The Neovascular Age-Related Macular Degeneration Database: Multicenter Study of 92 976 Ranibizumab Injections

Report 1: Visual Acuity

*Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group**

Purpose: To study real-world ranibizumab therapy for treatment-naïve eyes with neovascular age-related macular degeneration (nAMD) and to benchmark standards of care.

Design: Multicenter, national nAMD database study.

Participants: A total of 92 976 treatment episodes from 12 951 eyes of 11 135 patients.

Methods: Up to 5 years of routinely collected, anonymized data were extracted remotely from 14 United Kingdom centers to a central database using an electronic medical record (EMR) system. Participating centers used ranibizumab to treat nAMD using a loading phase of 3 monthly injections and a pro re nata retreatment regimen. The minimum data set defined before first patient data entry and mandated by the EMR system included age, Early Treatment Diabetic Retinopathy Study visual acuity (VA) at all visits, and injection episodes.

Main Outcome Measures: Baseline VA, change in VA, number of treatments and clinic visits, and baseline characteristics affecting VA change.

Results: Information from more than 300 000 clinic visits (2.8 million data points) were collated. Mean age at first treatment was 79.1 years, with a female preponderance of 1.7:1. Mean VA (letters) for eyes followed up for at least 3 years from a baseline of 55 letters was 57 (+2) letters at 1 year, 56 (+1) letters at 2 years, and 53 (−2) letters at 3 years. The proportion of eyes that avoided moderate vision loss at years 1, 2, and 3 were 90%, 84%, and 82%, respectively. The proportion of eyes with VA of 20/40 or better were: baseline, 16%; year 1, 30%; year 2, 30%; and year 3, 29%. The median number of treatments for eyes followed up for at least 3 years in years 1, 2 and 3 was 5, 4, and 4, respectively, and the median number of outpatient visits was 9.2, 8.2, and 8.2, respectively. Baseline VA was related inversely to mean vision gain at 3 months. Older age was associated with lower presenting VA.

Conclusions: Real-world visual outcomes achieved at a large number of centers across the United Kingdom do not match the results achieved in most randomized trials, but they were delivered with substantially fewer injections and hospital visits. This study provides important benchmark results that should be of interest to patients, retina specialists, and commissioners of health care. This study demonstrates the EMR system's potential usefulness for future phase 4 and 5 clinical trials. *Ophthalmology 2014;121:1092-1101 © 2014 by the American Academy of Ophthalmology.*

*Supplemental material is available at www.aaojournal.org.

Intravitreal injection of ranibizumab is an established therapy to treat neovascular age-related macular degeneration (nAMD) and is the most commonly performed retinal procedure in the United Kingdom's National Health Service (NHS). Clinical practice was informed initially by the Anti-Vascular Endothelial Growth Factor Antibody for the Treatment of Predominantly Classic Choroidal Neovascularization in Age-Related Macular Degeneration (ANCHOR) study and the Minimally Classic/Occult Trial of the Anti-VEGF Antibody Ranibizumab in the Treatment of Neovascular Age-Related Macular Degeneration (MARINA) study, which demonstrated that ranibizumab prevents central vision loss and improves mean visual acuity (VA) at 2 years when given at monthly intervals in eyes with subfoveal nAMD.[1,2] In the United Kingdom, the National Institute of Health and Clinical Excellence (NICE)[3] approved the use of ranibizumab in August 2008, leading to almost exclusive usage of ranibizumab for nAMD in the NHS. In contrast to the pivotal studies, in routine clinical practice in the United Kingdom, ranibizumab therapy is administered almost universally as a loading phase of 3 injections given at monthly intervals followed by pro re nata (PRN) treatment if active disease is detected at monthly assessment visits. Under strict trial conditions, PRN therapy is slightly but

ISSN 0161-6420/14/$ - see front matter
http://dx.doi.org/10.1016/j.ophtha.2013.11.031

statistically significantly worse than continuous monthly therapy, as shown in the Comparison of AMD Treatments Trials (CATT) and the Trial of Alternative Treatments to Inhibit VEGF in Age-Related Choroidal Neovascularisation.[4–7] In most published case series from routine clinical practice, the level of benefit of PRN treatment seen in randomized trials has not been achieved either using an attempted monthly follow-up or a treat-and-extend strategy.[8–13] Delivering the therapy with a recommendation of monthly assessment and re-treatment for active disease makes substantial demands on health care services and funding authorities. Given the cost and intensity of the intervention, it is important to understand what real-life outcomes are achieved and how different departments compare in translating clinical trial results into clinical practice. Clinical trials are limited by a restricted study population (entry criteria), for example, excluding second treated eyes and having a limited number of trial subjects, but results of such trials are widely assumed to reflect future clinical practice. Improvement in VA, although vital to prove the efficacy of a drug, may not be the best measure of the quality of clinical care where the ideal is to detect and maintain patients with excellent vision. Although phase 4 and 5 studies that occur after marketing authorization (such as the Observe the Effectiveness and Safety of Ranibizumab in Real Life Setting [Luminous] Trial; available at: http://clinicaltrials.gov/show/NCT01318941; accessed August 20, 2013) may help to produce additional information on efficacy and safety, their usefulness is limited by selective recruitment and possible changes in the behavior of treating physicians, so outcomes are likely to diverge from real-life outcomes. Traditional audits involve retrospective collection of incomplete data from small numbers of patients in single centers and may not reflect real-world results from entire populations of treated patients.

In addition, there is a risk of publication bias with single-center case series because they may be reluctant to report low success rates.[14] Robust real-world data are important to enable individual surgeons or centers to benchmark their own performance. The limitations of traditional audits and phase 4 studies could be overcome in part if the data were collected as a by-product of routine clinical care with a predefined structure to collect a core dataset, with compulsory data entry and missing data check, and from closer to the total number of patients treated in the population.

Appropriately designed and used electronic medical record (EMR) systems offer the ability to capture and pool a large proportion or even all of the treated patients' data to assess how clinical trial results translate into real-life clinical outcomes. They have the benefit that all data are collected as a by-product of routine clinical practice, and they can be designed to mandate capture of a defined minimum dataset. The United Kingdom has already demonstrated how a specialty-specific EMR system can be of benefit in ophthalmology to define benchmark clinical outcomes for cataract surgery and to individualize the risk of posterior capsular rupture for patients.[15–17] To date, the United Kingdom has avoided the danger that EMR systems can become simple data stores that do not help to improve the quality of care.[18] The aims of this study were to define benchmark standards of care for treatment-naïve eyes treated with ranibizumab for nAMD at a large number of United Kingdom centers using a loading phase of 3 monthly injections followed by a PRN re-treatment regimen.

Methods

Study Design

Two EMR systems from different companies in the United Kingdom were known to collect nAMD treatment and assessment data. Sites known to make comprehensive use of these systems were contacted; however, only sites using 1 EMR system met the deadline given with regard to permission to extract data. All data therefore were derived from 1 supplier (Medisoft Ophthalmology, Medisoft Limited, Leeds, UK). The lead clinician and Caldicott guardian (who oversees data protection) at each center gave written approval for the data extraction. Patient identifiers were stripped out completely and site and clinician data were pseudoanonymized, and on this basis, an ethics committee determined that formal ethics approval was not required. This study was conducted in accordance with the Declaration of Helsinki and the United Kingdom's Data Protection Act.

Settings

Fourteen NHS hospitals that deliver ranibizumab AMD treatment services in England and Northern Ireland submitted data to this study. Each site is the only NHS provider of nAMD care to their local population, and very few patients switch between providers. After NICE approval for the use of ranibizumab for nAMD in the NHS in August 2008, all sites used this drug almost exclusively. In 1 center, patients who were deemed nonresponders were switched to bevacizumab, but these numbers were extremely small (<1.0% in 1 of 14 centers), and any eye documented as receiving bevacizumab at any time point was excluded from the analysis. Before August 2008, some sites offered treatment with bevacizumab. Sites that gave approval for data extraction in the predetermined time frame were included. No sites declined to submit data, but a number of sites failed to deliver data within the time frame requested.

Dates for Data Collection

The study was initiated on February 1, 2012, with Caldicott guardian and lead clinician approval being achieved in 14 of the 18 centers contacted by March 2012, the date predetermined by the study team as the cutoff before data extraction was to occur. Data were delivered to the analysis team by the end of April 2012. All approvals and data extraction were performed by April 2, 2012.

Follow-up

All patients had data extracted from the time of the first injection of ranibizumab up to April 2, 2012. A number of patients were lost to follow-up, but it was not possible within the framework of this study to determine the cause of loss to follow-up. To explore whether incomplete follow-up had an impact on outcomes, change in VA was plotted only for patients who completed a defined follow-up period and was compared with a similar plot for all patients.

Variables

Analysis was restricted to treatment-naïve eyes undergoing ranibizumab therapy for nAMD. Eyes undergoing combined therapies

or having bevacizumab in either eye during the study period were excluded. The mode of data entry into the EMR system varied slightly between sites. At all sites, collection of demographic data (age, gender, and ethnicity) was dependent on automatic download from the hospital's patient administration system to the EMR system, and therefore the completeness of these variables was not under the control of the EMR system. When used optimally, pre-injection, injection procedure, and follow-up assessment data were entered live directly into the EMR system as an integral part of routine clinical care by all members of staff. Several sites run entirely paperless clinics and other sites have entirely electronic data collection but print a copy to maintain the paper notes. The EMR system used by centers in this study has a structured dataset for the management of nAMD that allows pooling of the data fields collected. Although this study itself is retrospective, the dataset was defined and set up before the date of first data collection in this study; that is, the mandated EMR data fields were defined prospectively and the EMR user could not exit a patient's chart unless these data were collected. This contrasts with a conventional retrospective chart review with unstructured data and is more akin to the electronic case report form used in clinical trials, but with the data captured as a by-product of routine clinical care. Data collected at all sites included VA for each eye (and the method of measurement) and treatment, if required (with procedure details and complications). The operative and postoperative local and systemic complications fields were mandatory within the software system, and a response had to be entered at each visit. In many centers, the EMR system was used to collect a larger optical coherence tomography dataset, including the presence or absence of parameters that influence re-treatment decision making.

Data Sources and Measurements

In this report, the best-measured VA before surgery was mostly the best VA with refraction, habitual correction, pinhole, or a combination thereof, as measured on an Early Treatment Diabetic Retinopathy Study chart letter score and then expressed as Early Treatment Diabetic Retinopathy Study letters and logarithm of the minimum angle of resolution (logMAR) vision in this study, but some sites measured a refracted best-corrected VA at baseline. Analysis for eyes with very low VA was undertaken by substituting counting fingers, hand movements, and light perception with 2.0, 2.3, and 2.7, respectively.[19]

Efforts to Reduce Bias

Any center with an EMR system that the authors were aware of via the EMR system providers were invited to submit data. An arbitrary cutoff of 2 months was made, and only centers whose data were extracted in this time were included. It is possible that centers that use EMR systems and responded rapidly to the data request are not reflective of the average treating center in the United Kingdom.

Number of Visits

Some centers run a 2-stop service (assessment and treatment on different days). For ease of analysis and to allow a standardized comparison of visit frequency between centers, additional visits within a ±2-week block were regarded as a single visit, with the last recorded VA used for analysis purposes; hence, the data on number of visits represents a normalized value to allow standardized comparison between centers, rather than the precise number of visits by the patient.

Statistical Methods

Data were extracted using Medisoft Ophthalmology (Medisoft Limited, Leeds, UK) for right and left eyes of patients who had had at least 1 intravitreal injection of ranibizumab. Both STATA software version 11 (StataCorp. 2009, Stata Statistical Software: Release 11. College Station, TX) and SPSS software version 19 (IBM Corp. Released 2010. IBM SPSS Statistics for Windows, Version 19.0. Armonk, NY) were used to combine, clean, reshape, merge, recode, and analyze the data. To check for errors in combining and reshaping large datasets, outcomes were verified separately in both statistical software databases by the lead author and statisticians (A.T., W.X., and C.B.). Regression analyses were performed in STATA. The method used to calculate a confidence interval for a proportion was the Wilson score method without continuity correction.[20]

Centers were chosen for this study on the basis that EMR systems were used consistently to record all VAs and ranibizumab injection procedures. In eyes for which data were not available for a particular visit or that had been lost to follow-up, no missing value substitutions were performed. The only exception to this rule was baseline VA. Some treatment centers brought patients back for an injection-only visit with no measurement of VA (n = 1670) after the initial treatment decision was made; hence the baseline VA was taken from the prior assessment visit, so long as this was within 2 weeks of the injection. This therefore was not missing data per se, but rather reflects variation in treatment delivery. Analyses were performed both including all patients initiated into the study and comparing these with a cohort of patients who completed follow-up to the final time point. The nature of the EMR system with a structured AMD assessment led to very low duplicate entries (0.02% overall in the worst data field).

Results

Participants

The 14 sites entered their first treatment episodes into the EMR systems during the following years: 2006 (2 sites), 2007 (5 sites), 2008 (4 sites), 2009 (1 site), and 2010 (2 sites). The first recorded ranibizumab injection was dated November 2006. Data were extracted for 12 951 eyes of 11 135 patients receiving a total of 92 976 ranibizumab injections during 317 371 clinic visits at 14 United Kingdom hospitals. During follow-up, 21.60% (n = 1816) of these patients required treatment to both eyes (Fig 1).

Age, gender, and ethnicity data were imported from the general hospital patient administration system and were not entered manually into the EMR system. Age was recorded in 100% of cases. The mean age at the time of the first injection was 79.7 years (Fig 2). Gender was recorded in all but 1 case (Table 1). The female-to-male ratio was 1.7:1, but when adjusted using national data from the 2011 census for ages 55 to 89 and assuming a similar gender and age mix in the study population, the female-to-male age-specific ratio decreased to 1.3:1. Data on ethnic origin were as shown in Table 1. Ethnic origin data were limited because such information often is not recorded in the hospital administration system, but in the available data, there was a preponderance of white patients (89.6% of recorded ethnicities).

Visual Acuity

Mean change in vision over time is shown in Figure 2. Data are plotted for 3 groups of eyes: those completing at least 52 weeks of follow-up, at least 104 weeks of follow-up, and at least 156 weeks of follow-up (nominally referred to as years 1, 2, and 3 in this article).

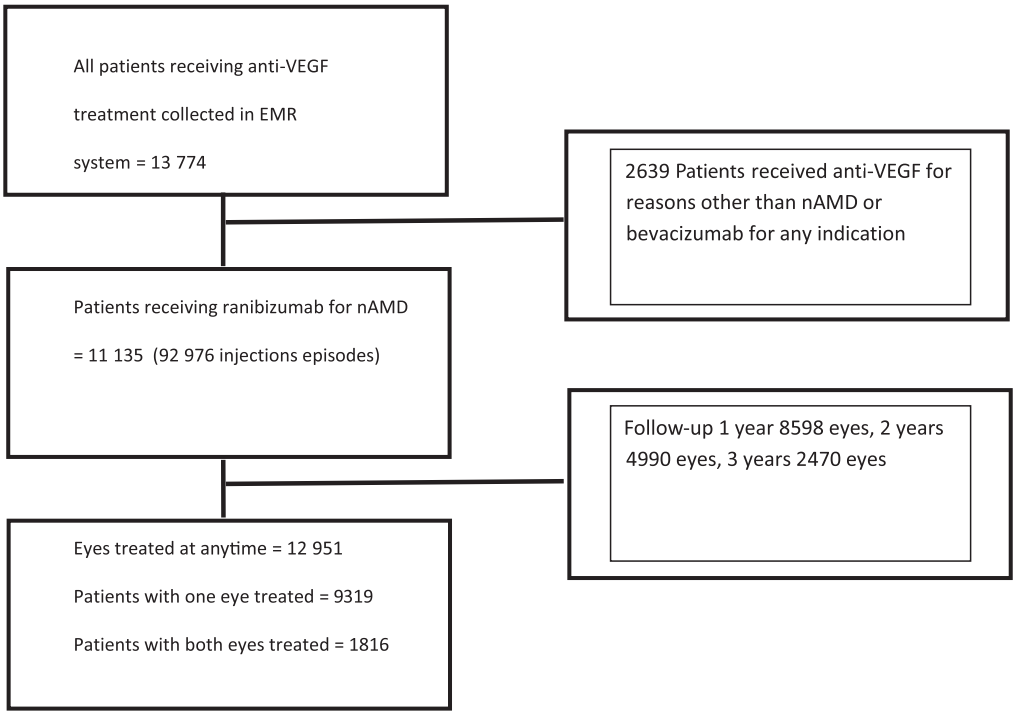

Figure 1. Consolidated Standards of Reporting Trials-style diagram showing the patients and eyes treated in the study. EMR = electronic medical record; nAMD = neovascular age-related macular degeneration; VEGF = vascular endothelial growth factor.

Visual acuity changes were as follows: for eyes followed up for at least 3 years, the mean change from baseline (55 letters) was 58 (+3) letters at peak gain time point, 57 (+2) letters at 52 weeks, 56 (+1) letters at week 104, 55 (+0) letters at week 120, and 53 (−2) letters at week 156 (Fig 3). To explore whether different cohorts of patients were associated with different profiles of mean change in vision over time, plots looking at cohorts followed up for at least 52, 104, and 156 weeks were plotted (Fig 3). These demonstrated a similar change in vision profile over their overlapping periods of follow-up.

The proportion of eyes that avoided moderate vision loss (15 letters) were 90% at year 1, 84% at year 2, and 82% at year 3 (Fig 4). The proportion of eyes with VA of 20/40 or better was 16% at baseline, 30% at year 1, 30% at year 2, and 29% at year 3 (Fig 4A). A more complete understanding of the change in

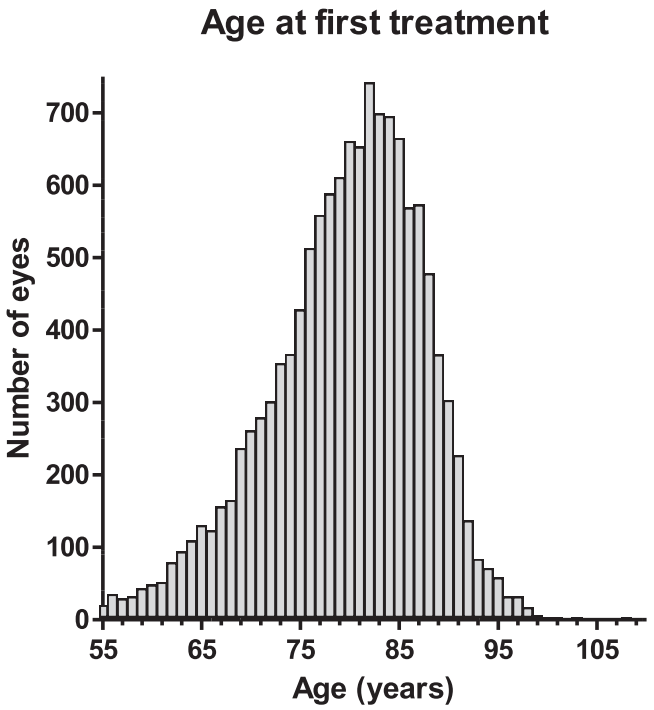

Figure 2. Bar graph showing the frequency of age at presentation for first eye treatment.

Table 1. Demographic Details

Variable	Male (n = 4071)	Female (n = 7062)	Not specified (n = 1)	Total (n = 11 135)
Age (yrs)				
Mean	78.8	80.1	79	79.7
Median	80	81	79	81
IQR	74–84	76–86	–	75–85
Range	55–103	55–108	–	55–108
Ethnicity, no.				
White	2208	3894	1	6103
Mixed	5	36	0	41
Asian	35	5	0	40
Black	9	20	0	29
Chinese	0	2	0	2
Other	0	5	0	5
Not recorded	212	379	0	591
Declined to state	1596	2728	0	4324

IQR = interquartile range.

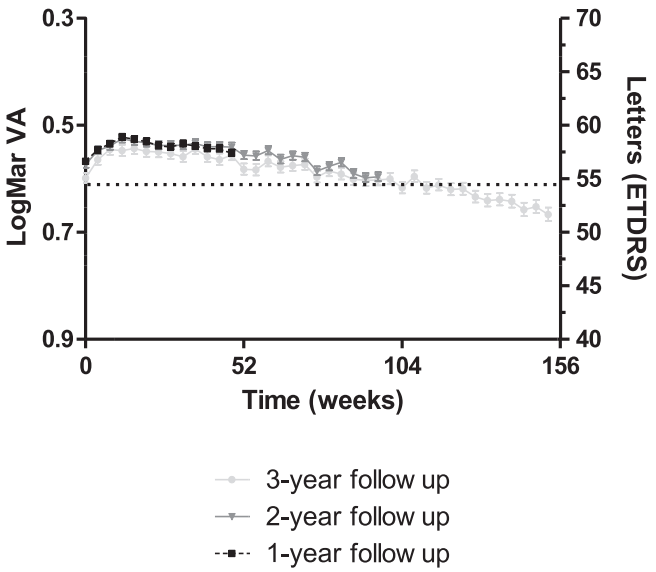

Figure 3. Graph showing the mean visual acuity (VA; with standard error bars) over time comparing patients with follow-up of at least 1, 2, or 3 years. ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution; SE = standard error.

vision in the population was obtained by box-and-whisker plots of VA at different time points (Fig 5, available at www.aaojournal.org) demonstrating median, mean, and dispersion of the data (interquartile range and 5th and 95th percentiles). To see if patients who did not complete follow-up were different from those followed up for at least 168 weeks, data were plotted both for (1) only eyes followed up for a complete 168 weeks (n = 1138) and (2) all eyes receiving at least 1 ranibizumab injection (n = 12 951 at time 0 and n = 1138 at month 42; Fig 5, available at www.aaojournal.org). Both boxplot profiles and change in mean VA were similar for these 2 groups. A comparison of outcomes and baseline demographics was made between eyes that had their first treatment 156 or more weeks before the date of data collation and that completed at least 156 weeks of follow-up versus those that did not. Eyes that completed follow up (n = 2241) compared with eyes that did not (n = 2009) were younger by almost 2 years (79.1 vs. 80.9 years), were more likely to be female (54% vs. 46%), and had better mean vision at last follow-up (0.65 logMAR [standard deviation {SD}, 0.31 logMAR] vs. 0.73 logMAR [SD, 0.35 logMAR]).

Effect of Baseline Characteristics on Visual Acuity Change

Visual acuity at 12 months was associated positively with baseline acuity (coefficient, 0.74; standard error [SE], 0.01; $P < 0.001$) and associated negatively with age (coefficient, −0.21; SE, 0.02; $P < 0.001$; adjusted R^2, 0.41). Change in VA at 12 months was associated negatively with baseline VA (coefficient, −0.28; SE, 0.01; $P < 0.001$) and age (coefficient, −0.24; SE, 0.02; $P < 0.001$; Fig 6).

Number of Visits

The mean number of outpatient visits (normalized to allow comparison of 1-stop and 2-stop services, as discussed in "Methods") in years 1, 2, and 3 were 9.2, 8.2, and 8.2 for patients followed up for up to, but not including, weeks 52, 104, and 156, respectively (Table 2).

Number of Injections

Eyes followed up for at least 52 weeks (but not including week 52) received a mean of 5.7 injections (median, 6; range, 1−13) in the first 52 weeks. Eyes followed up for at least 104 weeks received a mean of 3.7 injections (median, 4; range, 0−13) in their second year of therapy (weeks 52−104; Table 2). In the third year of treatment, eyes received a mean of 3.7 injections (median, 4; range, 0−12; Fig 7, available at www.aaojournal.org). The median number of treatments given for all eyes followed up for at least 3 years was 5 in year 1, 4 in year 2, and 4 in year 3.

Discussion

This study demonstrated that very large data sets of real-life outcomes data on ranibizumab therapy can be collated rapidly and efficiently. More than 92 000 treatment episodes, VA data from 300 000 outpatient visits, and more than 2.8 million data items were obtained in 5 weeks from initiation of the study. This wealth of data represents easily the largest dataset obtained for evaluating treatment burden and outcomes of ranibizumab therapy.[8,10,12,13] The structured data entry system within the EMR system, defined before the data collection started, resulted in very few duplicate entries (0.02% in the worst data field). In the EMR system used in this study, a mandated minimum dataset was constructed that forced users to enter complete data at each visit. This EMR system acted like an electronic case report form in a clinical trial, that is, these data fields were predefined before any data collection started and were entered prospectively, although in the study itself, data collection was retrospective. Unlike an electronic case report form, data were entered as part of routine clinical care and not as an additional entry on top of clinical records. The only data field of limited reliability was ethnicity, which relied on importing data from the hospital administration system into the specialty-specific EMR system.

The study confirmed that incidence of treated nAMD is higher in women, with a 1.7:1 female-to-male ratio (similar ratio to that of CATT), although when adjusted for the age- and gender-specific data available from the England and Wales 2011 census data (available at: http://www.ons.gov.uk/ons/dcp171778_277794.pdf; accessed January 1, 2013), the ratio falls to 1.3:1 for the age group 55 to 89 years where detailed national data are available. This excess female incidence supports that suggested in a previous meta-analysis.[21]

The MARINA and ANCHOR trials involved 24 injections over 2 years and 12 injections over 1 year, respectively. In contrast to these pivotal trials, the European product label for ranibizumab and clinical practice in the United Kingdom is to deliver 3 loading injections at monthly intervals followed by PRN dosing. A drug and disease model informed this practice, and a base-case analysis for the model predicting 8.1 injections in the first year and 6 injections in the second year were used with the assumption that the same clinical efficacy as the pivotal trial would be achieved with

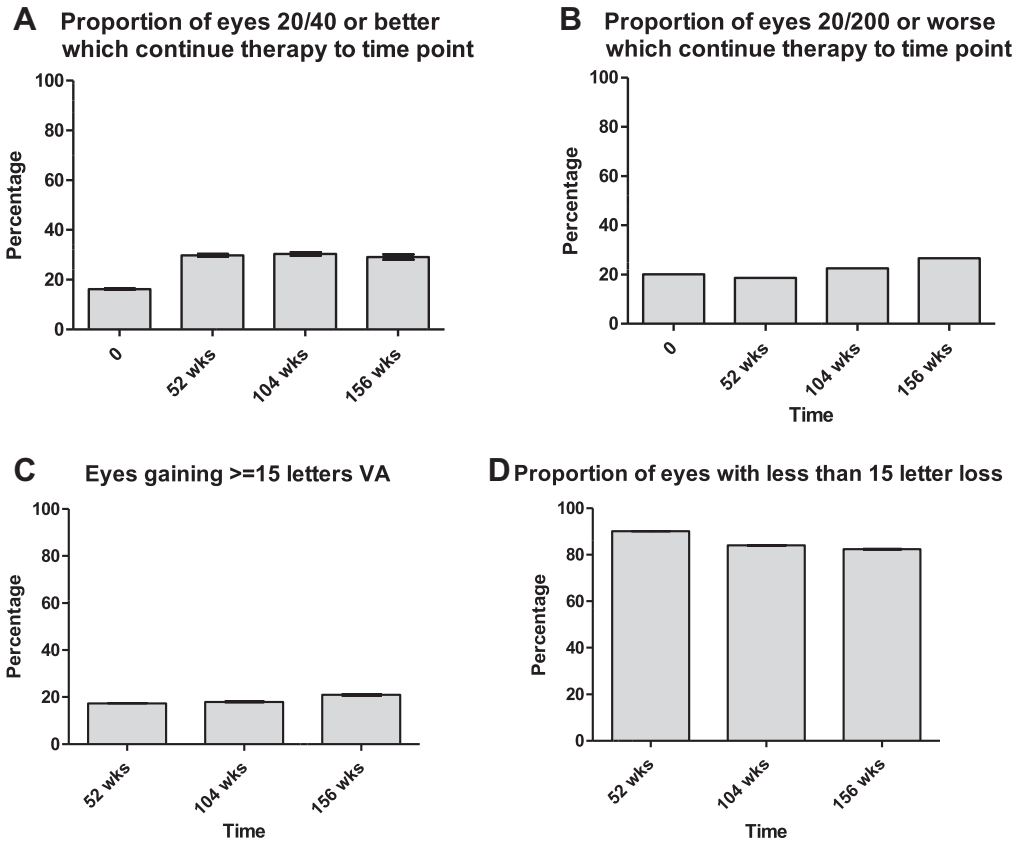

Figure 4. Bar graphs showing (**A**) the percentage of eyes with a Snellen equivalent of 20/40 or better and (**B**) the percentage of eyes with 20/200 or worse, respectively, at 0, 1, 2, and 3 years. Bar graph showing (**C**) the percentage of eyes that gained 15 letters or more (moderate gain) from baseline visual acuity (VA) at years 1 through 3 and (**D**) the percentage of eyes that lost fewer than 15 letters at the same time points. Error bars are 95% confidence intervals.

this lower dosing frequency.[3,22] The outcomes in the present study suggest that the VA outcomes achieved in the pivotal trials, ANCHOR and MARINA, are not translated into clinical practice in the United Kingdom. This may be explained by the much lower treatment frequency than expected either in the pivotal studies, in the CATT PRN arm, or in the NICE drug and disease model estimate.[3,22,23] Dichotomous VA outcomes (Fig 4) showed a lower proportion of patients gaining 15 letters of vision compared with baseline (17.4% at year 1 and 18% at year 2) than in the ANCHOR, MARINA, and CATT continuous arms by approximately 10% at week 52. Of note, the CATT PRN arm had a 25% rate of 15-letter gainers at 1 year, which increased to 30.7% at the 2-year time point. The difference may be explained by either a lower frequency of follow-up, fewer treatments, prolonged duration of symptoms, or inclusion of eyes with very good baseline VA. In the present study, the mean change in VA outcomes are somewhere between those found in the Phase IIIb, Multicenter, Randomized, Double-Masked, Sham Injection-Controlled Study of the Efficacy and Safety of Ranibizumab in Subjects with Subfoveal Choroidal Neovascularization [CNV] with or without Classic CNV Secondary to Age-Related Macular Degeneration (PIER study) (3 monthly loading injection then quarterly injections = 6 injections at fixed dosing)[24] and those found in CATT (6.9 ranibizumab injections in the PRN arm in year 1 and 5.7 ranibizumab injections in year 2).[5]

Other reasons for poor translation of clinical trial outcomes into clinical practice may be differences in patient population, which would affect the capacity for visual gain. In particular, real-world cohorts include eyes with some structural damage at the fovea, with subfoveal hemorrhage or where blood is the largest lesion component, and with very large lesions. Such patients usually are excluded from clinical trials on the basis that they have very limited scope for improvement. The mean age at presentation in this study was slightly older than that in the CATT ranibizumab PRN arm (79.7 vs. 78.4 years in CATT), and the mean baseline VA was worse than that in CATT (0.62 logMAR [55 letters] vs. 0.46 logMAR [61.5 letters]). Both the number of injections and number of visits (median, 10; interquartile range [IQR], 8–11) in the first year and a median of 9 visits (IQR, 7–10) in years 2 and 3 are fewer than expected in the drug and disease model used by NICE or in the CATT PRN arm. With regard to the proportion of eyes with VA of 20/40 or better, there was an increase from 16% at baseline to approximately 30% at year 1 in this study that was maintained to year 3 and that is lower than that found in the CATT PRN arm (39% of eyes 20/40 or better at baseline, increasing to 63% at 1 year), but the proportionate increase

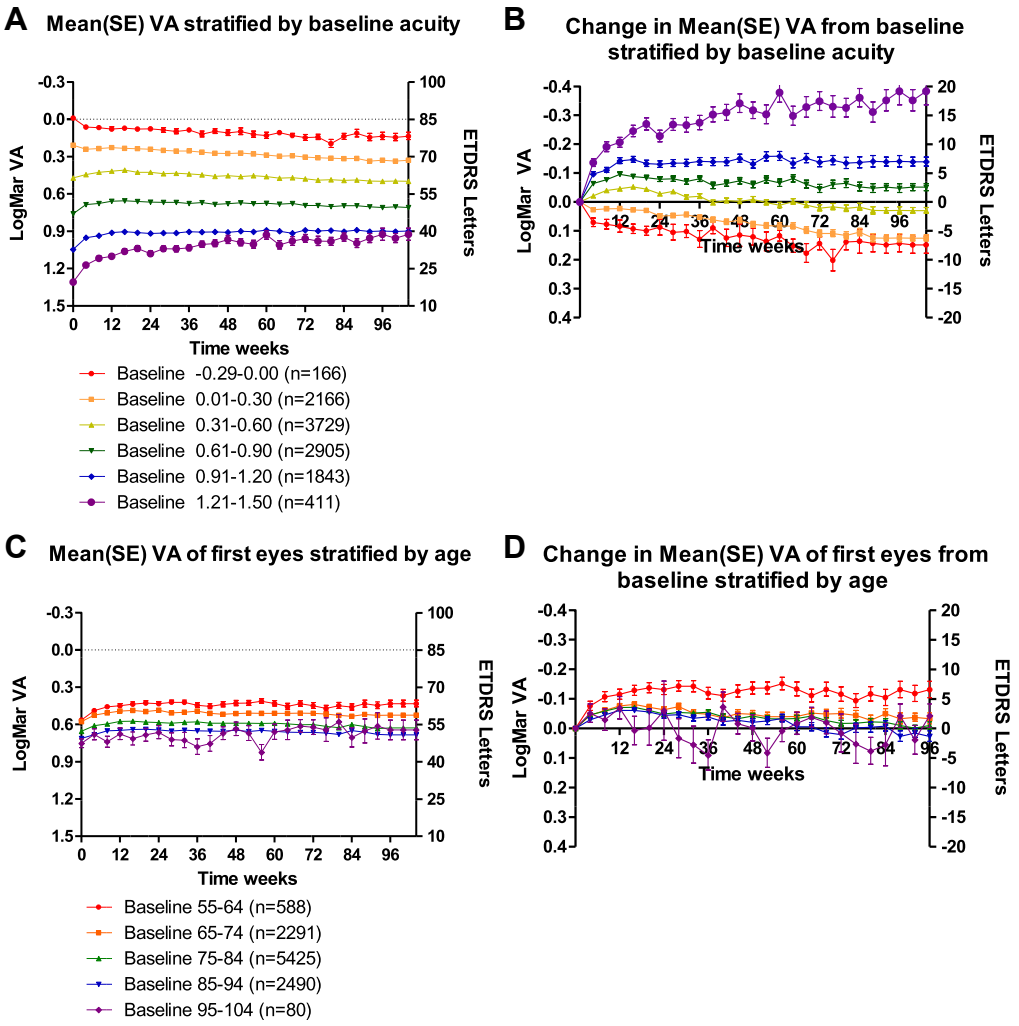

Figure 6. Graphs showing subgroups of mean visual acuity (VA; with standard error bars) over time. **A** and **B**, Mean visual acuity change stratified by baseline acuity for all eyes in 15-letter increments: (**A**) absolute acuity at each time point and (**B**) change from baseline. **C** and **D**, Mean visual acuity change stratified by age in years for first-treated eyes only in 10-year increments: (**C**) absolute acuity at each time point and (**D**) change from baseline. ETDRS = Early Treatment Diabetic Retinopathy Study; logMAR = logarithm of the minimum angle of resolution; SE = standard error.

in eyes shifting into the 20/40 or better state in this study relative to baseline was similar to that in CATT. This therefore underlines the importance of taking into account baseline status when trying to compare studies, although differences also may be attributable to either problems of delivery of therapy or difficulties for the patients in maintaining regular follow-up, or both.

Effect of Missing Data

A number of methods have been proposed to deal with missing data in controlled clinical trials, including using only complete cases and replacing missing values with the last observed value carried forward in longitudinal data or mean values in nonlongitudinal data. None of these approaches is satisfactory because they all have the potential to cause inefficiency of statistical estimators. Specifically, the last observation carried forward replacement of missing data would, in the case of mean VA declining (as in this study), bias the data toward a more positive outcome. In this article, we are describing patients still being followed up 3 years after starting treatment. Missing data would be a problem if we make inferences about patient prognosis 3 years after the start of treatment. Although imputation and techniques for dealing with missing data are becoming common in clinical trials, this is in part because of the need to preserve the randomization, which is not an objective here. We clearly describe patients who exit before 3 years, which enables readers to consider how this may impact on findings. Patients may leave because vision has improved and is stable or because their vision has deteriorated and they no longer wish to, or are unable to, attend clinics for injections. We do not know.

There was a high proportion of patients lost to follow-up, and those eyes that were lost to follow-up had a slightly worse VA at last visit. Eyes lost to follow-up were of slightly older age, which is associated with both a higher mortality rate and worse VA gain. Unlike clinical trials, patients in real-world clinics have preexisting morbidities

Table 2. Number of Visits and Treatments by Year

	Year 1	Year 2	Year 3
No. of ranibizumab injections*			
Mean	5.7	3.7	3.7
Median	6	4	4
Range	1–13	0–13	0–12
Visits per year*			
Mean (SD)	9.2 (2.3)	8.2 (2.1)	8.2 (2.1)
Median (range)	10	9 (7–10)	9 (7–10)
IQR	8–11		

IQR = interquartile range; SD = standard deviation.
*Only patients followed up for the entire year included.

where the risk of death and noncompliance is high, and the present trial had a loss to follow-up that was higher than that reported in the main clinical trials.

Effect of Baseline Characteristics on Visual Acuity Change

Baseline Visual Acuity. The very good baseline VA group (VA, −0.3 to 0 logMAR) had a mean drop of 0.12 logMAR (6-letter loss) by 52 weeks, and those with VA between 0 and 0.3 logMAR had a loss of 0.06 logMAR (3-letter loss). In the few studies with data on outcomes of eyes with baseline VA better than 70 letters (Snellen, 20/40), such as that by Williams and Blyth[25] and Ross et al,[13] the eyes with baseline vision better than 6/12 lost 0.5 letters and 1.5 letters at 1 year, respectively. This has been attributed to a ceiling effect in patients with very good vision at baseline. Our study supports the outcomes found in these previous studies in a much larger cohort of patients, as well as demonstrating this effect in patients with very good baseline VA (−0.3 to 0 logMAR), that has not been evaluated previously as a separate subgroup as well as demonstrating a significant relationship of both change in VA and VA at 12 months to baseline VA. If outcomes of therapy are just assessed by the metric of change in vision from baseline, then this would suggest that patients with good baseline vision are poor responders. In contrast, if we look at maintaining a good VA state and view Figure 7A, it shows that eyes in the very good baseline VA group maintained a VA of 0.09 logMAR (81 letters) and 0.27 logMAR (72 letters) at the 104-week time point. The mean VA lines for each of the VA subgroups separated at 0.3-logMAR (15-letter) intervals do not cross up to the 24-month point. This supports the use of ranibizumab at baseline VA better than the entry criteria of either ANCHOR, MARINA, or CATT. Although no single metric adequately describes all the different changes that occur with ranibizumab therapy over time, a useful metric for how ranibizumab is delivered in a population may be the proportion of patients with VA better than 20/40 at baseline and at subsequent time points, because this represents a measure of early access to treatment as well as effective delivery of the therapy over time. Patients with this VA level also would be able to meet the driving standard for the United Kingdom and in American states such as California.

Age. Unlike VA, age did not have such a major effect on VA gain for most of the age subgroups studied. Age at presentation of first eye treatment with ranibizumab peaked at 79 years for men and 80 years for women (Fig 2), and the proportion seeking treatment rapidly tailed off at older and younger ages. The youngest age groups gained more vision initially than the older subgroups (Fig 6). The oldest subgroup (95–105 years), although initially seeming to gain similar levels of vision as the other groups, then lost vision, and there was a lot of fluctuation in acuity over time. The oldest subgroup, however, had a relatively small number (80 eyes at baseline and only 16 eyes followed up for at least 2 years), which may explain the variability. Looking at baseline acuity by age, there was a trend for younger patients to have better baseline acuity of 0.56 logMAR (age, 55–65 years), 0.58 logMAR (age, 65–75 years), 0.65 logMAR (age, 75–85 years), 0.71 logMAR (age, 85–95 years), and 0.75 logMAR (age, 95–105 years). Eyes from patients in the younger cohorts (and better baseline vision) maintained a superior mean VA relative to the next oldest subgroup during the study follow-up, which supports the findings of the CATT study that age has an influence on VA outcomes.[26] It is possible that the better baseline VA at presentation in the younger age group is the result of earlier presentation, although the possibility of either more aggressive presentation of CNV or coexisting atrophy as a cause of lower presenting acuity in older cohorts cannot be excluded. The greater gain in VA in the younger groups is not explained by baseline VA because better baseline VA in general is associated with smaller VA gains.

What Is the Best Way to Plot Change in Visual Acuity over Time?

Figure 6 highlights the difference in plotting change in acuity relative to baseline versus actual logMAR or Early Treatment Diabetic Retinopathy Study letter score over time. Most studies plot mean change from baseline over time (CATT, ANCHOR, MARINA, etc.). This is relevant in trials to prove the efficacy of a drug, but for patients, it is more relevant to maintain better VA states over time because substantial improvements in acuity may have relatively little impact on activities of daily living if the final VA state is still poor. Plotting only mean change from baseline over time focuses attention away from whether good levels of VA are achieved and maintained. In contrast, plotting mean acuity at each time point (Fig 6A and B) describes the VA state of the study population and, given that baseline VA affects vision gain, allows an understanding of what VA gain potential there is in the study population.

Comparing box-and-whisker plots over time versus mean VA highlights the spread of the data in the population studied and shows the difference in median and mean. A combination of presenting mean acuity change over time together with a box-and-whisker plot (Fig 5, available at www.aaojournal.org) gives a more complete understanding of both the average and population change over time and gives a much better representation of the total data points available.

Role for Benchmarking Standards

Real-life delivery of therapy is problematic, with patients having intercurrent illness limiting follow-up, becoming lost to follow-up (death or moving to another area), or having difficulty achieving regular follow-up because of transportation or hospital capacity issues. To understand how well we are delivering care, we need to understand the real-life standard of care. United Kingdom clinical practice for delivering ranibizumab therapy for nAMD almost exclusively has been a loading phase of 3 monthly injections and PRN re-treatment based on disease activity as judged by optical coherence tomography scanning and fundal examination, although the compliance with the loading phase and PRN re-treatment criteria was not assessed formally in this study. The intended follow-up frequency has been monthly, although because of capacity constraints, this is not achieved at all sites. Unlike the pivotal trials and CATT PRN arm, there is less VA gain, vision tails off after the peak gain, and there is a lower proportion of patients gaining 15 letters of vision or maintaining vision of 20/40 or better. This represents what is currently being achieved in real life and acts as a real-life outcomes benchmark with which to compare local outcomes. These benefits, however, are obtained with fewer injections and fewer visits than the pivotal studies or in the CATT trial. The results, with a subsequent decrease in VA after maximum gain, are similar to those in outcome studies with most of the published treat-and-extend re-treatment approaches. Using change in VA alone is a problematic benchmark because unless it is adjusted for case mix, baseline VA and, to a lesser extent, age effect change in VA. Outcome measures such as the proportion of treated patients at baseline and 1, 2, and 3 years achieving specified VA states and stability of vision after the maximum achieved together may be good metrics to use as standards. The proportion of patients with VA of 20/40 or better will reflect not just the efficacy of the treatment but also how quickly patients can access the treatment, and this cutoff reflects the driving standard VA cutoff in many countries. The stability of vision after the maximum gained reflects the ability to follow up the patients and treat appropriately. Feedback of these outcomes to the community and comparing local outcomes with national averages may help treatment centers to alter their delivery of care to try to improve outcomes. The EMR systems such as the one used in this study provide a detailed audit of clinical outcomes at the click of a button, allowing each local site to compare their performance against the national benchmarks defined in this study.

Potential Role in Future Phase 4 and 5 Studies

Increasingly, EMR systems are being adopted with the aim that their implementation will improve quality, safety, and efficiency of care,[18] although published data to support their positive impact is limited.[27] Phase 4 trials involve safety surveillance (pharmacovigilance) and ongoing technical support of a drug after it receives permission to be sold. The EMR system used in this study captures a structured safety dataset for both local and systemic adverse events that are compulsory data entry fields at each visit after the initial ranibizumab injection visit (not presented in this article). Phase 5 is a growing term used in the literature of translational research to refer to comparative effectiveness research and community-based research; it is used to signify the integration of a new clinical treatment into widespread public health practice. The EMR study described in this article demonstrated the power and speed that very large datasets (>92 000 treatments episodes, more than 2 800 000 data fields) of high quality can be collated. The EMR used in this study already is being used to populate automatically the prospective part of the postapproval observational Luminous program (http://clinicaltrials.gov/show/NCT01318941; accessed August 2013). These data are captured as part of routine clinical care, thus avoiding the need for duplicate data entry into a study database. In future, this could be done for all patients receiving a new intervention because it comes to market providing both phase 4 and 5 datasets in a more rapid and complete way than currently at a much lower cost. In addition, because the outcomes data obtained are a by-product of normal clinical care, the outcomes obtained from an EMR approach are more likely to reflect real-life outcomes accurately than traditional phase 4 or 5 studies, where there may be both selection bias and changes in the behavior of patients and physicians who know that a study is being undertaken.

This study provided pooled, anonymized data on the demographics, visual outcome, treatment, and follow-up burden of ranibizumab treatment for nAMD. Both baseline VA and age influence VA outcome and change in VA. This study supports the use of ranibizumab therapy at baseline VA better than that used in the entry criteria of randomized controlled clinical trials. The visual outcomes achieved in this real-world cohort are worse than those achieved in the randomized controlled clinical trials. It is likely that this is because of a combination of capacity constraints preventing intended monthly review at some centers, reduced treatment frequency, and broader inclusion criteria (i.e., a different case mix) in the real world compared with clinical trials. Electronic medical record systems have the potential to collate very large volumes of data rapidly. This may enable retina specialist centers to benchmark their outcomes and facilitate cost-benefit analyses.

References

1. Rosenfeld PJ, Brown DM, Heier JS, et al; MARINA Study Group. Ranibizumab for neovascular age-related macular degeneration. N Engl J Med 2006;355:1419–31.
2. Brown DM, Kaiser PK, Michels M, et al; ANCHOR Study Group. Ranibizumab versus verteporfin for neovascular age-related macular degeneration. N Engl J Med 2006;355:1432–44.
3. National Institute for Health and Clinical Excellence. Ranibizumab and pegaptanib for the treatment of age-related macular degeneration. NICE technology appraisal guidance 155. Last modified May 2012. Available at: http://www.nice.org.uk/nicemedia/live/12057/41719/41719.pdf. Accessed August 7, 2013.
4. CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. N Engl J Med 2011;364:1897–908.

5. Comparison of Age-related Macular Degeneration Treatments Trials (CATT) Research Group, Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–98.
6. Tufail A, Patel PJ, Egan C, et al; ABC Trial Investigators. Bevacizumab for neovascular age related macular degeneration (ABC Trial): multicentre randomised double masked study. BMJ 2010;340:c2459. Available at: http://www.bmj.com/content/340/bmj.c2459?view=long&pmid=20538634. Accessed August 7, 2013.
7. IVAN Study Investigators, Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012;119:1399–411.
8. Gupta OP, Shienbaum G, Patel AH, et al. A treat and extend regimen using ranibizumab for neovascular age-related macular degeneration: clinical and economic impact. Ophthalmology 2010;117:2134–40.
9. Oubraham H, Cohen SY, Samimi S, et al. Inject and extend dosing versus dosing as needed: a comparative retrospective study of ranibizumab in exudative age-related macular degeneration. Retina 2011;31:26–30.
10. Bandukwala T, Muni RH, Schwartz C, et al. Effectiveness of intravitreal ranibizumab for the treatment of neovascular age-related macular degeneration in a Canadian retina practice: a retrospective review. Can J Ophthalmol 2010;45:590–5.
11. Rotsos T, Patel PJ, Chen FK, Tufail A. Initial clinical experience of ranibizumab therapy for neovascular age-related macular degeneration. Clin Ophthalmol 2010;4:1271–5.
12. Dadgostar H, Ventura AA, Chung JY, et al. Evaluation of injection frequency and visual acuity outcomes for ranibizumab monotherapy in exudative age-related macular degeneration. Ophthalmology 2009;116:1740–7.
13. Ross AH, Donachie PH, Sallam A, et al. Which visual acuity measurements define high-quality care for patients with neovascular age-related macular degeneration treated with ranibizumab? Eye (Lond) 2013;27:56–64.
14. Newcombe RG. Towards a reduction in publication bias. Br Med J (Clin Res Ed) 1987;295:656–9.
15. Johnston RL, Taylor H, Smith R, Sparrow JM. The Cataract National Dataset electronic multi-centre audit of 55,567 operations: variation in posterior capsule rupture rates between surgeons. Eye (Lond) 2010;24:888–93.
16. Sparrow JM, Taylor H, Qureshi K, et al. The Cataract National Dataset electronic multi-centre audit of 55,567 operations: risk indicators for monocular visual acuity outcomes. Eye (Lond) 2012;26:821–6.
17. Javitt JC. Rule Britannia. Eye (Lond) 2005;19:727–8.
18. Classen DC, Bates DW. Finding the meaning in meaningful use. N Engl J Med 2011;365:855–8.
19. Lange C, Feltgen N, Junker B, et al. Resolving the clinical acuity categories "hand motion" and "counting fingers" using the Freiburg Visual Acuity Test (FrACT). Graefes Arch Clin Exp Ophthalmol 2009;247:137–42.
20. Newcombe RG. Two-sided confidence intervals for the single proportion: comparison of seven methods. Stat Med 1998;17:857–72.
21. Rudnicka AR, Jarrar Z, Wormald R, et al. Age and gender variations in age-related macular degeneration prevalence in populations of European ancestry: a meta-analysis. Ophthalmology 2012;119:571–80.
22. Holz FG, Korobelnik JF, Lanzetta P, et al. The effects of a flexible visual acuity-driven ranibizumab treatment regimen in age-related macular degeneration: outcomes of a drug and disease model. Invest Ophthalmol Vis Sci 2010;51:405–12.
23. Center for Preventive Ophthalmology and Biostatistics. Comparison of Age-Related Macular Degeneration Treatments Trials. Available at: http://www.med.upenn.edu/cpob/studies/CATT.shtml. Accessed August 7, 2013.
24. Regillo CD, Brown DM, Abraham P, et al; PIER Study Group. Randomized, double-masked, sham-controlled trial of ranibizumab for neovascular age-related macular degeneration: PIER Study year 1. Am J Ophthalmol 2008;145:239–48.
25. Williams TA, Blyth CP. Outcome of ranibizumab treatment in neovascular age related macula degeneration in eyes with baseline visual acuity better than 6/12. Eye (Lond) 2011;25:1617–21.
26. Ying GS, Huang J, Maguire MG, et al. Comparison of Age-related Macular Degeneration Treatments Trials Research Group. Baseline predictors for one-year visual outcomes with ranibizumab or bevacizumab for neovascular age-related macular degeneration. Ophthalmology 2013;120:122–9.
27. Black AD, Car J, Pagliari C, et al. The impact of eHealth on the quality and safety of health care: a systematic overview. PLoS Med [serial online] 2011;8:e1000387. Available at: http://www.plosmedicine.org/article/info%3Adoi%2F10.1371%2Fjournal.pmed.1000387. Accessed August 7, 2013.

Footnotes and Financial Disclosures

Originally received: April 6, 2013.
Final revision: November 18, 2013.
Accepted: November 18, 2013.
Available online: January 24, 2014. Manuscript no. 2013-568.

*A complete list of members of the UK Age-Related Macular Degeneration EMR Users Group is available at www.aaojournal.org.

Writing Committee for the UK Age-Related Macular Degeneration EMR Users Group: Adnan Tufail, MD, FRCOphth; Wen Xing, MSc; Robert Johnston, FRCOphth; Toks Akerele, MD, FRCOphth; Martin McKibbin, FRCOphth; Louise Downey, MBChB, FRCOphth; Salim Natha, MBChB, FRCOphth; Usha Chakravarthy, MD, PhD; Clare Bailey, MD, FRCOphth; Rehna Khan, MB, ChB; Richard Antcliff, FRCOphth; Stewart Armstrong, FRCOphth; Atul Varma, MSCOphth; Vineeth Kumar, FRCSEd(Ophth); Marie Tsaloumas, MBBS, FRCOphth; Kaveri Mandal, FRCSEd(Ophth); and Catey Bunce, DSc.

Financial Disclosure(s):
The author(s) have made the following disclosure(s):

Robert L. Johnston: Employee — Medisoft Limited.

Supported in part by an unrestricted grant from Novartis Pharmaceuticals UK Limited, Frimley, UK. No member or affiliate of Novartis had any input into data analysis, interpretation of the data, or writing the manuscript. This research received a proportion of its funding from the Department of Health's NIHR Biomedical Research Centre for Ophthalmology at Moorfields Eye Hospital and UCL Institute of Ophthalmology. The views expressed in the publication are those of the authors and not necessarily those of the Department of Health.

Correspondence:
Adnan Tufail, MD, FRCOphth, Moorfields Eye Hospital NHS Trust, 162 City Road, London EC1V 2PD, United Kingdom. E-mail: Adnan.tufail@moorfields.nhs.uk.