Data Collection

We propose a hub and spoke structure, where each optometry practice liaises with its local secondary care site for the day-to-day operation of the trial, through the local site PI and trial co-ordinator. All sites, including secondary care and optometry practices will report data to Moorfields Reading Centre for quality assurance and data analysis.

FENETRE Study - Data flow structure



The sequence of data collection is shown in the table below:

Data Collection		Post randomisation (months)			
	Baseline	1-18	12	18	19
Medical History	✓	✓	✓	✓	
Consent/Randomisation	✓				
Clinical Pro-Forma	✓	✓	✓	✓	
Visual Acuity (ETDRS)	✓	✓	✓	✓	
Optical Coherence Tomography	✓	✓	✓	✓	
Standard clinical examination	✓	✓	✓	✓	
EQ-5D-5L	✓		✓	✓	
Health Care Utilisation Questionnaire	✓		✓	✓	
Time and travel questionnaire					✓
Classification (active/inactive/suspicious)		✓	✓	✓	

Tools and Source Document Identification: Content of the Case Report Forms will be provided by the Chief investigator according to the trial protocol. CRFs will be designed and produced by the research applications designer using the sponsor's CRF template. Moorfields CRF will develop the Case Report Forms in collaboration with King's CTU trial statistician and methodologist and the health economics team from Newcastle. This will occur prior to the commencement of the pilot study. All data will be handled in accordance with the Data Protection Act 1998. The Case Report Forms (CRFs) will not bear the subject's name or other personal identifiable data. A trial number will be used for identification on the CRFs. A separate log file which links the study ID and the patient's details, screening log and recruitment information will be kept on a protected computer. It will be the responsibility of the chief investigator or delegated trial member to ensure the accuracy of all data recorded on the CRFs. CRFs will be completed and signed off by the Chief Investigator or delegated/authorised individual as outlined in the delegation log, the completed CRFs will be checked for accuracy and completion by the trial co-ordinator prior to data entry.

Electronic Database: The front end will use a bespoke Microsoft Visual Studio application and the back end (data storage) will be hosted on Moorfields Research Database SQL servers. Local hospital trial-coordinator and local optometry staff will manage uploading both image and patient data (case report forms) on a monthly basis on a bespoke eCRF. This will be done using Moorfields remote log-in tokens, where the user will log onto clinical services and see the local drives of the PC they are using. The database will be validated to GAMP 5 standards.

Data analysis

With respect to data handling, the senior data manager in Moorfields CRF will independently ask the IT applications team to run missing data query and perform range check, logic check and data quality checks of the Electronic Database on a monthly basis. Data queries will be sent to trial co-ordinators for clarification and confirmation whenever picked up. Data entries on eCRFs will be compared for completion and accuracy, discrepancies will be checked against the paper CRFs. After all data queries are resolved and all errors are corrected, the database will then be locked with the agreement of King's CTU statistician and data will be exported by the applications manager and sent to trial statistician for data analysis. Pre-existing mechanisms for data transfer between Moorfields CRF and King's CTU will be utilised.

Statistical analysis: The primary analysis will be conducted following an intention to treat principle where all randomised patients are analysed in their allocated group whether or not they receive their randomised management plan. Whilst patients and clinicians cannot be masked to management status, those conducting the analysis will be masked. Baseline characteristics will be summarised for each management group (hospital or optometry practice). Continuous data will be summarised using means and standard deviations if data appear Guassian or medians and interquartile ranges. Categorical data will be reported as proportions and percentages. The primary outcome is whether or not a lesion is classified as a false negative. This will be compared between management groups using repeated measures logistic regression adjusting for randomisation stratifiers (treatment centre, treatment regimen and laterality). This analysis will allow information from each time point to be utilised up to the point at which a patient reactivates. Outcomes will be reported as adjusted odds ratios. Whilst our primary analyses will group suspicious and quiescent, a sensitivity analysis will be conducted where suspicious will be grouped with reactivated.

Secondary outcomes such as false positive rates and overall accuracy will be analysed in a similar fashion.

The percentage of patients experiencing adverse events in the two groups will be reported with 95% confidence intervals computed by the exact binomial method.

Loss to follow-up will be examined by study arm. Reasons for missingness may be important and these will be investigated using logistic regression of covariates based on an indicator of missingness. An available case analysis will be reported along with an analysis using imputed data based on best and worst case scenarios.

No formal interim analysis is planned but reports concerning patient safety will be prepared for review by the Independent Data Monitoring Committee (DMC). All tests will be two sided and will be assessed at the 5 % significance level unless otherwise specified. All confidence intervals will be 95 % and two sided. A detailed statistical analysis plan will be agreed with the TSC prior to any analysis of locked data. All statistical analysis will be performed using Stata (StataCorp, College Station, TX, USA).

Patients with Bilateral Disease: 1. Patients with bilateral QnAMD: The patient is the unit of analysis. In cases with bilateral disease where both eyes have reached quiescence in the course of the recruitment period, patients can be considered for involvement in the trial. For each follow-up visit in secondary or primary care, a classification will be made separately for each eye. An 'index eye' will be defined for each patient with bilateral disease at recruitment for the purposes of the primary outcome analysis. The 'index eye' will be the one with the better visual acuity at the time of randomisation or at random if equal visual acuity. 'Active' and 'suspicious' classification in either eye will trigger a referral to secondary care for review/treatment and corresponding patients will discontinue study visits but will remain in the study.

2. Fellow eye review in the course of follow up: In cases with unilateral disease, fellow unaffected eye will be assessed in the course of follow-up for signs of nAMD activity. nAMD detection and diagnosis will form part of the training package for community optometrists. If signs of new-onset fellow eye nAMD are detected, the patient will be referred to secondary care for review/treatment and will discontinue study visits but remain in the study. We estimate that this may occur in 5 % of cases over the one year of study. (Maguire et al, Mimura et al) The rate of fellow eye development of nAMD in the course of follow-up has been taken into consideration in the sample size calculations.

Economic analysis: *Within-trial analysis of costs and outcomes*

Costs and outcomes associated with the community based and the secondary care based care pathway will be collected over the 12 month follow-up period. Costs will be those that fall on the NHS, community optometry practices, personal social services, patients and their families. The use of secondary care and primary care optometry services will be collected on the eCRF. Other health service use will be collected via a participant completed questionnaire at 6 and 12 months. Costs to participants and their families for private health care and time away from usual activities will also be collected via the participant completed questionnaire noted above. The costs of accessing care will be informed by the results of a time and travel questionnaire completed at month 13 (this questionnaire asks about access costs for the last time a particular type of health care was used).

The cost of secondary care will be based on standard sources e.g. NHS reference costs (DoH Reference Costs), supplemented by micro costing to estimate the intervention cost. Similarly standard sources will be used to cost care provide in the community except for the intervention itself which will be the subject of a micro costing exercise. The responses to the time and travel questionnaire will be used to calculate unit costs for accessing different primary and secondary care services. These unit costs will be combined with the use of these services to estimate participant's time and travel costs. Health status, measured using the EQ-5D-5L will be collected from participants at baseline, 6 and 12 months. The response to the EQ-5D-5L will be converted into scores using population tariffs. (Devlin et al)

The within trial analysis will focus on analyzing the trial data such that it can be used to parametrise an economic evaluation model. Thus, we will explore how costs and health state utilities vary according to events that might occur e.g. referral, changes in treatments, cost to optometry practices etc. We will also explore how these outcomes might vary by location of care, clustering by care provider and practitioner experience.

Assessment of cost-effectiveness: An economic model will assess the cost-effectiveness of the alternative management option. Costs and health consequences, measured in terms of QALYs, associated with a policy of initial community based case or initial care in secondary care over the patient lifetime will be compared. The results of the model will be presented in terms of costs, QALYs and incremental cost per QALY gained. The model will be developed in accordance with the NICE reference case (NICE 2013) and we will characterise patients' treatment pathways and the impact of alternative strategies. At this stage we anticipate that the model will take the form of either a microsimulation or a discrete event simulation (if there is an element of queuing). These types of model would be most appropriate model type for this decision problem as they allow the representation of a clinical situation where patients can move between care settings and experience deterioration in health over time. The precise structure of the model will be developed during the project and will reflect the clinical decision question and the course of the condition. The data from the trial will be the main source of data for the economic model, but further data with which to model outcomes beyond the 12 month follow-up will be derived from the literature and other existing data sources following guidance for best practice (Caro et al). These data will include information on factors such as adverse events of missed deterioration of symptoms. The base case economic evaluation will be carried out from a UK NHS and PSS perspective, to take into account health care costs and longer-term social care costs. Both costs and QALYs will be discounted in the base case at 3.5% (NICE 2013). A wider cost perspective will be taken in sensitivity analysis. Other deterministic sensitivity analyses will include the impact of different unit costs and changes in discount rates. In order to characterize the uncertainty in the data used to populate the model, probabilistic sensitivity analysis will also be conducted. The results of this latter analysis will be presented as cost/QALY plots and cost effectiveness acceptability curves.

A budget impact model will also be produced. This will estimate the health service costs to the NHS of adopting the community based service. The model will follow best practice methods. The model will model costs for hypothetical cohort representative of the coverage of standard secondary care provided over a 10 year time horizon. It will present net budget impact and impact by sector (primary care or secondary care). Following best practice methods (Sullivan et al) all costs will be presented in a base year but no discounting will be performed. Both deterministic and probabilistic sensitivity analysis will be presented.

Process Evaluation-Main Study: A similar approach to collecting data for the process evaluation will be undertaken for the main study as was for the pilot study. On this occasion six of the optometry practices operating the QnAMD clinics and 6 hospitals in the control arm will be recruited. A triad of data collection will be undertaken again at each practice/hospital: patient and staff interviews, and observation of care delivery.

Qualitative interviews will be employed to learn whether the community based QnAMD clinics are acceptable to patients. A total sample of 27-36 patients (3-4 per clinic) will be selected from across the study and control arm depending on how quickly data saturation is reached. The sample will not be stratified per se, instead a purposive maximum variation sample will be selected to generate a broad range of views on whether and how the clinic is acceptable to patients. In other words, we will seek to recruit patients from a diverse range of backgrounds, ethnic groups, employment, housing, income, and geographical area. Questions will be oriented

to perceptions of what it meant in terms of time, travel, parking and quality of care to visit a community clinic or hospital for routine follow- up.
An independent researcher will also seek interviews with doctors and optometrists (12-18, 2-3 per clinic) involved with the study and the control arm. This approach will again aid differentiation between what is a common issue and that specific to the new clinic pathway. Open-ended questions will also focus on whether the right type of patient attends, issues concerning the practicalities in the organisation and management of the clinic, and resourcing including IT and digital equipment.
To supplement the data on the patient and staff interviews, we will also carry out semi-structured qualitative observation in practice by shadowing patients through their 'journey' there. As with the pilot study, we will use framework analysis (FA) but for the main study the purpose will be to map connections or relationships between different themes and interpret the data charts to identify the acceptability of community based QnAMD clinic.
Quality Standards: A number of consultations informed the quality standards put forward in this project, including input from the College of Optometrists, AMD-specific PPI input, liaising with the Macular Society and discussion with small group of community optometrists in Hertfordshire. They were also informed by the Royal College of Ophthalmologists and NICE guidance for management of Neovascular AMD and relevant COMET standards.
For System Performance:

- Compliance with 4-weekly review intervals (>95%)
- Time from diagnosis of re-activation to treatment in hospital-based eye service $\leq$ 1 week (>95%)
- Duration of visit $\leq$ 1 hour (>80%)

For Individuals:

- Completion of refresher courses (at least once a year)
- Success in re-accreditation test
- Perfromance of $\geq$ 40 clinical decisions per practitioner per year to maintain accreditation

Quality standards will be reviewed and discussed during PPI events in the course of the study. A representative of the College of Optometrists, a representative of the Macular Society and a Patient Expert will sit on the TSC and will review and advise on quality standards monitoring.
Artificial Intelligence Exploratory Study: We propose to use the opportunity provided by this trial to conduct a sub-study. The addition of this sub-study will be cost-neutral.
In this sub-study a Machine Learning algorithm will be introduced in the Reading Centre and will assess all OCT scans originating from secondary and community care. An automated segmentation algorithm will seek signs of nAMD activity such as subretinal and intraretinal fluid. On the basis of these findings, a classification task into reactivated and quiescent nAMD will be performed for each case at the Reading Centre. The rate of vision-threatening errors against the reference standard will be calculated. We will attempt to adapt the economic model to consider the cost-effectiveness of the AI-based decision making pathways in both secondary and primary care compared to conventional assessment.
The Machine Learning algorithm has been developed previously through the collaboration between Moorfields Eye Hospital and Google/Deepmind. This algorithm will be introduced in the Reading Centre, all data analysis will be performed within the Reading Centre and no research data will be shared or analysed externally to the research team.

We believe that the Machine Learning sub-study will add value and future-proof the research project. Furthermore, it will have no impact on the research budget requested or our ability to deliver on the main study elements.

Project management: The overall management structure of this study will consist of **Trial Management Group (TMG), Trial Steering Committee (TSC), Data Monitoring Committee (DMC) and a Quality Assurance Panel (QAP).** The **TMG** will be responsible for the day-to-day running and management of the trial. The Group will meet formally and informally regularly to discuss progress with trial and examine mitigating strategies in case of issues arising. The trial manager and CI will also send regular progress reports to all site PIs. TMG will meet twice in trial set-up and then bi-monthly or as required subsequently. The **TSC** will ensure the overall integrity of the study by monitoring its progress, investigating any serious adverse events, and taking account of regular reports from the **DMC and TMG**. It will include representatives of the Macular Society (its head of research would join if invited by NIHR), the College of Optometrists, two patient experts and a clinical commissioner. The **TSC** is expected to meet annually (or more often, if determined by the Chair). The **DMC** will monitor the trial data to ensure that the trial is being implemented in accordance with the highest standards of patient safety and ethical conduct. Throughout the trial, the **DMC** will monitor data on recruitment, emerging external evidence, sample characteristics and primary outcomes and make recommendations on whether an interim analysis is required. The **DMC** will consist of an independent Chair (a senior clinician with expertise in AMD) and three other members: a trial statistician not involved in the study; an optometrist; and a PPI representative. Patterns in rates of vision threatening errors identified during the monthly quality assurance process performed at the Reading Centre will be evaluated by a **Quality Assurance Panel** (consisting of the CI, two clinician co-applicants and a professor of Optometry) to introduce remedial measures if required (e.g. enhanced training, pausing recruitment).

Dissemination, Outputs and anticipated Impact

High-impact peer-reviewed publications in Ophthalmology and Health Service Research journals will be sought. Presentations in conferences, including the Royal College of Ophthalmologists national conference, the Annual conference of the College of Optometrists, the Association for Research in Vision and Ophthalmology conference, the American Academy of Ophthalmology conference, The College of Optometrists conference will be made. As part of this research project, an on-line training program will be developed with dedicated technical infrastructure and a library of clinical lectures and webinars, delivered by City University of London. This will form the basis of a sustainable training program for optometrists seeking to extend their scope of practice in the area of care for patients with AMD. The output of this program is expected to influence the healthcare market by validating care pathways for patients with AMD in the community by trained optometrists. The outcomes of this research will be communicated to NHS England and the Department of Health to inform policy on the role of primary care in the management of patients with AMD. The Research team and management team of the sponsor organisation will actively approach and engage key parties such as the College of Optometrists, stakeholders in the community optometry market, including multiples, LOCSU, NHS England and Clinical Commissioning Groups. A detailed engagement plan will be formulated to disseminate the results of this research in order to inform policy decisions for optimising patient care. We will also engage with Eye Charities such as the Macular Society, that is already

involved with the TSC for this project and Fight for Sight in order to ensure all channels of communication to the wider patient population are utilised to disseminate the results of this research and ensure they are acknowledged, selected and introduced for use in the health and care service.

Study Timetable

Months -3 to 0	Ethics and R&D approvals obtained, TSC and DMC formalised and approved by NIHR
Month 1-2	Development of Training Platform with input from Royal College of Optometrists
Months 3-5	Delivery of Training
Month 6	Accreditation testing for community optometrists
Months 7-12	Internal Pilot
Months 8-10	Delivery of qualitative research interviews for pilot phase
Months 11-12	Analysis of qualitative results to inform main study
Milestone end of Month 12	Progression Criteria assessment by TSC
Months 12-30	Patient recruitment and randomisation in Secondary Care
Months 12-42	Follow-up in Secondary and Primary care, data collection
Months 42-48	Reading Centre Reference Standard, Health Economics Analysis, Qualitative Research analysis, Statistical Analysis
Month 48	Final Report

Ethics: The research project will adhere to the UK Framework for Health and Social Care research. Ethics approval will be sought for this project. No particular challenges are expected given the robust quality assurance and safety controls embedded in the study design.

Project / research expertise: An outstanding multidisciplinary team covering the core competencies needed is combining forces to guarantee successful delivery of all aspects of the commissioning brief. The study is receiving methodological and statistical support by King's CTU. Senior statistical supervision will be provided by Dr Catey Bunce who has an unrivalled experience in providing statistical input for clinical trials in Ophthalmology. The research budget will also fund 25% of a junior statistician's time. Expert methodological input is provided by Prof Janet Peacock who has extensive relevant experience as NIHR senior investigator.

Trial management, randomisation, database development and management will be provided by the Clinical Research Facility of the Moorfields/UCL Institute of Ophthalmology Biomedical Research Centre. The Clinical Research Facility has dedicated resources in terms of database developers and managers and extensive experience in management of research in Ophthalmology and has recently been successfully inspected by the MHRA. A dedicated Trial Manager will be appointed by the CRF for the FENETRE study. The Trial Manager will oversee and co-ordinate the delivery of the trial across all sites. PPI organisation will also be within the remit of the Trial Manager.

Health Economics analysis will be provided by the University of Newcastle under the expert supervision of Prof Luke Vale, an internationally recognised expert in this field. He will supervise Ashleigh Kernohan, who is a trained health economist and an accredited optometrist. Similarly, process evaluation will be provided by the University of Cardiff under expert supervision of Prof Heather Waterman. A part-time research assistant will be employed for delivering the qualitative research component. Prof John Lawrenson and Prof Robert Harper are both senior academics with extensive expertise in the development and implementation of shared-care schemes involving optometrists for ophthalmic patients. Their input is invaluable for engaging the optometry profession through the College of Optometrists, the LOCSU and other optometry professional groups. They are also leading the development, delivery and quality assurance of

the training programme for community optometrists as well as the definition of quality standards for community optometry practices. CRF activity will be overseen by Richard Wormald (as a collaborator) who is a senior member of the BRC ACTIVE team supporting research projects within the CRF.

The Moorfields Ophthalmic Reading Centre will provide the reference standard and the quality assurance for this project. This will require 75% of a senior grader's time over the course of the project.

Clinicians of national standing with specialist interest in retinal disorders are joining this research proposal as co-applicants. Patient recruitment and follow-up will take place in 6 clusters surrounding 6 hospital-based eye units (Moorfields, Bristol, Manchester, Bradford, Leeds and York). The role of clinician co-applicants is extensive requiring considerable commitment of time and effort. They will be involved in the identification and recruitment of community-based optometry practices for this research project in the catchment areas corresponding to their geographical area. Their input will be crucial for providing the blended training programme for community optometrists that will involve educational material and local educational events during the course of the project. They will also be the point of reference for research governance for community-based optometry practices within their cluster for the duration of the study. They will finally facilitate the set-up of 'second wave' sites for corresponding areas. Taking on board comments made by the review panel and after detailed costing of the expected activity, the FTE involvement was decreased to 3% for Clare Baily (Bristol), Martin Mckibbin (Leeds), Faruque Ghanchi (Bradford), Sajjad Mahmood (Manchester) and Richard Gale (York). The head of the Medical Retina Service in Moorfields (Robin Hamilton, 3% FTE) will co-ordinate patient recruitment, engagement of community optometrists and delivery of training across the extensive catchment areas of Moorfields (central hub and satellites). Prof Adnan Tufail (3%) will contribute crucial methodological input given his extensive expertise in leading clinical trials in Ophthalmology nationally and internationally as well as in the interpretation of results and will also sit on the TMG and the QAP. Dr Praveen Patel (3%) is CRN Lead for North Thames and Clinical Trials Lead for Moorfields CRF, has crucial input in engagement of second wave sites and optometry practices across North Thames, provides methodological input to study design and will sit on the TMG and the QAP. Dr Dawn Sim (3% for first 12 months of the project) is pioneering tele-ophthalmology solutions linking primary care with secondary care and has a key advisory role in the development of the infrastructure and governance arrangements for data and image transfer between primary care and Moorfields CRF. Finally, all senior clinician co-applicants will have an active role in dissemination of results and act as champions of the community care model to ensure its widespread adoption, if validated by this trial. Dr Pearse Keane is contributing expertise in novel data analytics and the artificial intelligence sub-study as co-applicant, yet his involvement is not affecting the budget due to his capacity as NIHR Clinical Scientist.

Success criteria and barriers to proposed work

Success criteria

- Recruitment to time and target
- Meeting of progression criteria from the pilot to the main study
- Successful accreditation of at least one optometrist per community practice
- Retention of community optometry practices

Risks:

- Difficulties with recruitment due to local RnD set-up delays
- Recruitment rate inferior to set target
- Issues with community optometry uptake and retention
- Safety signals picked up by the Reading Centre safety control in the course of the study
- Qualitative research demonstrating issues around pathway acceptability in the pilot study

Mitigation Strategy:

- Efficient project management to assist sites with set-up and performance
- Recruitment reserve capacity embedded in the recruitment plan
- Possibility to set-up ‘third wave’ sites if needed
- Training of a wider pool of optometrists with a back-up list for involvement in the study in case of issues with retention
- Possibility for amendments to the key features of involved optometry practices and the quality standards in response to qualitative research findings from the pilot to the main study.