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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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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, multi-site, 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 NHS.

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

ClinicalTrials.gov Identifier: NCT03893474. Registered 28th March 2019.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- This study assesses the non-inferiority of a health 'technology' which aims to meet an immediate need of reducing the burden on hospital-based ophthalmology services.
- Clinical, patient-derived, and economic outcomes are all investigated to ensure this care pathway is both non-inferior and cost-effective.
- As part of the study, a bespoke training package for primary care optometrists has been developed in collaboration with the College of Optometrists, to enable immediate uptake by the NHS.

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 aging 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 to secondary care eye-clinics in correctly classifying re-activation 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 re-activation 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, multi-site 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 sub study 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. 35 primary care optometry practices of a range of sizes and types (independent, small group, 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 1-3 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 anti-Vascular 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 re-treatment interval to 12 weeks and maintenance of this interval for one or more consecutive occasions.

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, 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, 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 centralized 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 re-activated 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 re-activated in each trial arm (termed false positives).
2. The proportion of over-referrals in the intervention arm (community-based primary care) in comparison to the reference standard, i.e. 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 re-activations 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 post randomisation 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

Sub study: 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 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 participants. A total sample of 27-36 participants (3-4 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, 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 participants through their

'journey' there. We will use framework analysis (FA) 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 i.e. 6.2% (confidence interval of 4.8% to 7.9%).[6] 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[8]). This estimate requires adjustment for the fact that ECHOES figures were based upon 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] 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 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, $\pi_1 - \pi_o$, 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 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 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.

Data management and monitoring

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 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 co-ordinators 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% pseudo-anonymised 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 CI, two clinician co-applicants and a professor of optometry) whom will introduce remedial measures if required (e.g. 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 co-applicants and a professor of Optometry) to introduce remedial measures if required (e.g. enhanced training, 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 confidence intervals 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 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.

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 to the reference standard), as well as the proportion of participants correctly classified as having 're-activated' QnAMD at the confirmation hospital visit, will be reported with 95% confidence intervals 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% confidence intervals 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% confidence intervals 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 micro-costing 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 months and 12 month time points. 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 micro-costing 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. This data will be used to calculate an average journey cost for each different kind of care (e.g. hospital appointment, 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 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.

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 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 health care 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 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 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

An AMD-specific Patient and Public Involvement (PPI) group based at the Manchester Royal Eye Hospital have been involved in the study since it's 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 prioritization and dissemination of study results both to the public as well as relevant healthcare professionals.

Adjustments Made Because of COVID-19

Due to the coronavirus disease-2019 (Covid-19) pandemic, participant recruitment was suspended for 102 days between 26th March 2020 and 6th 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 HRA.

Firstly, the patient review period was reassessed by surveying 1st 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).

Secondly, 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- 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 (NIHR) Health Technology Assessment (HTA) programme supporting research which 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 sub-study 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 9-fold 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 not only improve the patient experience, but also 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 which will reduce demand on hospital appointments, reduce the cost to the NHS, and improve the patient experience.

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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, 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 utilized to disseminate the results of this research and ensure they are acknowledged, selected and introduced for use in the health and care service.

AUTHOR CONTRIBUTIONS

KB is the chief investigator of this study. AT, CB, PAK, AK, ER, AJ, SS, RAH, JGL, LV, HW and KB made significant contributions to the protocol development. AEL and AD are responsible for the planning of the statistical analysis. AEL, RAH, AD, and KB drafted and edited the manuscript. All authors have approved the final manuscript.

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FIGURE LEGEND

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.

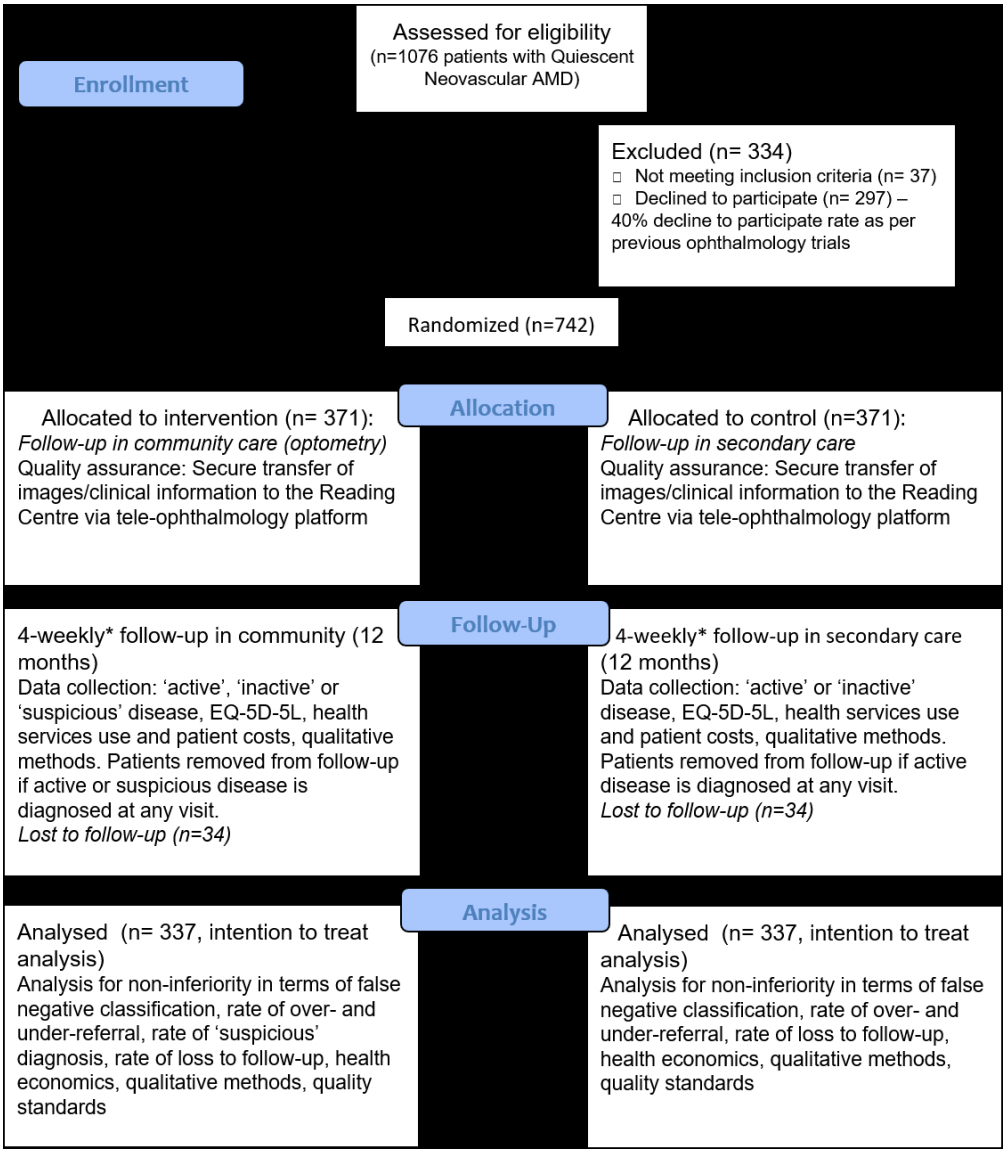

Figure 1 - Flow chart of study design and participant follow-up
Numbers of patients assessed, excluded, and lost to follow are estimated samples based on previous studies. * due to the COVID-19 pandemic the 4-weekly follow-up interval was changed to 8-weekly.

95x108mm (300 x 300 DPI)

Reporting checklist for protocol of a clinical trial.

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Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet	2

		registered, name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	N/A -Data not released yet
Protocol version	#3	Date and version identifier	v2 Oct 2019
Funding	#4	Sources and types of financial, material, and other support	19
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1&20
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	19
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	17-18
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the	12-13

		trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries	6

		where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	12
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	12
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion),	8-9

		and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6&16-17
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A - Only data analysts blinded and data only analysed after study completion.
Methods: Data collection, management, and analysis			

Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	11
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
Statistics: additional	#20b	Methods for any additional analyses (eg,	14-16

analyses		subgroup and adjusted analyses)	
Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	11
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	11-12
Auditing	#23	Frequency and procedures for auditing trial	12

		conduct, if any, and whether the process will be independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	16-17&20
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9-10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	N/A - Not included
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and	19

		each study site	
Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	5
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A - Not included in protocol documents but in collaboration agreement
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20

Appendices

Informed consent materials	#32	Model consent form and other related documentation given to participants and authorised surrogates	N/A - Not included in protocol documents
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A

Notes:

- 2b: N/A -Data not released yet
- 3: v2 Oct 2019
- 17b: N/A - Only data analysts blinded and data only analysed after study completion.
- 27: N/A - Not included
- 31b: N/A - Not included in protocol documents but in collaboration agreement
- 32: N/A - Not included in protocol documents The SPIRIT checklist is distributed under the terms of the Creative Commons Attribution License CC-BY-ND 3.0. This checklist was completed on 23. January 2021 using https://www.goodreports.org/, a tool made by the EQUATOR Network in collaboration with Penelope.ai

BMJ Open

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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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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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, multi-site, 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 NHS.

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

ClinicalTrials.gov Identifier: NCT03893474. Registered 28th March 2019.

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 world-wide health systems.
- However, interventions such as this are timely and relevant to the global trend towards decentralisation of health care.

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 aging 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 to secondary care eye-clinics in correctly classifying re-activation 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 re-activation 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, multi-site 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 sub study 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. 35 primary care optometry practices of a range of sizes and types (independent, small group, 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 1-3 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 anti-Vascular 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 re-treatment interval to 12 weeks and maintenance of this interval for one or more consecutive occasions.

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, 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, 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 centralized 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 re-activated 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 re-activated in each trial arm (termed false positives).
2. The proportion of over-referrals in the intervention arm (community-based primary care) in comparison to the reference standard, i.e. 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 re-activations 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 post randomisation 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

Sub study: 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 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 participants. A total sample of 27-36 participants (3-4 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, 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 participants through their

'journey' there. We will use framework analysis (FA) 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 i.e. 6.2% (confidence interval of 4.8% to 7.9%).[6] 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[8]). This estimate requires adjustment for the fact that ECHOES figures were based upon 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] 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 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, $\pi_1 - \pi_o$, 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 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 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.

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 supplementary material) which will be filed at the relevant hospital site responsible for the patient and is the only document which has patient identifiable data. Upon 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 is shared with the central study team, or the practices at point of consent and randomisation. All OCT's 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 tele-ophthalmology 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 co-ordinators 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% pseudo-anonymised 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 CI, two clinician co-applicants and a professor of optometry) whom will introduce remedial measures if required (e.g. 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 co-applicants and a professor of Optometry) to introduce remedial measures if required (e.g. enhanced training, 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 confidence intervals 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 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.

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 to the reference standard), as well as the proportion of participants correctly classified as having 're-activated' QnAMD at the confirmation hospital visit, will be reported with 95% confidence intervals 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% confidence intervals 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% confidence intervals 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 micro-costing 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 months and 12 month time points. 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 micro-costing 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. This data will be used to calculate an average journey cost for each different kind of care (e.g. hospital appointment, 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 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.

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 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 health care 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 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 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

An AMD-specific Patient and Public Involvement (PPI) group based at the Manchester Royal Eye Hospital have been involved in the study since it's 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 prioritization and dissemination of study results both to the public as well as relevant healthcare professionals.

Adjustments Made Because of COVID-19

Due to the coronavirus disease-2019 (Covid-19) pandemic, participant recruitment was suspended for 102 days between 26th March 2020 and 6th 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 HRA.

Firstly, the patient review period was reassessed by surveying 1st 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).

Secondly, 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- 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 (NIHR) Health Technology Assessment (HTA) programme supporting research which 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 sub-study 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 9-fold 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 not only improve the patient experience, but also 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 which will reduce demand on hospital appointments, reduce the cost to the NHS, and improve the patient experience.

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FUNDING

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COMPETING INTERESTS

The authors declare that they have no competing interests.

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, 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 utilized to disseminate the results of this research and ensure they are acknowledged, selected and introduced for use in the health and care service.

AUTHOR CONTRIBUTIONS

KB is the chief investigator of this study. AT, CB, PAK, AK, ER, AJ, SS, RAH, JGL, LV, HW and KB made significant contributions to the protocol development. AEL and AD are responsible for the planning of the statistical analysis. AEL, RAH, AD, and KB drafted and edited the manuscript. All authors have approved the final manuscript.

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FIGURE LEGEND

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.

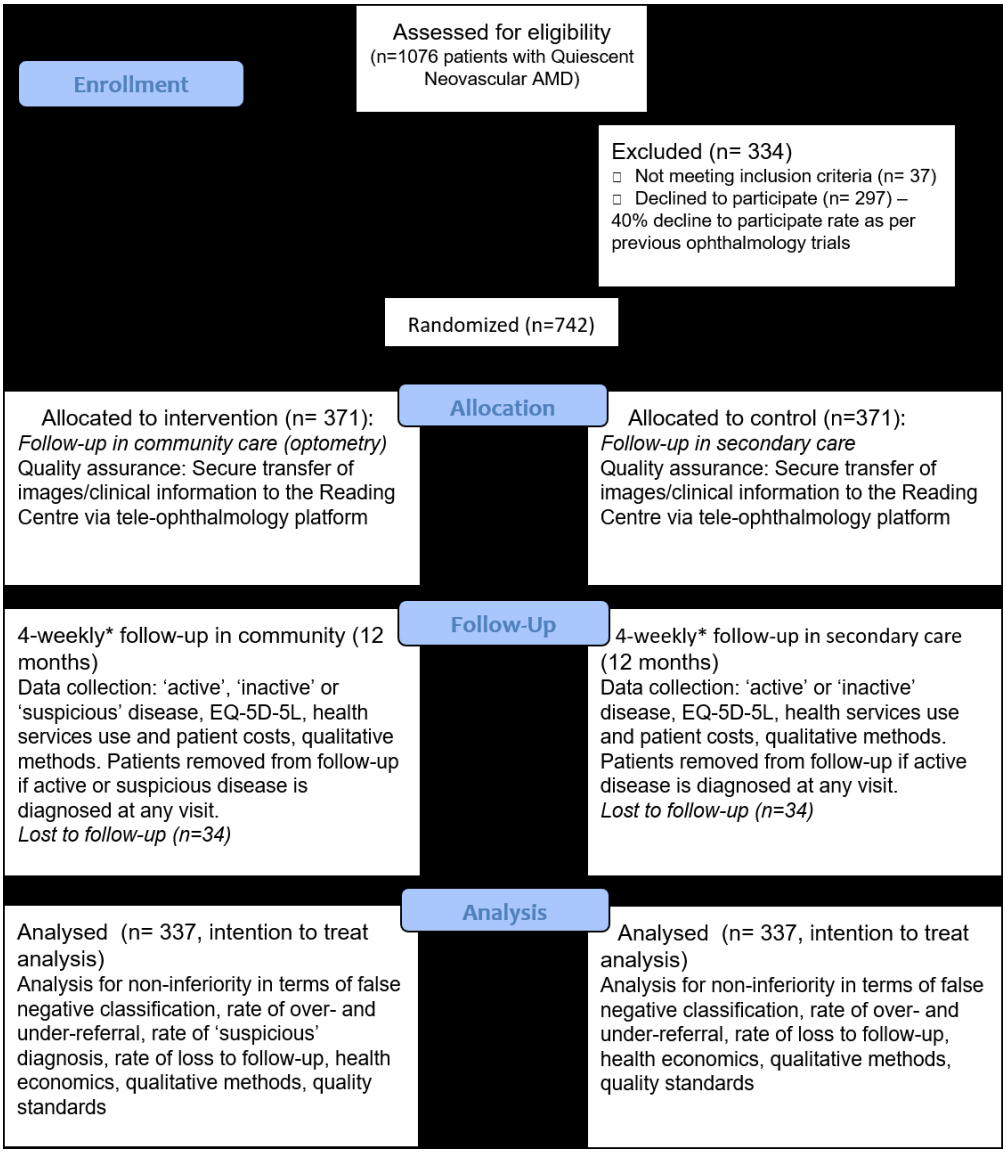

Figure 1 - Flow chart of study design and participant follow-up
Numbers of patients assessed, excluded, and lost to follow are estimated samples based on previous studies. * due to the COVID-19 pandemic the 4-weekly follow-up interval was changed to 8-weekly.

95x108mm (300 x 300 DPI)

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

Annastazia E Learoyd, Adnan Tufail, Catey Bunce, Pearse A Keane, Ashleigh Kernohan, Emily Robinson, Alijazy Jaber, Saqlain Sadip, Robert A Harper, John G Lawrenson, Luke Vale, Heather Waterman, Abdel Douiri, Konstantinos Balaskas on behalf of the FENTERE study group

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.

Reporting checklist for protocol of a clinical trial.

Based on the SPIRIT guidelines.

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Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

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Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the SPIRITreporting guidelines, and cite them as:

Chan A-W, Tetzlaff JM, Gøtzsche PC, Altman DG, Mann H, Berlin J, Dickersin K, Hróbjartsson A, Schulz KF, Parulekar WR, Krleža-Jerić K, Laupacis A, Moher D. SPIRIT 2013 Explanation and Elaboration: Guidance for protocols of clinical trials. BMJ. 2013;346:e7586

		Reporting Item	Page Number
Administrative information			
Title	#1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	#2a	Trial identifier and registry name. If not yet	2

		registered, name of intended registry	
Trial registration: data set	#2b	All items from the World Health Organization Trial Registration Data Set	Available in the trial registry
Protocol version	#3	Date and version identifier	v2 Oct 2019
Funding	#4	Sources and types of financial, material, and other support	20
Roles and responsibilities: contributorship	#5a	Names, affiliations, and roles of protocol contributors	1&21
Roles and responsibilities: sponsor contact information	#5b	Name and contact information for the trial sponsor	20
Roles and responsibilities: sponsor and funder	#5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	18-19
Roles and responsibilities: committees	#5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or	12-13

		groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	
Introduction			
Background and rationale	#6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3-4
Background and rationale: choice of comparators	#6b	Explanation for choice of comparators	4
Objectives	#7	Specific objectives or hypotheses	4
Trial design	#8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, non-inferiority, exploratory)	5
Methods: Participants, interventions, and outcomes			
Study setting	#9	Description of study settings (eg, community clinic, academic hospital) and list of countries	6

		where data will be collected. Reference to where list of study sites can be obtained	
Eligibility criteria	#10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	7
Interventions: description	#11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	5
Interventions: modifications	#11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving / worsening disease)	13
Interventions: adherance	#11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return; laboratory tests)	13
Interventions: concomitant care	#11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	N/A
Outcomes	#12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion),	8-9

		and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	
Participant timeline	#13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	Figure 1
Sample size	#14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	10-11
Recruitment	#15	Strategies for achieving adequate participant enrolment to reach target sample size	6&17
Methods: Assignment of interventions (for controlled trials)			
Allocation: sequence generation	#16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be	7

		provided in a separate document that is unavailable to those who enrol participants or assign interventions	
Allocation concealment mechanism	#16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	7
Allocation: implementation	#16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	7
Blinding (masking)	#17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	7
Blinding (masking): emergency unblinding	#17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	N/A - Only data analysts blinded
Methods: Data collection, management, and analysis			
Data collection plan	#18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any	11-12

		related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	
Data collection plan: retention	#18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	8
Data management	#19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	11-12
Statistics: outcomes	#20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13-14
Statistics: additional analyses	#20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	15-16

Statistics: analysis population and missing data	#20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13-14
Methods:			
Monitoring			
Data monitoring: formal committee	#21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	12-13
Data monitoring: interim analysis	#21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	12
Harms	#22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	12-13
Auditing	#23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be	12-13

		independent from investigators and the sponsor	
Ethics and dissemination			
Research ethics approval	#24	Plans for seeking research ethics committee / institutional review board (REC / IRB) approval	20
Protocol amendments	#25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC / IRBs, trial participants, trial registries, journals, regulators)	12-13
Consent or assent	#26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	11&17
Consent or assent: ancillary studies	#26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	9-10
Confidentiality	#27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	11
Declaration of interests	#28	Financial and other competing interests for principal investigators for the overall trial and each study site	20

Data access	#29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	20
Ancillary and post trial care	#30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	5
Dissemination policy: trial results	#31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	20
Dissemination policy: authorship	#31b	Authorship eligibility guidelines and any intended use of professional writers	N/A - Not included in protocol documents but in collaboration agreement
Dissemination policy: reproducible research	#31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	20
Appendices			
Informed consent	#32	Model consent form and other related	Included as

materials		documentation given to participants and authorised surrogates	supplementary material
Biological specimens	#33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	N/A