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The accuracy of home monitoring to detect disease activity during maintenance therapy for neovascular ARMD.

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Purpose: To report the reproducibility, sensitivity, specificity and predictive value of home monitoring for disease activity in neovascular age-related macular degeneration (ARMD).

Methods: Participants were trained to complete 3 separate home monitoring tasks, designed to identify subtle changes in visual function that may indicate increasing neovascular ARMD disease activity. These included measurement of near acuity and assessments of environmental distortion and overall visual function. The need for repeat intra-vitreal injection, as predicted by home monitoring, was compared to standard clinical assessment involving ETDRS distance acuity, slit lamp examination and spectral domain ocular coherence tomography.

Results: Although all participants were able to complete the home monitoring tasks, the reproducibility of each of the 3 tasks was modest. Cohen's kappa was 0.118 (p=0.54) for the comparison of the outcome of the home monitoring exercise with the gold standard of hospital assessment to determine disease activity. The sensitivity of the home monitoring exercise was 33.3% (95% CI 15.2-51.4) and the specificity was 77.8% (95% CI 61.8-93.8).

Conclusions: This study suggests that current tests of visual function, readily completed at home, cannot replace traditional clinic-based assessments for neovascular ARMD disease activity. Instead, such tests are likely to remain complementary to standard assessment in clinic.

Key words: Age-related macular degeneration, self-monitoring, sensitivity

Introduction: Age-related macular degeneration (ARMD) is the most common cause of certifiable visual impairment in England and Wales [1]. Until recently, first line therapy for neovascular ARMD has involved intra-vitreal injection of ranibizumab [2,3]. In the pivotal ANCHOR and MARINA trials, ranibizumab was given by intra-vitreal injection every 4 weeks over a two year period [2,3]. Since then other studies have investigated different approaches to treatment delivery [4,5]. Present UK practice for ranibizumab, now supported by the CATT and IVAN studies, involves a loading dose of fixed, monthly injections, followed by a maintenance phase involving regular monthly assessment with further injection as needed [6,7].

The need for regular assessment in the maintenance phase of intra-vitreal therapy is inconvenient for patients. This is particularly true for those patients with whom prior clinical experience of *pro re nata* therapy has identified that treatment every visit is not required. Furthermore many UK departments have inadequate capacity for the increasing number of assessment visits. This can delay the planned follow-up for all patients and adversely affect outcomes. The opportunity for large numbers of patients to monitor disease activity at home would be convenient for many and would help create additional capacity in hospital eye clinics. This pilot study was performed to collect data on the reproducibility, sensitivity and specificity of a novel, home monitoring programme to detect disease activity during the maintenance phase of ARMD treatment with ranibizumab.

Patients and Methods: Potential participants were recruited from the intra-vitreal injection clinics in the Leeds Teaching Hospitals NHS Trust. The project

was approved by the NRES Committee for Yorkshire & The Humber - Leeds central (12/YH/0195) and all applicable institutional and governmental regulations concerning the ethical use of human volunteers were followed during this research. Inclusion criteria were: age 60 years or over, neovascular ARMD treated with intra-vitreal ranibizumab for at least 6 months beyond the initial, loading phase of fixed injections, at least 1 injection during the prior 6 months of the maintenance phase of treatment, distance ETDRS letter score of at least 30 letters in the study eye at the start of the study. Exclusion criteria were significant hearing impairment likely to interfere with training and telephone communication and lack of informed consent.

Participants were trained by a hospital optometrist to perform three separate, home monitoring tasks, designed to identify subtle changes in visual function that may indicate neovascular ARMD disease activity. These three tasks involved the study eye alone and comprised: *i*, use of a double-sided LogMAR near acuity chart (Precision Vision, Illinois, USA) with current, near spectacle correction to record ETDRS letter score at 40cm, *ii*, careful observation of a familiar object in their home environment, such as a door frames or kitchen tiles, to look for new or increasing environmental distortion and *iii*, a general assessment of visual function, with an emphasis on the detection of new or increasing scotoma size, a change in the brightness or clarity of vision and ease of performing near visual tasks. For each task, the fellow eye was occluded. The results of the home monitoring exercises were recorded on data collection sheets, specific to the study. Participants were asked to perform the tasks at the same time of day, in the same location and

with the same lighting conditions. For the measurement of acuity, the two sides of the near acuity chart were marked with a colour symbol and the order in which the two sides were to be used was agreed in advance. Individual letters were read out to a friend or relative who marked all the letters read correctly on a scoring sheet. In the absence of a friend or relative, a research nurse completed the visual acuity scoring sheet over the telephone.

Following the training, participants were contacted by telephone and reminded to perform the home monitoring once on the day immediately before the next planned ARMD assessment visit and then three times, on consecutive days, before the second, planned ARMD assessment visit, a month later. At the time of the next, scheduled assessment visit after the training, the ability to perform the three tasks and to record the findings was reviewed and any problems addressed.

In order to evaluate the sensitivity and specificity of the home monitoring exercise, a comparison was made between the results of the final day of home monitoring and of the hospital assessment, performed the next day by an experienced, masked clinician and using a combination of distance ETDRS letter score, spectral domain OCT imaging and fundus examination. The following home monitoring outcomes were considered to indicate a need for repeat treatment: a decrease of more than 5 ETDRS letters, compared to the baseline or prior visit, in the study eye on near acuity testing, new or increasing environmental distortion in the home environment and new or increasing problems with general visual function. Statistical analysis comprised an evaluation of Fleiss' kappa and inter-class correlation for

reliability/reproducibility, Cohen's kappa for the agreement between the outcome of the home monitoring and hospital assessment and evaluation of sensitivity, specificity, negative and positive predictive value [8-10].

Results: Although 28 participants completed the home monitoring exercise, one lost his reading spectacles between the 2 home monitoring time points and so the results were considered to be invalid. The average age of the remaining 27 participants at the start of the exercise was 77 years (range 60-87) years. Other baseline characteristics are given in table 1. The median, distance, best corrected ETDRS letter score at 2m was 68 letters (range 39-85) at the start of the training period and median near acuity letter score, measured at 40cm and with current spectacle correction, was 48 letters (range 21-64).

Reproducibility for the detection of new or increasing distortion over the 3 days of consecutive assessment was modest (Kappa = 0.58, $P = 3.5 \times 10^{-7}$). The same applied to the general assessment of vision (Kappa = 0.45, $p = 7.2 \times 10^{-5}$). For the three consecutive near acuity letter score tests, the intra-class correlation was 0.95 (95% CI 0.91 – 0.98).

The outcomes of the home monitoring and standard clinical assessments are given in table 2. Cohen's kappa was 0.118 (p=0.54) for the comparison of the outcome of the home monitoring exercise with the gold standard of hospital assessment. The sensitivity of the home monitoring exercise was 33.3% (95% CI 15.2-51.4) and the specificity was 77.8% (95% CI 61.8-93.8). Negative predictive value was 70.0% (95% CI 52.4-87.6) and the positive predictive value was 42.9% (95% CI 23.9-61.9).

Discussion: This research was prompted by comments from two groups of patients: those who rarely require intra-vitreal injection with ranibizumab in the maintenance phase and who, as a consequence, find regular hospital monitoring to be inconvenient and unnecessary and those who require regular treatment but who feel that lack of follow-up capacity can result in their planned follow-up being delayed, with loss of the initial visual acuity gains. To reduce follow-up delays, this study investigated if patients could be taught to monitor their visual function at home and to detect the subtle changes in visual function that would suggest a need for repeat ranibizumab injection. Prior patient surveys in the Leeds intra-vitreal injection clinics have found that almost 70% of respondents would welcome the opportunity to monitor their visual function at home, if a reliable test were available. This view was supported by those attending a focus group study of members of a national charity, the Macular Society, all of whom were receiving regular intra-vitreal injections for ARMD.

For the 3 monitoring tests, reproducibility was greatest for the near acuity letter score, suggesting that most of the participants found it easy to use the double-sided, LogMAR near acuity chart. The chart has a 40cm string so that the chart is read at a fixed distance. Given the need to cover the fellow eye and to hold the chart and the string, accurate recording of the letter score required the help of a carer or friend at the time of testing, or the use of a research nurse to record the number of letters read correctly over the telephone. Reproducibility for the detection of distortion in the home environment and for the general assessment of vision was less good. Part of the difference may be attributable to the analysis method.

The 3 home monitoring tests were chosen to try to mimic the features used by clinicians in evaluating disease activity, namely a decrease in visual acuity, new or increasing sub-retinal fluid or oedema on OCT imaging and the presence of sub-retinal haemorrhage on slit-lamp examination. Although the traditional Amsler grid seems to have high sensitivity to detect new distortion, compliance with and the reliability to detect increasing distortion have been questioned. [11,12]. Detection of distortion in the home environment has however, been shown to be reliable. The general assessment of vision also focussed on the initial symptoms before the start of treatment or prior to re-treatment for disease activation. By combining these with an assessment of high contrast reading acuity, the study hoped to be able to use common patient symptoms as a guide to the need for repeat treatment.

Agreement between the outcome of the home monitoring exercise and the examination by a masked clinician was poor. The finding of higher specificity than sensitivity would suggest that participants in this study were more able to identify stable visual function than the subtle changes in visual function that were expected to be associated with renewed or increasing disease activity. In contrast, Sivaprasad found greater sensitivity compared to specificity in a prior study in which participants were asked to identify new or increasing environmental distortion or an overall decrease in visual function [12]. Participants in that study seemed better able to predict the presence of sub-retinal fluid or intra-retinal oedema on OCT imaging after further training to identify distortion in the home environment. Although the participants in this study also received both initial training and subsequent re-enforcement, we

were unable to reproduce the 87.5% sensitivity and 98.5% specificity reported by Sivaprasad [12]. The reasons for this are unclear but there may have been differences in the patient population, length of treatment or the training provided. Prior studies have identified that shape discrimination ability decreases with worse visual acuity, increasing age and more advanced ARMD [13,14]. However, an exploratory analysis of the agreement between sub-groups in this study failed to find a trend to suggest better agreement according to participant age, baseline near acuity letter score or a “dry” macula on OCT imaging at the prior examination.

The reasons for the poor agreement in this study between the subjective and objective measures of ARMD disease activity are also unclear. Visual acuity is only a measure of function across the central 1 degree of the retina and so may not detect anatomical changes elsewhere in the macula, present on either OCT imaging or slit lamp examination [15]. However, it was anticipated that disease activity away from the fovea would be identified through either the presence of environmental distortion or the general assessment of vision, particularly for near vision tasks. When used at the correct 30cm testing distance, the Amsler grid chart is believed to evaluate the central 20 degree visual field [15]. By combining near visual acuity with an assessment of environmental distortion and overall quality of vision, we had expected higher sensitivity and specificity for our home monitoring tasks. Quality of vision incorporates both contrast sensitivity and visual field and, like environmental distortion, was expected to be a better indicator of disease activity that high contrast acuity alone [16].

A variety of subjective tests have been proposed to help screen for neovascular ARMD [15-18]. However, few of the tests have been used successfully to monitor disease activity in those with established neovascular ARMD. The preferential hyperacuity perimeter (PHP, Carl Zeiss Meditec, Dublin, CA, USA) evaluates function in the central 14 degrees of the retina. PHP contour maps appear to show some correlation with resolution of intra- and sub-retinal fluid on OCT imaging after ranibizumab therapy [19]. In a small study involving 17 eyes, Querques also reported a sensitivity and specificity of 83% and 67% for the use of PHP alone in predicting the need for re-injection based on objective assessment by a clinician [20]. Although the study involved a clinic-based PHP system, a home-based version of the PHP system is now available (Foresee Home, Notal Vision, Tel Aviv, Israel). Furthermore, shape discrimination hyperacuity tests have also been developed for use on handheld devices and these are likely to be less expensive and therefore more widely available [13, 21]. Following a week to become familiar with the device and support during planned, monthly clinic visits, Kaiser reported that 93% of participants felt the device was easy to use and 83% would be willing to complete the test weekly [21]. The sensitivity and specificity of the handheld device when used in larger number of patients with ARMD are awaited.

Home monitoring for neovascular ARMD disease activity offers a number of potential advantages to patients, particularly for those being managed with *pro re nata* therapy. However, the results of this study suggest that while home monitoring may be acceptable to patients, it is not yet sufficiently sensitive to detect the subtle changes in visual function and anatomy that prompt repeat

treatment. This suggests that home monitoring for neovascular ARMD disease activity will remain complementary to traditional clinic assessment.

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Table 1: Baseline characteristics, distance visual acuity and number of prior treatments for the study and fellow eyes of participants.

		Baseline ETDRS letter score at 2m		Prior intra-vitreal injections	
Age	Sex	Study eye	Fellow eye	Study eye	Fellow eye
82	Male	56	35	7	8
81	Male	73	70	4	4
84	Female	84	73	5	26
79	Male	69	29	16	0
85	Female	53	55	11	1
76	Male	81	18	11	0
79	Female	65	45	4	13
83	Male	74	75	8	0
78	Male	70	84	10	0
83	Male	69	70	6	0
76	Male	78	6	6	0
74	Female	47	CF	12	0
83	Male	65	76	22	0
85	Female	50	83	6	0
79	Male	85	9	5	0
85	Female	75	15	4	0
76	Male	61	70	17	0
82	Female	41	CF	11	5
74	Male	40	3	25	0
72	Male	68	76	7	0
60	Female	57	84	10	0
68	Female	83	84	8	0
67	Female	58	37	16	0
76	Female	51	CF	14	0
87	Female	39	64	4	0
68	Female	70	80	7	0
67	Male	80	76	13	11

CF = Count fingers

Table 2: Comparison of the outcomes of the home monitoring and standard clinical assessments.

		Outcome of standard clinical assessment	
		Stable (No treatment indicated)	Active (Treatment indicated)
Outcome of home monitoring assessments	Stable (No treatment indicated)	14	6
	Active (Treatment indicated)	4	3