Home-monitoring for neovascular age-related macular degeneration in older adults within the UK: the MONARCH diagnostic accuracy study

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Scientific summary

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Scientific summary

Background

Neovascular age-related macular degeneration (nAMD) is the leading cause of blindness in older adults. Advanced nAMD causes substantial retinal damage, loss of central vision and reduced quality of life.

Several intravitreal drugs [anti-vascular endothelial growth factor (VEGF) that inhibits neovascularisation, i.e. anti-VEGF agents] are used to treat nAMD. Some eyes become fluid free after initial treatment over 3–6 months but relapse is common, and most patients require retreatment at some stage, with the disease typically becoming inactive for a period and then becoming active again. Hence, patients in the maintenance phase with inactive disease still need to be monitored regularly in hospital outpatient clinics for disease reactivation, when treatment is restarted. Monitoring places a substantial burden on hospital resources, patients and their family or carers. This burden would be substantially reduced if patients with inactive disease could self-monitor at home and attend hospital only when the disease reactivates.

Aim

To evaluate 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 (HES).

Objectives

1. Estimate the accuracy of three home-monitoring tests to detect active nAMD.
2. Determine the acceptability of home monitoring to patients and carers and barriers to adhering to regular testing.
3. Describe inequalities in recruitment, participants' ability to self-test and adherence to testing during follow-up.
4. Estimate the accuracy of home monitoring to detect conversion to nAMD in fellow eyes of patients with unilateral nAMD.
5. Describe the challenges experienced when implementing the tests.

Study design

Diagnostic test accuracy cohort study.

Setting

Participants recruited from six UK HES macular clinics (Belfast, Liverpool, Moorfields, James Paget, Southampton, Gloucester).

Methods

Participants

We invited patients to take part who had at least one study eye being monitored by HES for nAMD, were first treated > 6 and < 42 months earlier. We tried to recruit equal numbers by time since starting treatment in the first-treated study eye (6–17 months; 18–29 months; 30–41 months) to ensure test

performance was estimated across this range of duration of nAMD. Patients were followed for at least 6 months.

Reference standard

The reference standard was the reviewing ophthalmologist's decision about the activity status of a study eye at a HES monitoring visit, recorded as active, inactive or uncertain. There were no additional hospital visits for the study. Such decisions are usually based on clinical examination and the results of hospital-based retinal imaging investigations, for example, colour fundus photographs and ocular coherence tomograms (OCTs). The reference standard grouped uncertain with inactive judgements for analyses.

Index tests

Three home-monitoring ('index') tests were evaluated, spanning low to moderate cost and complexity. These were:

1. KeepSight Journal (KSJ): a paper-based booklet of near-vision tests presented as word puzzles developed in the United States and adapted by the study team for use in the study.
2. MyVisionTrack® (mVT®): electronic vision test, intended to be viewed on a tablet device.
3. MultiBit (MBT): electronic vision test, intended to be viewed on a tablet device.

Specific thresholds indicating a significant clinical change were not provided for any of index tests in advance by their developers.

Outcomes

The primary outcome was classification of a study eye at a monitoring visit as having active or inactive disease (active, inactive, uncertain), that is, the reviewing ophthalmologist's decision.

A secondary outcome (new reference standard) for Objective A was a change from inactive to active status from one management visit to the next. This was considered better to represent how home monitoring might be implemented.

For Objective C, outcomes investigated were willingness in principle to participate; ability to carry out index tests; adherence to weekly testing.

For Objective D, the outcome was conversion of a fellow eye to active nAMD as judged by an ophthalmologist, that is, same reference standard.

For Objective E, the following outcomes were described as measures of the technical and logistical challenges identified during the study:

Frequency and reason for incoming calls made to the helpline and outgoing calls made to participants.
Frequency and duration of events leading to the digital tests being unavailable for testing.

Other technical and logistical challenges.

Objective B study recruitment and data collection

Recruitment to the qualitative component began 3 months after the monitoring for neovascular age-related macular degeneration reactivation at home (MONARCH) study began recruiting. During the consent process for participation in the study, patients could consent to further contact from the qualitative research team to discuss participation in the qualitative study. Maximum variation sampling ensured a range of perspectives were captured in relation to: age (young-old 50–69 years and older-old > 70 years), gender, one or both eyes with nAMD, time since first treatment (defined as above) and adherence to home monitoring (test data from the two electronic tests were used to categorise

participants into 'regular' testers and 'irregular' testers). Patients who declined to participate in MONARCH but provided consent to be contacted about the qualitative study, informal 'carers', supporters or significant others in the lives of patients and healthcare professionals who interacted with participants at study sites visits were also approached to gather their perspectives about the acceptability of home monitoring.

Statistical analysis

Objective A: The test accuracy of index tests was estimated by fitting a logistic regression model to predict the reference standard from summary test scores for the interval between monitoring visits, adjusting for participants' baseline data. Accuracy was estimated for the primary outcome using all index test data, data only for the 4 weeks preceding the monitoring visit, the reference standard based on reading centre decisions made from OCT images and for the secondary outcome.

Test scores were summarised as: means (MBT and mVT); median (KSJ reported near visual acuity (VA), ordinal six-point scale); proportions (KSJ reported VA, Amsler grid and household object appearance reported worse than baseline vs. same or better). All four scores were fitted in the KSJ model and a single area under the receiving operator curve (AUROC) was estimated. Separate models were fitted for each test for the primary outcome, the two sensitivity analyses and the secondary outcome. Model performance was quantified by the odds ratio (OR) for the index test summary score(s) and the estimate of the AUROC and their respective confidence intervals (CIs). AUROCs were based on predicted probabilities calculated using only the fixed effects in the models. Sensitivity, specificity, positive and negative predictive values and 95% CIs were calculated using cut-off thresholds corresponding to Youden's index for each model, which minimises overall misclassifications. Average test scores above and below the thresholds were also calculated. Analyses took account of the structure within the data, that is, the nesting of visits and eyes within patients.

Objective B: All interviews were audio-recorded and transcribed. A directed content analysis approach based on deductive and inductive coding was used. NVivo version 12 was used to manage data and facilitate the analysis process, which, in summary, included the following stages: (1) independent transcription, (2) data familiarisation, (3) independent coding, (4) development of an analytical framework, (5) indexing, (6) charting and (7) interpreting data.

Objective C: Willingness in principle to participate was defined as an approached eligible patient agreeing to attend a research visit for training. Ability to perform an index test was defined as the proportion of monitoring visits for which some valid index test data were available. Adherence was defined as the proportion of weeks between monitoring visits for which some valid data for an index test were available. The ability and adherence models were performed for each test separately at the level of the patient.

Regression models estimated associations of age, sex, Index of Multiple Deprivation (IMD), stratum of time since first diagnosis and baseline visual acuity at diagnosis on the outcomes of willingness to participate, ability to perform tests and adherence to weekly testing; models for the latter two outcomes were fitted for each index test. Associations were reported with 95% CIs. Analyses of adherence and ability took account of nesting of visits within participants.

Objective D: The test accuracy of the index tests for the reference standard of an ophthalmologist's classification of a fellow eye as having active disease at a monitoring visit, that is, conversion to active nAMD, was estimated by the same methods as described for Objective A. Two sensitivity analyses were carried out: (1) the same reference standard but using test data only for the 4 weeks preceding the management visit and (2) the alternative reference standard of classification of a fellow eye having active disease based on reading centre grading of OCTs carried out during the monitoring visits.

Objective E: This objective used descriptive summary descriptive statistics only.

Results

The study recruited 297 patients (consented participants) between 21 August 2018 and 31 March 2020. Half of recruited participants were first treated for nAMD 6–17 months before consenting, 28% 18–29 months before consenting and 22% 30–41 months before consenting. At the end of the study, data for at least one monitoring visit after starting to use the index monitoring tests were available for 357 study eyes in 297 patients. Data were available for at least one complete monitoring visit after starting to use the index monitoring tests for 317 study eyes of 261 patients. More participants were women (58.6%). Participants' mean age was 74.9 (6.6) years [standard deviation (SD)]. The mean visual acuity of study eyes (better seeing eyes if participants had two study eyes) was 0.2 (0.2) Logarithm of the minimum angle of resolution (LogMAR) (SD).

Objective A: Median testing frequency was three times per month. In the primary analysis, estimated AUROCs were < 0.6 for all index tests, and only KSJ summary score was significantly associated with the lesion activity (OR = 3.48, 95% CI 1.09 to 11.13; $p = 0.036$). Estimated AUROCs were < 0.6 for all tests in both sensitivity analyses and for the secondary outcome of change from inactive to active status between adjacent management visits.

Objective B: Two overarching meta-themes emerged from the qualitative studies related to acceptance or non-acceptance of home monitoring. Meta-theme 1 encompassed four main themes: (1) the role of home monitoring; (2) suitability of procedures and instruments; (3) experience of home monitoring; and (4) feasibility of home monitoring in usual practice. Meta-theme 2 consisted of one main theme covering key inhibitors to acceptability. The main factors influencing acceptability included a participant's understanding about the purpose of home monitoring and their experience of using it. While home monitoring was generally seen as a relatively straightforward exercise to undertake and non-burdensome, training and ongoing support were regarded as essential to its success. Home monitoring was acceptable to patients and its potential to reduce clinic visits during non-active treatment phases was recognised.

Objective C: A minority of patients who were approached were willing in principle to participate. Increasing age and worse deprivation index for home address were associated with being unwilling in principle to participate ($\chi^2 = 50.5$ and 24.3, respectively, both $p \leq 0.001$). Recruiting site was also associated with willingness in principle to participate, believed to be due to sites adopting different strategies for approaching and recruiting patients. Increasing age and worse deprivation were not consistently associated with either being able to self-monitor with the index tests or adherence to weekly testing (χ^2 for all tests < 5, $p > 0.08$ for ability and adherence, except for worse IMD being associated with better adherence for the KSJ, $\chi^2 = 12.15$, $p = 0.016$). Recruiting site was also associated with being able to test and adhering to weekly testing.

Objective D: There were 132 fellow eyes with data from 544 monitoring visits, 17 of which (12.9%) had nAMD recorded at one or more management visits over about 100 participant-years. This rate of conversion was higher than expected based on epidemiological studies of conversion rates in unaffected fellow eyes, potentially due to study eyes having had nAMD longer ago. Some predictors could not be fitted in models and estimates of associations were imprecise. The no-test model predicted conversion better than for Objective A (AUROC = 0.73) and electronic tests did not increase this (AUROCs = 0.73 and 0.76 for MBT and mVT, respectively). The estimated AUROC for the KSJ was 0.85, due to a strong positive association of the household object summary score with conversion (OR 15.3, $p = 0.036$).

Objective E: Despite two-thirds of the population having previously used a smartphone, there were still a variety of challenges experienced with the electronic devices while testing at home that contributed to both reduced adherence and ultimately withdrawals from the study.

Strengths and limitations

The study had several strengths. Estimates of the diagnostic test accuracy of index tests were at low risk of bias: the study population was appropriate for the intended use of the tests, and summary test scores were not available to ophthalmologists providing the reference standard, which was judged after the index test data were collected.

Limitations

A smaller-than-planned sample size (less than half the target number of monitoring visits); nonetheless, 95% CIs for AUROCs were narrow (± 0.04) and estimates were able to rule out tests providing adequate accuracy for diagnosing active nAMD to enable patients to be monitored without hospital review.

Tests were sometimes not available for technical reasons that were beyond the control of the research team.

The study had no control over monitoring visits and participants are likely to have reported their subjective visual experience to their consultants, which might have influenced the reference standard.

We could not define test thresholds a priori, and instead estimated AUROCs. We did not compare AUROCs for tests due to their poor accuracy.

The ways in which patients were approached and screened varied across sites, generating a site effect in analyses of potential inequalities; variations may have reflected the pre-conceptions of research staff regarding the capabilities of patients to use the electronic tests.

Conclusions

Based on the detection of lesion activity assessed by clinicians in the clinic, we have shown that none of the index tests provides acceptable test accuracy for home monitoring in this context. Associations of increasing age and deprivation index for home address with unwillingness in principle to participate despite provision of hardware highlight the potential for inequality with interventions of the kind evaluated. While a proportion of nAMD patients are willing and interested in the potential for home monitoring, substantial practical and technological issues are encountered in the implementation of such, requiring a significant support infrastructure, including a study helpline.

Future work

Future research should focus on the methodological challenge of efficiently evaluating mobile health technologies which deal with constantly emerging new technology. The clear evidence of inequalities in participation and retention should prompt future research on ways to encourage participant and adoption of mobile health technologies by underserved populations. Focus should also be placed on methods to improve adherence and retention in longitudinal studies involving electronic testing, particularly around the nature of feedback to participants.

Trial registration

This trial is registered as ISRCTN79058224.

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