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1 **The UK Neovascular AMD Database Report 3: Inter-Centre Variation in Visual Acuity Outcomes and**
2 **Establishing Real-World Measures of Care.**

3 Subtitle: Real world Outcomes in UK centres.

4

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18 Record software provider from which data were extracted. All other authors have no relevant financial
19 conflicts of interest to disclose.

20

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23

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25

26

27

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51 **Financial Disclosures**

52 Robert L Johnston is the Medical Director of Medisoft Limited, the Electronic Medical Record software
53 provider from which data were extracted. All other authors have no relevant financial conflicts of interest
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57

59 **Abstract**

60 **Aims:** International variations in visual acuity (VA) outcomes of eyes treated for neovascular age-related
61 macular degeneration (nAMD) are well documented, but intra-country inter-centre regional variations are
62 not known. This data is important for national quality outcome indicators. We aimed to determine intra-
63 country, inter-centre regional variations in outcomes for treatment of nAMD.

64 **Methods:** Prospective multi-centre national database study of 13 UK centres that treated patients
65 according to a set protocol (3 loading doses, followed by pro-re-nata re-treatment). 5,811 treatment naive
66 eyes of 5,205 patients received a total of 36,206 ranibizumab injections over 12 months.

67 **Results:** Mean starting VA between centres varied from 48.9 to 59.9 ETDRS letters. Mean inter-centre VA
68 change from baseline to 12 months varied from +6.9 letters to -0.6 letters (mean of +2.5 letters). The
69 proportion of eyes achieving VA of 70 letters or more varied between 21.9% and 48.7% at 12 months.
70 Median number of injections (visits) at each centre varied from 5 to 8 (9 to 12) with an overall median of 6
71 (11). Age, starting VA, number of injections and visits but not gender were significantly associated with
72 variation in these VA outcomes ($P < 0.01$). Significant variation between centres persisted even after
73 adjusting for these factors.

74 **Conclusions:** There are modest differences in VA outcomes between centres in the UK. These differences
75 are influenced, but not completely explained, by factors such as patient age, starting VA, number of
76 injections and visits. These data provide an indication of the VA outcomes that are achievable in real world
77 settings.

78

79 **Introduction**

80 Age-related macular degeneration (AMD) is one of the leading causes of irreversible blindness in patients
81 aged over 60 years. Since the introduction of anti-Vascular Endothelial Growth Factor (VEGF) agents to
82 treat neovascular AMD (nAMD) in 2006, rates of blindness and visual impairment from AMD have declined
83 dramatically.¹⁻³ Data from several randomized clinical trials suggest patients gain on average 6-11 letters
84 using the most aggressive monthly dosing posology in the first year of treatment.⁴⁻⁷ A less resource
85 intensive Pro-Re-Nata (PRN) dosing posology has been found in the Comparison of Age-related macular
86 degeneration Treatment Trials (CATT)^{6;8} and Inhibit VEGF in Age-related choroidal Neovascularisation
87 (IVAN)^{7;9} trials to produce outcomes similar to monthly dosing. This has provided a sound empirical basis
88 for use of PRN posology in the National Health System (NHS) in the United Kingdom (UK).

89

90 Although PRN dosing posology in theory is able to achieve excellent outcomes, 'real-world' studies have not
91 matched the outcomes achieved in clinical trials.¹⁰⁻¹³ We have previously reported longitudinal results from
92 a cohort of patients recruited from hospitals in the UK.^{10;11;14} Patients had standardised data recorded at
93 the point of care into an Electronic Medical Record (EMR) system and the grouped national findings
94 showed that PRN retreatment after 3 loading doses resulted in moderately stable vision.¹¹ National data
95 have also been reported from Australia for a treat and extend posology.¹⁵ International multi-country real
96 life comparisons have reported some international differences in VA outcomes and treatment
97 patterns,¹⁶ which may be influenced by different reimbursement and health system structures. However,
98 what remains unclear is how much, if any, intra-country inter-centre regional variation occurs. This data is
99 obscured by aggregate national data, and is important as it permits understanding of the factors that
100 influence outcomes in a real world setting and allows national quality benchmarks to be set. In this report
101 we examine inter-centre variations in patient characteristics, the number of treatments delivered and their
102 impact on visual outcomes in 13 geographically distinct UK centres.

103

104 **Methods**

105 **Study Design**

106 The study design is described in detail in previous reports from the UK-nAMD Database Study group.^{10;11;14}
107 In brief, sites known to make comprehensive use of Electronic Medical Records (EMR) systems were
108 contacted and requested to contribute data. Patient identifiers were completely removed and site and
109 clinician data were pseudo-anonymised. On this basis an ethics committee determined that formal ethics
110 approval was not required. The study was conducted in accordance with the declaration of Helsinki and the
111 UK's Data Protection Act.

112 **Study Centres**

113 Thirteen NHS hospitals that deliver ranibizumab AMD treatment services in England and Northern Ireland
114 submitted data to this study. Each site is the sole NHS provider of nAMD care to their local population and
115 very few patients switch between providers. Following NICE approval for the use of ranibizumab for nAMD
116 in the NHS in August 2008 all sites used this drug almost exclusively, although prior to this date some sites
117 offered limited treatment with bevacizumab. The study was initiated on 1st Feb 2012, all approvals and data
118 extraction was performed by 02 April 2012. Data was delivered to the analysis team by the end of April
119 2012.

120 **Data variables**

121 Analysis was restricted to treatment-naïve eyes undergoing ranibizumab therapy conforming to 3 monthly
122 loading dose followed by PRN posology for nAMD that completed at least 12 months of follow up.
123 In this report the 'best-measured VA' was the best VA with refraction or habitual correction and/or pinhole
124 as measured on an ETDRS chart and expressed as LogMAR vision and ETDRS letters. The vast majority of
125 sites measured VA with habitual correction rather than best-corrected refracted VA at all time points and
126 used ETDRS charts. Analysis for eyes with very low VA was undertaken by substituting counting fingers (CF),
127 hand movement (HM), and perception of light (PL) with 2.0, 2.3, and 2.7, respectively.
128 We examined the outcome measures commonly reported in clinical trials (VA change from 0 to 12 months,
129 proportion of eyes gaining and losing 15 ETDRS letters etc) as well as other measures such as VA change
130 from 3 to 12 months and proportion of eyes achieving 70 ETDRS letters at 12 months (Snellen equivalent of
131 20/40 or 6/12, driving equivalent in many jurisdictions).

132 **Statistical methods**

133 Medisoft Ophthalmology (Medisoft Limited, Leeds, UK) was the EMR system used for data extraction. Data
134 for right and left eyes of patients who had had at least one intravitreal injection of ranibizumab for nAMD
135 were extracted. Both STATA version 11 and SPSS version 19 were used to analyse data. Perl and R package
136 ggplot2 was used for multivariable analyses, construction of generalised linear models and creation of
137 funnel plots.

138 **Results**

139 **Participants**

140 Over the 1 year of follow up analysed in this study, 36,206 ranibizumab injections were performed in 5,811
141 eyes. Table 1 shows the baseline demographics of each of the 13 centres. The number of eyes treated
142 ranged from 39 (Centre M) to 923 (Centre C). Patients treated at each centre were of similar age, ranging
143 from a mean of 78.3 (J) to 81.7 years at the time of the first injection (K).

144 Treatment and outcome characteristics of each centre are shown in Table 2. The median number of
145 injections in each centre was 6 with one centre providing a median of 8 injections (J) and 2 centres
146 providing a median of 5 (L, M). Mean starting VA across all centres was lowest in centre F (48.9 ETDRS
147 letters) and highest in centre L (59.9 letters). VA after 12 months of treatment was highest in centre I (63.2
148 letters) and lowest in centre M (52.9 letters). The centres with the higher mean starting VA did not
149 necessarily finish 12 months with the highest VA at 1 year, nor did the centres with the lowest starting VA
150 finish with the lowest VA at 1 year. Centres that saw patients the most frequently (B) or injected most
151 frequently (J) achieved the 5th and 2nd best VA at 1 year respectively and showed the least variation
152 between 3 and 12 months.

153 At 12 months, the mean change in VA across 13 centres varied from +6.9 letters (centre I) to -0.6 letters
154 (centre L), a difference of 7.5 letters, with a mean VA gain of +2.5 letters. Figure 1 shows these results
155 graphically, with further details in Table 2. The funnel plot in Figure 1 shows the distribution of centres and
156 95% and 99% confidence intervals. Two centres (L, D) were slightly outside the 99% confidence intervals;
157 these were the only centres reporting a slight reduction in VA. One of these centres had the lowest number
158 of injections (5, L); however the other centre had the median number of injections (6, D). Starting VA in

159 centre D was near the middle of the distribution, at 53.7 letters, while in centre L, eyes commenced
160 treatment with the best starting VA at 59.9 letters. In contrast, Figure 2 (supplement) shows that there was
161 less variation in VA change from 0 to 3 months, with a tighter clustering of results. Figure 3 (supplement)
162 shows the VA change from 3 months to 12 months, with most centres clustered within the 95% confidence
163 intervals, and the previous 2 centres that were outside the 99% CI when considering change from 0-12
164 months are now either within or very close to the limits (L, D).

165 The proportion of eyes that gained 15 ETDRS letters or more at 12 months ranged from 7.7% (A) to 29.5%
166 (K). When examined on the funnel plot (Figure 4 supplement), these proportions showed little variation
167 from centre to centre, with all centres within or above the 99% CI. The proportion of eyes that lost 15
168 ETDRS letters or more at 12 months showed an even tighter distribution, with all centres within the 99% CI,
169 and all except one (L) within the 95% CI (Figure 5 supplement). The actual proportions ranged from 4.6% (I)
170 to 11.7%(L). We also examined the proportion of eyes maintaining or achieving driving vision of 70 ETDRS
171 letters or more and found all centres performed above the lower 99% CI limit.(Figure 6)

172 It should be noted that the centre with the lowest number of visits and injections (M, median 9 visits,
173 median 5 injections, Table 2) had outcomes in the middle of the distributions for all the VA measures
174 studied (Figures 1-6). Similarly, the centres with the highest number of visits (B, 12 visits) and highest
175 number of injections (J, 8 injections), generally had outcomes either in the middle of the distribution or
176 higher than average but still within the 95% CI (Figures 1-6).

177 We performed multivariable analyses to determine which factors were associated with better visual
178 outcomes. Younger age, worse starting VA, and higher number of injections and visits but not gender were
179 significantly associated with variation in these VA outcomes ($P<0.01$). Significant variation between centres
180 persisted even after adjusting for these factors.

181 **Discussion**

182 There is considerable published data on VA outcomes derived from clinical trials but limited data describing
183 real-world outcomes. Real-world outcomes indicating what is possible when trial results translate to clinical
184 practice are ultimately the most important measure as they reflect what happens to whole populations of
185 patients rather than the rarefied cohorts included in trials. They are also important for establishing

186 benchmarks standards that are achievable in busy public systems, and for defining measures of quality care
187 that take into account the heterogeneity of patient populations and care delivery systems. This study
188 provides some of the first real-world outcomes from a single national health system, namely 13 UK public
189 hospital centres using a PRN treatment posology. We report that there was some inter-centre variation in
190 VA outcomes up to a maximum difference of 7.5 letters between the highest and lowest VA achieved from
191 0-12 months. Age, starting VA, number of injections and visits but not gender were significantly associated
192 with variation in these VA outcomes.

193 The median performance of these 13 centres is comparable to results from clinical trials, once the lower
194 starting VA and lower number of injections is taken into account. Table 3 compares findings from this study
195 with clinical trial results. The CATT⁶ and IVAN^{7,9} studies achieved mean improvement from 0-12 months of
196 6.8 and 5.0 letters, respectively with 7 injections, while the Groupe d'Etude Français Avastin versus Lucentis
197 dans la DMLA néovasculaire (GEFAL)¹⁷ and Multicentre Anti-VEGF Trial in Austria (MANTA)¹⁸ studies
198 showed mean improvement of 2.9 and 4.1 letters respectively with 6 injections, as compared with mean
199 improvement of 2.5 letters with 6 injections in this study. These results suggest that a similar benchmark of
200 +2.5 letters improvement (0-12 months) with 6 injections represents quality ongoing care that is achievable
201 in a real-world, public hospital setting.

202 There are few other real-world studies with which to compare our results. A large database observational
203 study from Australia, the Fight Retinal Blindness Study,¹⁹ reported mean VA gains of 5.3 letters after 2 years
204 and 13 injections of a treat and extend posology. These results are superior to those achieved in this report
205 but direct comparisons are difficult due to differences in health systems, patient mix, and different follow-
206 up periods.

207 It should be noted that the difference in 0-12 month VA change between the highest and lowest scoring
208 centres was 7.5 ETDRS letters, a difference that is only marginally beyond what some studies have
209 considered non-inferior. The CATT⁶ and GEFAL¹⁷ considered a difference of 5 EDTRS letters to represent
210 noninferiority, while the MANTA¹⁸ considered a difference of 7 letters to be noninferior.¹⁸

211 Due to the 'ceiling effect' whereby eyes starting treatment with good VA have little room for further
212 improvement, many measures are dependent on the starting VA.^{11;12;20} Adjusting for age, starting VA,
213 number of injections and visits reduced, but did not eliminate the significant variation between centres,
214 suggesting there are other unmeasured factors that contribute to these variations in outcomes.

215

216 This study has several strengths including a large sequential sample, collection of a standardised minimum
217 dataset as mandated by the use of an EMR reflecting routine, real-world clinical practice and the large
218 number of centres involved. A weakness of this study is the loss to follow up of a number of patients over
219 time, as is inevitable in a real-world clinical setting. Although there were differences in baseline
220 demographics between patients lost to follow-up and those who completed follow-up, we have previously
221 shown that VA changes are similar in both groups.¹¹ Best-corrected VAs were not routinely measured,
222 instead the VAs with habitual correction were reported in this study which may underestimate absolute VA
223 measurements compared with clinical trials. It should be noted that clinical treatment decisions were based
224 on these VAs and we believe these represent real-world outcomes and may better reflect patients' visual
225 experience than protocol determined best-corrected VAs. A possible reason for differences in injection
226 numbers may be individual differences in centre / physician thresholds for retreatment using a PRN
227 posology.

228

229 In summary, we report that 13 UK centres using a PRN treatment posology for managing neovascular AMD
230 achieved broadly similar VA outcomes with modest variability in outcomes. The difference between the
231 highest and lowest VA gain at 12 months was 7.5 letters with a mean of +2.5 letters gained. Age, starting
232 VA, number of injections and visits but not gender were significantly associated with variation in these VA
233 outcomes. These data may be considered as establishing an achievable benchmark for the quality of PRN
234 posology in real-world settings, and is likely to be relevant to many sites worldwide.

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257

258

259
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261 the accuracy of the data analysis.

262

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266 denmark: year 2000 to 2010. *Am J Ophthalmol*. 2012; 153:209-213.
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316 degeneration treated with ranibizumab? *Eye (Lond).* 2013; 27:56-64.
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319

320 Figure Legends.

321 **Figure 1:** *Funnel plot showing the change in ETDRS letters from baseline to 12 months by centre. Solid black*
322 *lines represent the 95% confidence intervals, dashed lines the 99% confidence intervals. ETDRS refers to*
323 *Early Treatment Diabetic Retinopathy Study.*

324
325 **Figure 2 (supplement):** *Funnel plot showing the change in ETDRS letters from baseline to 3 months by*
326 *centre. Solid black lines represent the 95% confidence intervals, dashed lines the 99% confidence intervals.*
327 *ETDRS refers to Early Treatment Diabetic Retinopathy Study.*

328
329 **Figure 3 (supplement):** *Funnel plot showing the change in ETDRS letters from 3 months to 12 months by*
330 *centre. Solid black lines represent the 95% confidence intervals, dashed lines the 99% confidence intervals.*
331 *ETDRS refers to Early Treatment Diabetic Retinopathy Study.*

332
333 **Figure 4 (supplement):** *Funnel plot showing the proportion of eyes gaining 15 ETDRS letters or more from*
334 *baseline to 12 months by centre. Solid black lines represent the 95% confidence intervals, dashed lines the*
335 *99% confidence intervals. ETDRS refers to Early Treatment Diabetic Retinopathy Study.*

336
337 **Figure 5 (supplement):** *Funnel plot showing the proportion of eyes losing 15 ETDRS letters or more from*
338 *baseline to 12 months by centre. Solid black lines represent the 95% confidence intervals, dashed lines the*
339 *99% confidence intervals. ETDRS refers to Early Treatment Diabetic Retinopathy Study.*

340
341 **Figure 6:** *Funnel plot showing the proportion of eyes maintaining driving vision of 70 ETDRS letters or better*
342 *at 12 months by centre. Solid black lines represent the 95% confidence intervals, dashed lines the 99%*
343 *confidence intervals. ETDRS refers to Early Treatment Diabetic Retinopathy Study.*

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