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FENETRE study: quality-assured follow-up of quiescent neovascular age-related macular degeneration by non-medical practitioners: study protocol and statistical analysis plan for a randomised controlled trial

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ABSTRACT

Objective Management of age-related macular degeneration (AMD) places a high demand on already constrained hospital-based eye services. This study aims to assess the safety and quality of follow-up within the community led by suitably trained non-medical practitioners for the management of quiescent neovascular AMD (QnAMD).

Methods/design This is a prospective, multisite, randomised clinical trial. 742 participants with QnAMD will be recruited and randomised to either continue hospital-based secondary care or to receive follow-up within a community setting. Participants in both groups will be monitored for disease reactivation over the course of 12 months and referred for treatment as necessary. Outcomes measures will assess the non-inferiority of primary care follow-up accounting for accuracy of the identification of disease reactivation, patient loss to follow-up and accrued costs and the budget impact to the National Health Service.

Ethics and dissemination Research ethics approval was obtained from the London Bloomsbury Ethics Committee. The results of this study will be disseminated through academic peer-reviewed publications, conferences and collaborations with eye charities to insure the findings reach the appropriate patient populations.

Trial registration number NCT03893474.

Strengths and limitations of this study

- The main strength of this study is its potential to demonstrate the safety and cost-effectiveness of a community-based model of care for patients with stable age-related macular degeneration.
- The assessed care pathway promotes decentralisation of care out of the hospital environment and enables shared care with non-medical healthcare practitioners.
- The study involves a comprehensive economic and process evaluation and a training package allowing this care pathway to be quickly implemented within healthcare systems.
- This care pathway is designed for the UK health setting and may not be immediately generalisable for worldwide health systems.
- However, interventions such as this are timely and relevant to the global trend towards decentralisation of healthcare.

BACKGROUND

Neovascular age-related macular degeneration (nAMD) is the most frequent cause of blindness and accounts for 50% of all certifications of visual impairment in the UK.[1 2] Current treatment involves intravitreal injections of drugs to inhibit vascular endothelial growth factor (anti-VEGF) to ameliorate the pathology behind nAMD, improving the morphological appearance of the retina and stabilising/improving visual acuity. This treatment process means that the disease becomes quiescent and standard clinical practice includes long-term follow-up of patients with quiescent nAMD (QnAMD) to monitor for the return of active disease and the need for further treatment.

While regular clinical review is an effective management strategy, this method is stressful for patients with frequent hospital visits and long waits in crowded clinics and burdensome for the National Health Service (NHS), requiring ophthalmologist availability on a regular basis within a service that is already severely constrained. Demand for these

services are predicted to increase further due to an ageing population. As a result, reviews to optimise the current care pathways and improve patient management have been published outlining possible options, including virtual or combined clinics, faster referral processes and the use of trained non-medical healthcare professionals within the hospital setting.[3–5]

Following these calls for improved clinical services, in 2016, the Effectiveness of Community versus Hospital Eye Service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES) trial was undertaken to examine the possibility of primary care optometrists managing patient follow-up, with the aim of developing a shared care pathway for monitoring QnAMD. This study showed that the ability of optometrists to detect reactivated nAMD is non-inferior to that of ophthalmologists,[6] did not incur significantly higher costs[7] and could reduce demands on hospital resources.[6 7]

This study continues investigating the potential of a community-based, non-medical practitioner-led pathway for the management of QnAMD. We believe this is an important development in AMD care. 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. Assessing the clinical and cost-effectiveness of community-based primary care QnAMD follow-up, we will examine:

1. The safety of non-medical practitioner follow-up of QnAMD in the primary care setting compared with secondary care eye clinics in correctly classifying reactivation due to nAMD (primary objective).
2. The efficiency (rate of over-referral) of primary care and secondary care QnAMD pathways against an enhanced reference standard.
3. The non-inferiority of non-medical practitioner follow-up of QnAMD in the primary care versus secondary care eye-clinics in correctly classifying reactivation due to nAMD.
4. The cost-effectiveness and budget impact of community-based primary care optometry QnAMD pathways against secondary care pathways.

METHODS

Study design

This is a prospective, randomised, multisite clinical trial testing the non-inferiority of primary care optometry follow-up of participants with QnAMD over 12 months. Participants with QnAMD will be randomised to continue secondary care within a hospital setting (control arm) or be monitored for disease reactivation in a community setting by non-medical healthcare practitioners (primary care optometrists; intervention arm).

In both trial groups, participants will be reviewed at 4-weekly intervals to monitor for disease reactivation, as per routine clinical practice in QnAMD clinics (figure 1). Participants in the intervention arm who are determined to have 'active' or 'suspicious' (where the assessing optometrist cannot determine with certainty whether the disease is active or inactive) disease classification will be referred to the hospital eye service for a confirmatory review of their disease and will discontinue participation in the study. Any participants with reactivated disease from either trial group will be referred for treatment and will discontinue participation in the study.

Trial phases

The study will involve three phases: (1) a development phase consisting of training for primary care optometrists using an in-house bespoke training package developed by City, University of London, in collaboration with the College of Optometrists, (2) an internal pilot phase assessing the feasibility of the recruitment plan, performing quality assurance of the training package and a process evaluation with criteria for progression to the full trial and (3) the full trial. This pilot will only involve recruitment at a selection of the available locations (the first wave sites). The full trial will involve recruitment up to the final determined sample size, include an assessment of economic outcomes and incorporate a substudy undertaking a process evaluation of the community-based optometry follow-up (intervention arm).

Setting

This study will take place at a number of locations across the UK, including London (Moorfields Eye Hospital), Manchester, Bristol, Bradford, Leeds and York (first wave sites) with further locations joining part way through the study.

Recruitment will take place at hospital-based eye units within each city, which will also deliver the secondary care (control) arm of the study. Thirty-five primary care optometry practices of a range of sizes and types (independent, small group and multiples) and geographical locations will be recruited to deliver the community-based primary care for the intervention arm of the study. This number of optometry sites has been selected within an expectation that each site will perform an average of one to three appointments per week (up to 144 per year), and the distribution of practice sizes/types/locations has been selected to allow judgements to be made about applicability of findings to the wider UK population.

Participants

Participants considered for recruitment will be those with nAMD currently undergoing treatment with antivascular endothelium growth factor injections whom have reached disease quiescence. For the purposes of this study, disease quiescence for nAMD will be defined as:

- For participants on monthly pro renata regimens, a period of at least 3 months during which treatment has not been required.
- For participants on treat and extend regimens, successful extension of retreatment interval to 12 weeks and maintenance of this interval for one or more consecutive occasions.

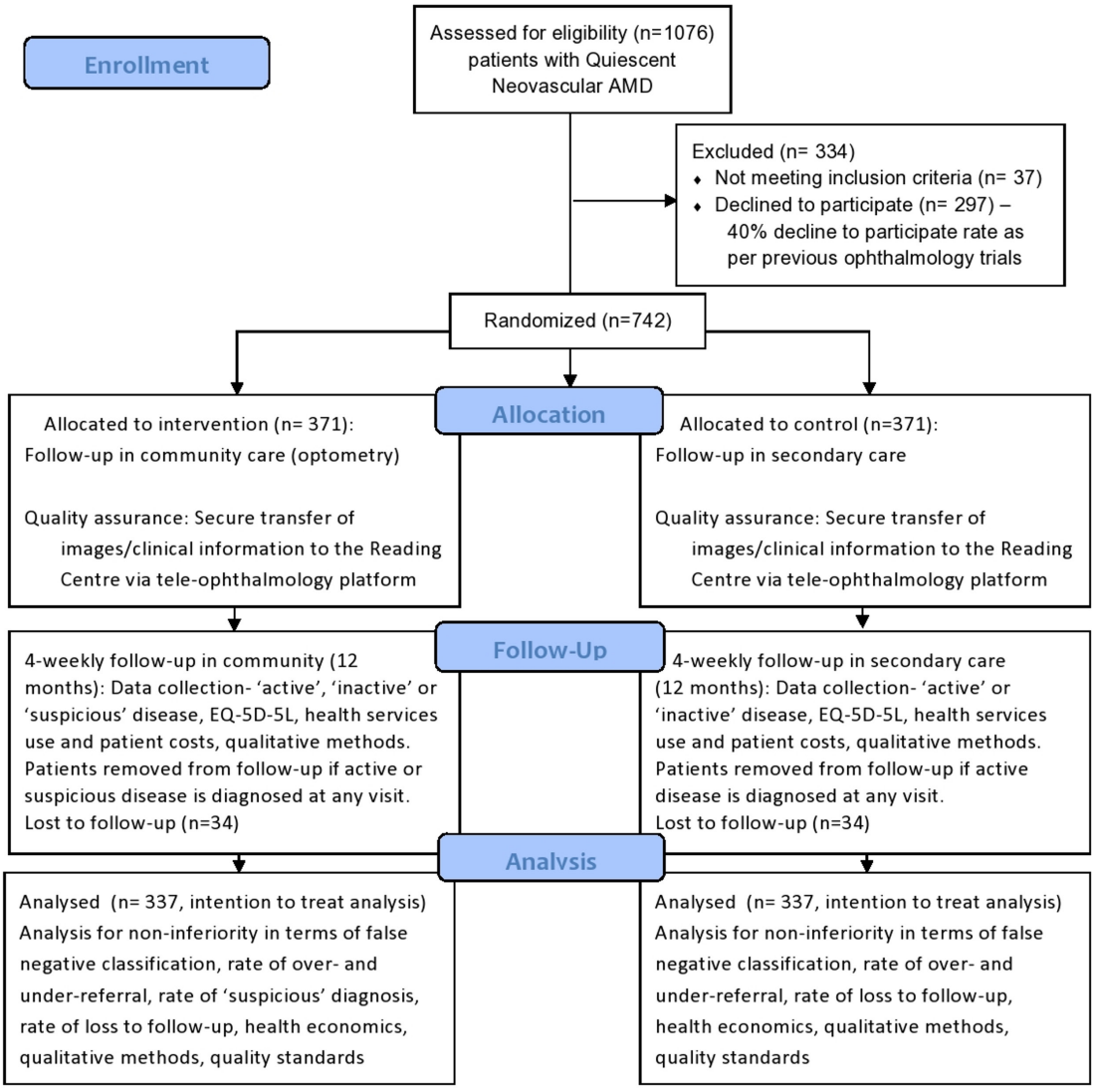

Figure 1 Flow chart of study design and participant follow-up. Numbers of patients assessed, excluded and lost to follow are estimated samples based on previous studies. *Due to the COVID-19 pandemic, the 4-weekly follow-up interval was changed to 8-weekly follow-up interval. AMD, age-related macular degeneration.

Patients with bilateral nAMD will be considered for the study if both eyes have reached disease quiescence. For each follow-up visit in either trial group, a classification will be made separately for each eye. 'Active' and 'suspicious' classification in either of the participant's eyes will trigger a referral to secondary care for review/treatment, and corresponding participants will discontinue study visits.

Eligibility criteria

The inclusion criteria for this study are the achievement of disease quiescence, aged 55 years or older, have provided informed consent and have the ability to perform study specific procedures.

Participants will be excluded if they have the following:

- Significant media opacities (cataract and 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.
- Or a history of other causes of choroidal neovascularisation (myopic, angioid streaks, inflammatory, retinal dystrophies, secondary to central serous chorioretinopathy and idiopathic).

Randomisation and blinding

Randomisation will be performed by site staff using the web-based randomisation tool: Sealed Envelope (www.sealedenvelope.com). Sealed Envelope provides a proven reliable and centralised randomisation system. The system will be custom designed to the trial requirements. The method of randomisation will be minimisation with a ratio of 1:1. The minimisation algorithm will stratify (minimise) by centre and number of eyes eligible at baseline (unilateral or bilateral). This is performed with an 80%

probability of allocating to the trial arm that reduces the imbalance.

Patients will be randomised into the control arm or the intervention arm.

The only masking in this study will be the statisticians and health economists so that the analyses can be performed masked to treatment.

Outcome measures

Primary outcome

The primary outcome measure for this study is the proportion of participants who reactivate within 12 months of randomisation (determined by the reference standard) but who are not identified as having reactivated in each trial arm (termed false negatives).

Secondary outcomes

The following secondary outcome measures will also be examined:

1. The proportion of participants who do not reactivate within 12 months of randomisation (determined by the reference standard) but are incorrectly identified as having reactivated in each trial arm (termed false positives).
2. The proportion of over-referrals in the intervention arm (community-based primary care) in comparison with the reference standard, that is, when classification is 'reactivated' or 'suspicious' but disease is classified at the hospital visit to be 'inactive'.
3. The proportion of participants in the intervention arm who are correctly classified as reactivations at the confirmation visit (termed true positives).
4. The mean change in visual acuity (measured with habitual correction and pinhole) between baseline and 12 months postrandomisation in each trial group.
5. The proportion of 'suspicious' lesion classifications in the intervention arm.
6. The proportion of patient non-attendance and loss to follow-up in each trial group.

Economic outcomes

The principal economic outcome measure for this study is to examine the incremental cost per quality-adjusted life year (QALY) gained over the estimated patient lifetime estimated from an economic model informed by trial data. Additional economic outcomes include:

1. The use of health services and patient costs collected via study case report forms and participant completed questionnaires.
2. The costs of interventions and subsequent care to the NHS modelled over the estimated lifetime.
3. The budget impact to the NHS.
4. The modelled estimates of visual impairment and QALYs based on responses to the EQ-5D-5L.

Substudy: process evaluation of the intervention arm

The process evaluation in the internal pilot will determine how the implementation of the community-based QnAMD clinics can be improved and identify corresponding contextual factors that underpin how and why the clinics work. Six optometry practices operating the QnAMD clinics and six 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 participants. A total sample of 27–36 participants (three to four per clinic) will be selected from across the study and control arms 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 participants. In other words, we will seek to recruit participants 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, two to three 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 semistructured qualitative observation in practice by shadowing participants through their 'journey' there. We will use framework analysis with the purpose of mapping connections or relationships between different themes and interpret the data charts to identify the acceptability of community-based QnAMD clinics.

Sample size calculation

The ECHOES study has shown that the rate of false negatives per lesion assessment when conducted by an ophthalmologist was 62/994, that is, 6.2% (95% CI of 4.8% to 7.9%).[6] Over the course of 1 year, a patient will typically have lesions assessed on 12 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*).[8] This estimate requires adjustment for the fact that ECHOES figures were based on scenarios and vignettes and did not factor in additional patient information that may be available to the clinician, 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.[9] While approval has been made on the basis of a non-inferiority design with a one-sided alpha of 5%, this is generally frowned on 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 margin 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%, the same as 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[6] and attracted no criticism or referee comment about it being too high.

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, $\varpi_1 - \varpi_0$, 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. Seven per cent loss to follow-up was observed in the first year of the IVAN study[10] 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 participants. Of these, 72 participants 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 V.8.1.2.0.

Data confidentiality

Patient consent will be completed by the hospital site responsible for patient care. This includes the completion of a written consent form (blank form provided in the online supplemental material), which will be filed at the relevant hospital site responsible for the patient and is the only document that has patient identifiable data. On patient consent, each patient is assigned a study ID, which is used to complete the case report forms used for data collection. This is the only way the patient is identified in the study.

No personal patient data are shared with the central study team, or the practices at point of consent and randomisation. All Optical Coherence Tomography (OCTs) uploaded onto the database are also anonymised manually to remove patient identifiable data.

Data management and monitoring

Data (images and case report forms) will be sent via secure teleophthalmology link on an electronic database hosted in the Reading Centre at Moorfields/UCL Institute of Ophthalmology Biomedical Research Centre.

Classification as active or inactive nAMD by the Reading Centre on the basis of optical coherence tomography and clinical vignettes (standardised pro forma with visual acuity, systemic and ocular history and patient symptoms completed for each case) will be performed to provide the enhanced reference standard used to assess the study outcome measures. Quality-assured processes of grading will be used in the Reading Centre based on double reading with adjudication by the Reading Centre lead. Grading by the Reading Centre will be masked to patient identifiers and the site of origin.

Missing data queries, range checks, logic checks and data quality checks of the electronic database will be performed on a monthly basis by the IT applications team at Moorfields. Data queries found will be sent to trial coordinators for clarification and confirmation. Data entries within the electronic database will compared for completion and accuracy with discrepancies checked against paper data forms.

No formal interim data analysis has been planned.

Quality assurance/safety control

A random sample of 20% pseudoanonymised cases for each community optometrist will be reviewed every month at the Moorfields Reading Centre with feedback sent to the respective clinical teams. Patterns in rates of vision threatening errors will be evaluated by a quality assurance panel (consisting of the Chief Investigator (CI), two clinician coapplicants and a professor of optometry) who will introduce remedial measures if required (eg, enhanced training, pausing recruitment).

Trial oversight

The overall management structure of this study will consist of a 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, meeting regularly to discuss trial progression and examine mitigating strategies in case of issues arising.

The TSC will ensure the overall integrity of the study, safeguarding the rights and well-being of the participants and ensuring that this trial is conducted to the rigorous standards set out as Good Clinical Practice. This role includes ensuring appropriate ethical approvals are obtained, monitoring trial progress, investigating any serious adverse events, reviewing proposals for project amendments and recommendations made by the DMC.

The DMC will monitor the trial data to ensure that the trial is being implemented in accordance with the highest standards of patient's safety and ethical conduct. Through the trial, the DMC will monitor recruitment, protocol compliance, emerging external evidence, sample characteristics and primary outcome measures, as well as make recommendations to the TSC, such as whether interim analysis is required.

Patterns in rates of vision-threatening errors identified during the monthly quality assurance process performed at the Reading Centre will be evaluated by the QAP (consisting of the chief investigator, two clinician coapplicants and a professor of optometry) to introduce remedial measures if required (eg, enhanced training and pausing recruitment).

Statistical analysis

The primary analysis will be conducted following an intention-to-treat principle where all randomised participants are analysed in their allocated group whether, or not, they receive their randomised management plan. All tests will be two sided and will be assessed at the 5% significance level unless otherwise specified. All CIs will be 95% and two sided. All statistical analysis will be performed using R (The R Foundation for Statistical Computing Platform).

Analysis of primary outcome

The primary outcome is whether, or not, a patient has a lesion classified as a false negative within 12 months. This classification rate will be compared between management groups using logistic regression adjusting for randomisation stratifiers (minimisation factors: treatment centre and laterality). This analysis will allow information from each time point to be used up to the point at which a patient reactivates. Outcomes will be reported as adjusted ORs. While our primary analyses will group suspicious and quiescent, a sensitivity analysis will be conducted where suspicious will be grouped with reactivated.

Survival analysis will then be used (in a secondary analysis) to test whether the time to false negative classification differs between the two trial arms.

Analysis of secondary outcome

The secondary outcome of the proportion of false positives in each trial arm within 12 months will be compared using logistic regression, adjusting for randomisation stratifiers (minimisation factors: treatment centre and laterality) as described for the primary outcome.

The proportion of over-referrals in the intervention arm (in comparison with the reference standard), as well as the proportion of participants correctly classified as having 'reactivated' QnAMD at the confirmation hospital visit, will be reported with 95% CIs computed by the exact binomial method.

Mean change in visual acuity (between baseline and 12 months) in each trial arm will be compared using logistic regression adjusting for randomisation stratifiers (minimisation factors: treatment centre and laterality) as described for the primary outcome.

The proportion of 'suspicious' lesion classifications in the intervention arm will be reported with 95% CIs computed by the exact binomial method.

The proportion of patient non-attendance in each trial arm will be compared using logistic regression adjusting for randomisation stratifiers (minimisation factors: treatment centre and laterality) as described for the primary outcome.

The percentage of participants experiencing adverse events in the two groups will be reported with 95% CIs in the same way. 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 different possible scenarios.

Economic analysis

Costs and outcomes associated with either trial group will be collected over the 12-month follow-up period. The costs for this within trial evaluation will be derived from published reference costs and microcosting for the intervention pathways. The use of secondary care and primary care optometry services will be collected from the study's case report forms. Any additional costs will be measured using a bespoke resource allocation questionnaire, which will measure NHS costs, personal and social services costs and patient out of pocket costs. This questionnaire will be administered at baseline, 6-month time point and 12-month time point. Cost estimates will be derived from published NHS resources costs.[11 12] The number of appointments or treatments will be multiplied by the unit costs. The cost of the intervention itself will be subject to a microcosting exercise, which include staff, equipment, administration and any other relevant costs for delivering the intervention. The costs of participant time and travel when accessing care will be informed by the results of a bespoke time and travel questionnaire completed at month 13. These data will be used to calculate an average journey cost for each different kind of care (eg, hospital appointment and optometry appointment), which will be multiplied by the number of each journeys taken.

Health-related quality of life will be measured by use of the EQ-5D-5L questionnaire. 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.[13] The results from the EQ-5D-5L will be used to produce utility values at baseline, 6 and 12 months for each participant. This approach will be used to estimate the QALYs produced for each arm of the trial using the under the curve approach. The within trial analysis will focus on analysing 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, for example, 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.

An economic model will assess the cost-effectiveness of the alternative management options. Costs and health consequences, measured in terms of QALYs, associated with a policy of initial community-based primary care 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

National Institute of Clinical Excellence (NICE) reference case,[14] and we will characterise participants 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. These types of model would be most appropriate model type for this decision problem as they allow the representation of a clinical situation where participants can move between care settings and experience deterioration in health over time, which would be appropriate given the nature of nAMD. 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.[15] 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 personal and social services perspective to take into account healthcare costs and longer term social care costs. Both costs and QALYs will be discounted in the base case at 3.5%.[14] 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 characterise 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 model will estimate the health service costs to the NHS of adopting the community-based primary care service and will follow best practice methods. The approach will model costs for hypothetical cohort representative of the coverage of standard secondary care provided for up to a 10-year time horizon. It will present net budget impact and impact by sector (primary care or secondary care). Following best practice methods,[16] all costs will be presented in a base year, but no discounting will be performed. Both deterministic and probabilistic sensitivity analysis will be presented.

Patient and public involvement (PPI)

An AMD-specific PPI group based at the Manchester Royal Eye Hospital has been involved in the study since its development. This group consists of contributors who have previously or are currently receiving care for AMD. Contributors meet at least once a year with provision for additional face-to-face or 'virtual' meetings when input is required for potential protocol amendments or issues arising during the course of the study. An end-of-study debrief is planned with all PPI contributors, which will include discussions of the prioritisation and dissemination of study results both to the public as well as relevant healthcare professionals.

Adjustments made because of COVID-19

Due to the COVID-19 pandemic, participant recruitment was suspended for 102 days between 26 March 2020 and 6 July 2020. This suspension period affected 67 patients and caused 10 to withdraw from the trial.

As a result of the pandemic, two adjustments have been made to the trial protocol and formally approved via Health Research Authority (HRA).

First, the patient review period was reassessed by surveying first wave NHS sites and community-based primary care practices. It was recommended that the 4-weekly intervals are changed to 8-weekly intervals as per routine clinical practice in QnAMD clinics post-COVID-19 lockdown (March–May 2020).

Second, to minimise the number of hospital visits and aid patient recruitment during the COVID-19 pandemic, the protocol was amended to allow for verbal consent over the phone, as well as written consent provided in person at hospital appointments.

DISCUSSION

This study aims to assess the clinical effectiveness and cost-effectiveness of a community-based, non-medical practitioner-led pathway for the management of QnAMD. Recommendations for the development of community-based eye care services have been proposed in the Royal College of Ophthalmologists 'Way Forward' report as one possible way of reducing demand for overstretched hospital-based services.[5] In addition, 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.[17] These recommendations mean that this study is a timely and much needed investigation, which will offer a possible integrated care pathway for the management of QnAMD.

The FENETRE trial is funded through a National Institute for Health Research Health Technology Assessment programme supporting research that is immediately useful to patients, clinical practice and policy/decision makers, comparing proposed 'technologies' with the current best alternative while examining the clinical and cost-effectiveness of the new intervention. As a result of this funding, this trial is structured to meet the criteria in a number of ways:

1. It compares community-based primary care to the current best alternative: secondary care within a hospital setting.
2. It examines clinical, patient-derived and economic outcomes, demonstrating whether community-based primary care is both non-inferior to current practices and cost-effective.
3. It includes a substudy evaluating the community-based primary care pathway and how it impacts patients' quality of life.

4. It includes a development of a bespoke training package, developed in collaboration with the College of Optometrists.

If this study shows the non-inferior and cost–benefits of community optometry follow-up of participants with QnAMD, we believe that the included aspects of this study design will allow immediate response to be implemented including further development of this care pathways across the NHS. Not only would this implementation lead to a reduction in the clinical burden on hospital services, but it can also help to standardise AMD treatment across the UK. Recent work has highlighted inequalities in the access to AMD treatment within the NHS with a ninefold difference in procedure rates between areas of high treatment use and low treatment use.[18] This difference can lead to wide variation in the number of injections patients receive to treat their nAMD and addressing the high demand on AMD services may go some way to correct this inequality.

Measures such as moving to community-based primary care can also improve the patient experience. Patient involvement work in preparation for this study highlighted that people with QnAMD place great importance on receiving care closer to home, in a timely and convenient way, and are also keen on a community service, which allows a closer relationship to develop between the treating optometrist and the patient. This feedback was reminiscent of the perspectives of health professionals and patients interviewed as part of the ECHoES trial,[19] which emphasised that the current services does not fit the needs and preferences of patients with nAMD who could be better served by an integrated care pathway. Alongside this work, a recent systematic review assessing adherence to nAMD treatment has shown that distance to treatment centre and poor experiences within treatment centres are contributing factors to non-adherence,[20] suggesting that changes to the current service would improve the patient experience and improve treatment outcomes.

In conclusion, this study aims to show the non-inferiority of community-based, non-medical practitioner-led care for patients with QnAMD, allowing a new clinical pathway to be adopted by ophthalmology services that will reduce demand on hospital appointments, reduce the cost to the NHS and improve the patient experience.

ETHICS AND DISSEMINATION

This study will adhere to the UK Framework for Health and Social Care research. Prior to participations, all subjects provide informed consent and are informed in advance that they can withdraw from the study at any time without penalty. The study was approved by the London Bloomsbury Ethics committee.

Once the study is completed, data will be accessible by the FENETRE study groups for analysis and dissemination. Results of any analyses will be presented at national and international conferences and published in peer-reviewed scientific journals. We will also engage with Eye Charities such as the Macular Society, which 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 used to disseminate the results of this research and ensure they are acknowledged, selected and introduced for use in the health and care service.

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The FENETRE Study - Quality-Assured Follow-Up of quiescent neovascular age- related maculaR dEgeneration by non-medical practitioners: study protocol and statistical analysis plan for a randomised controlled trial

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Supplementary material

To be inserted onto the header

Study Number: Centre Number (*if appropriate*):
Participant identification Number for this trial:
Version: 3.0
IRAS number: 254025
Date: 23/04/2019

CONSENT FORM

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

Name of Researcher: _____

Please initial box

1. I confirm that I have read and understand the information sheet dated..... (version.....) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study, may be looked at by individuals from the sponsor of the trial, responsible persons authorised by the sponsor, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. I understand that anonymised data collected during the study, including eye scans (Optical Coherence Tomography) and clinical data may be used for future research projects. ☐

4. I agree to take part in the Artificial Intelligence sub-study. ☐

5. I agree to my GP being informed of my participation in the study. ☐

6. I agree to take part in the above study. ☐

Name of Participant	Date	Signature
Name of Person taking consent	Date	Signature

When completed: 1 for participant; 1 (original) for researcher site file; 1 to be kept in medical notes.