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Randomized Trial of a Home Monitoring System for Early Detection of Choroidal Neovascularization-HOme Monitoring of the Eye (HOME) Study

The AREDS2-HOME Study Research Group*

Abstract

Objective—To determine whether home monitoring with ForeseeHome device, using macular visual field testing with hyperacuity techniques and tele-monitoring, results in earlier detection of age-related macular degeneration associated choroidal neovascularization (CNV), reflected in better visual acuity, when compared with standard care. The main predictor of treatment benefit from anti-vascular endothelial growth factor (VEGF) agents is the visual acuity at the time of CNV treatment.

Design—Unmasked, controlled, randomized clinical trial.

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Participants—1970 participants, aged 53 to 90 years, at high risk of developing CNV were screened; 1520, mean age 72.5 years enrolled in the **HO**me **M**onitoring of the **E**ye (HOME) Study in 44 Age-Related Eye Disease Study2) clinical centers.

Interventions—1) Standard care arm: investigator-specific instructions were provided for self-monitoring vision at home followed by report of new symptoms to clinic. 2) Standard Care and Device arm: device provided with recommendation for daily testing. The device monitoring center received test results and reported changes to the clinical centers who contacted participants for examination.

Main Outcome Measures—The difference in best-corrected visual acuity scores between baseline and detection of CNV. The event was determined by investigators based on clinical exam, color fundus photographs, fluorescein angiography, and optical coherence tomography. Masked graders at central reading center evaluated the images using standardized protocols.

Results—763 participants were randomized to device monitoring and 757 to standard care, and followed for a mean of 1.4 years between July 2010-December 2013. At the pre-specified interim analysis, 82 participants progressed to CNV, 51 in the device arm and 31 in the standard care arm. The primary analysis achieved statistical significance with the participants in the device arm demonstrating a smaller decline in visual acuity with fewer letters lost from baseline to CNV detection (median (interquartile range [IQR]):−4 [−11.0, −1.0] letters) compared with standard care (median [IQR]:−9 [−14.0, −4.0] letters) (p=0.021), resulting in better visual acuity at CNV detection in the device arm. The Data and Safety Monitoring Committee recommended early study termination for efficacy.

Conclusions—Persons at high risk for developing CNV benefit from the home monitoring strategy for earlier detection of CNV development which increases the likelihood of better visual acuity results following intravitreal anti-VEGF therapy.

Introduction

Age-related macular degeneration (AMD) is the leading cause of blindness in persons over 50 years of age in the United States and worldwide.[1-3] A major cause of severe vision loss in AMD is the development of choroidal neovascularization (CNV), which consists of abnormal vessels within or under the retina. Treatment with intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents can potentially improve visual acuity by 3 lines or more in 30 to 40% and maintain visual acuity at the presenting level of acuity at the time of CNV diagnosis in 95% of eyes.[4-9] Visual acuity at the time of initiation of anti-VEGF treatment is demonstrated to be the best predictor of the visual acuity at 1 and 2 years following therapy.[4,10] For example, eyes with visual acuity of 20/25 to 20/40 at initiation of anti-VEGF therapies, have a mean visual acuity of 20/30 one year after initiation of treatment whereas eyes with pre-treatment visual acuity of 20/100 to 20/160 have mean 1 year post-treatment visual acuity of 20/63.[4] Current monitoring of individuals at risk for CNV consists of periodic in-office examinations by eye care providers with a recommendation for self-monitoring, which may include the use of an Amsler grid. Using such monitoring strategies, only 13 to 36% of individuals with new onset CNV present to their ophthalmologists with visual acuity of 20/40 or better.[4,11] With increasing time between onset of symptoms and initiation of treatment, the visual acuities both at presentation and following treatment were demonstrated to be markedly decreased.[12] Detection of CNV prior to substantial vision loss is critical to maximize successful visual outcomes following treatment.

This report describes the results of the **HO**me **M**onitoring of the **E**ye (**HOME**) Study, a Phase 3, unmasked, randomized clinical trial evaluating the role of home monitoring with

the ForeseeHome device (Notal Vision Ltd., Israel) plus standard care compared with standard care alone for eyes at high risk of progression to CNV.

Home Monitoring Device

The home monitoring device (a visual field monitoring device, which has been approved by the FDA since 2009, is based on hyperacuity (or vernier acuity) a process by which the human visual system is able to perceive even the most minute differences in the relative localization of two objects in space.[13] CNV causes subtle separation of the different layers of the retina, resulting in localized metamorphopsia and scotoma. The monitoring device presents images of artificial distortion of different magnitude. Due to brain preferential awareness, the user is able to detect more significant distortions while ignoring smaller ones. This mechanism allows for creation of a quantified visual field map of the metamorphopsia for each eye and longitudinal detections of changes in such maps as well as deviation from the normal population. This monitoring strategy was previously tested in an out-patient setting in a cross-sectional evaluation.[14] This monitoring, coupled with telemedicine is currently tested for home use prospectively.

Methods

The HOME study compared the strategy of home monitoring plus standard care with standard care alone in eyes at high risk of progression to CNV to determine if the addition of the home monitoring device improves detection of progression to CNV, as reflected by better visual acuity at the time of CNV detection. The main clinical question was whether early detection would result in better visual acuity at diagnosis of CNV, a major predictor of future visual function following anti-VEGF therapy.

The study was conducted in 44 clinical sites of the Age-Related Eye Disease Study2 (AREDS2), a clinical trial of nutritional supplements for the treatment of AMD.[15,16] Men and women aged 53 to 90 years were enrolled from July 30, 2010, through November 16, 2012, with planned follow up until May 31, 2014. The Institutional Review Boards for human subject research from the individual clinical sites approved the protocol and all participants signed informed consents. The research was conduct with adherence to the tenets of the Declaration of Helsinki and the research was Health Insurance Portability and Accountability Act (HIPAA)-compliant. The study was registered at clinicalTrials.gov with the following number: NCT01103505.

Study Population

Participants enrolled were at risk for developing CNV, with either bilateral large drusen (potentially 2 study eyes) or large drusen in one eye (study eye) and advanced AMD in the fellow (non-study) eye, and best corrected visual acuity of 20/60 or better in the study eye(s). Participants were screened in at least one eye using a brief tutorial on the home monitoring device in the clinic to ensure they could operate the device and did not have visual field defects that would prevent future device monitoring. Participants could not have media opacities that prevented quality fundus photography, other retinal disorders such as diabetic retinopathy that might confound the evaluation of the outcome measurement, or a follow-up plan that required examinations or treatments more frequent than every 4 months.

This study, supported by National Institutes of Health (NIH), was required to gather information on race. Using guidelines from the NIH Health Policy on Reporting Race and Ethnicity Data: *Subjects in Clinical Research*, self-reported race and ethnicity of the AREDS2 participants were collected with two ethnic categories (Hispanic or Latino and Not Hispanic or Latino) and five racial categories (American Indian or Alaska Native, Asian,

Black or African American, Native Hawaiian or Other Pacific Islander, and White). Participants were able to select more than 1 racial category.

Randomization was balanced by using permuted block size of 4 and stratified by study site. Participants were randomly assigned (1:1) into one of two arms; the device arm, which received standard care plus device for home monitoring; and the standard care arm, which received only standard care. The study by design was unmasked as the participant, investigator and the clinical coordinator were aware of the random assignment of the two arms. The reading center personnel who graded the ocular images were masked to all medical knowledge or treatment assignment of the study participants.

Randomized Arms

Standard Care (Control Arm)

The participants randomized to the standard care only arm received instructions that were investigator-specific for self-monitoring of vision at home to detect progression of AMD. Aids such as Amsler grids may be recommended. This arm will be referred to as the standard care arm. When participants experienced symptoms, they were instructed to call their clinical center immediately to schedule an appointment within 72 hours.

Home Monitoring Device (Device Arm)

In addition to receiving the same standard care instructions, the participants received a home monitoring device, with instructions for installation and use. This arm will be referred to as the device arm. In instances in which baseline visual field measurements could not be established due to a pre-existing field defect in at least one study eye, the participant returned the device and continued monitoring with standard care only, but nonetheless were included in the final analyses in the intent-to-treat (ITT) cohort as part of the device arm.

Participants were encouraged to use the device on a daily basis and results were transmitted automatically via cellular modem to a central data monitoring center. When the device testing suggested a change compared with the baseline measurements, an alert was sent from the monitoring center to the participant's clinical center prompting the staff to schedule a visit with the study ophthalmologist within 72 hours.

Study Visits and Procedures

At baseline, all participants had best-corrected visual acuity testing (BCVA) and color fundus photography of 3 stereoscopic fields (Figure 1) in both eyes. Certified examiners used a standardized protocol to obtain visual acuity using the electronic version of the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity charts.[17] During visits where an alert was initiated by either symptoms or a change detected by the device, or if the examining physician suspected CNV presence on a scheduled visit, the same ocular imaging with fluorescein angiography (FA) and spectral domain optical coherence tomography (SDOCT) were performed in addition to the visual acuity testing and color fundus photography. These images were submitted to a reading center for grading of lesion characteristics of CNV.

The two types of study visits to the clinical center included scheduled visit, which may be an AREDS2 study visit, or a pre-determined routine care visit; or unscheduled visit, initiated by the participant, usually due to new symptoms or triggered by a device alert. A participant's initial report of new symptoms at scheduled visits would not be considered as prompting an alert unless the participant also contacted the clinical center prior to the scheduled visit to arrange an unscheduled visit. Regardless of the type of study visit, each participant

underwent a protocol eye examination and when CNV was suspected, ocular images were obtained and submitted to the reading center.

Study Objectives and Primary Outcomes

The primary objective of this study was to determine whether home monitoring Preferential Hyperacuity Perimetry and tele-monitoring based on the device plus standard care in participants at high risk for progression to CNV results in earlier detection of progression to CNV as reflected by better visual acuity at the time of CNV detection, when compared with standard care alone. Progression to CNV was determined by the investigator, based upon standardized ocular imaging with color fundus photography, FA and OCT. At the reading center, these events were confirmed by gradings conducted by masked, certified independent personnel who had no knowledge of the treatment assignment. Events from both arms are graded using a standardized protocol.

Secondary vision function objectives at the time of CNV detection included the comparison of the proportion of eyes in each monitoring strategy that at the time of CNV detection maintained visual acuity of 20/40 or better, lost ≤5 letters, lost ≥ 15 letters, or had visual acuity of 20/200 or worse. In addition, the sensitivity and specificity of the performance of alerting modalities in both arms for detecting CNV were analyzed.

Statistical Methods

A sample size of 1400 participants (700 per arm) was considered adequate to determine the magnitude of effect for the primary efficacy analysis. Assuming that 100 participants would have a study eye convert to CNV, this provided at least 80% power to detect a minimum difference between the study arms of at least 5 letters in the mean decrease in BCVA at the time of CNV conversion in a study eye, assuming a standard deviation of 10 letters and a 0.05 one-sided significance level.

All comparisons were made on the intent-to-treat (ITT) cohort, which included all participants who had an investigator-confirmed CNV event assigned to the two arms regardless of the adherence to the use of the device. Additional analysis was conducted on the initial per protocol population (PP1), in which the device arm is restricted to those participants who were using the device at the time of CNV detection regardless of adherence to minimal recommended frequency of monitoring and on a second per protocol population (PP2), which further restricts the device arm to only those participants who met the minimum use criteria of two tests per week in their study eye(s) prior to the CNV event.

The analysis of the primary efficacy endpoint was conducted with the Mann-Whitney test. The distribution of change in visual acuity from baseline was strongly negatively skewed (Shapiro-Wilks p-value < 0.01), requiring the use of non-parametric tests rather than a t-test. The van Elteren test, a type of stratified Wilcoxon-Mann-Whitney test, compared the two arms, accounting for strata, to detect differences in the distributions of the primary outcome variable between the two treatments.[18] Fisher's Exact tests were used to compare proportions between the two treatment groups. All p-values presented are based on one-sided tests and are unadjusted for multiple comparisons. All analyses were conducted using SAS version 9.2 (SAS Institute Inc.) at a significance level of 0.05.

Interim Analyses

Interim analyses were planned for the following scenarios: to stop early for efficacy, recalculate the number of CNV events to increase the power of the study, or to stop early for futility. Two interim analyses were planned at approximately 50% and 75% of the total

planned number of CNV events. Guidelines were followed for each of these scenarios (see Protocol, available at http://aaojournal.org). For interim monitoring of efficacy, the group sequential method with O'Brien-Fleming alpha spending function was used.

Results

A total of 1970 participants were screened and 1520 (77%) were randomized to one of the two arms. The most common reasons participants failed screening were pre-existing significant visual field defects identified on the qualification test by the device at the clinic (N=351, 58%), and high rate of unreliable responses (N=79, 13%). Among the eyes randomly assigned to the device arm, 105 eyes (8.0%) of 88 participants failed to establish baseline values during initial home testing due to visual field defects not identified during the inclinic device screening. Of these 88 participants 17 participants did not establish baseline in either study eye; of these 17 participants, 16 continued in the study and one dropped out. Figure 2 provides the flow sheet of the participants screened and enrolled in the HOME Study.

The demographic characteristics of the 1520 participants are summarized in Table 1 with 895 (59%) women and mean (SD) age 72.5(7.7) years. A total of 1250 (83%) participants had bilateral large drusen (2 potential study eyes) and 243 (16%) participants had large drusen in the study eye and advanced AMD in their non-study eye. A total of 763 participants (1,313 eyes) were randomized to device arm and 757 participants (1,273 eyes) were randomized to standard care. The mean baseline BCVA of the study eyes was 81.7 letters (Snellen equivalent 20/25). There were 564 (37.1%) participants who were also enrolled in AREDS2. There were no statistically significant differences in the baseline characteristics between the participants in the two arms of the study. The mean (SD) study follow-up period was 1.4 (0.6) years with only 44 (3%) participants lost to follow-up.

Home monitoring device arm - frequency of testing

Of the 763 subjects randomized to the device arm, 728 (95%) used the device during part of the study period while 156/763 (20%) returned the device or stopped for at least 1 month before CNV developed, study termination, or were lost to follow-up. In the device arm, the average (SD) weekly usage throughout the study period, among those that continued to test with the home device (607 participants), was 4.4 (1.8) times per week, and in 70 subjects less than twice a week.

Timing from Alert or Symptom to Exam

The median (IQR) time intervals from alerts or symptoms to the exam were 5 (3-8) and 7.5 (4-18.5) days for device arm and standard care arm, respectively. It took participants in the standard care arm, 2.5 days longer to schedule an exam than participants in the device arm (p-value < 0.001). Within the device arm, the median (IQR) days from alert to exam were 5 (3-8) days and from symptoms to exam were 7 (3-17) days.

Progression to CNV

As of April 2, 2013, 82 participants (ITT cohort) progressed to CNV in at least one of their study eyes based on the study investigator's determination, 51 were detected in the device arm and 31 in the standard care arm. There were no statistically significant differences in baseline characteristics between those who progressed to CNV between these two arms (Table 1).

The Data and Safety and Monitoring Committee (DSMC) reviewed results from these 82 CNV events excluding 1 participant with missing visual acuity at the time of CNV event, (approximately 80% of planned sample size) during a pre-specified interim analysis. The interim analyses used the O'Brien-Fleming stopping boundary of <0.02385. Our p-value fell within the stopping boundary (p-value = 0.0210), suggesting that the study met statistical significance. The DSMC recommended early termination of the study since the results demonstrated that eyes at high risk of developing progression to CNV can be identified with better levels of vision when they are detected with the use of the FH monitoring device plus standard care.

Accumulation of events over time

The accumulation of CNV events over time in each arm and the difference in number of events between the arms is presented in Figure 3. The device arm accumulated events initially at a higher rate with the standard care arm lagging behind. The events rate became virtually identical in each of the monitoring arms later in the study as can be seen in the graph representing the difference in number of events between the arms. A piecewise linear regression assessment indicates that the slope was significantly different from zero ($p<0.001$) between January 2012 until January 2013. Starting February 2013 the slope was not significantly different from zero ($p = 0.88$) confirming that accumulation of more events early in the study resulted from earlier detection. In order to verify the stability of the slope of this regression line, it was initially calculated up to the point of the data lock to include the 82 CNV events in this report. The regression line was then extended beyond the data lock to include additional 23 CNV events. The additional events resulted in a slope that remained approximately zero, indicating no significant difference in the event rates in both arms.

BCVA at time of CNV detection

Table 2 summarizes the BCVA at the time of CNV detection in the ITT, PP1 and PP2 cohorts. In the ITT cohort, the device arm exhibited a significantly smaller decline in BCVA with fewer letters lost from baseline to CNV detection (median, [IQR], −4 [−11.0, −1.0] letters compared with the standard care group (median, [IQR]: −9 [−14.0, −4.0] letters ($p=0.021$).

At the time of the CNV diagnosis, the device arms lost median, [IQR]: −3 [−10.0, −1.0] letters and median, [IQR]: −3 [−9.0, −1.0] letters in the PP1 cohort (39 eyes) and PP2 cohort (35 eyes), respectively. The difference between each of these cohorts and the standard care arm (30 eyes) showed a significant difference with a preservation of 6.0 letters ($p=0.007$) and 6.0 letters ($p=0.005$) in the PP1 and PP2 device groups, respectively. The device group remained superior (p-value < 0.05) compared to the standard care group after stratification for baseline AMD status, baseline visual acuity and participation in AREDS2 (Table 3, available at http://aaojournal.org). Results of the visual acuity changes were similar when analyses were conducted on a subset of 68 CNV events confirmed by the reading center (Table 4, available at http://aaojournal.org).

Other visual acuity outcomes

Secondary visual acuity outcomes are summarized in Table 5. A higher percentage of eyes were detected with BCVA of 20/40 or better at the time of their CNV event in the device arm (40 [87%] eyes) compared with the standard care (18 [62%] eyes) (p-value = 0.014). In the device arm, 27 (53%) eyes maintained BCVA within 1 line of their baseline visual acuity, 6 (12%) eyes lost 15 or more letters from baseline, and 1 (2%) eye had visual acuity of 20/200 or worse at the time of the CNV event. In the standard care group 12 (40%) eyes

maintained BCVA within 1 line of their baseline visual acuity, 7 (23%) eyes lost 15 or more letters from baseline, and 1 (3%) eye had visual acuity of 20/200 or worse at the time of the CNV event. The proportions between groups for these secondary visual acuity outcomes generally favored the device arm, but did not meet statistical significance (p-value = 0.185; 0.146 and 0.607, respectively). In both the PP1 and PP2 cohorts, 91% and 94%, respectively of the devices users maintained visual acuity of 20/40 or better compared with 62% in the standard care arm at CNV diagnosis (p-value=0.005 and p-value=0.003, respectively). A statistically significant advantage was also seen in the device plus standard care arm for a reduction in the proportion of CNV events diagnosed with at least 15 letters vision loss in comparison with the standard care only arm in the PP2 cohort (6% vs. 23%, p-value=0.045).

Performance of the Home Monitoring System

The sensitivity of the home monitoring device and the strategy that included tele-monitoring was evaluated by comparing the two study arms in the analyses of the “first modality to alert”, which included alerts generated by the device, reported symptoms, both device and symptoms and clinical signs at scheduled clinic visit. The specificity of the device and symptoms were evaluated by calculating the annual false positive rate.

Home Monitoring Sensitivity

First to Alert: Of the 51 patients who were randomized to the device regardless of whether they were using a device at the time when they developed CNV (ITT), the combination of device alert or symptoms, representing CNV detected between scheduled visits, triggered the first alerts in 37 eyes (72.5%). The device alone was the first modality to alert in 26 eyes (51.0%), symptoms were the first modality to alert in 11 eyes (21.6%), while the remaining 14 eyes (27.5%) had diagnosis of CNV at a scheduled visit for routine care or an AREDS2 study visit. In the PP1 and PP2, the combination of device alert or symptoms triggered the first alerts in 29 eyes (74.4%) and 28 eyes (80.0%), respectively. Of the 31 eyes in the standard care arm that developed CNV, symptoms was the first modality to alert in 17 (54.8%) while 14 (45.2%) events were identified during scheduled or AREDS2 visits.

Home Monitoring Specificity

A total of 237 false alerts visits (107 participants with one false alert, 36 with two, 15 with three, 2 with four and 1 with five false alerts), precipitated by a change detected by the device although CNV was not confirmed, resulting in 0.24 alerts/year. Extrapolation of the per-patient false positive rate indicates that on average, there will be one false positive device alert per 4.2 years for every device user. The rates of false alerts triggered by symptoms in the device arm and the standard care arm were similar, 44 (0.04 annually) and 48 (0.05 annually) respectively and 79% of participants had no device false alert.

Visual Acuity by Modality of Alert

In the ITT population, the standard care arm lost significantly more letters when compared with the device arm (median values of −11.5 vs. −3.0; p-value = 0.03) when the alert was triggered between pre-scheduled office visits (Table 6). When CNV was suspected during scheduled visits there was no statistical difference in the letters lost between groups (p=0.449). The inference from these data is that in addition to the effect of standard care, the beneficial effects may be attributed and isolated to the device monitoring. When standard care arm was compared with the PP1 and PP2 populations, the differences in the median number of letters lost were similar (−11.5 for standard care vs. −3.0 for both PP1 and PP2, p-values <0.001 and 0.01).

Discussion

The HOME Study results showed that participants randomized to the device arm had significantly better visual acuity at the time of detection of incident CNV when compared to those randomized to standard care only. The primary analyses demonstrated that the decrease in the visual acuity score at the time of the CNV detection was at least 5 letters lower in the median decrease in BCVA in the device arm compared with the standard care arm. This resulted in median acuity among the device users of 20/32 with nearly 90% of eyes maintaining 20/40 or better vision at CNV detection. The independent DSMC reviewed the results at a pre-planned interim analysis and recommended early stopping of the randomized trial in April 2013.

This is the first time that tele-monitoring has been tested within a randomized-controlled trial of a strategy of self- monitoring with the device and standard care. The use of the monitoring device using preferential hyperacuity perimetry has been tested previously in a cross-sectional evaluation in an out-patient, office setting for detection of CNV associated with advanced AMD and demonstrated good sensitivity and specificity which was significantly better than the Amsler grid.[19] Although not mandated by study protocol, the Amsler grid was used as the standard care routine in some of the clinical centers in both arms of the current study. Previous studies of the Amsler grid had demonstrated low sensitivity for detecting CNV as well as low compliance.[20,21] Other studies of preferential hyperacuity perimetry have compared this technique directly with that of the Amsler grid, noting increased sensitivity of the preferential hyperacuity perimetry for detecting CNV development.[22] In other studies, the utility of the preferential hyperacuity perimetry for following the course of CNV was tested in the outpatient offices.[23,24] However, none of these studies were longitudinal or evaluated in randomized controlled trials, making the results of our study unique.

The study demonstrated that the proportion of participants who maintained 20/40 or better visual acuity at the time of the detection and initiation of treatment for CNV was 87% in the device arm (Table -5) and 62% in the standard care arm (p-value =0.014). In participants who used the device at the recommended frequency, the proportion maintaining 20/40 or better was 94%. In comparison to other clinical studies of anti-VEGF therapies, the proportion presenting 20/40 or better vision at the time of detection and initiation of anti-VEGF therapy in this study is greater than previously reported which ranged from 13 to 36%.[4,11]

A long term plot and analysis of the accumulation of events over time showed that while initially there seemed to be a higher CNV event rate in the device arm compared to the standard care arm, the event rate at the later stages of the study was found to be similar the two monitoring strategies.. This finding supports the study conclusion that the home monitoring device detects CNV earlier than standard care since it would be expected that a true early detection modality tested in a prospective longitudinal study would result in accumulation of more events in the earlier phases of the study compared to its control. This gap will then become constant over time as demonstrated in this study (Figure 3).

The study was designed to replicate the standard care delivered in clinical practice among retina specialty clinics while utilizing clinical trial methodology to answer clinically relevant study questions. The study population represented patients who were at risk for developing advanced AMD but they were restricted to have visual acuity of 20/60 or better. Participants whose planned treatment/exam schedule was more frequent than every 4 months were excluded purposefully to evaluate the device monitoring strategy in a population that was not frequently receiving in office monitoring of their disease.

The overall compliance using the home monitoring device was good. While the majority of participants were able to successfully install and use the device consistently, this technology could not be used by all participants with AMD because of preexisting visual field defects that resulted in an approximate 20% screen failure rate. Additional 8 % of the eyes could not establish baseline measurements after randomization and 20% stopped monitoring at different time points during the study. The performance of the device was considered good with an annual false positive event rate for the device of 0.24/year. On extrapolation, on average the device would trigger an unscheduled visit for “false alarm” approximately once every 4.2 years of device use time. In a typical follow up plan of an AMD patient of 2 clinic visits per year,[25] it is expected that the additional burden due to false alerts would be minimal.

The strengths of this study include the high statistical power of the study and the use of a clinical trial infrastructure that had a ready pool of individuals who met the clinical inclusion and exclusion criteria for the study. This led to efficiency in recruitment. The research team was experienced in conducting clinical trials in determining CNV development. The ocular images were evaluated by the reading center that was masked to the randomization as well as the medical information. The BCVA was obtained by certified personnel using a standardized electronic ETDRS visual acuity testing method which was developed to have less technician-related bias.[17]

Persons 65 years of age or older should have dilated eye examinations to determine their risk of developing advanced AMD, especially CNV.[26] In contrast to current home monitoring strategies, those with intermediate AMD (bilateral large drusen), or advanced AMD in one eye would benefit from home monitoring with the device to detect the development of CNV at an earlier stage with better preservation of their visual acuity to maximize visual acuity results following intravitreal therapy with anti-VEGF agents.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Emily Chew and Traci Clemons had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analyses. The investigators designed and executed the study in collaboration with the sponsors of the study. The analyses were performed independently in the Coordinating Center. The Data and Safety Monitoring Committees evaluated both the study design and the study data. The manuscript was drafted by the investigators with collaboration and input from the sponsors.

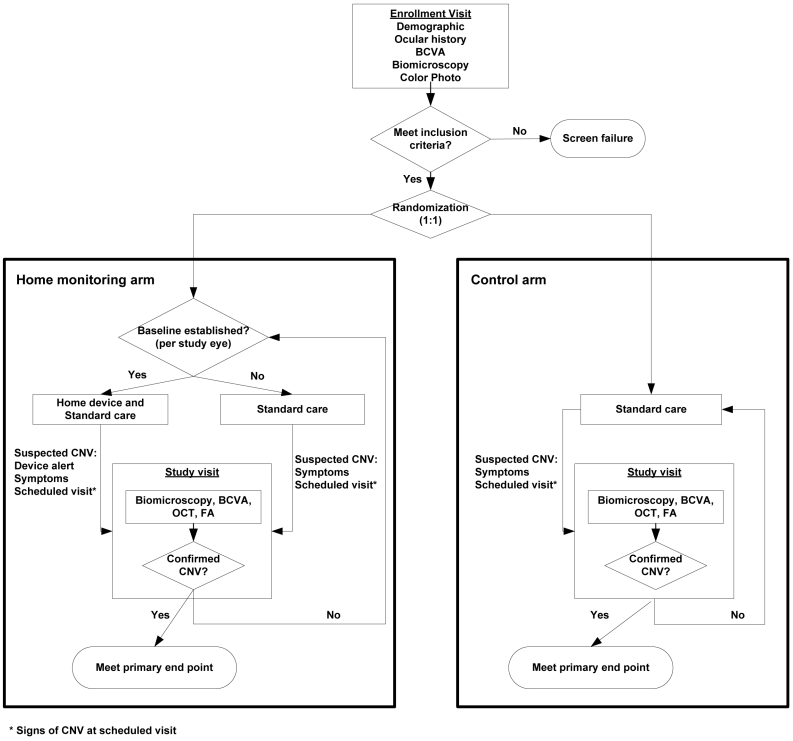

Figure 1. Study Visits by Randomization in the HOme Monitoring of the Eye (HOME) Study
Abbreviations:

BCVA: Best-corrected visual acuity

CNV: Choroidal neovascularization

FA: Fluorescein angiography

OCT: Optical coherence tomography

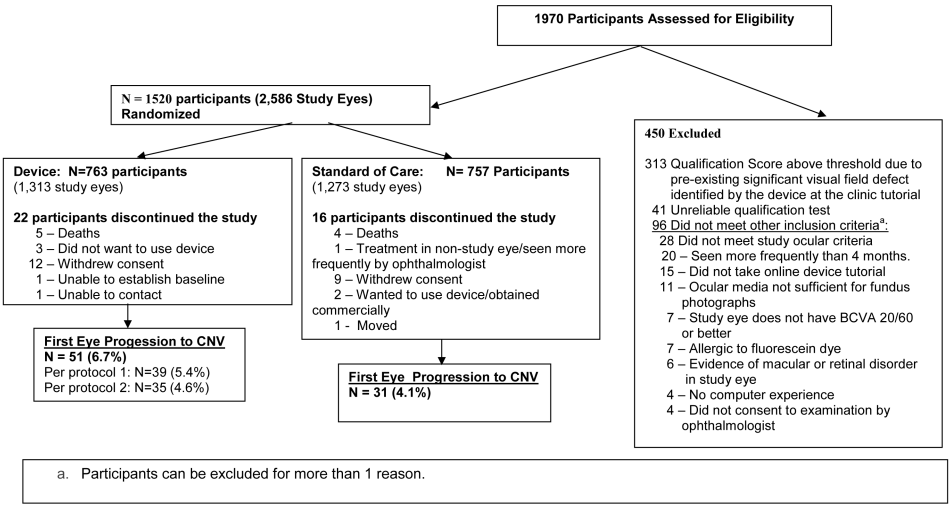

Figure 2. Study Flow and Randomization (Consort Diagram)

BCVA: Best-corrected visual acuity

CNV: Choroidal neovascularization

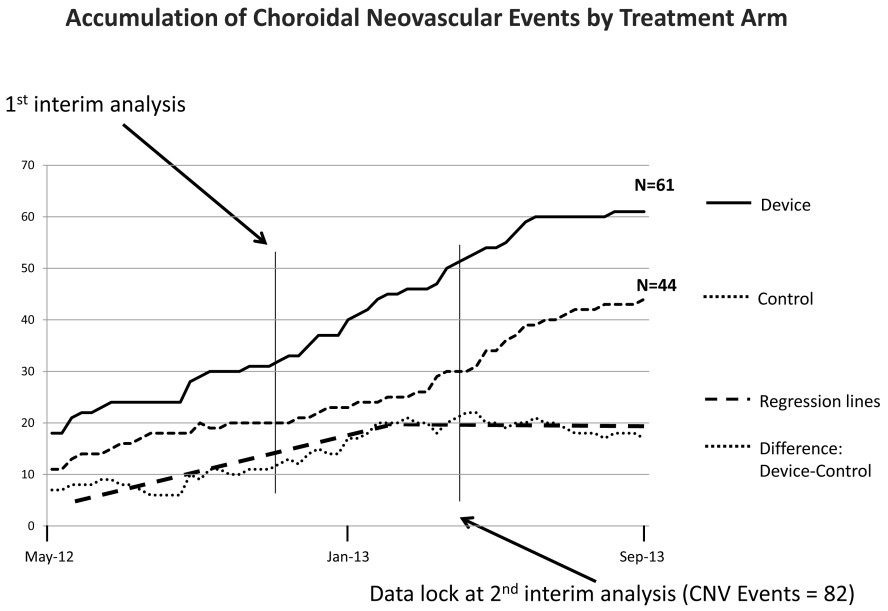

Figure 3. Accumulation of Treatment Events by Treatment Arms

CNV: Choroidal neovascularization

The piecewise linear regression lines evaluate the slopes of the curve that represent the difference in number of accumulated choroidal neovascularization events between the two study arms. The slope becomes zero as the rates of these events become equal just prior to the second interim analyses.

Table 1

Baseline Characteristics by Treatment Group in the HOme Monitoring of the Eye (HOME) Study

	Full Cohort			ITT Population*		
	Treatment			Treatment		
Baseline Characteristic	**Device Monitoring N=763**	**Standard Care N=757**	**Total N=1520**	**Device Monitoring N=51**	**Standard Care N=31**	**Total N=82**
Gender						
Male	319 (41.8)	306 (40.4)	625 (41.1)	21 (41.2)	10 (32.3)	31 (37.8)
Female	444 (58.2)	451 (59.6)	895 (58.9)	30 (58.8)	21 (67.7)	51 (62.2)
Baseline Age: Mean (SD)	72.6 (7.7)	72.3 (7.7)	72.5 (7.7)	73.0 (7.7)	73.2 (7.6)	73.1 (7.6)
Race						
Non-Caucasian	30 (3.9)	27 (3.6)	57 (3.8)	0 (0)	0 (0)	0 (0)
Caucasian	733 (96.1)	730 (96.4)	1463 (96.3)	51 (100)	31 (100)	82 (100)
Ethnicity						
Not Hispanic origin	750 (98.3)	749 (98.9)	1499 (98.6)	51 (100)	30 (96.8)	81 (98.8)
Hispanic origin	13 (1.7)	8 (1.1)	21 (1.4)	0 (0)	1 (3.2)	1 (1.2)
Participant Type						
Non-AREDS2 Participant	468 (61.3)	488 (64.5)	956 (62.9)	25 (49.0)	13 (41.9)	38 (46.3)
AREDS2 Participant	295 (38.7)	269 (35.5)	564 (37.1)	26 (51.0)	18 (58.1)	44 (53.7)
Baseline AMD Category Graded by Reading Center						
Missing	6 (0.8)	11 (1.5)	17 (1.1)			
Bilateral Large Drusen	642 (84.1)	608 (80.3)	1250 (82.2)	37 (72.5)	24 (77.4)	61 (74.4)
Large Drusen, AAMD	111 (14.5)	132 (17.4)	243 (16.0)	14 (27.5)	7 (22.6)	21 (25.6)
Other**	4 (0.5)	6 (0.8)	10 (0.7)			
Baseline VA: Mean (SD) Snellen equivalent	81.5 (7.5) 20/25	81.9 (7.1) 20/25	81.7 (7.3)	51, 79.7 (8.0) 20/25	31, 80.5 (5.8) 20/25	82, 80.0 (7.2)
Median (min,max) Snellen equivalent	83.0 (54.0, 100) 20/20	83.0 (51.0, 100) 20/20	83.0 (51.0, 100)	81.0 (62.0,93.0) 20/25	82.0 (68.0,90.0) 20/25	81.0 (62.0,93.0)

ITT: Intent To Treat (participants who developed choroidal neovascularization prior to the second interim analyses of the study data.(75 percentile of the events)

AREDS2: Age-Related Eye Disease Study 2

AAMD: Advanced age-related macular degeneration

SD: Standard Deviation

VA: Visual Acuity

CNV: Choroidal Neovascularization

*Determined for study eyes that progressed to CNV only

**Other group: < large drusen, cannot grade (N = 1); Cannot grade bilateral (N=1); Bilateral advanced age-related macular degeneration (N=8)

Table 2

Primary Visual Acuity Outcome at Diagnosis of Choroidal Neovascularization by Treatment Group

ITT Population					
		Treatment			
		Device Monitoring N=51	**Standard Care N=30***	**Total N=81**	**P-value****
VA Score at Baseline	Mean (SD)	79.7 (8.0)	80.7 (5.7)	80.1 (7.2)	0.021
	Median (IQR)	81.0 (73.0, 86.0)	82.0 (77.0, 85.0)	81.0 (75.0, 85.0)	
VA Score at CNV Event	Mean (SD)	72.3 (13.8)	68.1 (16.1)	70.8 (14.8)	
	Median (IQR)	75.0 (70.0, 82.0)	72.0 (64.0, 77.0)	73.0 (67.0, 80.0)	
VA Score Change from Baseline at Event	Mean (SD)	−7.4 (11.4)	−12.6 (16.5)	−9.3 (13.7)	
	Median (IQR)	−4.0 (−11.0, −1.0)	−9.0 (−14.0, −4.0)	−7.0 (−12.0, −2.0)	
PP1 Population					
		N=39	**N=30 ***	**N=69**	
VA Score at Baseline	Mean (SD)	79.7 (7.9)	80.7 (5.7)	80.1 (7.0)	
	Median (IQR)	80.0 (73.0, 85.0)	82.0 (77.0, 85.0)	81.0 (75.0, 85.0)	
VA Score at CNV Event	Mean (SD)	73.7 (12.9)	68.1 (16.1)	71.3 (14.5)	
	Median (IQR)	75.0 (70.0, 82.0)	72.0 (64.0, 77.0)	74.0 (69.0, 80.0)	
VA Score Change from Baseline at Event	Mean (SD)	−5.9 (9.5)	−12.6 (16.5)	−8.8 (13.3)	0.007
	Median (IQR)	−3.0 (−10.0, −1.0)	−9.0 (−14.0, −4.0)	−6.0 (−11.0, −2.0)	
PP2 Population					
		N=35	**N=30 ***	**N=65**	
VA Score at Baseline	Mean (SD)	79.6 (8.0)	80.7 (5.7)	80.1 (7.0)	
	Median (IQR)	80.0 (73.0, 85.0)	82.0 (77.0, 85.0)	81.0 (75.0, 85.0)	
VA Score at CNV Event	Mean (SD)	74.3 (11.6)	68.1 (16.1)	71.5 (14.1)	
	Median (IQR)	75.0 (70.0, 82.0)	72.0 (64.0, 77.0)	73.0 (69.0, 80.0)	
VA Score Change from Baseline at Event	Mean (SD)	−5.2 (8.3)	−12.6 (16.5)	−8.6 (13.2)	0.005
	Median	−3.0 (−9.0, −1.0)	−9.0 (−14.0, −4.0)	−6.0 (−11.0, −2.0)	

ITT: Intention to Treat

VA: visual acuity

SD: standard deviation

IQR: interquartile range

CNV: choroidal neovascularization

PP1: Per protocol 1

PP2: Per protocol 2

* The above excludes the participant from the standard care only arm who did not have any visual acuity determination at the time of the event.

** p-value from a one-sided Mann-Whitney test

Visual Acuity Scores and Snellen Equivalents:

85 to 90=20/20

77 to 84= 20/25

71 to 76= 20/30

66 to 70= 20/40

Table 5

Secondary Visual Acuity Outcomes at Diagnosis of Choroidal Neovascularization by Treatment Group

	Treatment			
	Device Monitoring	**Standard Care***	**Total**	**P-value****
ITT Cohort				
	N=51 (%)	**N=30 (%)**	**N=81 (%)**	
Maintained 20/40 or better***	40 (87)	18 (62)	58 (77)	0.014
Maintained Vision (loss of no more than 5 letters)	27 (53)	12 (40)	39 (48)	0.185
15+ letter loss from baseline	6 (12)	7 (23)	13 (16)	0.146
Declined to 20/200 or worse	1 (2)	1 (3)	2 (2)	0.607
PP1 Cohort				
	N=39 (%)	**N=30 (%)**	**N=69 (%)**	
Maintained 20/40 or better****	32 (91)	18 (62)	50 (78)	0.005
Maintained Vision (loss of no more than 5 letters)	22 (56)	12 (40)	34 (49)	0.134
15+ letter loss from baseline	3 (8)	7 (23)	10 (14)	0.069
Declined to 20/200 or worse	1 (3)	1 (3)	2 (3)	0.684
PP2 Cohort				
	N=35 (%)	**N=30 (%)**	**N=65 (%)**	
Maintained 20/40 or better****	29 (94)	18 (62)	47 (78)	0.003
Maintained Vision (loss of no more than 5 letters)	20 (57)	12 (40)	32 (49)	0.129
15+ letter loss from baseline	2 (6)	7 (23)	9 (14)	0.045
Declined to 20/200 or worse	1 (3)	1 (3)	2 (3)	0.714

ITT: Intention to Treat

PP1: Per protocol 1

PP2: Per protocol 2

Table 6

First Modality to Lead to Choroidal Neovascularization (CNV) Detection and Change in Visual Acuity at CNV Diagnosis by Treatment Group

	Treatment							
	Device Monitoring							
	ITT N=51		PP1 N=39		PP2 N=35		Standard Care N=31	
Visit Type	**N (%)**	**Change in VA (mean/median)**	**N (%)**	**Change in VA (mean/median)**	**N (%)**	**Change in VA (mean/median)**	**N (%)**	**Change in VA (mean/median)**
Device Alert* + Symptom Visits* + Follow-up for Device Alert or Symptom*	37 (72.5)	−6.8 / −3.0	29 (74.4)	−4.6 / −3.0	28 (80.0)	−4.8 / −3.0	N/A	N/A
Device Alert Visit* + Follow-up for Device Alert*	26 (51.0)	−5.6 / −3.0	25 (64.1)	**−3.8 / −3.0**	**24 (68.6)**	−4.0 / −3.0	N/A	N/A
Symptom Visit* + Follow-up for Symptom*	11 (21.6)	−9.7 / −7.0	4 (10.3)	−9.5 / −8.0	4 (11.4)	−9.5 / −8.0	17 (54.8)	−16.5 /−11.5
Scheduled Visit + Follow-up	14 (27.5)	−8.9 / −8.5	10 (25.6)	−9.8 / −8.5	7 (20.0)	−6.9 / −8.0	14 (45.2)	−8.1 / −8.0

p-values for comparisons of interest (comparator is Standard of Care: Device + Symptom compared with Symptom (Standard Care): ITT, PP1, and PP2 (p-values = 0.03, <0.001 and 0.01, respectively); Symptom Visit + Follow-up: ITT, PP1, and PP2 (p-values 0.26, 0.25 and 0.25, respectively); and Scheduled Visit + Follow-up: ITT, PP1 and PP2 (p-values = 0.44; 0.50; and 0.41, respectively)

*Unscheduled visit

ITT: Intention to Treat

PP1: Per protocol 1

PP2: Per protocol 2

VA: Visual Acuity

N/A: Not Applicable