Monitoring for **n**eovascular **A**ge-**r**elated macular degeneration (AMD) Rea**c**tivation at **H**ome:
The MONARCH study

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- **KeepSight** have provided access to KeepSight branded vision monitoring and education tools and use of the KeepSight Journal, adapted for UK use for the duration of the study

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Glossary / abbreviations

AMD	Wet age-related macular degeneration
App	Software application
AUROC	Area Under the Receiver Operating Characteristic
BCVA	Best Corrected Visual Acuity
BRI	Bristol Royal Infirmary
CARF	Central Angiographic Resource Facility
CF	Colour fundus images
CRF	Case report form
CTEU	Clinical Trials and Evaluation Unit
EDTRS	Early Treatment Diabetic Retinopathy Study
HES	Hospital Eye Service
HTA	Health Technology Assessment
KSJ	Keep Sight Journal
MHRA	Medicines and healthcare products regulatory agency
MRC	Medical Research Council
MBT	MultiBit vision test
mVT®	MyVisionTrack® vision test
nAMD	Neovascular Age-related Macular Degeneration
NHS	National Health Service
NIHR	National Institute for Health Research
OCT	Optical Coherence Tomography
PIL	Participant information leaflet
PPI	Patient and Public Involvement
REC	Research ethics committee
ROC	Receiver Operating Characteristic
SMG	Study management group
SOP	Standard operating procedure
SSAR	Suspected serious adverse reaction
SSC	Study steering committee
VEGF	Vascular Endothelial Growth Factor

1. Study summary

Wet age-related macular degeneration (neovascular AMD, nAMD) is the commonest cause of blindness in the UK. It involves new vessels growing and leaking at the back of the eye. Recent treatments for wet AMD have led to a significant reduction in the number of wet AMD patients being registered blind. However, providing prompt access to clinics for regular surveillance and treatment has proved a major challenge for the National Health Service (NHS). Most patients need a series of monthly injections followed by a period of regular check-up visits in case more injections are required. AMD can often flare up after a period when treatment has not been required, so check-ups are usually needed for several years.

Home monitoring to detect the need for treatment could mean that patients would not need regular hospital check-ups, allowing Hospital Eye Services (HES) clinic appointments to be kept for patients likely to require treatment. If home monitoring indicated treatment might be required, patients could request an urgent clinic appointment. Home monitoring would be more convenient and less costly for both the patient and the NHS. The main aim of our study is to find out whether our chosen home monitoring tests can detect when wet AMD needs to be treated as well as the surveillance tests currently carried out at hospital check-ups.

We have chosen three home monitoring tests for which some promising results have already been reported. The tests span a range of both technical complexity and cost. The most simple and inexpensive is a paper booklet (KeepSight journal, KSJ) of self-administered “reading tests” with space for patients to record their results on a weekly basis. The other two tests are software applications (apps) that display shapes or patterns on an Apple iPod touch and patients indicate by entering information on the screen which of four shapes is the ‘odd-one-out’ or articulate what numbers appear briefly on the screen. Their responses will be sent to the research team through the internet.

Approximately 1620 existing patients having treatment or check-ups at participating NHS hospitals will be invited to take part in home monitoring (see Study Schema at section 5.1). They will be asked to perform the home monitoring tests weekly at home in between standard hospital check-ups over a period of 1 to 2 years. To ensure our results will apply to most patients needing treatment or surveillance, we will recruit patients first treated for wet AMD 6 to 41 months previously. Patient participants will be trained by appropriately qualified members of the local research team (an optometrist or research nurse with experience in communicating to patients with AMD is preferred) to perform the home monitoring tests, and will have the opportunity for refresher training throughout their participation in the study. At selected participating NHS sites we will undertake an integral qualitative study; a sample of patients and their carers will be interviewed to find out their experiences of performing the tests, focusing on the difficulties experienced and what could be done to make the home monitoring tests more acceptable.

1.1 Study Summary Table

Short Title	The MONARCH study
Full Title	**Mo**nitoring for **n**eovascular **a**ge-**r**elated macular degeneration (nAMD) rea**c**tivation at **h**ome
Study Design	Diagnostic test accuracy study
Study Type	Non-interventional basic science study involving procedures with human participants (see section 12.6 for justification)
Sponsor	Queen's University Belfast
Funder	National Institute for Health Research (NIHR) Health Technology Assessment (HTA) Programme (15/97/02)
Setting	Participant's homes and participating NHS hospitals
Study Hypothesis	Self-monitoring vision tests performed by patients with neovascular AMD at home can detect reactivation of disease with comparable accuracy to tests currently performed by hospital eye services.
Index Tests (Home monitoring tests)	KeepSight paper journal (KSJ) MyVisionTrack® App on iPod touch MultiBit test App on iPod touch
Reference Standard	Routine monitoring of nAMD activity status in hospital eye service clinics as part of usual care in the NHS
Study Objectives	**A** Estimate the test accuracy of three tests to self-monitor reactivation of nAMD compared to the reference standard of detection of reactivation during hospital follow-up with Optical Coherence Tomography (OCT) imaging, clinical examination and Early Treatment Diabetic Retinopathy Study (EDTRS) visual acuity.
	B Determine the acceptability of the tests to patients and carers and their adherence to home monitoring testing regimens. (This is the integrated qualitative study being run at selected participating centres only).
	C Explore whether inequalities (by age, sex, social economic status and visual acuity in the better -seeing eye) exist in recruitment to the study, and impact the ability of participants to do the tests during follow-up and the adherence of participants to weekly testing.

	D Provide pilot data for the use of home monitoring to detect conversion to nAMD in the fellow eyes of patients with unilateral disease, compared to the reference standard of detection of conversion during hospital follow-up with EDTRS visual acuity and OCT imaging.
Main Eligibility Criteria	**Inclusion criteria:** A participant may enter study if the participant has at least one eye meeting the inclusion criteria. A potential study eye may be included if ALL of the following apply: 1. Eye diagnosed with active nAMD (≥ 6 months earlier) in a potential participant ≥ 50 years old and currently being treated with an anti-VEGF drug or being monitored (i.e. with active or inactive nAMD) by the NHS 2. Within 42 months of first treatment for nAMD in the first-treated study eye **Exclusion criteria:** A participant may not enter study if the participant does not have at least one study eye. A potential study eye will be excluded if ANY of the following apply: 1. Vision in the potential study eye limited by another eye condition 2. Surgery in the potential study eye in the previous 6 months 3. Refractive error in the potential study eye >-6D 4. Retinal or Choroidal neovascularization in the potential study eye not due to nAMD In addition, a participant will be excluded if ANY of the following apply: 5. Inability to do one or more of the proposed tests as assessed during 'further information and training' session (see sections 5.8.1 and 5.8.2) 6. Unable to understand English 7. Unable to comply with proposed home testing **Participants can contribute data for both eyes if both eyes meet the criteria for eligibility.**
Study Population	**Objectives A, C & D:** Patients with active nAMD currently being treated with an anti-VEGF drug or monitored by NHS, stratified by time since starting treatment (6-17 months; 18-29 months; 30-41 months) in the study eye with the longest duration from first treatment.

<table>
<tr><td></td><td colspan="2">Objective B:
As for objectives A, C & D plus carers of participants, patients and their carers who have declined to participate in home monitoring and sub-groups of participants and their carers who complete one, two or three tests, who start and stop and who drop out</td></tr>
<tr><td>Sample Size</td><td colspan="2">Objectives A, C & D:
>=400 participants

Objective B:
One-to-one interviews during home visits with participants (n=~75 across selected NHS sites). Carers of participants interviewed separately via telephone or e-interview (n=~60). Patients and their carers who have declined to participate in home monitoring will also be interviewed (n= ~30; 15 patients, 15 carers). Participants and their carers from sub-groups who complete one, two or three tests, who start-and-stop and who drop out will be completed (n= ~40; 20 participants, 20 carers).

Total: ~510 participants</td></tr>
<tr><td>Follow-Up</td><td colspan="2">As per usual NHS follow-up care for ≥12 months, accruing on average 6 clinic attendances from registration until end of study

Participants will complete weekly home monitoring tests at home (KeepSight Journal, MyVisionTrack® and MultiBit test) and continue to attend usual care HES clinics.</td></tr>
<tr><td>Duration</td><td colspan="2">Total duration, 42 months</td></tr>
<tr><td rowspan="4">Software and Equipment Used in Study for Non-Medical Purposes</td><td>iPod touch</td><td rowspan="3">Software and equipment not used for the purposes of diagnosis, prevention, monitoring, treatment or alleviation of disease</td></tr>
<tr><td>Mobile broadband router (e.g. “Mi-fi” router) (only provided if participant does not have home wireless internet)</td></tr>
<tr><td>KeepSight Journal (paper booklet)</td></tr>
<tr><td>MyVisionTrack® (software application)</td><td></td></tr>
<tr><td></td><td>MutliBit test (software application)</td><td></td></tr>
<tr><td>Image Collection</td><td colspan="2">Retinal images taken during usual care follow up to be anonymised and submitted to the Central Angiographic Resource Facility (CARF) in Belfast (see Study Manual for instructions)</td></tr>
</table>

2. Background

Treatment for nAMD with drugs that inhibit vascular endothelial growth factor (anti-VEGF antibodies), generally starts with a loading phase of 3 injections over 3 consecutive months. A proportion of eyes become fluid free in the subsequent maintenance phase but relapse is common and most patients will require re-treatment in affected eyes at some stage, with the disease typically becoming inactive for a period then becoming active again. Patients in the maintenance phase with inactive disease still need to be monitored in hospital by measurement of best-corrected visual acuity (BCVA) and optical coherence tomography (OCT). When disease reactivation is detected, treatment is restarted.

A recent large study has shown that, while many patients have many months of treatment-free periods, a significant burden falls on hospitals (as well as patients) with respect to the need for regular and repeated review (1). Thus methods that might allow the patient to self-monitor at home would reduce the burden on hospitals.

When diagnosis of active nAMD is confirmed, treatment with anti-VEGF therapy is almost always initiated. In most cases patients receive 3 injections every 4-6 weeks initially (loading phase) and then patients are reassessed at each subsequent visit in the treatment cycle to determine lesion activity and decide whether retreatment is necessary (maintenance phase). Monitoring visits use a combination of visual acuity, clinical biomicroscopic examination and optical coherence tomography (OCT) to determine if the neovascular lesion is active (wet) or inactive (dry). It is these monitoring appointments which are causing a significant strain on NHS out -patient clinics in eye hospitals.

During the maintenance phase, patients are monitored for relapse at regular monitoring out patients visits at eye hospitals. The frequency of monitoring depends on the drug being used (ranibizumab or aflibercept) and the preferred treatment regimen (treat [active disease] -as-necessary or treat-and-extend). Ranibizumab is licensed for monthly treatment as required, and aflibercept every two months, during the maintenance phase. For treat-as-necessary regimens, a lesion found to be active is treated and a further monitoring visit is arranged; treatment is withheld if the nAMD lesion is inactive, and a further monitoring visit is arranged. For treat-and extend regimens, ‘prophylactic’ treatment is administered to an eye with an inactive lesion, extending the interval between monitoring visits providing the disease remains inactive; if the nAMD lesion is found to be active, the interval between monitoring visits returns to the standard interval (one month for ranibizumab or two months for aflibercept) until the lesion becomes inactive, and the interval is then extended again). A disadvantage of the treat-and-extend treatment regimen is that it can lead to unnecessary overtreatment.

In this test accuracy study, monitoring of patients will continue as usual in eye hospitals. All the study will do is to add weekly home monitoring, using three different tests (time 20- 40 minutes), to the usual care pathway. Ophthalmologists in eye hospitals will continue to use their preferred drug and treatment regimen to monitor and treat nAMD in their patients. Participants can contribute data for both eyes if both eyes meet the criteria for eligibility. Data will be collected for fellow non-study eyes in order to inform objective D.

An efficient feature of the study is the choice of the reference standard to be the usual care clinical decision about the activity of nAMD in the study eye at the hospital out-patient appointment. Each participant will remain in the study throughout the follow-up period. Therefore, there will be some monitoring visits when the study eye is judged by the participant’s

ophthalmologist to have active disease and some visits when the study eye is judged to have inactive disease. The study will compare the results of the home monitoring tests during the interval preceding the monitoring visit with the reference standard assessed at the monitoring visit.

Because of (a) the clinic workload in treating and monitoring nAMD patients and (b) the high cost of establishing a robust reference standard for people at high risk of nAMD but not currently being monitored by the NHS, we decided that the most urgent priority is to identify a home monitoring test that can detect reactivation in the patients currently being managed in the NHS. We imagine that, ideally, after diagnosis patients would have injections in a hospital clinic over a number of months (typically three) and would then be discharged with the home monitoring test; if the test indicated a deterioration in their vision, they would arrange an urgent appointment. The focus of NHS hospital nAMD clinics would then shift to providing urgent appointments to administer treatment, rather than regular monitoring.

3. Rationale for the study

The development and implementation of care pathways for anti-VEGF treatment for a large and growing number of patients has put considerable pressure on Hospital Eye Services (HES). Many patients remain under regular review for several years after starting treatment. If patients could self-monitor their vision for reactivation of nAMD at home, this would be a significant advantage. Mobile phone technology allows data to be transmitted to a hospital without the need for patients to interpret tests results, making home monitoring practicable.

3.1 Test accuracy of tests for self-monitoring nAMD activity

The advent of tablet computers and mobile/wireless technology has led to the development of devices for self-monitoring of visual function in nAMD (2). The disadvantages of the standard Amsler chart have long been recognised; its sensitivity to detect the onset of nAMD has been estimated to be only 50-70% (3). Perceptual completion (4) and the inability of patients to understand the test or reliably report the results are thought to contribute to poor performance (2).

Reactivation of nAMD is more difficult to detect because some patients have distortion due to scarring and photoreceptor disorganization in the absence of disease activity; therefore, a test has to enable patients to perceive an *increase* in distortion rather than solely its *presence*. Newer technologies such as visual and memory stimulating grids (5), preferential hyperacuity perimetry home devices (6, 7) and shape discrimination tests (8-12) have been reported to quantify distortion more accurately than either the Amsler grid or visual acuity in clinical settings (2).

This study investigates the test accuracy of “index” tests to detect reactivation with supporting peer-reviewed literature and usability data; one uses paper-and-pencil and two use modern information technology, implemented as software applications (apps) on an iPod touch.

3.2 Potential inequalities in uptake

The study also aims to address the question: How do demographic, socioeconomic and visual function factors influence the uptake of home monitoring tests for detecting active nAMD? Outcomes characterising uptake and exposures of interest are defined in section 5.2.6.

A survey by Age UK in 2013 found that internet use among people aged 65 year or over varied across the UK, with a "north-south" divide; more than 50% in the south (Surrey, Bedfordshire, Buckinghamshire, Suffolk and Oxfordshire) used the internet but less than a third in the north (Cumbria, Yorkshire, Hull, Tyne and Wear) (13). With respect to smartphone use, only 20% of 65-74 year olds used such a device to access the internet in 2013 (14); perhaps more importantly, this percentage had increased from only 12% in 2012, suggesting that the situation is changing rapidly over time. The potential importance of failure to access the internet has been highlighted by a study of men and women in the English Longitudinal Study of Ageing from 2004 to 2011 (15) internet use was found to be significantly "protective against health literacy decline."

The small percentage of regular internet and smartphone users is a potential threat to the study, especially if potential participants feel alienated by the technology and are not prepared to try out the solutions we propose. Assuming that we are able to recruit our target sample size, it is still important to determine the extent to which the technology is a barrier to consent and participation in order to project wider adoption of home monitoring in the future if it is found to have satisfactory performance. Moreover, among participants, it is possible that some tests will be easier to do for participants with limited experience of smart devices and the internet. This would be an important factor to weigh against test performance if differences in test performance were found to be small.

We have designed the study by including the following features to try to minimise the extent to which technology is a barrier to home monitoring:

a) We have included a simple paper-based home monitoring test, which we hope will feel familiar to participants. This test is designed like a series of puzzles which require participants to use their near vision correction.
b) We are providing a mobile broadband device (if a participant does not already have home wi-fi) so that participation is not limited by the lack of home wi-fi. This device has a simple on/off switch; the only things that a participant needs to remember to do is to keep the device charged (a mains micro-USB charger will be provided) and to switch on the device before performing the home-monitoring tests that use the iPod. The iPod will interact with the wi-fi device automatically to transmit data.

We will explain use of the devices during an initial training and information session with each potential participant (see section 5.8.2) and provide a help line for participants to call in the event of the experiencing difficulty (see section 5.8.6 for further details).

4. Aim and objectives

The aim of the MONARCH study is to quantify the performance of three non-invasive test strategies for use by patients at home to detect active nAMD compared to diagnosis of active nAMD during usual monitoring of patients in the Hospital Eye Service.

The study has four objectives:

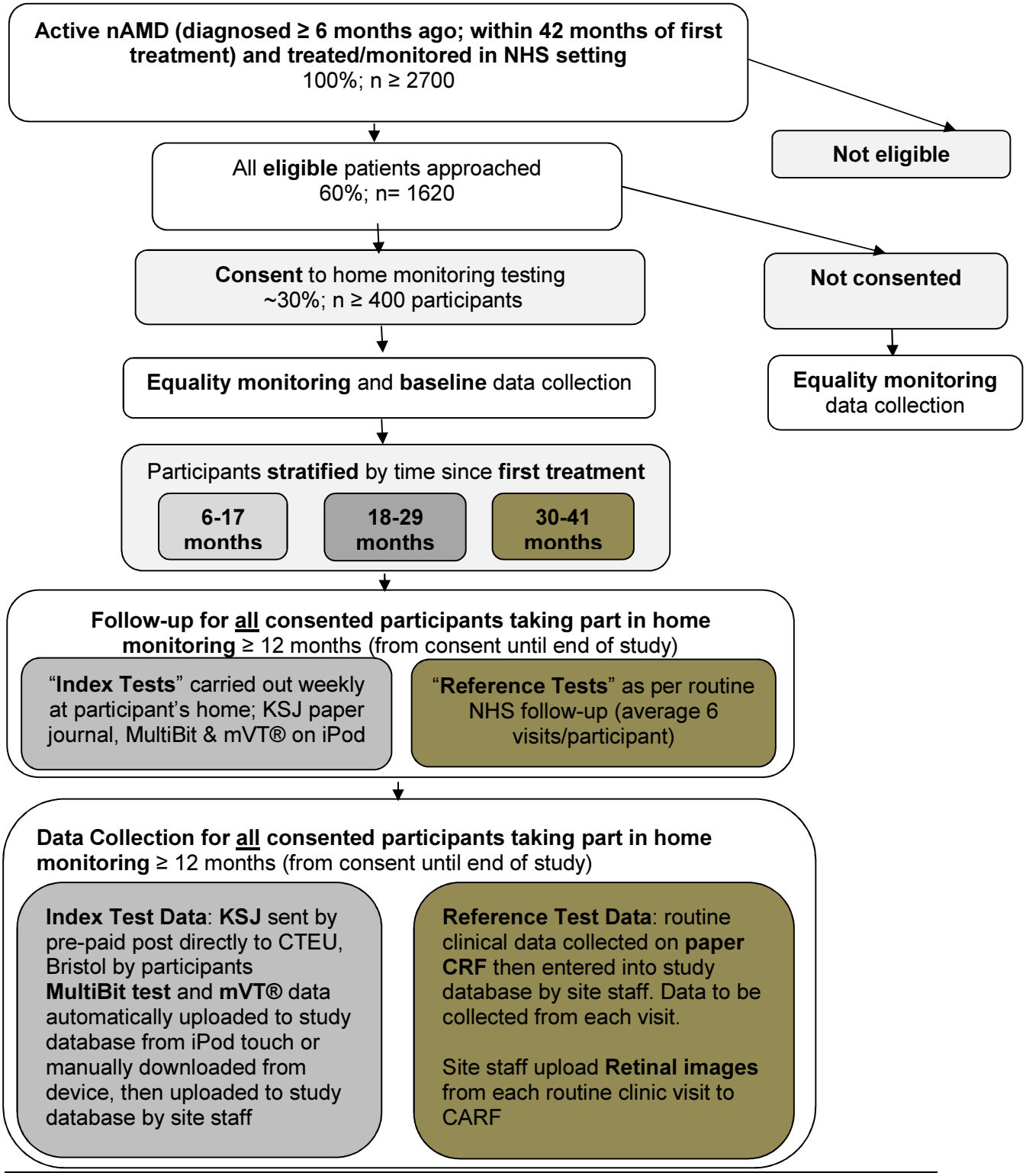
- **A.** Estimate the test accuracy of three tests to self-monitor reactivation of nAMD compared to the reference standard of detection of reactivation during hospital follow-up with Optical Coherence Tomography (OCT) imaging, clinical examination and Early Treatment Diabetic Retinopathy Study (EDTRS) visual acuity.
- **B.** Determine the acceptability of the tests to patients and carers and their adherence to home monitoring testing regimens.
- **C.** Explore whether inequalities (by age, sex, social economic status and visual acuity in the better -seeing eye at diagnosis) exist in recruitment to the study, and impact the ability of participants to do the tests during follow-up and the adherence of participants to weekly testing.
- **D.** Provide pilot data for the use of home monitoring to detect conversion to nAMD in the fellow eyes of patients with unilateral disease, compared to the reference standard of detection of conversion during hospital follow-up with EDTRS visual acuity and OCT imaging.

The plan of investigation for objectives A, C and D is described in section 5.

The study population to be recruited for objective B (the integrated qualitative study) differs substantially from that required for objectives A, C and D. Only selected NHS centres will be participating in procedures and data collection for objective B. Therefore, the plan of investigation for objective B is described separately in section 6.

5. Plan of Investigation: Objectives A, C & D

5.1 Study schema: Objectives A, C & D to detect reactivation of nAMD lesions



5.2 Study design: Objectives A, C & D

This is a multi-centre diagnostic test accuracy cohort study to estimate the sensitivity and specificity of home monitoring tests to detect active nAMD in patients previously diagnosed with nAMD and quiescent after treatment.

MONARCH is designed to compare the results of the home monitoring tests being evaluated ("index tests", see section 5.2.1) with the results of a reference standard (see section 5.2.5) for study eyes (and fellow eyes for objective D). These comparisons allow the accuracy of the index tests to be quantified with respect to the reference standard.

Participants will be followed for at least 12 months, accruing on average 6 clinic attendances at which home monitoring and reference test results can be compared.

The nature of active nAMD may change over time since diagnosis, if the disease progresses despite monitoring and treatment. Therefore, we will structure the study population in order to study participants at varying times since diagnosis and first treatment of nAMD in the first-treated study eye (see section 5.4; see main study Flow Chart). This design avoids the prolonged duration of follow-up which would be required if, instead, we were to follow participants from diagnosis to an equivalent time in the natural history of their condition.

5.2.1 Index tests (Home monitoring tests)

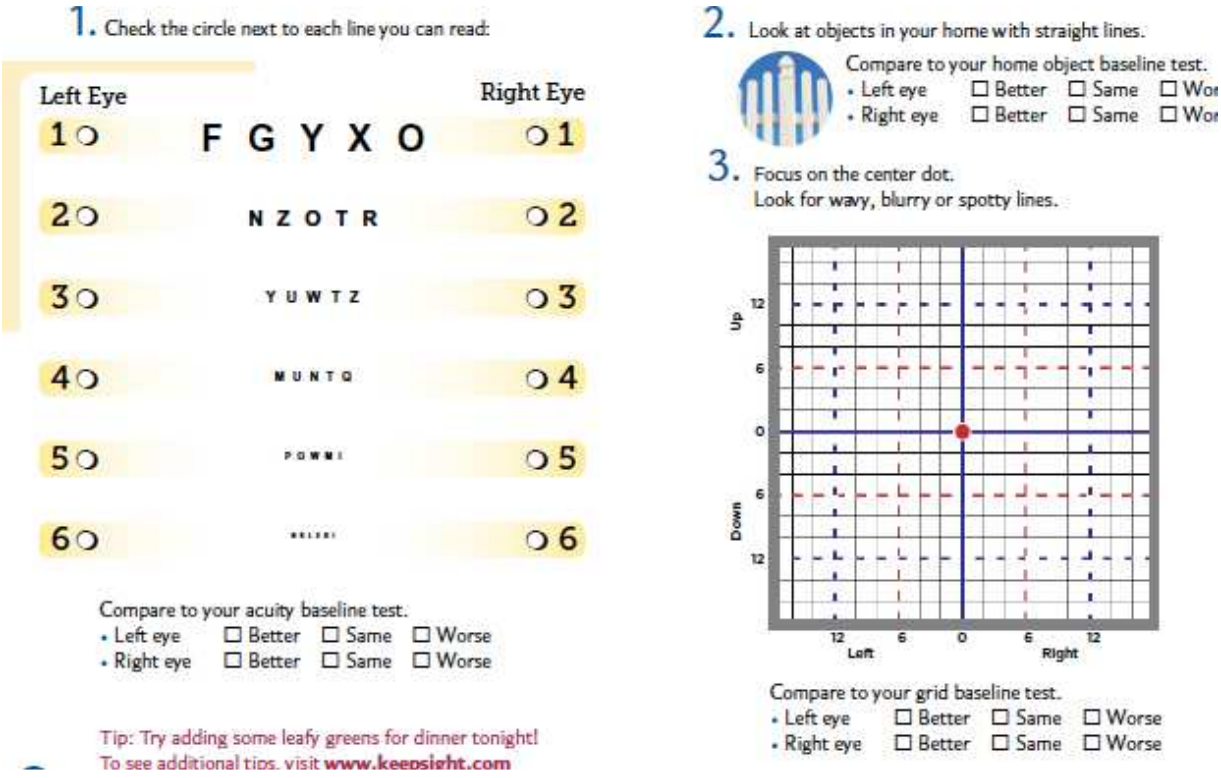
There are 3 home monitoring ("index") tests spanning low to moderate cost and complexity. These are:

1. KeepSight Journal (KSJ) adapted for UK use (a paper-based booklet of near vision tests)
2. MyVisionTrack® (mVT®) electronic vision test, developed by Vital Art and Science Inc.
3. MultiBit (MBT) electronic vision test, developed by Visumetrics, licensed by Novartis

5.2.2 The KeepSight Journal (KSJ) (5)

The KeepSight Journal (KSJ) encourages weekly monitoring using a paper journal. It includes 3 different monitoring strategies, viewed one eye at a time. Firstly, near visual acuity is assessed using a puzzle (crossword or word search) employing a variety of font sizes (an example is shown in Figure 1). Secondly, patients are encouraged to view objects with straight lines in the home to check for distortion (wall panelling, floor tiles, venetian blinds, etc.). Finally, they use a modified amsler chart (Visual and memory stimulating grid (VMS grid)) to record areas of distortion or scotoma in their vision. The KSJ has been used before; 198 patients with intermediate AMD (at high risk of progression to late stage), were randomized to use the KSJ to self-monitor or usual care, with follow-up at 6 and 12 months to assess adherence (5). The results showed significantly better adherence in the journal group with the findings supporting the efficacy of the journal for increasing vision self-monitoring adherence and confidence while promoting persistence in weekly monitoring.

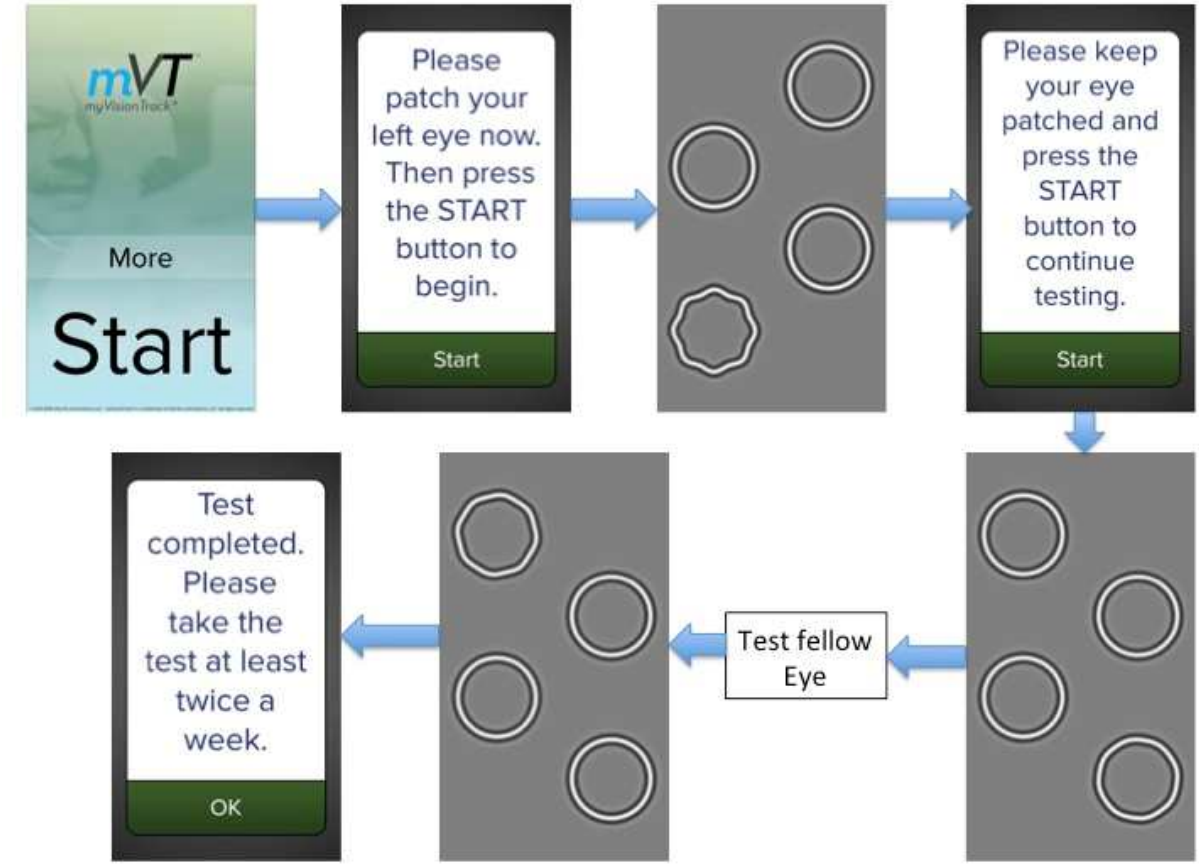
Figure 1: example of a visual puzzle in the KSJ



5.2.3 MyVisionTrack (mVT®) (8-10)

MyVisionTrack is a software application (app) on an iPod touch. It is a shape discrimination test which measures hyperacuity, by displaying 4 circles, one of which is radially deformed ("bumpy" rather than perfectly circular). Viewing the display monocularly, the patient has to identify the odd-one-out (see Figure 2). Studies have shown that the task implemented on an iPod touch can distinguish between intermediate and advanced nAMD and a survey reported that 98% of patients found the test easy to use (8). Studies at the Liverpool site led by Paul Knox (co-investigator) have successfully used the test in macular clinics and patients have found the test straightforward to complete (16). In a recent study, 33 patients with Diabetic macular oedema receiving anti-VEGF treatments used the mVT and they were followed up for 6 months. There was no change in visual acuity at 3 or 6 months visits but shape discrimination hyperacuity improved in parallel with a clinical impression that their condition had improved (17).

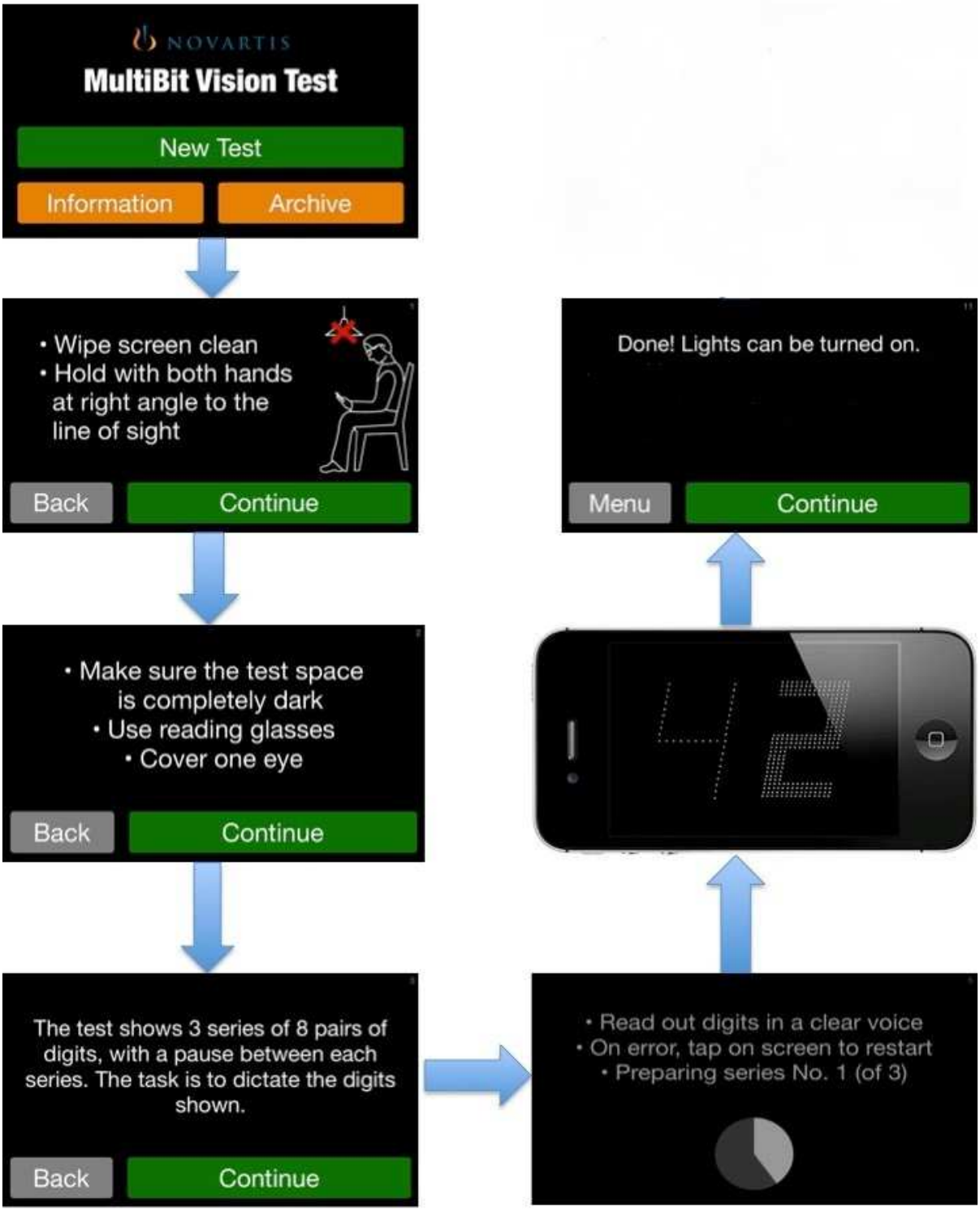
Figure 2: diagram illustrating steps when self-monitoring with the mVT app



5.2.4 MultiBit test (MBT) (18, 19)

MultiBit test is also an app on an iPod touch. It is a near acuity threshold test of neuro-retinal damage. Traditional tests fail to detect such damage because they are supra -threshold. The MBT displays receptive field sized dots or “rarebits”, which provide a miniscule amount of information to the visual system compared to conventional targets (see Figure 3). Patients are presented with pairs of numbers, they state the numbers that they see out loud and the numbers are then represented at high contrast together with a recording of the patient’s responses. MultiBit test is the only test with published data describing its performance to alongside changes in nAMD activation (18). It was used to track 29 patients during treatment and monitoring in NHS out-patient clinics (average 39 weeks follow-up), with patients monitoring themselves at home with an iPod touch. MBT performance improved gradually after treatment, stabilized during periods of disease inactivity and deteriorated gradually preceding reactivation. MBT performance also agreed well with retinal imaging clinical assessments but not with visual acuity (known to be an insensitive test of reactivation).

Figure 3: diagram illustrating steps when self-monitoring with the MBT app



5.2.5 Reference tests (routine NHS follow-up)

The reference standard (sometimes called the "gold standard") is a test that classifies an observation in a way that is considered “definitive.” In the case of MONARCH. This is the nAMD status of a study eye being monitored. The reference standard is sometimes imperfect but represents how diagnostics decisions are currently being made.

The reference standard test for the study is the reviewing ophthalmologist’s decision at a monitoring visit about the activity status of a study eye. This decision will be made on the basis of clinical examination and the results of hospital-based investigations such as colour fundus (CF) photographs and OCT images. It is possible that the reviewing ophthalmologist sometime misjudges the status of a study eye at a monitoring visit (the judgements required are complex and can be difficult; even experts can disagree when judging the activity status of a nAMD lesion (20)) but the decisions made by ophthalmologists currently represent the best reference standard.

5.2.6 Potential inequalities in uptake of home monitoring (Objective C)

In order to assess potential inequalities in uptake of home monitoring (a requirement of the NIHR commissioning brief and a feature of the study that is consistent with Cochrane Equality Methods Group guidance) the following characteristics, captured as an “equality monitoring dataset”, will be investigated as potential predictors of the of uptake of home monitoring tests:

a) Age

b) Sex

c) Ethnicity

d) Index of Multiple Deprivation for place of residence (21)

e) Visual function in better seeing eye

A linked-anonymised equality monitoring dataset will be captured for all patients who are approached with a Patient Information Leaflet, including those who decline to consent to take part in home monitoring (see section 5.9.1 for details).

5.2.7 Pilot data for use of home monitoring to detect conversion to nAMD in fellow eyes (Objective D)

The framework for this objective is essentially the same as the framework for objective A. The setting, index tests and data collection are the same. There are the following differences:

a) The research question of interest is the ability of the index tests to detect conversion of a fellow eye, not being treated or monitored at the time of recruitment, to active nAMD with the initiation of treatment.

b) Therefore, the study population will only include participants with a fellow eye confirmed as not having nAMD at the time of recruitment (expected to be about 350; see section 5.6).

c) The reference standard for this research question is the reviewing ophthalmologist's decision at a monitoring visit that the fellow has converted to active nAMD and requires treatment. This decision will be made on the basis of clinical examination and the results of hospital-based investigations such as colour fundus photographs and ocular coherence tomography (OCT) images. Fluoroscein angiography may also be carried out to confirm that active disease is present.

5.3 Study setting: Objectives A, C & D

The study will be run in the homes of patients being monitored by HES for nAMD at participating NHS hospitals and in the participating NHS hospitals.

Participants will be recruited in secondary care (HES clinics). During the study the reference standard for an eye being monitored will be determined at HES clinic visits. During intervals between clinical visits participants will use home monitoring tests to test their vision themselves. We will ask participants to complete the home monitoring tests themselves weekly at home.

5.4 Study population: Objectives A, C & D

The study population for this part of the study are patients with at least one study eye being monitored by HES for nAMD, stratified by time since starting treatment in the first-treated study eye (6-17 months; 18-29 months; 30-41 months) to ensure test performance is estimated across this range of duration of nAMD.

5.4.1 Eligibility of patients with unilateral or bilateral nAMD

Participants will contribute data to the study for both eyes, except when an eye would not be classified as a study eye if it were to be diagnosed with nAMD (likely to be an eye in which the tests could not be applied). If both eyes of patient meet the criteria for eligibility, then the participant will contribute data for two study eyes, with stratification according to the time since first treatment in the first-treated eye (see section 5.4.4). If one eye meets the criteria for eligibility but second "fellow" eye does not because it is not affected by nAMD, then the participant will still contribute data for both eyes, with the data collected for non-study fellow eyes informing objective D (see section 5.9.3). Data will not be collected for ineligible eyes without "useful" vision (see section 5.9.3). See section 5.4.5 for some illustrative examples.

5.4.2 Inclusion criteria

A participant may enter study if the participant has at least one eye meeting the inclusion criteria.

A potential study eye may be included if ALL of the following apply:

1. Eye diagnosed with active nAMD (≥ 6 months earlier) in a potential participant ≥ 50 years old and currently being treated with an anti-VEGF drug or being monitored (i.e. with active or inactive nAMD) by the NHS
2. Within 42 months of first treatment for nAMD in the first-treated study eye

5.4.3 Exclusion criteria

A participant may not enter study if the participant does not have at least one study eye.

A potential study eye will be excluded if ANY of the following apply:

1. Vision in the potential study eye limited by another eye condition
2. Surgery in the potential study eye in the previous 6 months
3. Refractive error in the potential study eye >-6D
4. Retinal or Choroidal neovascularization in the potential study eye not due to nAMD

In addition, a participant will be excluded if ANY of the following apply:

5. Inability to do one or more of the proposed tests as assessed during 'further information and training' session (see sections 5.8.1 and 5.8.2)
6. Unable to understand English
7. Unable to comply with proposed home testing

5.4.4 Stratification of study population

Home monitoring to detect active nAMD is relevant at any stage of the condition after diagnosis, apart from any initial loading phase of treatment (usually 3 months). In order to recruit a study population that evaluates home monitoring across the time spectrum of monitoring, we will stratify recruitment into 3 strata according to time since first treatment for nAMD in the first-treated study eye: (a) 6-17 months; (b) 18-29 months; (c) 30 to 41 months.

5.4.5 Illustrative examples for classification of eligibility of study and fellow eyes

Left eye	Classification for study	Data collection	Right eye	Classification for study	Data collection
nAMD diagnosis meeting eligibility criteria	**Eligible-** Study eye	✓	nAMD diagnosis meeting eligibility criteria	**Eligible-** Study eye	✓
nAMD diagnosis meeting eligibility criteria	**Eligible-** Study eye	✓	No nAMD diagnosis; vision not excessively limited by another condition and meeting all other eligibility criteria	**Not eligible-** Fellow eye	✓
nAMD meeting eligibility criteria	**Eligible-** Study eye	✓	No nAMD diagnosis; vision limited by another condition not meeting eligibility criteria	**Not eligible-** Non-seeing eye	X

5.5 Primary and secondary outcomes: Objectives A, C & D

The primary outcome is classification of a study eye at a visit as having active or inactive disease. For the reference classification, this is the reviewing ophthalmologist's decision at a monitoring visit about the activity status of the study eye (definitely active, definitely inactive, ambiguous). We will also collect data on whether an injection is ordered/given, though this may not correlate perfectly with classification by lesion activity as (a) a patient may decide to refuse further injections or a patient's health may preclude it or (b) an injection may be given when a lesion is inactive, e.g. in the context of a treat-and-extend regimen. For the index texts, alternative threshold criteria for classification will be explored to maximise test performance.

5.5.1 Secondary outcomes

For Objective C the following uptake outcomes will be investigated as measure of uptake of home monitoring tests:

a) **Participation in the study**, defined as consent (yes/no) among eligible patients approached to take part.
b) **Ability of participants to do the tests during follow-up**, defined as the proportion of visits for which some data for an index test are available
c) **Adherence of participants to weekly testing**, defined as the proportion of weeks for which data for an index test are available, aggregated across intervals between visits for which the reference standard assessment is available

5.5.2 Predictors of outcome to be studied: Objectives A, C & D

See section 8.1.3 for discussion of analysis of objective D, where we will explore the extent to which variables, captured to characterise equality of provision/participation, predict secondary outcomes.

5.6 Justification of target sample size: Objectives A, C & D

5.6.1 Objectives A & C

It is assumed that the reference standard will be 'active' for 30% of monitoring visits; correlations between tests and reference standard will be 0.6 for both active and inactive lesions (22). We will recruit at least 400 participants with test and reference data for about 2300 clinic visits (average 6 visits/participant, 5% attrition). Multiple visits per participant are not independent and measurement error will dilute power to discriminate test performance, so we have assumed an effective sample size of 1200 visits, giving 90% power to detect a difference of 0.06, or 80% power to detect a difference of 0.05, in the area under the receiver operating characteristic curves (AUROC) for 2 tests if the AUROC is 0.75 (22).

5.6.2 Objective D

Estimates of the rate of conversion to nAMD among fellow eyes vary, ranging from 4% to 16% (23-26). Assuming the risk in unselected patients is 5-6% per year, up to 50 patients may have

nAMD in both eyes at the time of recruitment. Among the remaining 350 patients, we expect to identify conversion of fellow eyes to nAMD in about 25-30 patients.

5.7 Measures taken to avoid bias: Objectives A, C & D

Risk of bias is considered with respect to bias domains described in an appraisal tool for diagnostic accuracy studies (27). Information here should be read in conjunction with information about the proposed methods of analyses (see section 8.1).

i. Bias due to selection of participants

Bias in this domain will be avoided by using a cohort study design and recruiting a representative sample of eligible patients. We cannot guarantee that consecutive eligible patients will be recruited but factors such as absence of research staff (e.g. annual leave) or other logistical issues will not be associated with the characteristics of patients. Therefore, we anticipate that, when staff are available, research teams will invite consecutive eligible patients to take part and hence recruit a representative sample of patients. The exclusion criteria are appropriate, i.e. they would prevent a person self-monitoring using one or more of the tests even if the test(s) were implemented as part of usual care (if shown to detect nAMD reactivation accurately).

ii. Bias in the assessment of the index tests

Bias in this domain will be avoided by ensuring that the index tests will be 'scored' without knowledge of the results of the reference standard. We will pre-specify the methods for defining threshold scores based on the knowledge of the distribution of scores and expert judgements about weights for false positive and false negative misclassifications. We cannot specify test thresholds at the outset because there are no available data to inform these definitions.

iii. Bias in the assessment of the reference standard

Bias in this domain will be avoided by ensuring that the reference standard is assessed without knowledge of the results of the index tests. The reference standard represents a usual care decision about the reactivation of nAMD and, although this decision will not always be accurate (28), it can reasonably be considered likely to classify participants correctly with respect to reactivation of nAMD.

iv. Bias due to exclusion of participants or inappropriate intervals between the times of index testing and the reference standard

Bias in this domain will be avoided by ensuring the analysis includes all follow-up visits for which the reference standard is assessed and by carefully describing the time intervals between index tests and the reference standard. We will also account for all patients recruited into the study e.g. using a flow diagram and tables as appropriate. We will acknowledge potential differences between participating centres and present information that may characterise this, e.g. variation in methods used to obtain the reference standard and the centre-specific rate of reactivation of nAMD.

5.8 Study Methods: Objectives A, C & D

5.8.1 Participant identification and invitation to participate

Potential study participants will be identified by local teams from established clinical databases of patients and via outpatient clinics. Potential participants will be screened for eligibility by the healthcare team through review of their medical notes and any existing imaging.

All potential participants will be sent by post or given an invitation letter and patient information leaflet (PIL) (approved by a Research Ethics Committee, (REC)) describing the study. An appropriately trained and qualified member of the local research team (e.g. study clinician/research nurse/optometrist) will also discuss the study with them by telephone or in person. The potential participant will have time to read the PIL and to discuss their participation with others outside the research team (e.g. relatives or friends) if they wish. All potential participants who are provided a PIL will be given a unique study number against which details including reason(s) for non-participation (e.g. reason for being ineligible or patient refusal) along with equality monitoring data will be collected (see section 5.9.1 for further details). The study number will be the primary way in which the participant will be identified and will be used in all correspondence and during data collection.

Usually at least 24 hours after receipt of the PIL, potential participants will be telephoned or seen by a member of the local research team who will answer any questions and confirm whether or not the potential participant is interested in participating and attending a further information and training session.

5.8.2 Further information and training session, equipment and consent

Verbal consent to attend the further information and training session will be taken by a member of the local research team and will be recorded in the patient's hospital record. Potential participants who have had less than 24 hours to consider the study will only be booked to attend a further information and training session if they feel they have had sufficient thinking time.

The information and training session should be led by an appropriately qualified member of the local research team with experience of working with patients. It is strongly suggested that training is led by an optometrist or research nurse.

At the further information and training session, the potential participant will be shown the equipment and how it should be used for the study. The local research team member will answer any further questions, check and confirm the participant's eligibility and take written informed consent if the potential participant is eligible and agrees to participate. Participants will also be asked for consent to receive optional SMS text reminders during the study, and an optional copy of the final study results at the end of the study.

Following consent, the participant will be provided with the following to take home: an iPod touch, the KSJ plus a pre-paid envelope and a mobile broadband router (if required).

The local study team will send a letter to the participant's GP to inform them of study participation.

A study manual will be provided to the local research team with details of the training and equipment, and this will be covered in site initiation.

5.8.3 Return of study equipment

At the end of the study a participant who has completed at least 12 months of follow-up will be allowed to keep possession of the iPod touch.

If a participant withdraws early (before the end of the study) their iPod touch and mobile broadband router must be returned to the local study team (see section 5.12 for further details).

Please refer to the study manual for details on equipment return for local study teams. This will be covered in site initiation.

5.8.4 Home monitoring tests

Participants will be asked to complete home monitoring "index" tests weekly at their home.

Each electronic test takes approximately 5 minutes to complete though some participants may take up to 10 minutes, the KeepSight Journal can take between 10-20 minutes depending on the difficulty of the puzzle, therefore weekly monitoring is likely to range from 20-40 minutes.

Participants should complete all three of the index tests (i.e. KSJ paper journal, MultiBit test and mVT®) for both eyes (unless a fellow eye doesn't have 'useful vision', see section 5.9.3)

Each KSJ booklet should last approximately 6 months. Once a booklet is completed, participants should be instructed to return the completed booklet in a pre-paid envelope to the study management team at CTEU Bristol (see section 5.9).

Data will be collected automatically from the electronic tests. See section 5.9 for further details.

5.8.5 Reference tests (routine NHS follow-up)

There is no specific follow-up schedule required for the study. Participants should be monitored in routine NHS follow-up monitoring clinics and any imaging required should continue as per the discretion of the local healthcare team according to local standard of care and patient need.

However, local site teams should collect data for both participant's eyes (again unless a fellow eye doesn't have 'useful' vision, see section 5.9.3) at each routine follow-up appointment and this must be entered into the study database in a timely manner (ideally within 2 weeks of hospital check-up).

5.8.6 Technical support with home monitoring tests

Participants and local research team members having difficulty with use of the applications, iPod touches, mobile broadband devices, automatic data upload or other technical queries should contact the MONARCH technical helpline.

Details of the MONARCH technical helpline are provided in the Study Manual.

5.8.7 Retinal Image Collection

Patients are asked to provide consent to retinal image collection. This is optional; participants can take part in home monitoring without consenting to retinal image collection. For participants who agree to retinal image collection all retinal images (e.g. Colour Fundus, OCT) taken during follow-up are to be uploaded in an anonymised form to CARF by the local research team in a timely manner following collection during routine hospital follow-up. Please refer to the study manual for instructions on retinal image upload. This will be covered in site initiation.

Retinal images are to be stored at CARF for use in future ethically approved research.

5.8.8 Blinding

All personnel carrying out "reference tests" (routine NHS follow-up monitoring) will be blinded to the results of the "index" (home monitoring) tests; this will minimise detection bias.

Under no circumstances should any member of the site team, particularly optometrists, look at completed index test results for any participant. Deviations from this should be reported to the study coordinating centre using the relevant CRF.

5.9 Data collection: Objectives A, C & D

All data recorded on paper relating to the participant will be located in CRF folders, which will be stored securely. Staff with authorisation to make changes to the study records, including the study database, will be listed on the study delegation log maintained at each centre. Data collection will include the following elements:

(a) A screening log of all patients diagnosed with nAMD who are approached for the study (including the date when they are given/posted the PIL).

(b) Patients approached and assessed against the eligibility criteria and, if ineligible, reasons for ineligibility and any reasons for declining to participate.

(c) Equality monitoring data (see section 5.9.1).

5.9.1 Equality monitoring data

The following equality monitoring data will be collected for all patients approached with a patient information leaflet.

a) **Age**: when approached for the study as recorded in the hospital patient information system

b) **Sex**: as recorded in the hospital patient information system

c) **Ethnicity**: as recorded in the hospital patient information system

e) **Index of Multiple Deprivation** for place of residence (21) derived from the participant's residential postcode, as recorded in the hospital patient information system. Northern Ireland has its own Multiple Deprivation Measure, (29) which we use for participants recruited in Belfast. Recommended methods will be used to analyse associations of outcomes with different deprivation indices for England and Northern Ireland (30).

f) **Visual function**: visual acuity in the better-seeing eye when approached for the study.

The equality monitoring data will be entered onto the study database with records identified by a study number only in a linked anonymised format.

5.9.2 Data collection for patients consenting to home monitoring testing

For participants who provide consent to completion of home monitoring the following data will be collected:

- Baseline information (e.g. history).
- Data from standard of care hospital follow-ups (this is the "reference test data") .
- Data from home monitoring:
  - KSJ booklet vision test completed weekly by participant at home and sent directly to CTEU Bristol ("index test data").
  - Data from home monitoring app based vision tests collected weekly during follow-up until the end of study and automatically uploaded to clinical study database (or downloaded at next clinic visit, if required) ("index test data").
- [*Optional*] Retinal images (e.g. Colour, OCT, fluorescein angiography images) taken as part of routine follow-up uploaded to CARF *(Participants can take part in home monitoring without providing their consent to retinal image collection).*

Table 1 Data collection

	Approach and Consent		***Follow-Up ≥12 months (consent until end of study)***	
Data item	*Approach*	*Consent*	*Home monitoring tests weekly at home*	*Routine NHS follow-up monitoring clinics*
Equality monitoring data #	✓			
Baseline data		✓		
*Index Tests (Home monitoring tests) **			✓	
Reference Test Data (CRFs completed following standard of care hospital follow-up)$				✓

**Completed KSJ booklets to be sent directly to CTEU Bristol in pre-paid envelopes by participants; data from MyVisionTrack® and MultiBit tests automatically uploaded to clinical study database, or downloaded by local research team at next clinic visit before patient is seen in clinic, then uploaded to clinical study database, if required*

 # socio-demographic details and visual acuity in better-seeing eye are to be collected for <u>all patients</u> who are approached for the main study <u>including those who decline</u> to participate in home monitoring (See sections 5.2.6 and 5.9.1)

$ *follow-up may be approximately every 1-3 months (frequency is as per discretion of local healthcare team). CRF data is to be collected for <u>every follow-up appointment</u>*

Data will be collected in secondary care (HES clinics) and in participants' homes.

Data will be collected in secondary care in a conventional manner, on paper case record forms (CRFs), which will then be transcribed into the study database. Alternatively, data may be directly transcribed into the study database from hospital records.

Data from the paper based home monitoring test (KeepSight Journal) will be sent by participants directly to CTEU, Bristol using pre-paid envelopes.

Data from the app based home monitoring tests (MultiBit test and MyVisionTrack®) will be captured automatically over the internet, by participant's home wireless internet or mobile broadband 'router' (e.g. MY WIFI device). This device will provide a local wi-fi facility to which the iPod testing device can connect. After a test has been completed, the app will submit the data automatically via a web service to study coordinating centre, where the data will be integrated in the study database. The data file will include the date and time of testing and the participant's study number but no other identifiable information.

In the event that automatic data collection cannot be implemented for a participant for a period of time (e.g. interruption in the mobile broadband service which cannot be repaired remotely), data will be downloaded from the iPod testing device by site staff at the next clinic visit and submitted using the same process through the site's internet connection. Data must be downloaded before the patient is seen in clinic for assessment. This method of data collection will also be used for participants who do not have reception for the mobile broadband router at home.

Automatic transmission of data has the added advantage of allowing the central coordinating team to monitor adherence to the weekly testing schedule. With participants' consent, these data will allow us to send SMS text messages to participants (either to a mobile phone or to the iPod device) that are customised, e.g. "well done for doing the tests weekly" or polite reminders if data have not been received "we have not received home monitoring data from you for 2 weeks; please ring XXXXX XXXXXX if you are experiencing difficulty."

The study manual will include instructions on data collection.

5.9.3 Instruction to collect data for both eyes

Data will be collected for both eyes of a participant throughout the study, this is customary practice at out-patient monitoring visits. The standard instructions for the index home monitoring tests direct patients to test both eyes, one at a time.

If a participant does not have useful vision in their fellow eye (defined as Snellen score of 6/60, LogMar 1.0 or 33 letters), data may be collected for one eye only.

5.10 Source data: Objectives A, C & D

The primary source data for this part of the study will include: Raw data extracted from MyVisionTrack® and MultiBit test apps, Keep Sight Journals, Electronic Health Records at HES clinics, patient notes, retinal images.

5.11 Planned recruitment rate: Objectives A, C & D

Projected timetable: Recruitment is expected to last 18 months. Assuming that each centre has >500 patients being actively monitored (at varying times since first treatment), that 60% will be eligible and >25% of eligible patients will consent, we estimate that sites will each recruit ~80 participants in 18 months.

Approximately equal recruitment is planned into each stratum (see section 5.4 for details). It is possible that one stratum may close to recruitment early (before the end of the study) if sufficient numbers of participants are recruited ahead of time. Recruitment data will be reviewed and monitored by the Study Management Group (SMG, see section 9.1) during recruitment.

Based on information from the nAMD clinics at the Belfast Health and Social Care Trust, we have assumed that each site will have a "stock" of ≥ 500 patients being actively monitored for nAMD activity (at varying times since first treatment), giving rise to a pool of about 2,700 patients from which we can recruit. Patients who are being monitored and those who are newly diagnosed can be recruited at any time, simply entering the appropriate stratum when they are recruited. New patients will accrue to the 'stock' and a 'stock' patient eligible for the 6-17 month stratum when recruitment at a site starts could be recruited to the 18-29 month stratum at the time of actual recruitment. Therefore, a potential participant is unlikely to be 'missed' (only becoming ineligible when the time since first treatment exceeds 41 months).

5.12 Discontinuation/withdrawal of participants: Objectives A, C & D

Each participant has the right to discontinue their part in the study at any time. In addition, the investigator may withdraw a participant at any time. It is unlikely for this study that there would be any reason for the investigator to withdraw the participant from the study.

All discontinuations and withdrawals will be documented. If a participant wishes to discontinue or withdraw, data collected up until that point will be included in the analyses, unless the participant expresses a wish for their data to not be used. For participants who discontinue or withdraw within 12 months of consent, the local study team should ensure that the equipment (iPod touch and mobile broadband router) is returned to the local study team (see section 5.8.3).

Adherence rates will be reported in the results including the number of participants that have been withdrawn, lost to follow-up or died.

The study manual will include instructions on procedures required at discontinuation or withdrawal.

5.13 Discharge from routine hospital follow up

It is possible that patients will be discharged from routine hospital follow-up during the study. The study manual will include instruction on data collection and procedure required at discharge.

5.14 Frequency and duration of follow up: Objectives A, C & D

Participants will be followed for a minimum of 12 months from consent, or until the end of study, whichever occurs soonest.

Participants being followed-up for 12 months will have, on average, 6 clinic visits at which home monitoring and reference test results can be compared.

5.15 Likely rate of loss to follow-up: Objectives A, C & D

We have allowed for 5% attrition (see section 5.6). Loss to follow-up and patient adherence to data collection will be monitored by the Study Management Group (SMG).

5.16 Expenses: Objectives A, C & D

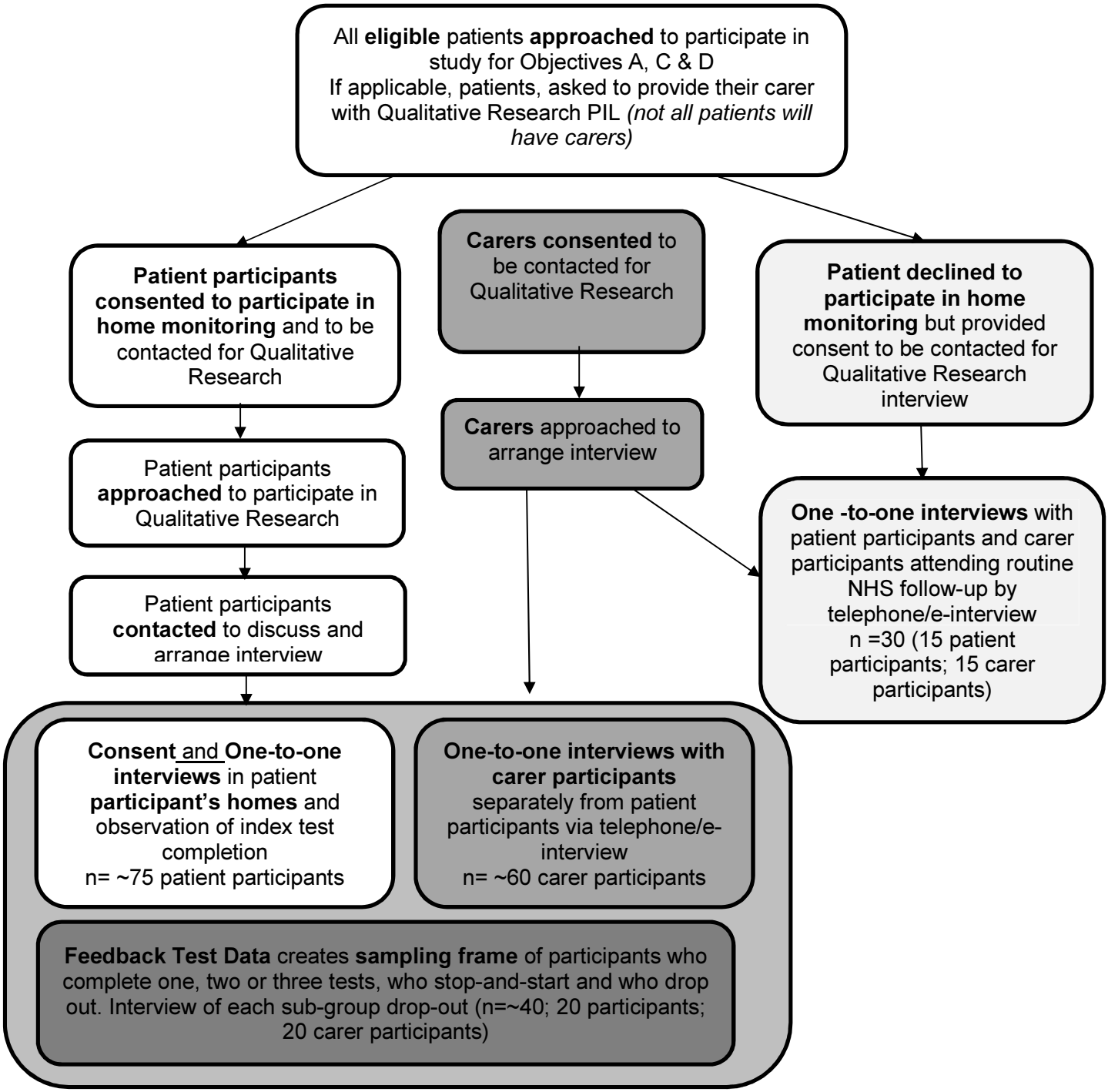
Participation in the study does not require any additional hospital, GP or any other health professional visits beyond standard of care. All equipment required to complete home monitoring tests will be provided to participants. It is not anticipated that participants will generate any expenses for this study.

Participant travel expenses will not be reimbursed for hospital visits as these would be expected to occur as part of routine follow up care.

6. Plan of Investigation: Objective B (Integrated Qualitative Research)

6.1 Study schema: Objective B

Multi-centre (3 select sites), non-interventional qualitative study



6.2 Study design: Objective B

The main aims of the integrated qualitative component of the study are to investigate (i) patient acceptability of using each test including which test is preferred most by patients; (ii) patient adherence at home to weekly monitoring; and (iii) the role of carers in patient acceptance. The qualitative analysis will contribute to an appraisal of the feasibility of the routine implementation of nAMD home monitoring. We do not plan to undertake a formal technical usability study (as the tests have been used already in similar contexts including by some members of this research team) though we will gather qualitative data about the factors that inhibit and facilitate the successful implementation of the tests. The qualitative component of the study will be informed by insights from relevant research regarding factors that influence the acceptance by older people of new telehealth/technology aids (31) as well as key theoretical models such as the technology acceptance model and its variants (32) and the theory of reasoned action (33). The conduct and content of data collection will be guided by these theoretical and empirical insights whilst affording ample opportunities and scope to elicit and capture in a bottom-up way the views and experiences of patients and carers, respectively, as they engage or assist to varying degrees with the three monitoring tests/methods.

In brief, we will conduct interviews with various groupings across three of the five hospital sites spanning London, Belfast and Southampton, and covering home-based patient interviews including interviews with patients who do not have a carer. We will conduct one-to-one interviews with patients in their homes including observing patients perform the tests in order to gain an in-situ understanding of the tasks faced by patients and carers. We will interview carers and other relevant groupings using telephone or e-interviews (see below). The conduct of the interviews will be person-centred in terms of capturing difficulties, concerns, fears, benefits and so on, about the proposed monitoring tests. The use of interviews will enable us to acquire a research-informed understanding of the acceptability of the monitoring tests from the perspective of patients and the role of carers in home monitoring. We will also gain a better understanding about the particular factors that influence successful implementation for specific patient subgroups such as patients without carers and patients who are reluctant, initially, to change to home monitoring (34).

We will observe test completion and conduct one-to-one interviews during home visits (n=~75 across 3 sites). Carers will be interviewed separately via telephone or e-interview mode (n=~60). Transcripts will be analysed using established qualitative research methods.

6.3 Study setting: Objective B

Study interviews will be conducted with various groupings across three participating NHS hospital sites.

6.4 Study sample: Objective B

The sample for objective B will dovetail with, or draw upon, the sampling approach used for objectives A, C and D.

In brief, we will use maximum-variation and purposive sampling in order to capture the range of patient- and related-factors that may be potentially relevant to assessing acceptability (e.g. age, gender, socio-economic status and eye health history) and the role of carers. Patients will be

asked to 'nominate' a carer or person who offers personal support to them. Overall, the sample will comprise the following subgroups.

1. We will observe test completion and conduct one-to-one interviews with patients during home visits at three sites (London, Belfast and Southampton; n=~25 x 3 sites: ~75) in order to gain an in-depth understanding of the tasks faced by patients and carers. We will observe and note the physical and social context of each home environment including the presence and interaction of a carer.

2. Approximately up to five of the 25 patient interviews at each site will be with patients who state that they do *not* have a carer in order to make relevant analytic comparisons and illuminate further the role of carers in home monitoring.

3. In addition to completing field notes of observations, meetings and discussions with carers during the home visit, family carers or friend-carers of patient interviewees will be interviewed separately from patients via telephone or e-interview mode (n=~60 carer interviews).

4. Feedback test data will be used to create a sampling frame of patients who complete one, two or three tests, who stop-and-start and who drop out. Up to ~20 patients and ~20 carers (n=~40 interviewees in total) from these subgroups will be invited to participate in phone or e-interviews.

5. We will conduct telephone or e-interviews with patients who decline the invitation to participate in trying tests at all and prefer to attend the hospital clinic for review (~5 patients and 5 carers per site x 3: n=~15 patients; n=~15 carers).

Patients and carers who consent to participate will be approached directly by the qualitative research team running this part of the study (see section 6.8.1 for further information).

6.4.1 Patient participant eligibility criteria

Patient participant eligibility does not need to be assessed separately for the integrated qualitative component of the study. Any patient who is eligible to participate in home monitoring testing (see section 5.4 for criteria) is eligible to participate in the qualitative component.

6.4.2 Carer participant eligibility criteria

Inclusion Criterion
A carer participant may take part in the integrated qualitative component of the study if ALL of the following apply:

1. They have been nominated as a person who provides personal support by a patient who is eligible to participate in MONARCH
2. 18 years of age or older

Exclusion Criteria
A carer participant may not take part in the integrated qualitative component of the study if ANY of the following apply:

1. Unable to understand English
2. Individuals who are paid to provide care services

6.5 Primary and Secondary outcomes: Objective B

Patient acceptability of home monitoring is the primary outcome of study objective B and it will be assessed via interviews and the qualitative analysis of interview transcript data.

6.6 Justification of target sample size: Objective B

Sample size will be guided via the procedures of maximum-variation sampling and data saturation – indicative sample sizes are specified in section 6.4.

6.7 Measures taken to avoid bias: Objective B

In so far as it is possible and acceptable to refer to qualitative research in terms such as bias and its avoidance, we will follow the procedures listed in the 'consolidated criteria for reporting qualitative research' (COREQ) including respondent validation, recording transparency and team discussion of data and its coding and analysis.

6.8 Study Methods: Objective B

6.8.1 Patient participant identification and consent

All eligible patients approached to participate in the study will be contacted, or seen in clinic by an appropriate member of the local research team for their decision on whether or not they would like to participate in home monitoring testing. At the same time, patients will be asked to confirm whether they agree for a member of the qualitative research team to contact them with further information on the qualitative component of the study. Each patient will complete a consent form to confirm their decisions.

Patients may consent to take part in home monitoring testing without consenting to participate in the qualitative component of the study. Patients can consent to the qualitative component without consenting to participation in home monitoring.

Patients will also be asked whether or not they have a carer. If they do have a carer a member of the local research team will ask the patient to pass an invitation letter and an information sheet (approved by the REC) describing the study to their carer.

All patients approached will have a study number which will be the primary way in which the patient participant will be identified and will be used in all correspondence.

A member of the qualitative research team will post an invitation letter, PIL and consent form to patient participants who consented to be contacted about the qualitative study. The letter and PIL will be followed-up with a phone call from the qualitative research fellow who will answer any remaining queries and then enquire whether or not the patient would like to participate in the qualitative study.

For patients participating in home monitoring:
The qualitative research fellow will arrange a home-visit at a convenient time for patients who agree to take part and written consent will be obtained at the start of the visit. With patient participant consent the qualitative research fellow will observe completion of the "index" tests, the home environment and will conduct a one-to-one interview. The home visit for patient

participants taking part in home monitoring is expected to last up to 60 minutes. Discussions with carers may also be held by the researcher during home-visits, if appropriate.

For patient participants not taking part in home monitoring:
The follow-up phone call after receipt of the PIL and invitation letter will be used to request patient participants to return a signed consent form and arrange a time to conduct a telephone or e-interview at a time convenient for the patient. This interview is expected to last up to 20 minutes.

6.8.2 Carer participant identification and consent

Carer participants will be given an invitation letter, an information sheet (approved by the REC) and a pre-paid envelope by the patient they are supporting on behalf of the study team. The information sheet for the carer will contain an invitation to be contacted by the qualitative study team. If carers wish to be contacted they will be asked to complete the written consent to further contact form providing their contact details and return this to the study coordination centre at CTEU, Bristol in the pre-paid envelope provided.

The qualitative research fellow will then telephone carers to answer any remaining queries and then enquire whether or not the carer would like to participate. The follow-up phone call will also be used to request carer participants to return a signed consent form and arrange a time to conduct a telephone or e-interview at a time convenient for the carer participant. This interview is expected to last up to 20 minutes.

6.8.3 Subgroup patient and carer participant identification and consent

The qualitative research fellow will design a sampling frame “feedback loop” to identify participants who complete one, two or three tests, who stop-and-start and who drop out. The qualitative research fellow will contact suitable participants and their carers from each of these sub-groups who have provided consent to be contacted by the qualitative team.

The qualitative research fellow will post an information sheet (approved by the REC) to carers and participants of the subgroupings described above who consented to be contacted about the qualitative study. The information sheets will be followed up with a phone call from the qualitative research fellow who will answer any remaining queries and then enquire whether or not they would like to participate. The follow-up phone call will also be used to request patient and carer participants to return a signed consent form and arrange a time to conduct a telephone or e-interview at a time convenient for the patient or carer participant. These interviews are expected to last up to 20 minutes.

6.8.4 GP letters for qualitative component of study

GP letters will not be sent for the qualitative component of the study.

6.9 Data collection (Interviews): Objective B

Data collection will be conducted according to usual procedures for this kind of investigative approach (35, 36). The procedures that will be required to conduct sensitive and responsive data collection with each subgroup will be piloted at the Belfast site, initially, and then discussed with the research team members and service colleagues at other sites and refined accordingly and on an iterative basis. Data collection will comprise semi-structured, approximately one hour face-to-face home interviews with participants and patients along with observation-based notes of test completion (37); telephone (38, 39) or e-interviews (40) of approximately similar structure and content will be conducted with carers and other participant, patient and carer groups as noted in the schema for objective B (see section 6.1).

The interview guides will be developed based on the collective experience of the research team and informed by relevant published and theoretical studies regarding the social and psychological determinants of the acceptance of new technological monitoring aids.

Interviews will be audio-recorded, transcribed verbatim and analysed thematically (41) . Results of the experience and analysis from ongoing interviews will inform and refine subsequent interviews and the final analysis regarding patient acceptability and factors that impact on acceptance of the tests and the role of carers in home monitoring from the perspective of patients as well as their relatives. Overall, interview data will enable a fine grain analysis pertinent to patients developing an acceptance of homebased monitoring tests.

Data collected will include audio recordings, interview transcripts and field notes. Each audio recording will have a unique ID number; and reference to any name on a transcript will the anonymised and replaced with the participant's unique study number. Observations of test completion will be recorded by the qualitative research fellow on a form/grid that will be designed specifically for the study and refined iteratively (if required) following the first few interviews. Every form will contain the unique study number of a participant and will not contain personal identifiers. Linked anonymised interview data and field notes will be stored, managed and analysed using standard qualitative software such as NVivo on a password protected PC in a combination lock-secure office in the Centre for Public Health, Queen's University Belfast.

6.10 Source data: Objective B

The source data for the interview transcripts will be the audio recordings.

6.11 Planned recruitment rate: Objective B

Recruitment will mirror as closely as possible the recruitment of patients in the main study.

6.12 Discontinuation/withdrawal of participants: Objective B

Participants may withdraw from the qualitative component of the study at any time by informing the qualitative research fellow directly or indirectly via their informal carer or professional care staff; and current and planned data collection will stop immediately. Data collected up to the point of withdrawal will be included in qualitative analyses. A withdrawal note will be completed by the qualitative research fellow and entered onto the NVivo software. The study coordination centre CTEU Bristol will also be informed.

6.13 Frequency and duration of follow up: Objective B

The follow-up of patient is not a focus of the qualitative study.

6.14 Likely rate of loss to follow-up: Objective B

Patients who complete one, two or three tests, who stop-and-start and who drop out will be included in the qualitative interview study. Up to ~20 patient participants and ~20 carer participants (n=~40 interviewees in total) from these subgroups will be invited to participate in phone or e-interviews.

6.15 Expenses: Objective B

It is not anticipated that participants will generate any expenses for this part of the study.

7. Definition of end of study

The study will end for a participant when the follow-up period is completed for the whole study or they discontinue with the study.

The end of the study as a whole will be after all data has been collected, all data queries have been resolved, the database locked and the analysis completed.

8. Statistical analyses

8.1 Plan of analysis: Objectives A, C & D

8.1.1 Objective A

The study will be analysed and reported in line with the reporting guidelines for studies of diagnostic accuracy (42) and will follow a statistical analysis plan that will be written in advance of the analyses being carried out. We are unable to prespecify the analyses in as much detail as would usually be expected because of the early stage of evaluation of the index tests. The following are some examples of the constraints affecting our ability to pre-specify the study analyses completely:

a) Although preliminary data have to some extent indicated that eyes with active lesions have poorer scores than eyes with inactive lesions, these data cannot be used to pre-specify optimal thresholds for classification of study eyes on the basis of the results of index tests.
b) Preliminary data for index tests have been collected in the context of a cross-sectional design, i.e. the association between index test results and reference classification being explored on a one-to-one basis. However, in the study, we expect the index tests to be scored on multiple occasions between one hospital review visit and the next (varying in number according the length of the interval). We do not currently have any information to guide the choice of optimal parameters to characterise test performance in this situation (e.g. worst index test score, mean/median index test score, most recent index test score, variability of index test score).
c) It is possible that better performance of home monitoring can be achieved by combining information for multiple index tests (since the underlying rationale for the index tests varies).

As for (b), we do not currently have any information to guide how the results of multiple tests might be combined optimally to maximise the performance of home monitoring overall.

d) It is possible that better performance of home monitoring can also be achieved by combining information across eyes, e.g. taking into account changes in the difference in performance between the participant's two eyes over time. As for (b), we do not currently have any information to guide how the results of tests in the two eyes might be combined optimally to maximise the performance of index tests.

Therefore, we propose exploratory analyses to specify how best to maximise performance (both for index tests and combined home monitoring data), inspecting receiver operator characteristic (ROC) curves that characterise the performance of different analytic choices to address the above constraints. In order to minimise bias, we will pre-specify the method of choosing test thresholds.

Diagnostic accuracy, that is the sensitivity, specificity, positive and negative predictive values of each test, will be reported with 95% confidence intervals. The overall performance of the tests will be quantified by the area under the ROC curve (AUROC) and the AUROCs for the tests will be compared to determine if one or more tests is superior to one or more of the others. Analyses will take account of the structure within the data (see (b) above), i.e. the nesting of visits (and eyes) within patients.

The number of home monitoring assessments between each clinic visit will vary by visit and by participant due the timing of the hospital visits and how closely the participant adheres to the weekly monitoring schedule. We will create a summary measure for the home monitoring scores obtained between two hospital visits and will use weighting in the analysis to reflect the precision of the summary (i.e. according the number of scores contributing to the summary). The choice of appropriate summary will be decided in discussion with the clinicians on the team and by examining the profiles of participants scores blinded to any other information or test results.

Other analyses may be explored to investigate whether the performance of home monitoring overall can be improved by, for example, combining information: (a) from multiple index tests; (b) from adjacent home monitoring periods preceding a monitoring visit (to see if there is evidence that index tests provide 'advance warning' of nAMD becoming active); (c) information for the study eye and an unaffected fellow eye (to see if differences in scores between affected and unaffected eyes contribute to test accuracy).

8.1.2 Objective C

Logistic regression models will be fitted to explore inequalities in participation, ability to carry out the home monitoring tests and adherence to the weekly testing schedule. Specifically, the influence of age, sex, social economic status and visual acuity in the better-seeing eye at diagnosis on the outcomes of: consent to take part (among all patients approached); ability of a participant to complete a test, analysed separately for each home monitoring test (among all participants); and adherence to the study protocol (among all participants). The influence of these factors will be reported as odds ratios with 95% confidence intervals. As for objective A, analyses will take account of the structure within the data, i.e. the nesting of visits within participants where necessary.

8.1.3 Objective D

All analyses for objective D will be descriptive only. With a small number of fellow eyes converting to nAMD, estimates of the sensitivity will be less precise than for objective A. Nevertheless, we will explore how test accuracy for detecting conversion changes as a function of index test scores and report the test accuracy statistics as described for objective A for detecting conversion for each test, with 95% confidence intervals.

8.1.4 Frequency of analyses

For study objectives A, C and D, the primary analysis will take place when follow-up is complete for all recruited participants. No formal interim analysis is planned.

8.2 Plan of analysis: Objective B

8.2.1 Objective B

Interviews will be audio-recorded and transcribed for analysis and reporting. The research team will review results iteratively and data will be managed and analysed using NVivo software and content and thematic analytical strategies (41, 43). The focus of the analysis will be on, for example, the acceptability of the tests, the factors that facilitate or impede such acceptability, ease/difficulty of using each test and the perceived benefits as well as the role of carers and family members (44). The transcripts of individual interviews at each site will be analysed to produce an integrated and synthesised account and interpretation of the acceptance of the new tests. The qualitative researchers and wider research team will meet to discuss iteratively and early on the results of the analysis including the generation of codes and categories from the content of the transcripts (37). Overall, the rigour, transparency and sensitivity of the methodology (45) will be enhanced by following the consolidated criteria for reporting qualitative research (COREQ) such as respondent validation, reflexivity and discussion of analytical codes and categories (46).

8.2.2 Frequency of analyses

Data for objective B will be analysed iteratively during the study.

8.3 Subgroup analyses

There are no planned subgroup analyses. We will report the study findings descriptively by strata.

8.4 Economic issues

There are no planned economic analyses for this study.

9. Study management

9.1 Study Management Group

The study will be managed by a Study Management Group (SMG), which will meet either face-to-face or by teleconference, as required and approximately monthly. The SMG will be chaired by a Chief Investigator and will include all members of the named research team (see *Chief Investigators & Research Team Contact Details)*. Other members of the research team will be invited to join as required.

The SMG will be supported by the Clinical Trials and Evaluation Unit (CTEU) Bristol. The CTEU Bristol is an UK Clinical Research Collaboration registered Clinical Trials Unit. The CTEU Bristol will prepare all the study documentation and data collection forms, develop and maintain the study database, check data quality as the study progresses, monitor recruitment and carry out study analyses in collaboration with the clinical investigators associated with objectives A, C and D. Prof Donnelly and the post-doc appointed in Belfast will prepare all the study documentation, data collection forms and databases associated with objective B and will complete the analyses (qualitative study).

9.2 Day-to-day management

An appropriately qualified member of the local research team (e.g. a research nurse/optometrist) in each centre will be responsible for identifying potential study participants, seeking informed participant consent, collecting study data and ensuring the protocol is adhered to.

9.3 Monitoring of sites

9.3.1 Study Initiation

Before the study commences training session(s) will be organised by CTEU Bristol. These sessions will ensure that personnel involved fully understand the protocol, CRFs and the practical procedures for the study.

9.3.2 Site monitoring

CTEU Bristol will carry out central monitoring and audit of compliance of centres with the principles of Good Clinical Practice (GCP) and data collection procedures. As monitoring will be carried out centrally CTEU Bristol will not check CRFs against the data entered and source data, unless there are good reasons to visit the site to complete a monitoring visit (e.g. the central monitoring highlights a problem).

9.4 Study Steering Committee (SSC)

A Study Steering Committee (SSC) will be established to oversee the conduct of the study. The CI will nominate potential independent members for HTA to invite to join the SSC. The SSC will monitor study progress (from reports from the SMG and discussions with study representatives at SSC meetings).

The SSC will consist of an independent Chair and other independent members (likely to include a retinal specialist, a physician, a Patient & Public Involvement representative and an eye research network representative); other SSC members with observer status will be invited to represent the study team, the Sponsor and the funder.

9.5 Patient and Public Involvement

The patient and public involvement group will meet regularly to review / provide feedback on aspects of the study (e.g. participant documents).

10. Safety reporting

This study does not require participants to undergo any additional investigations. Therefore, it is not possible for clinical adverse events to be attributed to study specific procedures.

There are no safety reporting procedures to be followed for this study.

11. Ethical considerations

11.1 Review by an NHS Research Ethics Committee

Ethics review of the protocol for the study and other study related essential documents (e.g. PIL and consent form) will be carried out by a UK Research Ethics Committee (REC).

Any amendments to these documents, after a favourable opinion from the REC has been given, will be submitted to the REC for approval prior to implementation.

11.2 Risks and anticipated benefits

11.2.1 Potential benefits and harms to participants:

There should be no additional risk to patient participants when taking part in this study This is a non-interventional diagnostic test accuracy study that will not change the patients' standard care.

The main risk to the participants (including carer participants) is the risk of failure to protect personal data. Consent will be sought for collection and storage of personal data from participants and carers. Strict confidentiality will be maintained at all times.

The integral qualitative part of this study will gather data on the perceived benefits and drawbacks of home monitoring to meet Objective B.

11.2.2 Potential benefits to society:

Information gained from this study may help us to improve the future treatment of patients with nAMD, streamline the care pathway enabling a more efficient use of resources resulting in better use of resources.

11.3 Informing potential study participants of possible benefits and known risks

Information about possible benefits and risks of participation will be described in the PILs to be formulated with service user involvement and confirmed acceptable by review by an NHS research ethics committee.

11.4 Obtaining informed consent from participants

11.4.1 Objectives A, C & D

All participants will be required to give written informed consent. An appropriately qualified member of the local research team will be responsible for the consent process. This process, including the information about the study given to patients in advance of consent, is described above in section 5.8.25.8.1.

11.4.2 Objective B

All patient and carer participants taking part in the integral qualitative part of the study (Objective B) will be required to give consent in writing. The qualitative research fellow will be responsible for the consent process. This process, including the information about the study given to patients and carers in advance of recruitment, is described above in sections 6.8.1 and 6.8.2.

11.5 Co-enrolment

Co-enrolment with another interventional or observational study will be permitted; as long as this does not result in any changes to the routine clinical follow-up schedule of the patient.

12. Research governance

This study will be conducted in accordance with:

- Good Clinical Practice (GCP) guidelines
- Research Governance Framework for Health and Social Care

12.1 Sponsor approval

Any amendments to the study documents must be approved by the sponsor prior to submission to the REC.

12.2 NHS approval

Approval from the local NHS Trust is required prior to the start of the study.

Any amendments to the study documents approved the REC will be submitted to the Trust for information or approval as required.

12.3 Investigators' responsibilities

Investigators will be required to ensure that local research approvals have been obtained and that any contractual agreements required have been signed off by all parties before recruiting

any participant. Investigators will be required to ensure compliance to the protocol and study manual and with completion of the CRFs. Investigators will be required to allow access to study documentation or source data on request for monitoring visits and audits performed by the Sponsor or CTEU Bristol or any regulatory authorities.

Investigators will be required to read, acknowledge and inform their study team of any amendments to the study documents approved the REC that they receive and ensure that the changes are complied with.

12.4 Monitoring by sponsor

The study will be monitored and audited in accordance with the Sponsor's policy, which is consistent with the Research Governance Framework. All study related documents will be made available on request for monitoring and audit by the sponsor (or CTEU Bristol if they have been delegated to monitor), the relevant REC and for inspection by other licensing bodies.

12.5 Indemnity

This is a University sponsored research study. The sponsor (Queen's University Belfast) has a suite of indemnity policies in place to cover research conducted by staff and students.

The University of Bristol (of which the study coordination centre, CTEU is a part) holds professional negligence insurance to cover the legal liability of the University of Bristol as the employer of staff engaged in the research (CTEU staff) for harm to participants arising from the design of the research where the research protocol was designed by the University of Bristol.

12.6 Notification of no objection from Medicines and Healthcare Regulatory Authority (MHRA) devices

This study is considered a basic science study as it requires the use of software and apparatus for ***non-medical*** purposes only.

The software and apparatus to be used within this study are not classed medical devices for the purposes of this study as they are not being used for diagnosis, prevention, monitoring, treatment or alleviation of disease within this study. The data gathered during this study will not be used to support an application for CE marking for *any* of the software or apparatus used within the study.

Monitoring AMD disease status and determination of each participant's diagnosis and any required treatment will be carried out by the reviewing ophthalmologist based solely on clinical examinations carried out at a participant's routine NHS monitoring clinic visit. The reviewing ophthalmologist will be "blinded" to the results of the home monitoring index tests.

Therefore a notification of no objection from MHRA Devices is not required.

13. Data protection and participant confidentiality

13.1 Data protection

Data will be collected and retained in accordance with the UK Data Protection Act 1998.

13.2 Data handling, storage and sharing

13.2.1 Data handling: Objectives A, C & D

Data will be entered onto a purposed designed server database hosted on the NHS network. Access to the database will be via a secure password-protected web-interface (NHS clinical portal). The participants will be identified using their unique study number on the secure database.

Data will be entered promptly and data validation and cleaning will be carried out throughout the study. The study manual will cover database use, data validation and data cleaning. The study manual will be available and regularly maintained. Where electronic patient medical notes are used, local Trust policies will be followed.

Data from MultiBit test and mVT® will be captured by the software applications themselves and transmitted automatically (or following download) to the secure study database. Participants will be identified using minimal study identifiers only.

Data captured in the KeepSight Journals will be sent directly to CTEU Bristol and transcribed into the secure study database. Participants will be identified using minimal study identifiers only.

13.2.2 Data handling: Objective B

Audio-recordings and transcriptions, field notes and observations and results of thematic analyses will be stored a password protected PC in a combination lock-secure office in the Centre for Public Health, Queen's University Belfast. Participant's will be identified using minimal study identifiers only.

13.2.3 Data handling: Retinal Images

Retinal images will be upload in an anonymised form to CARF, Belfast.

13.2.4 Data storage

All study documentation will be retained in a secure location during the conduct of the study and for 5 years after the end of the study, when all patient identifiable paper records will be destroyed by confidential means. Where study related information is documented in the medical records, these records will be identified by a label bearing the name and duration of the study, or an equivalent electronic flag in an electronic health record. In compliance with the MRC Policy on Data Preservation, relevant 'meta'-data about the study and the full dataset, but without any participant identifiers other than the unique participant identifier, will be held indefinitely (University server). A secure electronic 'key' with a unique participant identifier, and key personal identifiers (e.g. name and date of birth) will also be held indefinitely, but in a

separate file and in a physically different location (NHS hospital server). These will be retained because of the potential for the raw data to be used subsequently for secondary research.

13.2.5 Data sharing

Data will not be made available for sharing until after publication of the main results of the study. Thereafter, anonymised individual patient data will be made available for secondary research, conditional on assurance from the secondary researcher that the proposed use of the data is compliant with the MRC Policy on Data Preservation and Sharing regarding scientific quality, ethical requirements and value for money. A minimum requirement with respect to scientific quality will be a publicly available pre-specified protocol describing the purpose, methods and analysis of the secondary research, e.g. a protocol for a Cochrane systematic review. The second file containing patient identifiers would be made available for record linkage or a similar purpose, subject to confirmation that the secondary research protocol has been approved by a UK REC or other similar, approved ethics review body.

14. Dissemination of findings

The findings will be disseminated by usual academic channels, i.e. presentation at international meetings, as well as by peer-reviewed publications and through patient organisations and newsletters to patients, where available.

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16. Department of Health Disclaimer

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the HTA programme, NIHR, NHS or the Department of Health.

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18. Amendments to protocol

Amendment number (i.e. REC number)	Previous version	Previous date	New version	New date	Brief summary of change	Date of ethical approval (or NA if non-substantial)