E.4 Referral

E.4.1 Organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow-up people with suspected and confirmed AMD

RQ5: How do different organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow up influence outcomes for people with suspected AMD (for example correct diagnosis, errors in diagnosis, delays in diagnosis, process outcomes)?

RQ16: How do different organisational models for ongoing treatment and follow up influence outcomes for people with diagnosed neovascular AMD (for example disease progression, time to treatment, non-attendance)?

RQ 24: How soon should people with neovascular AMD be diagnosed and treated after becoming symptomatic?

Bibliographic reference	**Muen Wisam J; Hewick Simon. Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study. 2011; JRSM Short Reports; 2(8): 2042-5333**
Country/ies where the study was carried out:	UK
Study type	Prospective study
Aim of the study	To assess the use and quality of referrals to a neovascular age-related macular degeneration clinic from optometrists using the standard rapid access referral form from the Royal College of Ophthamologists
Study dates	Referrals made between December 2006 and August 2009
Setting	Eye department at NHS Highlands Trust
Source of funding	Not reported
Sample size	54 rapid access referrals forms
Inclusion criteria	All patients referred to the eye department at NHS Highlands Trust using the RARF
Exclusion criteria	Not specified
Baseline characteristics	Not specified

<table>
<tr><th>Bibliographic reference</th><th>Muen Wisam J; Hewick Simon. Quality of optometry referrals to neovascular age-related macular degeneration clinic: a prospective study. 2011; JRSM Short Reports; 2(8): 2042-5333</th></tr>
<tr><td>Methods</td><td>Prospective data were gathered from all optometry referrals using the rapid access referral form(RARF), between the periods of December 2006 to August 2009. These were assessed for accuracy of history, clinical signs and final diagnosis as compared to a macula expert.
The specific points recorded in the history were:
Reduction of vision
Distortion
Central scotoma
The clinical signs assessed were:
Haemorrhage
Exudates
Drusen
Subretinal fluid/macular oedema
All patients were seen within 2 weeks of receipt of the referral. The optometrist history was taken from the RARF, and this was compared with the history obtained by the ophthammologists on the same three points.</td></tr>
<tr><td>Results</td><td>The overall agreement between the specialist and optometrist on all three history findings was 57.4%;

The total number of patients with a correct diagnosis of neovascular AMD was 37% (n=20).
<table>
<tr><td>Diagnosis</td><td>Patients (n, %)</td></tr>
<tr><td>Exudative</td><td>20 (37.0)</td></tr>
<tr><td>Dry AMD</td><td>10 (18.5)</td></tr>
<tr><td>Branch retinal vein occlusion</td><td>4 (7.4)</td></tr>
<tr><td>Central serous retinopathy</td><td>4 (7.4)</td></tr>
<tr><td>Macular scar</td><td>3 (5.6)</td></tr>
<tr><td>Posterior vitreous detachment</td><td>2 (3.7)</td></tr>
</table></td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Dobbelsteyn D ; McKee K ; Bearnes R D; Jayanetti S N; Persaud D D; Cruess A F; What percentage of patients presenting for routine eye examinations require referral for secondary care? A study of referrals from optometrists to ophthalmologists.2015; Clinical & Experimental Optometry; 98(3):214-17.</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Nova Scotia, Canada:</td></tr>
<tr><td>Study type</td><td>Retrospective cohort case study</td></tr>
<tr><td>Aim of the study</td><td>To investigate the percentage of asymptomatic patients presenting for routine optometric eye examinations that have pathology or pathology-related risk factors warranting referral for ophthalmological consultation</td></tr>
<tr><td>Study dates</td><td>Patients presented for routine eye care between 2007 and 2010</td></tr>
<tr><td>Setting</td><td>2 large multi-practitioner optometric clinics</td></tr>
<tr><td>Source of funding</td><td>Financial support of the Canadian optometric trust fund.</td></tr>
<tr><td>Sample size</td><td>23,330 individual patients were examined during study period.</td></tr>
<tr><td>Inclusion criteria</td><td>(i) The patient presented for routine optometric eye care during a specified period of time; (ii) the patient was found to have pathology (or showed enough risk of pathology) resulting in referral to an ophthalmologist; and (iii) a referral report was received from the consulting ophthalmologist stating the diagnosis and the treatment plan</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>A retrospectively review of patients files to indicate if patients were symptomatic or asymptomatic of the indicated pathology. Patient’s files were obtained at clinics through an electronic programme, which enabled the identification of patients meeting the inclusion criteria. Researchers then created a database including the patients’ ID, date of referral, clinical reasons for the referral, presence or absence of symptoms of pathology, diagnosis and treatment plan. Clinical reasons for referral were extracted from referral letters and sorted into 6 categories: AMD, cataract, glaucoma, diabetic, retinopathy, retinopathy and other.</td></tr>
<tr><td>Results</td><td>Referrals for symptomatic and asymptomatic patients
<table>
<tr><th></th><th>All referrals</th><th>symptomatic</th><th>asymptomatic</th><th>Total patients seen</th></tr>
<tr><td>Referrals for all ages</td><td>4,076</td><td>2,992</td><td>1,084</td><td>45,232</td></tr>
<tr><td>% of patients seen</td><td>9%</td><td>6.6%</td><td>2.4%</td><td></td></tr>
</table>
Reasons for referrals</td></tr>
</table>

Bibliographic reference	**Dobbelsteyn D ; McKee K ; Bearnes R D; Jayanetti S N; Persaud D D; Cruess A F; What percentage of patients presenting for routine eye examinations require referral for secondary care? A study of referrals from optometrists to ophthalmologists.2015; Clinical & Experimental Optometry; 98(3):214-17.**

	Number of asymptomatic patients referred (total=1084) (%)	Number of symptomatic patients referred (total=2992) (%)	Relative risk (95%CI)
Retina	555 (51.2)	564 (18.8)	2.72 (2.47 to 2.98)
Glaucoma	307 (28.3)	199 (6.6)	4.26 (3.61 to 5.02)
Diabetic retinopathy	74 (6.8)	72 (2.4)	2.84 (2.07 to 3.89)
Other	67 (6.2)	991 (33.1)	0.19 (0.15 to 0.24)
Cataract	51 (4.7)	1,013 (33.8)	0.14 (0.11 to 0.18)
AMD	30 (2.7)	153 (5.1)	0.54 (0.37 to 0.80)

Bibliographic reference	**Azzolini C ; Torreggiani A ; Eandi C ; Donati S ; Oum M A; Vinciguerra R ; Bartalena L ; Tartaglia V. A teleconsultation network improves the efficacy of anti-VEGF therapy in retinal diseases. 2013. Journal of Telemedicine & Telecare; 19(8): 437-442.**
Country/ies where the study was carried out	Italy
Study type:	Cohort study
Aim of the study	To investigate the care of patients with age-related macular degeneration (AMD) managed via a physician-to-physician teleconsultation network for ophthalmology.
Study dates	June 2011 and December 2012.
Setting	10 cities across Italy, 11 groups of ophthalmologists, each group was based on retina centre located at a university or hospital
Source of funding	Not reported
Sample size	678 patients including 360 network patients and 318 control patients (consecutive undergoing usual care during the 3 months before the use of the network)
Inclusion criteria	Not specified
Exclusion criteria	Not specified

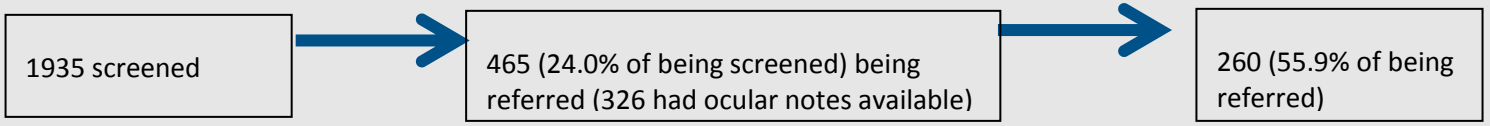
Bibliographic reference	**Azzolini C ; Torreggiani A ; Eandi C ; Donati S ; Oum M A; Vinciguerra R ; Bartalena L ; Tartaglia V. A teleconsultation network improves the efficacy of anti-VEGF therapy in retinal diseases. 2013. Journal of Telemedicine & Telecare; 19(8): 437-442.**
Baseline characteristics	Not specified
Methods	A longitudinal comparison of patient care in sites using the new telemedicine network, named as Reading Centre 2.0. The main components of the network are: • a central service, • a web accessible database, • storage and forwarding functions, • dedicated electronic medical records • short message service • email notification between physician, guaranteed privacy and confidentiality • a central help desk Main development in the software are: • application software for both computer and ipad/iphones • a grading system accounting for 5 variables providing key information about the risk of exudative AMD: age, visual acuity, Amsler test, macular haemorrhage and the status of second eye • an interactive booking system to make an appointment directly with the Retina centre from outside with SMS notification for patients • successive multiple masks for comparing images of the same electronic medical record during follow-up • pop-up window to assist physicians and ensure correct data entry A tablet computer (ipad) was given to each participant. Web consultation tests were carried out on site. After the initial meeting, the general ophthalmologist used the teleconsultation network for a trial period of 7-10 days to exchange clinical data with retina specialists from retina centres. After the trial period, the ophthalmologist began to exchange real data over the following 3-month period. At the end of the 3 month period, the ophthalmologist at each site discussed the following results at a final audit meeting: Degree of access to the network, Acceptability of technology and medical efficacy

Bibliographic reference	**Azzolini C ; Torreggiani A ; Eandi C ; Donati S ; Oum M A; Vinciguerra R ; Bartalena L ; Tartaglia V. A teleconsultation network improves the efficacy of anti-VEGF therapy in retinal diseases. 2013. Journal of Telemedicine & Telecare; 19(8): 437-442.**
Results:	

	Telemedicine network (n=360)	Usual care (n=318)	Effect (95%CI)
Visual acuity			
First visit, log MAR (range)	0.29 (0.23 to 0.34)	0.29 (0.24 to 0.35)	0
Post-treatment	0.22 (0.18 to 0.25)	0.27 (0.23 to 0.32)	-0.05
Time from first visit to general ophthalmologist to treatment, mean days (SD)	5.5 (1.4)	28.7 (4.0)	-23.20 (-23.66 to -22.74)

Notes	Not randomised trial (before-after study)

Bibliographic reference	**Chasan J E; Delaune B ; Maa A Y; Lynch M G; Effect of a teleretinal screening program on eye care use and resources. 2014; JAMA Ophthalmology, 132 (9).; 1045-51.**
Country/ies where the study was carried out	United State
Study type	Retrospective study
Aim of the study	To evaluate the effect of a community-based diabetic teleretinal screening program on eye care use and resources
Study dates	October 1, 2008, to March 31, 2009
Setting	Community based clinics
Source of funding	Not reported
Sample size	1935 underwent diabetic telerentinal screening in the primary care community-based clinics.
Inclusion criteria	Patients underwent diabetic telerentinal screening in the primary care community-based clinics and were referred for an ophthalmic examination in the eye clinic.
Exclusion criteria	Not specified
Baseline characteristics	Not reported

Bibliographic reference	**Chasan J E; Delaune B ; Maa A Y; Lynch M G; Effect of a teleretinal screening program on eye care use and resources. 2014; JAMA Ophthalmology, 132 (9).; 1045-51.**
Methods	Clinical medical records were reviewed for a 2-year period after patients were referred from teleretinal screening. The following information was collected for analysis: patient demographics, referral and confirmatory diagnoses, ophthalmology clinic visits, diagnostic procedures, surgical procedures, medications, and spectacle prescriptions. Retinal cameras are used to capture images, which are remotely interpreted by an eye care professionals in a centralised reading centre.
Results	Between October 1 2008 to March 31 2009, a total of 1935 people underwent diabetic teleretinal screening in the primary care community-based clinical. Of those screened, 465 (24.0%) were referred to the eye clinic for an ophthalmic examination, 326 had ocular notes available (70.1% being referred) Of those referred, 260 (55.9%) underwent an ophthalmic examination within 2 years of the teleretinal screening.  Patients number by referral diagnoses Referral diagnoses / No. of patients (%) (total=465) Nonmacular diabetes retinopathy: 201 (43.2) Never-related disease: 143 (30.8) Lens or media opacity: 89 (19.1) Age-related macular degeneration: 60 (12.9) Diabetic macular edema: 26 (5.6) other: 67 (14.4) unreadable: 45 (9.7) Accuracy of telretinal screening in detecting diagnosis categories (n=326)

Bibliographic reference	**Chasan J E; Delaune B ; Maa A Y; Lynch M G; Effect of a teleretinal screening program on eye care use and resources. 2014; JAMA Ophthalmology, 132 (9).; 1045-51.**
	<table><tr><td>Referral diagnoses</td><td>Sensitivity, %</td></tr><tr><td>Nonmacular diabetes retinopathy</td><td>81.2</td></tr><tr><td>Never-related disease</td><td>88.4</td></tr><tr><td>Lens or media opacity</td><td>56.0</td></tr><tr><td>Age-related macular degeneration</td><td>81.6</td></tr><tr><td>Diabetic macular edema</td><td>75.3</td></tr><tr><td>other</td><td>36.6</td></tr><tr><td>unreadable</td><td>73.6</td></tr></table>
Notes	The percentage of agreement of the teleretinal imaging programmer was calculated by comparing the referral diagnosis to the confirmation diagnosis. Sensitivity was calculated by dividing the total number of referral diagnosis confirmed by ophthalmic examination by number of diagnoses detected by ophthalmic examination. Study populations were not AMD specific.

Bibliographic reference	**Tschuor P ; Pilly B ; Venugopal D ; Gale R P. Optimising assessment intervals improves visual outcomes in ranibizumab-treated age-related neovascular degeneration: using the stability phase as a benchmark.2013. Graefes Archive for Clinical & Experimental Ophthalmology; 251 (10): 2327-30.**
Country/ies where the study was carried out	UK
Study type	Cohort study
Aim of the study	To observe visual acuity change in the stability phase when follow-up intervals are decreased in ranibizumab-treated neovascular age-related macular degeneration
Study dates	Data collected between October 2009 and December 2012
Setting	A base hospital to a community eye clinic
Source of funding	Not reported

<table>
<tr><th>Bibliographic reference</th><th>Tschuor P ; Pilly B ; Venugopal D ; Gale R P. Optimising assessment intervals improves visual outcomes in ranibizumab-treated age-related neovascular degeneration: using the stability phase as a benchmark.2013. Graefes Archive for Clinical & Experimental Ophthalmology; 251 (10): 2327-30.</th></tr>
<tr><td>Sample size</td><td>62 patients (72 treated eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were 50 years or over and have had a fluorescein angiogram confirmed diagnosis of nvAMD. In addition to this, the patients must have been in stability phrase of treatment, defined as the period following their 3 initial treatment with ranibizumab.</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Number of female (n=45); mean age, years=82.0</td></tr>
<tr><td>Methods</td><td>154 patients with nvAMD treated with intravitreal ranibizumab in routine clinical practice. Patients were transferred from a base hospital to a community eye clinic. Prior to transfer, the first 3 injection of ranibizumab were given at monthly intervals. However, following this, the follow-up interval could not be guaranteed to be monthly.
The patients must have attended at least 12 visits in the stability phrase consisting of 6 visits at the base hospital followed by 6 visits at the community eye centre. Both the base hospital and the community eye clinic used a “one-stop” mode enabling assessment and re-treatment to be performed at the same visit.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td>Community eye clinic (7 to 12 visits)</td><td>Base hospital (1 to 6 visits)</td><td>Effect (95%CI)</td></tr>
<tr><td>Mean follow-up time between each visit, days (range)</td><td>31.81 (21 to 139)</td><td>56.81 (21 to 288)</td><td>-25.0 (-30.48 to -19.52)</td></tr>
<tr><td>Mean BCVA , letters(SD)</td><td>55.7 (15.5)</td><td>54.5 (14.0)</td><td>1.20 (-4.00 to 6.40)</td></tr>
<tr><td>VA changes over 6 visits, letters</td><td>+4.6</td><td>-1.1</td><td>P<0.001</td></tr>
<tr><td>% of eyes had a gain of 15 letters (n)</td><td>12.5 (n=9)</td><td>1.3 (n=1)</td><td>9.00 (1.18 to 68.92)</td></tr>
<tr><td>% of eyes lost 15 letters (n)</td><td>4.1 (n=3)</td><td>9.5 (n=7)</td><td>0.43 (0.12 to 1.58)</td></tr>
<tr><td>Mean number of injections</td><td>3.39</td><td>3.69</td><td>-0.30 (-2.70 to 2.10)</td></tr>
<tr><td>Predicted mean number of injection</td><td>3.90</td><td>2.37</td><td></td></tr>
</table>
</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Ghazala Fadi ; Hovan Marta ; Mahmood Sajjad. Improving treatment provision of Wet AMD with intravitreal ranibizumab 2013. BMJ Quality Improvement Reports; 2(1).</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>UK</td></tr>
<tr><td>Study type</td><td>Audit</td></tr>
<tr><td>Aim of the study</td><td>To identify improvement in visual acuity of patients treated for wet AMD following changes made to the appointment system, hospital macular treatment centre facility.</td></tr>
<tr><td>Study dates</td><td>2009-2011</td></tr>
<tr><td>Setting</td><td>Manchester Royal Eye hospital’s macular treatment centre (MTC)</td></tr>
<tr><td>Source of funding</td><td>not reported</td></tr>
<tr><td>Sample size</td><td>162 patients (2009); 53 (2010); 80 (2011)</td></tr>
<tr><td>Inclusion criteria</td><td>Patients attending the AMD clinic</td></tr>
<tr><td>Exclusion criteria</td><td>not specified</td></tr>
<tr><td>Baseline characteristics</td><td>not reported</td></tr>
<tr><td>Methods</td><td>The study design was audit of patient treatment and visual measures and continuous re-audit to measure the impact of changes taken. Through regular re-audit it was possible to measure the effect of change made at the MTC on treatment time and the corresponding effect on the mean visual acuity.
<table>
<tr><th>Staffing capacity</th><th>Original</th><th>Improvement</th></tr>
<tr><td></td><td>Medical retinal consultants (3)
Ophthalmic fellows (2)
Specialist nurse (1)
Optometrist (1)
Imaging technician (1)</td><td>Medical retinal consultants (4)
Vitreo-retinal consultants (2)
Medical retinal fellows (4)
Vitreo-retinal fellows (2)
Associate specialist (2)</td></tr>
<tr><td>Number of treatment rooms</td><td>2</td><td>3</td></tr>
</table>
Other action plans were carried out between 2009 and 2011, including</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td colspan="4">Ghazala Fadi ; Hovan Marta ; Mahmood Sajjad. Improving treatment provision of Wet AMD with intravitreal ranibizumab 2013. BMJ Quality Improvement Reports; 2(1).</td></tr>
<tr><td></td><td colspan="4">Fast-track referral pathway into hospital eye service for wet AMD patients was implemented;
Application process for funding of ranibizumab injections from primary care trusts was streamlined so that no prior approval was required before commencing treatment;
With the agreement of hospital management, proposal changes to clinics templates were made and new protected slot became available for new patients to improve delay in initiation of treatment;
In order to ensure review intervals were being met, service capacity was increased through implementation of a training programme to involve optometrists in the assessment of patients;</td></tr>
<tr><td>Results</td><td colspan="4"><table>
<tr><td></td><td>2010 (n=53)</td><td>2011 (n=60)</td><td>Effect (95%CI)
(2011 vs 2010/2009) (n=53)</td></tr>
<tr><td>% of patients maintained vision</td><td>79% (n=42)</td><td>88% (n=53)</td><td>1.11 (0.94 to 1.45)</td></tr>
<tr><td>% of patients had a gain of 15 letters or more BCVA</td><td>6% (n=3)</td><td>20% (n=12)</td><td>3.53 (1.05 to 11.85)</td></tr>
<tr><td>VA changes, letters</td><td>-3.69</td><td>+2.72</td><td></td></tr>
<tr><td></td><td>2009 (n=100)</td><td>2011 (n=20)</td><td></td></tr>
<tr><td>% of patients being referred to 1st assessment within 1 week</td><td>28% (n=28)</td><td>60% (n=12)</td><td>2.14 (1.33 to 3.45)</td></tr>
<tr><td>Mean time interval between treatment decision to 1st treatment</td><td>70 days</td><td>15 days</td><td></td></tr>
</table></td></tr>
<tr><td>Notes</td><td colspan="4">The majority of the changes that were made between 2009 and 2011 were implemented after the 2010 audit.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Goudie C; Lunt D; Reid S; Sanders S; Ophthalmic digital image transfer: benefit to triage, patient care and resource. 2014. Ophthalmic and physiological optics; 34(6): 628-35.</th></tr>
<tr><td>Country/ies where the study was carried out:</td><td>UK</td></tr>
<tr><td>Study type</td><td>Retrospective study</td></tr>
<tr><td>Aim of the study</td><td>To quantity the effect of attaching digit image to ophthalmic referrals. In particular the effect of digital images on appointment priority, the need for an appointment and the disease categories involved.</td></tr>
<tr><td>Study dates</td><td>September 2010 to Jan 2011</td></tr>
<tr><td>Setting</td><td>Ophthalmic referral centre, the Queen Margaret hospital, Dunfermline</td></tr>
<tr><td>Source of funding</td><td>Not reported</td></tr>
<tr><td>Sample size</td><td>358 consecutive electronic referrals with attached digital images. (794 consecutive electronic referrals without attached images were interrogated)</td></tr>
<tr><td>Inclusion criteria</td><td>All electronic referrals with or without attached image</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>All electronic referrals with and without images received from community optometry were reviewed and actioned on the day of receipt. When reviewed, the referring optometrist was sent an immediate email acknowledging receipt and outcome of referral.
Initial triage was performed by a specially trained team, consisting of 2 hospital optometrists and 3 specialist ophthalmic nurses.
Any referrals deemed urgent was reviewed by the on call consultant on the day, usually resulting in a patient appointment within 24hour. Non-urgent referral with images were collectedly reviewed at the end of the week by the consultant on call for the weekend. The decision not to see a patient was always made by the consultant, with a subsequent explanatory letter to patient, optometrist and general practitioner.</td></tr>
<tr><td>Results</td><td>Over 90% of referrals without attached imaged resulted in a hospital appointment, but there was no other data reported.

Referral pathway
<table>
<tr><td>Nurse led triage</td><td>On-call consultant</td><td>Urgent HES appointment, n=64 (18%)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Goudie C; Lunt D; Reid S; Sanders S; Ophthalmic digital image transfer: benefit to triage, patient care and resource. 2014. Ophthalmic and physiological optics; 34(6): 628-35.**

<table>
<tr><td></td><td>On-call consultant/Consultant review</td><td>Routine HES appointment, n=170 (47%)</td></tr>
<tr><td></td><td>Consultant review</td><td>Discharge, n=122 (34%)</td></tr>
</table>

Relative risk between new nurse led triage and old referral=47%/90%=0.53 (95%CI 0.47 to 0.59)

Ophthalmological diagnosis given for optometry referrals vetted by the central ophthalmic electronic referral unit as “urgent”

Diagnosis	Number of referrals (total=64)
Wet macular pathology	28
Papilloedema	6
Retinal detachment	3
Central retinal vein occlusion	2
Corneal pathology	2
Macular haemorrhage	2

Notes	Older referral pathway took between 2 and 32 weeks being referred to the hospital eye service; while new triage referral pathway takes less than 12 weeks. Not AMD specific clinic

Bibliographic reference	**Bo Li; Anne-Marie Powell; Philip L Hooper; Thomas G Sheidow. Prospective evaluation of teleophthalmology in screening and recurrent monitoring of neovascular age-related macular degeneration. A randomised clinical trial. 2015. JAMA Ophthalmol; 133 (2): 276-282.**
Country/ies where the study was carried out	Canada
Study type	Prospective randomised clinical trial

<table>
<tr><th>Bibliographic reference</th><th>Bo Li; Anne-Marie Powell; Philip L Hooper; Thomas G Sheidow. Prospective evaluation of teleophthalmology in screening and recurrent monitoring of neovascular age-related macular degeneration. A randomised clinical trial. 2015. JAMA Ophthalmol; 133 (2): 276-282.</th></tr>
<tr><td>Aim of the study</td><td>To evaluate the use of teleophthalmology both in the initial screening and recurrence monitoring of neovascular AMD.</td></tr>
<tr><td>Study dates</td><td>November 2011 to November 2012</td></tr>
<tr><td>Setting</td><td>Retina service at the Ivey eye institute in London, Ontario, Canada</td></tr>
<tr><td>Source of funding</td><td>The Academic Health Science Centre Alternate Funding Plan from the Academic Medical Organisation of Southwestern Ontario.</td></tr>
<tr><td>Sample size</td><td>106 patients (106 eyes) enrolled for screening of nAMD, and 63 patients were enrolled in the monitoring of nAMD recurrence.</td></tr>
<tr><td>Inclusion criteria</td><td>Not specified</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>Teleophthalmology has the ability to provide localised communit-based evaluations, limiting patient travel and inconvenience. Teleophthalmologic screening program replied on store-forward approach where a series of digital images are obtained by a technician locally and electronically forwarded to a retinal specialist for grading and evaluation. Along with the digital image, a standard ophthalmic examination, including a short patient history, visual acuity and intraocular pressure measurement, can also be sent electronically to the retinal specialist. After reviewing the teleophthalmologic data set, any patient believed to require clinical assessment and treatment is then transferred to the nearest retinal specialist.

Patients with suspected neovascular AMD
The patients were randomised into routine screening or teleophthalmologic screening during the 1-year period.
<table>
<tr><td>Intervention (1T)</td><td>Control (1R)</td></tr>
<tr><td>Teleophthalomologic screening</td><td>Routine screening</td></tr>
<tr><td>Community-based stand-alone clinics operated by community and general ophthalmologists</td><td>Retinal specialists at the Ivey Eye Institute</td></tr>
<tr><td>In person assessment</td><td>Being assessed electronically by retinal specialists</td></tr>
</table>
Patients who previously treated for neovascular AMD</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><td>Bo Li; Anne-Marie Powell; Philip L Hooper; Thomas G Sheidow. Prospective evaluation of teleophthalmology in screening and recurrent monitoring of neovascular age-related macular degeneration. A randomised clinical trial. 2015. JAMA Ophthalmol; 133 (2): 276-282.</td></tr>
<tr><td></td><td>Patient who were previously treated for neovascular AMD and did not have evidence of disease activity at the time of enrolment (Jan 2010-November 2012)
<table>
<tr><td>Intervention (2T)</td><td>Control (2R)</td></tr>
<tr><td>Teleophthalmologic monitoring</td><td>Routine monitoring</td></tr>
<tr><td>Assessed and followed at the ocular health centre every 2 months</td><td>Regular appointment every 2 months</td></tr>
<tr><td>Patients data obtained at each visit were stored in the ocular health centre database and electronically sent to retinal specialist for formal evaluation of neovascular AMD reoccurrence.
Patients were followed up at the OHC on a bimonthly if there was no evidence of disease reoccurance of neovascular AMD. Patients with evidence of neovascular AMD reoccurance based on teleophthalmologic data were recalled to the Eye institute for treatment and continued to be followed up as needed</td><td>In-person evaluation by a retinal specialist</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Bo Li; Anne-Marie Powell; Philip L Hooper; Thomas G Sheidow. Prospective evaluation of teleophthalmology in screening and recurrent monitoring of neovascular age-related macular degeneration. A randomised clinical trial. 2015. JAMA Ophthalmol; 133 (2): 276-282.**
Results	

	Intervention (IT, n=52)	Control (1R, n=54)	Effect (95%CI)
Average time, referral to diagnostic imaging, days	22.5	18.0	4.5 (-2.80 to 11.80)
Time referral to treatment for patients being diagnosed with nAMD and required treatment, days	39.1	30.4	8.7 (-5.29 to 22.69)
	Intervention (2T, n=27)	Control (2R, n=36)	
Average time to recurrence, days	103.9	108.1	-4.2 (-47.77 to 39.15)
Average detection of disease recurrence to treatment time, days	13.6	0.04	13.5 (9.0 to 18.2)
BCVA at time of recurrence	20/154.2	20/155.2	
BCVA at the end of follow-up	20/184.8	20/180.7	

Bibliographic reference	**Markun Stefan, Dishy Avraham, Neuner-Jehle Stefan, Rosemann Thomas, Frei Anja. The Chronic care for wet age-related macular degeneration (CHARMED) study: a randomised controlled trial. 2015. Plos One**
Country/ies where the study was carried out	Switzerland
Study type	RCT
Aim of the study	To investigate the implementation of chronic care model to improve visual function and quality of live
Study dates	Study populations were recruited between April 2011 and Jan 2013, and being followed up for 12 months.
Source of funding	This study was supported by non-commercial foundation Zukunft Hausarzt, Zuricher.
Sample size	169 patients (190 eyes)

<table>
<tr><th>Bibliographic reference</th><th>Markun Stefan, Dishy Avraham, Neuner-Jehle Stefan, Rosemann Thomas, Frei Anja. The Chronic care for wet age-related macular degeneration (CHARMED) study: a randomised controlled trial. 2015. Plos One</th></tr>
<tr><td>Inclusion criteria</td><td>People aged 50 years or older, with wet AMD, who were eligible for therapy with anti-VEGF drugs, had a BCVA of at least 20 letters assessed with the ETDRS chart and provided written consent in study participant. In cases where both eye were affected by wet AMD both eyes were included and followed in the study</td></tr>
<tr><td>Exclusion criteria</td><td>Serious general or psychological illness (advance malignant diseases, severe depressive disorders or dementia) and insufficient German or French language skills (for completing the self-administrated questionnaire).</td></tr>
<tr><td>Baseline characteristics</td><td>Mean age 76.7 (SD=8.0) years; no. of females=107 (633%);</td></tr>
<tr><td>Methods</td><td>People were randomised either in intervention and control groups.
<table>
<tr><th>Intervention (chronic care model) group</th><th>Control group</th></tr>
<tr><td>Evidence based core elements of the chronic care model (CCM). Delivery of CCM was organised as followed: in every study site a practice assistant was assigned to be the “Chronic Care Coach” (CCC). The CCCs attended a one day training course comprising the instruction and materials to utilize as means to introduce the CCM core elements. The following elements were introduced:
Organisation of health care delivery system;
Self-management support;
Decision support;
Clinical information systems</td><td>No study specific intervention</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Markun Stefan, Dishy Avraham, Neuner-Jehle Stefan, Rosemann Thomas, Frei Anja. The Chronic care for wet age-related macular degeneration (CHARMED) study: a randomised controlled trial. 2015. Plos One**
Results	

	Intervention CCM (n=84)	Control (n=85)	Effect (95%CI)
Visual acuity			
Mean changes of ETDRS at 6 months	+0.3 (95%CI -3.4 to 4.0)	+2.7 (95%CI -1.0 to +6.4)	-2.40 (-12.65 to 7.85)
Mean changes of ETRDS at 12 months	-0.3 (95%CI -4.4 to +3.8)	+4.5 (95%CI +0.1 to +8.9)	-4.80 (-11.31 to 1.71)
NEI VFQ-25			
Score at 6 months	+2.1 (95%CI -0.4 to +4.6)	+2.4 (95%CI -0.3 to +5.1)	-0.30 (-3.89 to 3.29)
Score at 12 months	+3.4 (95%CI +1.1 to +5.7)	+1.3 (95%CI -1.2 to +3.8)	2.10 (-0.96 to 5.16)
Patients assessment of chronic illness care (PACIC) at 12 months	+0.6 (95%CI +0.1 to 1.0)	+0.6 (95%CI +0.2 to 1.0)	0
Number of ophthalmologist visits at 12 months, median (IQR)	12 (9 to 12)	12 (7 to 13)	

Notes	The study was stopped early due to recruitment difficulties. Open label study design (awareness of allocation in the intervention group)

Bibliographic reference	**Reeves Barmaby; Scott Lauren; Taylor Jodi; Harding Simon; Peto Tunde, Muldrew Alyson, Hogg Ruth; Wordsworth Sarah; Mills Nicola; O'Reilly Dermot; Rogers Chris; Chakravarthy. Effectiveness of community versus hospital eye service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual non-inferiority trial. 2016. BMJ Open.**
Country/ies where the study was carried out	UK
Study type	RCT
Aim of the study	To compare the ability of ophthalmologists versus optometrists to correctly classify retinal lesions due to neovascular age-related macular degeneration (nAMD).

Bibliographic reference	**Reeves Barmaby; Scott Lauren; Taylor Jodi; Harding Simon; Peto Tunde, Muldrew Alyson, Hogg Ruth; Wordsworth Sarah; Mills Nicola; O'Reilly Dermot; Rogers Chris; Chakravarthy. Effectiveness of community versus hospital eye service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual non-inferiority trial. 2016. BMJ Open.**
Source of funding	The Queen's university Belfast. The ECHoES trial was funded through the rapid trials funding call advertised by the National Institute for Health Research Health Technology Assessment programme.
Sample size	155 healthcare professional including 62 ophthalmologists and 67 optometrists
Inclusion criteria	Ophthalmologists were required to have 3 years' post-registration experience in ophthalmology, have passed the part 1 examination of the Royal College of Ophthalmologists or the Diploma in Ophthalmology or equivalent and have experience within the AMD service (no minimum duration specified). Optometrists were required to be fully qualified, registered with the General Optical Council for at least 3 years and not be participating or have participated in any AMD shared care scheme.
Exclusion criteria	Not specified
Baseline characteristics	Not specified
Methods	A non-inferiority trial designed to emulate a parallel group design. Decision about the reactivation status of lesions were made from vignettes, consisting of sets of retinal images (colour and spectral domain OCT) with accompanying clinical information, rather than by examining actual patients. Re-treatment decision-making on the basis of review of image, in the absence of the patient, is a strategy that is increasing being used by the HES to improve the efficiency of nAMD clinics. A database consisting 288 vignettes was created from the clinical and image repository of a previously conducted trial (HTA ref: 07/36/01). The vignette consisted of a brief clinical summary that provided a patient's age, gender, cardiovascular health and smoking status; 2 sets of images comprising colour fundus and radial pattern spectral domain OCT from 2 separate visits with the corresponding visual acuity from each visit. The 2 sets of images were termed baseline and index, with the former from a visit when the lesion was quiescent and the latter from a visit when the lesion could have been either quiescent or reactivated. All participants received the same training. Ophthalmologists and optometrists are qualified to detect retinal pathology, but optometrists may not have the skills to detect lesion reactivation. Eligible ophthalmologists may also not have been fully trained to detect lesion reactivation since doctors without specialist skills (grade ST1 and above) often staff retina clinics in the HES. There were 2 aspects of training. First, participants had to attend 2 online webinars; second, each participant had to assess a set of training vignettes and achieve a criterion level of performance.

Bibliographic reference	**Reeves Barmaby; Scott Lauren; Taylor Jodi; Harding Simon; Peto Tunde, Muldrew Alyson, Hogg Ruth; Wordsworth Sarah; Mills Nicola; O'Reilly Dermot; Rogers Chris; Chakravarthy. Effectiveness of community versus hospital eye service follow-up for patients with neovascular age-related macular degeneration with quiescent disease (ECHoES): a virtual non-inferiority trial. 2016. BMJ Open.**
Results	The primary outcome was correct classification of the activation status of the nAMD lesion characterised in the vignette at the index visit from the image and other information the vignette contained. Participants' classifications (reactivated, quiescent or suspicious) were judged against an expert reference standard.

	Ophthalmologists	Optometrists	Effect RR (95%CI)
No. of correctly classified the nAMD lesion in the index images	1722/2016 (85.4%)	1702/2016 (84.4%)	1.01 (0.99 to 1.04)
No. of correctly classified a vignette as reactivated	736/994 (74.0%)	795/994 (80.0%)	0.93 (0.88 to 0.97)
No. of correctly classified a vignette as quiescent/suspicious	986/1022 (96.5%)	907/1022 (88.7%)	1.09 (1.06 to 1.11)
Error occurred for the vignette that were classified as reactivated	62/994 (6.2%)	57/994 (5.7%)	1.09 (0.77 to 1.54)

Bibliographic reference	**Engman S, Edwards A, Barkri S. Administration of repeat intravitreal anti-VEGF drugs by retina specialists in an injection-only clinical for patients with exudative AMD: patient acceptance and safety. 2011. Ophthalmology 26(6): 380-86.**
Country/ies where the study was carried out	USA
Study type	Retrospective case review
Aim of the study	To examine patient acceptance and safety of repeated intravitreal injections of anti-VEGF agents for exudative AMD, by retina specialist, without an eye examination before every injection.
Source of funding	This study was supported by Research to prevent blindness and the central for translational science activities grant.

<table>
<tr><th>Bibliographic reference</th><th>Engman S, Edwards A, Barkri S. Administration of repeat intravitreal anti-VEGF drugs by retina specialists in an injection-only clinical for patients with exudative AMD: patient acceptance and safety. 2011. Ophthalmology 26(6): 380-86.</th></tr>
<tr><td>Sample size</td><td>110 patients (115 eyes)</td></tr>
<tr><td>Inclusion criteria</td><td>All intravitreal injections of bevacizumab and ranibizumab performed between June 2008 and May 2009 for the treatment of wet AMD.</td></tr>
<tr><td>Exclusion criteria</td><td>Not specified</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>Retrospective chart review. 115 eyes (110 patients) with exudative AMD underwent repeated intravitreal anti-VEGF injections with limited interval examination and diagnostic testing. Medication, laterality, number of injection cycles started and completed, number of injections per injection cycle, subjective visual changes, pre- and post-injection visual acuity (VA), pre- and post-injection intraocular pressure (IOP), nurse- and patient-initiated phone calls, emergency (non-scheduled) clinic visits, complications, new diagnoses, and patient complaints after each injection were recorded. The main outcome measures were complications and patient complaints.</td></tr>
<tr><td>Results</td><td>An injection clinic cycle is defined as the period of time from enrolment in the injection clinic until return for a full examination at the conclusion of the prescribed number of injections in the designated injection clinic.
A total number of intravitreal injections was 549 for 110 patients during a total of 175 injections clinic cycles. Of 549 injections were given at the clinical appointment at the time of enrolment, with remaining 396 given on subsequent visits to the designated injection clinic.
Patients were considered to have an “interrupted” injection circle cycle if they had a dilated examination at any time during an injection cycle prior to their scheduled post-injection clinical appointment.
<table>
<tr><th>Mean number of injection given per cycle (including injections given at the time of enrolment in the injection clinic)</th><th>Mean number of injection given in the designated injection clinic only (not including those given at the time of enrolment)</th></tr>
<tr><td>3.1</td><td>2.2</td></tr>
</table>
<table>
<tr><td rowspan="3">175 injection cycles(110 patients, 549 injections)</td><td>134 uninterrupted cycles (76.6%)</td><td>-</td></tr>
<tr><td rowspan="2">41 interrupted cycles (23.4%)</td><td>17 emergency visits</td></tr>
<tr><td>14 injection clinic evaluations</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	**Engman S, Edwards A, Barkri S. Administration of repeat intravitreal anti-VEGF drugs by retina specialists in an injection-only clinical for patients with exudative AMD: patient acceptance and safety. 2011. Ophthalmology 26(6): 380-86.**
	Of 175 injection cycles, cycles were more likely to be interrupted cycles compared to interrupted (RR=3.27, 95%CI 2.47 to 4.32)

Bibliographic reference	**Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.**
Country/ies where the study was carried out	Denmark
Study type	Systematic review
Aim of the study	This review searched the existing literature was to provide an overview of the experiences in non-physicians such as nurses are trained to give injections into the vitreous body of the eye for intravitreal therapy with vascular endothelial growth factor inhibitors against common eye diseases, e.g. age-related macular degeneration and diabetic retinopathy.
Source of funding	Not reported
Sample size	5 included studies
Inclusion criteria	Studies had to address any outcome based on non-physician delivered intravitreal injection therapy. Being non-physician was defined as the injecting personel not being a physician.
Exclusion criteria	Non-English studies Case studies Comments
Baseline characteristics	N/A
Methods	The study searched the literature using electronic bibliographic databases of PubMed, EMBASE, the Cochrane library, CINAHL and the Web of Science on 22 Septermber 2015. The following search strategy (nurse OR orthoptists OR optometrist OR non-physicial) AND (intravitreal) All references were screened by title and abstract by one author who excluded in irrelevant references, duplicates and studies not written in English. No date restrictins were applied.

<table>
<tr><th>Bibliographic reference</th><td>Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.</td></tr>
<tr><td></td><td>All remaining references were retrieved in full-text. Full-text artciles were read for eligibility and data extraction by 2 authors, and reference for all included studied were read to find additional eligible studies.</td></tr>
<tr><td>Results</td><td>5 studies were included in the review.
All studies used nurses for non-physician intravitreal injections therapy.
<table>
<tr><th>Studies</th><th>Country</th><th>Design</th><th>Non-physician characteristics</th><th>Supervised injections, n</th><th>Injections</th><th>Prevalence of injection related AE, %</th><th>Patient satisfaction</th></tr>
<tr><td>DaCosta 2014</td><td>UK</td><td>Retrosective Cohort 2 yrs</td><td>3 nurses trained in 1 1-day course after which they observed practice</td><td>20</td><td>4,000</td><td>Endophthalmities: 0
Cataract: 0
Loss of central artery perfusion: 0
Uveitis: 0
Retinal detachment: 0
Vitreous haemorrhage: 0
Subconjunctival haemorrhage: 57</td><td>62% (31/50) patients were completedly satisfied (score 5/5); 38% (19/50) were satisfied (score 4/5)</td></tr>
<tr><td>Hasler 2015</td><td>Denark</td><td>Retrosective Cohort 5 yrs</td><td>4 nurses traing by vitreoretinal surgeons</td><td>8-10</td><td>12,542</td><td>Endophthalmities: 0.032</td><td></td></tr>
<tr><td>Michelotti 2014</td><td>UK</td><td>Retrosective Cohort 17mo</td><td>2 nurse and 1 senior nurse were trained and supervised by ophthammologist</td><td>200</td><td>3,355</td><td>Endophthalmities: 0
Retinal tear: 0
Uveitis: 0
Retinal detachment: 0
Vitreous haemorrhage: 0</td><td>Formal survey ongoing; no formal or informal patient complaints reported</td></tr>
</table></td></tr>
</table>

Bibliographic reference	Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.							
							Subconjunctival haemorrhage and corneal abrasion:3.6	
	Simcock 2014	UK	Prosective Cohort 5.5 yrs	2 nurses practitioners trained 1-on-1 by a vitreoretinal surgeon	20	10,006	Endophthalmities: 0.40	
	Verma 2013	UK	Prosective Cohort 5mo	4 nurses with surgical backgrounds trained in a 1-day course	25	1,400	Endophthalmities: 0 Cataract: 0 Retinal detachment: 0 Exacerbation of blepharitis: 0.71 Corneal punctate epitheliopathy: 5.0 Subconjunctival haemorrhage:8.6	97% patients (1,351/1,400) gave pain score of 0-1 out of 5 (max); survey showed high levels of satisfaction.
Comments	1. Was an “a priori” design? it was unclear whether inclusion criteria were established before the conduct of the review; 2. Was there duplicate study selection and data extraction? all reference were screened by title and abstract by one author who exluded irrelevant references, duplications and studies not written in Engliish. Full text articles were read for eligibility and data extraction by 2 authors. The following search strategy (nurse OR orthoptists OR optometrist OR non-physicial) AND (intravitreal). 3. Was a comprehensive literature search performed? The search used the electronic bibliographic database of PubMed, EMBASE, the Cochrane Libraray, CINAHL and the web of science. 4. Was the status of publication used as as an inclusion crierion? non-English studies were excluded. 5. Was a list of studies (included and excluded) provided? Included studies were listed; 6. Were the characteristics of the included studies provided? Table 1 in the study summarised included studies.							

Bibliographic reference	**Rasul A ; Subhi Y ; Sorensen T L; Munch I C. Non-Physician delivered intravitreal injection service is feasible and safe - A systematic review. Danish Medical Journal 63 (5) 2016.**
	7. Was the scientific quality of the included studies assessed and documented? Studies were included in a qualitative analysis to provide an overview of the existing literature. After reading the included studies, four topics were identified which we used to systematise the presentation of the review. Quality of included was not stated. 8. Was the scientific quality of the included studies used appropriately in formulating conclusions? 9. Were the methods used to combine the findings of studies appropriate? N/A 10. Was the likelihood of publication bias assessed? Not stated 11. Was the conflict of interest included? Yes Amstar score 3/11.
Notes	There was another systematic review (Li, Greenberg and Krzystolik 2015, nurse-administered intravitreal injections: a systematic review. Graefes Arch Clin Exp Ophthalmol 253: 1619-21), which included patients satisfaction as one of study outcomes.

Bibliographic reference	**Arias L ; Armada F ; Donate J ; Garcia-Arumi J ; Giralt J ; Pazos B ; Pinero A ; Martinez F ; Mondejar J J; Ortega I ; Zlateva G ; Buggage R . Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. 2009. Eye 23: 326-333.**
Country/ies where the study was carried out	Spain
Study type	Retrospective study
Aim of the study	To assess the impact on visual acuity of delays between diagnosis and treatment in patients with subfoveal neovascular age-related macular degeneration (NV-AMD) and to evaluate NV-AMD patients' emotional status before therapy initiation.
Setting	Patients registered in the Spanish national health system and referred to regional health centre for evaluation/treatment by a retinal specialist
Source of funding	The study was funded by Pfizer.
Sample size	100
Inclusion criteria	Patients diagnosed with subfoveal neovascular AMD, aged 50 years or over, either gender with untreated AMD in one or both eyes were identified at the time diagnosis upon referral to a regional health centre for treatment. Patients were eligible for

<table>
<tr><th>Bibliographic reference</th><td>Arias L ; Armada F ; Donate J ; Garcia-Arumi J ; Giralt J ; Pazos B ; Pinero A ; Martinez F ; Mondejar J J; Ortega I ; Zlateva G ; Buggage R . Delay in treating age-related macular degeneration in Spain is associated with progressive vision loss. 2009. Eye 23: 326-333.</td></tr>
<tr><td></td><td>inclusion if they were capable of understanding and responding to study instruments and if they provided consent to participate.</td></tr>
<tr><td>Exclusion criteria</td><td>diagnosis of choroidal neovascularisation secondary to eye conditions other than AMD; participant or planned participation in any other clinical trial during the study period; or clinical or psychological conditions the effects of which might interfere with the collection or interpretation of study findings.</td></tr>
<tr><td>Baseline characteristics</td><td>Mean age (SD)=74.2 (7.9) years; no. of female=50 (50%); mean number of co-morbidities (SD)=2.2 (1.5);</td></tr>
<tr><td>Methods</td><td>This study included newly diagnosed NV-AMD patients registered in the Spanish national health system and referred to regional health centers for evaluation/treatment by a retinal specialist from 09/2005 to 03/2006. Records were reviewed and data abstracted at referring physicians' offices (diagnosis visit) and regional health centers (treatment visit). Treatment was at physicians' discretion. The Hospital Anxiety and Depression Scale was administered at the treatment visit (before therapy).</td></tr>
<tr><td>Results</td><td>The median time from the diagnosis visit to treatment visit was 2.3 months (95%CI 0.2 to 10.8).
50% patients received treatment within 2.3 months, 25% experience delays of > 2.3 to 4.2 months, and 25% had delays > 4.2 to 11.7 months.

Correlation between months to treatment and mean change in visual acuity score (n=98)
<table>
<tr><th>Time to treatment</th><th>Change in visual acuity score, mean (SD)</th><th>Effect (95%CI)</th></tr>
<tr><td><1 months (n=29)</td><td>0.1 (0.4)</td><td>-</td></tr>
<tr><td>1 to 2 months (n=12)</td><td>0.2 (0.4)</td><td>0.10 (-0.17 to 0.37)</td></tr>
<tr><td>2 to 3 months (n=18)</td><td>0.4 (0.6)</td><td>0.30 (-0.01 to 0.61)</td></tr>
<tr><td>>3 months (n=39)</td><td>0.4 (0.9)</td><td>0.30 (-0.02 to 0.62)</td></tr>
</table></td></tr>
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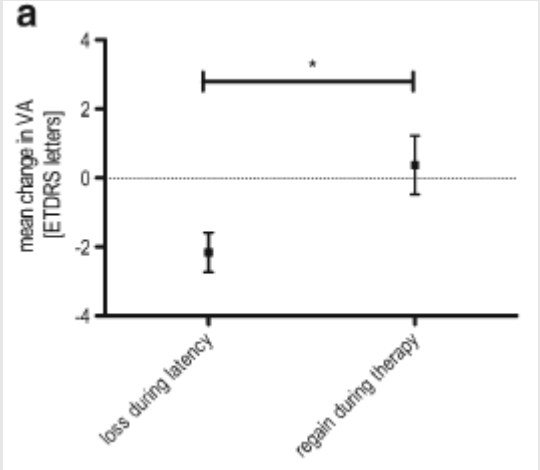
<table>
<tr><th>Bibliographic reference</th><td>Muether P S; Hermann M M; Koch K ; Fauser S . Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. 2011. Graefes Archive for Clinical & Experimental Ophthalmology; 249 (5): 633-37.</td></tr>
<tr><td>Country/ies where the study was carried out</td><td>Germany</td></tr>
<tr><td>Study type</td><td>Prospective non-randomised trial</td></tr>
<tr><td>Aim of the study</td><td>To evaluate changes in visual acuity and central retinal thickness over time, and their consequences for the patients concerned</td></tr>
<tr><td>Source of funding</td><td>The study was supported by the Koeln Fortune programme/Faculty of Medicine, University of Cologne</td></tr>
<tr><td>Sample size</td><td>90</td></tr>
<tr><td>Inclusion criteria</td><td>Neovascular AMD of all subtypes (occult, predominantly classic, minimally classic, classic, and retinal angiomatous proliferative lesions). Diagnosis was established by fluorescence and indocyanine green angiography at baseline</td></tr>
<tr><td>Exclusion criteria</td><td>Patients with massive hemorrhages or advanced fibrosis were excluded. Further exclusion criteria included any previous CNV treatment, previous vitrectomy, central laser coagulation, peripheral laser coagulation within the last year, cataract surgery within the last 3 months, diabetic retinopathy, and progressive glaucoma.</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>First treatment (n=69)</td><td>Recurrent treatment (n=21)</td></tr>
<tr><td>Mean age (SD)</td><td>77.7 (6.9)</td><td>77.0 (7.3)</td></tr>
<tr><td>VA at diagnosis, logMAR (SD)</td><td>0.62 (0.31)</td><td>0.44 (0.26)</td></tr>
<tr><td>VA at time of treatment, logMAR (SD)</td><td>0.60 (0.30)</td><td>0.47 (0.27)</td></tr>
<tr><td>Time from indication to treatment days (SD)</td><td>27.4 (25.2)</td><td>23.0 (13.7)</td></tr>
</table>
</td></tr>
<tr><td>Methods</td><td>Sixty-nine patients indicated for first-time ranibizumab treatment and 21 patients with necessary re-treatment were included in the study. Visual acuity and spectral domain optical coherence tomography (SD-OCT) central retinal thickness at the time of the indication examination were compared to values at the first-time treatment and during recurrent ranibizumab treatment.
First treatment: time between treatment indication and first injection.
Recurrent treatment: time between diagnosis of persistent or recurrent CNV activity and subsequent re-treatment indication and first re-injection.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td colspan="2">First treatment (n=69)</td><td></td><td colspan="2">Recurrent treatment (n=21)</td><td></td></tr>
<tr><td></td><td>Visual loss</td><td>No visual loss</td><td>Effect (95%CI)</td><td>Visual loss</td><td>No visual loss</td><td>Effect (95%CI)</td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Muether P S; Hermann M M; Koch K ; Fauser S . Delay between medical indication to anti-VEGF treatment in age-related macular degeneration can result in a loss of visual acuity. 2011. Graefes Archive for Clinical & Experimental Ophthalmology; 249 (5): 633-37.						
	No. of patients (%)	31 (44.9)	38 (55.1)	0.82 (0.58 to 1.14)	11 (52.4)	10 (47.6)	1.10 (0.60 to 2.02)
	Time delays, days	31.6	24.0	MD=7.6 (1.07 to 14.13)	25.6	20.2	5.4 (-3.54 to 14.34)
		Had a loss of more than one logMAR (equivalent to more than 5 ETDRS letters)	No a loss of more than one logMAR (equivalent to more than 5 ETDRS letters)		Had a loss of more than one logMAR (equivalent to more than 5 ETDRS letters)	No a loss of more than one logMAR (equivalent to more than 5 ETDRS letters)	
	No. of patients (%)	12 (17.4)	57 (82.6)	0.21 (0.12 to 0.36)	2 (9.5%)	19 (90.5)	0.11 (0.03 to 0.40)
	Time days, days	36.5	25.5	MD=11.0 (-0.27 to 22.27)	52.0	20.0	32.0 (10.05 to 53.93)

Bibliographic reference	Muether P S; Hoerster R ; Hermann M M; Kirchhof B ; Fauser. Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration. 2013. Graefes Archive for Clinical & Experimental Ophthalmology 251 (2): 453-58.
Country/ies where the study was carried out	Germany
Study type	Prospective interventional case series
Aim of the study	To investigate the efficacy of a monthly spectral domain optical coherence tomography (OCT) controlled PRN treatment regimen in clinical routine with the described delay between indication to treat and treatment.
Source of funding	The study was supported by the Koeln Fortune Programme, Faculty of Medicine, University of Cologne

Bibliographic reference	**Muether P S; Hoerster R ; Hermann M M; Kirchhof B ; Fauser. Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration. 2013. Graefes Archive for Clinical & Experimental Ophthalmology 251 (2): 453-58.**
Sample size	102
Inclusion criteria	Patients with primary diagnosis of exudative AMD based on fluorescein and indocyanine green angiography and SD-OCT were enrolled following informed consent. All patients received three initial consecutive monthly ranibizumab.
Exclusion criteria	Not specified
Baseline characteristics	102 patient enroled, and 89 patients were followed up for 12 months, and 83 were included in the analysis. Of those included in the analysis, mean age was 76.8 (SD=6.9). The CNV subtype was occult in 52 cases, minimally classic in 4 cases, predominantly classic in 5 cases, and classic in 12 cases
Methods	Eighty-nine patients with neovascular AMD were followed for 12 months. Early treatment diabetic retinopathy study (ETDRS) visual acuity (VA), Radner reading VA and spectral domain optical coherence tomography were performed monthly, with additional fluorescein angiography if needed. After an initial loading phase of three consecutive monthly intravitreal injections with ranibizumab, re-injections were performed when recurrent activity of choroidal neovascularization (CNV) was detected. Ranibizumab in Germany is only refunded by the health insurance company following a written request of the ophthalmologist including VA scores, FA and SD-OCT findings. Latency and approval of the request varies depending on the case and the insurance, as well as short-term surgical capacities for appointment of treatment. IN this study, latency between indicator for treatment and subsequent treatment was determined for every patients for the analysis.
Results	To determine the influence of latency between indication to treat and eventual treatment, the study analysed the loss of VA during latency and therapy period. During latency visual acuity decreased by -2.16 (SD=4.97) letter ETDRS. After conduction of the subsequent treatment series with 3 monthly injection, visual acuity recovered by +0.37 (SD=7.44) letter EDTRS. Thus recovery of ETDRS VA was significant lower than visual loss during latency period.

Bibliographic reference	Muether P S; Hoerster R ; Hermann M M; Kirchhof B ; Fauser. Long-term effects of ranibizumab treatment delay in neovascular age-related macular degeneration. 2013. Graefes Archive for Clinical & Experimental Ophthalmology 251 (2): 453-58.
	

Bibliographic reference	Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.
Country/ies where the study was carried out	Canada
Study type	Prospective case series
Aim of the study	To determine whether a change in visual acuity occurred between time of initial (referral) diagnosis and the time of assessment and treatment by a retinal specialist.
Source of funding	The study was funded in part by Pfizer Global Pharmaceuticals, Pfizer Inc
Sample size	38

Bibliographic reference	Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.
Inclusion criteria	Patients who presented with a newly diagnosis subfoveal CNV. Patients included in they had new-onset wet AMD, defined as acuity onset (<30 days) of visual loss, visual distortion, change in colour vision or development of central blurring of vision, in conjunction with angiographic evidence of subfoveal CNV.
Exclusion criteria	Patients were excluded of their CNV was not related to AMD.
Baseline characteristics	32 out of 38 enrolled patients included in the analysis. Included patietns had a mean age of 77 (SD=8.66), and 24 (75%) were female; 6% had purely classic membranes, 44% predominantly classic lesions, 19% minimally classic lesions and 31% occult CNV. Nearly all of the patients (94%) had evidence of macular degeneration in both eyes; most patients (72%) had the dry type in their contralateral eye.
Methods	A prospective pilot study of 38 consecutive AMD patients who presented with newly diagnosed subfoveal choroidal neovascularization was conducted in a tertiary care retinal practice. All eligible subjects underwent clinical examination and digital fluorescein angiography at the time of assessment by a retinal specialist. Correlations were performed to assess the association between continuous independent variables and any visual deterioration since initial diagnosis. Multivariate linear regression models with stepwise techniques were used to evaluate any association between visual progression and time elapsed, while controlling for potential clinical covariates.
Results	Conceptual model of AMD pathway

Bibliographic reference	**Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.**

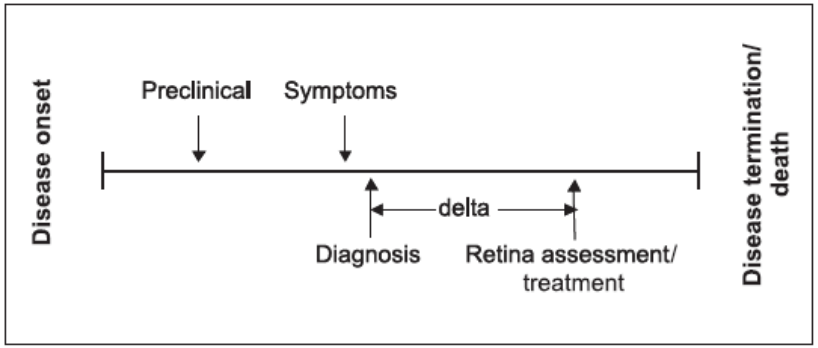


Fig. 1—Conceptual model of age-related macular degeneration (AMD).

The median time elapsed between initial diagnosis and referral assessment and treatment was 28 days; 14 (44%) of the subjects had some degree of visual loss, and 5 (16%) lost > 3 lines of distance visual acuity . Multivariate linear regression demonstrated that only time elapsed and lesion type based on fluorescein angiography were associated with progression of visual loss. Co-efficient for time elapsed=0.00674 (t=-4.148, 95%CI -0.010 to -0.003), p=0.000

Bibliographic reference	Oliver-Fernandez A ; Bakal J ; Segal S ; Shah G K; Dugar A ; Sharma S. Progression of visual loss and time between initial assessment and treatment of wet age-related macular degeneration 2005. Canadian Journal of Ophthalmology 40(3): 313-19.

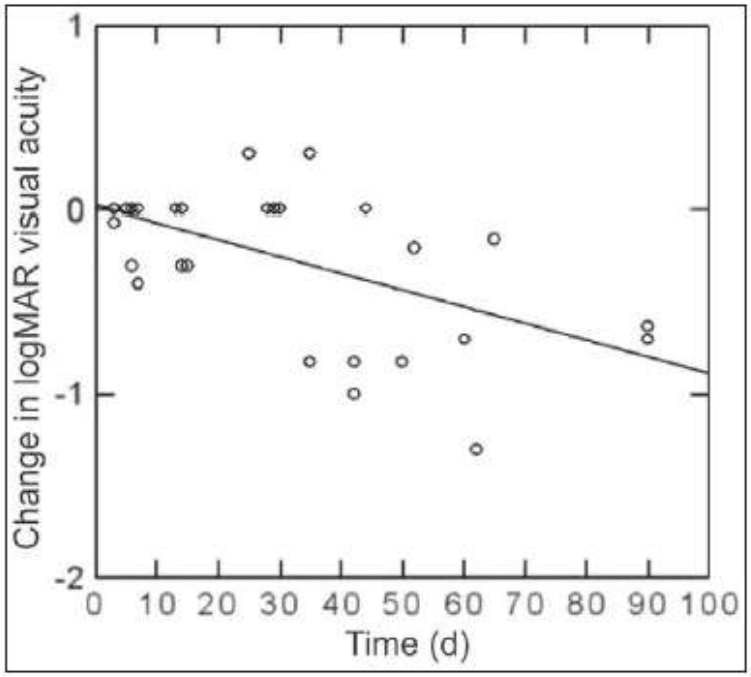


Fig. 2—Relation of degree of loss in visual acuity (calculated as the logarithm of the minimum angle of resolution [logMAR]) to time between initial diagnosis and specialist assessment and treatment.

Bibliographic reference	**Rauch R; Weingessel B; Maca S M; Vecs. Time to first treatment: the significance of early treatment of exudative age-related macular degeneration. 2012. Retina 32 (7): 1260-64.**
Country/ies where the study was carried out	Austria
Study type	Retrospective case series
Aim of the study	To determine whether the duration of neovascular AMD, defined as the time elapsed between first symptoms and treatment, has an impact on the visual outcome after ranibizumab therapy.
Source of funding	Not reported
Sample size	45 patients
Inclusion criteria	Patients included when a subfoveal CNV showing activity of the disease was present, for instance, presence of retinal haemorrhage, intraretinal edema, subretinal fluid, or fibrovascular pigment epithelial detachment and fluorescein leakage during angiography. Furthermore, patients had to have received 2 ranibizumab injections at an interval of 4 weeks and had to be able to precisely state the onset and kind of visual symptoms (visual distortion, change in colour vision, or development of central blurring of vision)
Exclusion criteria	Patients were excluded from the study If the CNV was not subfoveal or not related to AMD, if they were not able to give precise information upon visual symptoms, or if they have received any other treatment than 2 injections of ranibizumab
Baseline characteristics	Mean age (SD)=76.9 (9.1) years; no. of female=33 (73%).
Methods	In the study, 45 patients with exudative age-related macular degeneration were split into 3 groups depending on the duration of visual symptoms--Group I: <1 month, Group II: 1 month to 6 months, and Group III: >6 months. Best-corrected visual acuity, clinical ophthalmologic examination, and central retinal thickness as measured by optical coherence tomography were recorded at baseline and 2 months later. Fluorescein angiography was performed at baseline. Treatment consisted of 2 intravitreal injections of 1.25 mg of ranibizumab at baseline and after 4 weeks. Non-parametric correlations were calculated using the Spearman rho test. For comparing differences in mean values and standard deviation of variables, a two-tailed t test was performed.
Results	

	Group 1 (duration symptoms <1m)	Group 2 (1-6m)	Group 3 (>6m)	Effect (G3-G1) (95%CI)

Bibliographic reference	Rauch R; Weingessel B; Maca S M; Vecs. Time to first treatment: the significance of early treatment of exudative age-related macular degeneration. 2012. Retina 32 (7): 1260-64.				
	No. of patients	22	17	6	
	Mean symptom duration, days (SD)	18 (9)	63.1 (21.3)	201 (14)	183 (171.18(-194.82)
	Baseline VA, logMAR	0.4 (0.19)	0.31 (0.16)	0.09 (0.07)	-0.31 (-0.41 to 0.21)
	VA after treatment, logMAR	0.49 (0.20)	0.38 (0.16)	0.16 (0.13)	-0.33 (- 0.46 to 0.20)
	Mean VA change from baseline to treatment	0.09	0.07	0.06	-0.03 (-0.05 to -0.01)
	Visual acuity by patients groups (symptom duration)				

Bibliographic reference	Rasmussen A ; Brandi S ; Fuchs J ; Hansen L H; Lund-Andersen H ; Sander B ; Larsen M . Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Opthalmologica 93 (7), 2015.
Country/ies where the study was carried out	Denmark
Study type	Retrospective case series
Aim of the study	To study the relation between the interval from diagnosis to initiation of intravitreal injection therapy and visual outcome in neovascular age-related macular degeneration (nAMD) and to report changes over time in fellow-eye status.
Study date	2007, 2009, 2011 and 2012
Source of funding	This study was supported by the VELUX Foundation, the Lundbeck Foundation and Glostrup Hospital.
Sample size	1099 people (1185 eyes)
Inclusion criteria	Patients aged≥50 years with active choroidal neovascularisation associated with AMD Patients had BCVA≥0.05 Patients' CNV involvied the foveal centra and absecen of extensive subretinal fibrosis
Exclusion criteria	Patients had previous PDT, retinal photocoagulation or intraocular pharmacotherapy Patients failed to complete the 3 monthly loading-phase injections Patients had missing data for baseline or 3 month BCVA
Baseline characteristics	Year (no.) | age median (IQR) | BCVA (confidence limit)

<table>
<tr><th>Bibliographic reference</th><td colspan="2">Rasmussen A ; Brandi S ; Fuchs J ; Hansen L H; Lund-Andersen H ; Sander B ; Larsen M . Visual outcomes in relation to time to treatment in neovascular age-related macular degeneration. Acta Opthalmologica 93 (7), 2015.</td></tr>
<tr><td></td><td colspan="2">
<table>
<tr><td>2007 (296)</td><td>80 (10)</td><td>0.23 (0.21-0.25)</td></tr>
<tr><td>2009 (267)</td><td>80 (9)</td><td>0.24 (0.22-0.26)</td></tr>
<tr><td>2011 (301)</td><td>80 (10)</td><td>0.23 (0.21-0.25)</td></tr>
<tr><td>2012 (321)</td><td>79 (12)</td><td>0.23 (0.21-0.26)</td></tr>
</table>
</td></tr>
<tr><td>Methods</td><td colspan="2">The retrospective analysis of a clinical database included all eligible patients who began intravitreal ranibizumab treatment for nAMD during the first 6 months of years 2007, 2009, 2011 and 2012. The periods were chosen to represent the first and the most recent year with full implantation of intravitreal VEGF inhibitor treatment for nAMD with arbitrarily chosen years in between and intervals between cohorts that were large enough to enhance contrast between clinical practices.
The treatment protocol prescribed 3 initial 0.5mg ranibizuma injections at intervals of 4 weeks followed by a renvewed clinical exmainiation 1 month after the third injection.</td></tr>
<tr><td>Results</td><td colspan="2">Time to treatment and mean ETDS letters gain
<table>
<tr><td>Year (no.)</td><td>Time to treatment, median (days)</td><td>Mean ETDRS letter gain in eyes with nAMD (confidence limits)</td><td>Mean ETDRS letter gain in fellow eyes with nAMD (confidence imits)</td></tr>
<tr><td>2007 (296)</td><td>16</td><td>2.6 (1.1 to 4.1)</td><td>5.1</td></tr>
<tr><td>2009 (267)</td><td>11</td><td>0.4 (-1.8 to 2.5)</td><td>4.3</td></tr>
<tr><td>2011 (301)</td><td>2</td><td>5.3 (3.6 to 7.0)</td><td>4.6</td></tr>
<tr><td>2012 (321)</td><td>1</td><td>6.3 (4.8 to 7.7)</td><td>4.8</td></tr>
</table>
<table>
<tr><td></td><td colspan="2">Time to treatment</td><td>Effect (95%CI)</td></tr>
<tr><td></td><td>13.5 days</td><td>1.5 days</td><td></td></tr>
<tr><td>Mean ETDRS letter giain (SD)</td><td>1.56 (15.42)</td><td>5.8 (14.12)</td><td>-4.24 (-5.93, -2.55)</td></tr>
</table>
</td></tr>
<tr><td>Notes</td><td colspan="2">The estimated effect showed that 4 more letters lost of those waited longer to treatment. (4 letters differences for 12 days different time to treatment.</td></tr>
</table>

<table>
<tr><th>Bibliographic reference</th><th>Real J P; Luna J D; Urrets-Zavalia J A; De Santis ; M O ; Palma S D; Granero G E. Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration. 2013. European Journal of Ophthalmology 23(6): 857-864.</th></tr>
<tr><td>Country/ies where the study was carried out</td><td>Argentina</td></tr>
<tr><td>Study type</td><td>Retrospective cohort study</td></tr>
<tr><td>Aim of the study</td><td>To evaluate the impact on therapeutic effects and visual outcome of the different accessibilities to neovascular treatment.</td></tr>
<tr><td>Source of funding</td><td>No financial support was received for the study</td></tr>
<tr><td></td><td>Sample size: 96 eyes (78 patients)
Inclusion criteria: patients aged over 50 years with treatment-naïve subfoveal choroidal neovascularisation secondary to neovascular AMD, confirmed by fluorescein angiogram (FA) or optical coherence tomography (OCT), who were managed within bevacizumab or ranibizumab in one of 3 opthalmologic centres.
Exclusion criteria: patients with CNV related to degeneration myopia, angioid streaks, chorioretinal inflammatory diseases, hereditary retinal disorderd, or central serous chorioretinopathy were excluded from the analysis, as well as those with CNV secondary to PCV ore RAP, or with a history of laser photocoagulation treatment, PDT, or prior intravitreal therapy. Patients who during the monitoring year had received a combined treatment with other drugs and/or surgical treatment that could have modified the VA were also excluded.
Baseline characteristics:
<table>
<tr><th></th><th>Bevacizumab (n=52 eyes, 41 patients)</th><th>Ranibizumab (n=44 eyes, 37 patients)</th><th>P value</th></tr>
<tr><td>Male, n(%)</td><td>17 (33)</td><td>17 (39)</td><td>0.66</td></tr>
<tr><td>Mean age, years (SD)</td><td>73.9 (9.28)</td><td>78.6 (6.76)</td><td><0.01</td></tr>
<tr><td>Occult CNV lesion</td><td>22 (44)</td><td>17 (13)</td><td>0.83</td></tr>
<tr><td>Classic CNV</td><td>19 (28)</td><td>18 (29)</td><td>0.68</td></tr>
<tr><td>VA≥20/40, n(%)</td><td>8 (15)</td><td>6 (13)</td><td>0.99</td></tr>
<tr><td>20/40 to 20/320</td><td>32 (62)</td><td>31 (70)</td><td>0.39</td></tr>
<tr><td>VA≤20/320</td><td>12 (23)</td><td>7 (16)</td><td>0.45</td></tr>
</table></td></tr>
</table>

Bibliographic reference	**Real J P; Luna J D; Urrets-Zavalia J A; De Santis ; M O ; Palma S D; Granero G E. Accessibility as a conditioning factor in treatment for exudative age-related macular degeneration. 2013. European Journal of Ophthalmology 23(6): 857-864.**
	Mean VA, logMAR (SD) 0.79 (0.42) 0.77 (0.39) 0.8
Methods	A retrospective analysis of the charts of 78 patients with previously untreated exudative AMD, who were treated with ranibizumab or bevacizumab between January 2009 and December 2011. The main outcomes measured included time delay and change in mean best-corrected visual acuity (BCVA) between diagnosis and treatment and mean BCVA change at 1-year follow-ups.
Results	

	Bevacizumab (n=52 eyes, 41 patients)	Ranibizumab (n=44 eyes, 37 patients)	Effect (long delay vs short delay) (95%CI)
Average waiting time, days (SD)	36.06 (21.86)	153.80 (76.36)	117.74 (-143.24 to 92.24)
Diagnostic confirmation time (elapsed time between baseline and diagnostic confirmation date)	19.21 (14.96)	28.4 (27.66)	9.19 (-0.83 to 19.21)
VA at baseline, logMAR (SD)	0.80 (0.43)	0.77 (0.39)	-0.03 (-0.21 0.15)
VA at diagnostic confirmation	0.91 (0.44)	1.03 (0.4)	0.12 (-0.07 to 0.31)
VA change between diagnosis and treatment, letter (SD)	-5.46 (9.90)	-13.01 (13.82)	-7.55 (-12.94 to -2.16)

Bibliographic reference	**Lim J H; Wickremasinghe S S; Xie J ; Chauhan D S; Baird P N; Robman L D; Hageman G ; Guymer R H. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. 2012. American Journal of Ophthalmology 153 ($): 678-86.**
Country/ies where the study was carried out	Australia
Study type	Prospective interventional case series

<table>
<tr><th>Bibliographic reference</th><td>Lim J H; Wickremasinghe S S; Xie J ; Chauhan D S; Baird P N; Robman L D; Hageman G ; Guymer R H. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. 2012. American Journal of Ophthalmology 153 ($): 678-86.</td></tr>
<tr><td>Aim of the study</td><td>To investigate the potential influences that affect visual acuity (VA) outcome in a clinic-based cohort of age-related macular degeneration (AMD) patients undergoing anti-vascular endothelial growth factor (anti-VEGF) treatment for choroidal neovascularization.</td></tr>
<tr><td>Source of funding</td><td>Publication of the study was funded by national health and medical research council.</td></tr>
<tr><td>Sample size</td><td>185 eyes of 185 patients</td></tr>
<tr><td>Inclusion criteria</td><td>Patients were over the age of 50 years and were diagnosed with subfoveal CNV secondary to AMD.</td></tr>
<tr><td>Exclusion criteria</td><td>The main exclusion criteria: 1) diagnosis of CNV secondary to other eye condition; 2) laser photocoagulation or PDT prior to anti-VEGF injections; 3) non white ancestry</td></tr>
<tr><td>Baseline characteristics</td><td>Not specified</td></tr>
<tr><td>Methods</td><td>Patients with subfoveal choroidal neovascularization (CNV) secondary to AMD were recruited. A detailed questionnaire was given to patients at time of enrollment, to collect information relating to demographics, history of visual symptoms, visual acuity (VA), and treatment scheduling. Delay from symptoms to treatment ("Treatment delay") was measured in terms of weeks and analyzed in tertiles. Information pertaining to treatment outcomes was collected over a 6-month period.</td></tr>
<tr><td>Results</td><td>
<table>
<tr><td></td><td colspan="3">Time delay: symptoms to treatment</td><td></td></tr>
<tr><td></td><td>Lowest tertile (<7 week) (n=55)</td><td>Middle tertile (7-21 weeks) (n=54)</td><td>Highest tertile (>21 weeks) (n=54)</td><td>Effect (highest vs lowest tertile) (95%CI)</td></tr>
<tr><td>No. of patients had a gain of more than 2 lines (%)</td><td>21 (38)</td><td>16 (30)</td><td>11 (20)</td><td>0.53 (0.29 to 1.00)</td></tr>
<tr><td>No. of patient had a gain or loss of less than 2 lines</td><td>28 (51)</td><td>30 (56)</td><td>36 (67)</td><td>1.31 (0.95 to 1.80)</td></tr>
<tr><td>No. of patients had a loss of more than 2 lines</td><td>6 (11)</td><td>8 (14)</td><td>7 (13)</td><td>1.19 (0.43 to 3.31)</td></tr>
<tr><td></td><td colspan="3">Time delay: diagnosis to treatment</td><td></td></tr>
<tr><td></td><td>Lowest tertile (<1 week) (n=84)</td><td>Middle tertile (1-3 weeks) (n=50)</td><td>Highest tertile (>3 weeks) (n=50)</td><td></td></tr>
</table>
</td></tr>
</table>

Bibliographic reference	Lim J H; Wickremasinghe S S; Xie J ; Chauhan D S; Baird P N; Robman L D; Hageman G ; Guymer R H. Delay to treatment and visual outcomes in patients treated with anti-vascular endothelial growth factor for age-related macular degeneration. 2012. American Journal of Ophthalmology 153 ($): 678-86.				
	No. of patients had a gain of more than 2 lines (%)	24 (29)	17 (34)	11 (22)	0.77 (0.41 to 1.43)
	No. of patient had a gain or loss of less than 2 lines	48 (57)	26 (52)	33 (66)	1.16 (0.88 to 1.52)
	No. of patients had a loss of more than 2 lines	12 (14)	7 (14)	6 (12)	0.84 (0.34 to 2.10)

Bibliographic reference	Takahashi H ; Ohkubo Y ; Sato A ; Takezawa M ; Fujino Y ; Yanagi Y ; Kawashima H. Relationship between visual prognosis and delay of intravitreal injection of ranibizumab when treating agerelated macular degeneration. Retina 35 (7): 1331-38. 2015
Country/ies where the study was carried out	Janpan
Study type	Retrospective case
Aim of the study	In age-related macular degeneration, various factors in clinical practice cause delays to arise between the time exudative change is observed and the time antivascular endothelial growth factor drugs are actually injected. We investigated the influence of injection delay on prognosis.
Study date	Published in 2015
Source of funding	Not reported
Sample size	50 people (50 eyes)
Inclusion criteria	Patients were diagnosed with exudative AMD. Patietns received PRN ranibizuma monotherapy for 1 year since exudative change as first noted.
Exclusion criteria	Patients had injections of antiVEGF drugs other than ranibumab or receipt of PDT in the target eye Patients had intraocular surgey to the target eye exluding cataract surgey performed in either 3 months before exudative change was first noted or in the 12 month follow-up period Patients had a history of vitreous surgey such as vitreactomy or submacular surgey in the target eye Patients had any intraocular, extraocular or periocular inflammation or infection affecting either eye

<table>
<tr><th>Bibliographic reference</th><td>Takahashi H ; Ohkubo Y ; Sato A ; Takezawa M ; Fujino Y ; Yanagi Y ; Kawashima H. Relationship between visual prognosis and delay of intravitreal injection of ranibizumab when treating agerelated macular degeneration. Retina 35 (7): 1331-38. 2015</td></tr>
<tr><td></td><td>Patients had a history of uneitis in either eye</td></tr>
<tr><td>Baseline characteristics</td><td>
<table>
<tr><td></td><td>Patient being treated in hospital A</td><td>Patient being treated in hospital B</td></tr>
<tr><td>Number</td><td>25</td><td>25</td></tr>
<tr><td>Mael, n(%)</td><td>12 (48)</td><td>17 (68)</td></tr>
<tr><td>Age, mean (SE) years</td><td>75.5 (1.6)</td><td>71.2 (1.6)</td></tr>
<tr><td>Initial BCVA (logMAR) Snellen</td><td>0.19 (20/31)</td><td>0.47 (20/59)</td></tr>
<tr><td>Mean injectin dealys, days</td><td>9</td><td>47</td></tr>
</table>
</td></tr>
<tr><td>Methods</td><td>The study retrospectively investigated BCVA on the date that exudative change was first noted as initial BCVA, BCVA after 1 year, number of injection per year, and mean and total delay in days from the time exudative change was observed until injection for each injection.
Four types of delay were categoried as follow:
1.Referal delay, the numerb of days between the date of AMD diagnosis at the preivous institution (if made) and the data of the first visit to the institution where the first IVR was performed;
2.Specialist outcome clinic appointment delay, the number of days between the date the patient fulfilled the injection criteria at the general outpatient clinic and the date they were examined at the specialist outpatient clinic;
3.Patient refusal delay, the number of days between the date the patient fulfilled the injection criteria at the specialist outpatient clinic and the date the actual injection was scheduled at which time the patient refused injection
4. Appointment injection delay, all other delays.</td></tr>
<tr><td>Results</td><td>Predicted change in visual acuity is expressed by:
Change in visual acuity=0.000477-0.448 *(initial BCVA) + 0.00304 *(mean injection delay)

Expected visual acuity after 1 year for each patient’s VA at initial examiniation, and number of appointment waiting delays for intravitreal</td></tr>
</table>

Bibliographic reference	Takahashi H ; Ohkubo Y ; Sato A ; Takezawa M ; Fujino Y ; Yanagi Y ; Kawashima H. Relationship between visual prognosis and delay of intravitreal injection of ranibizumab when treating agerelated macular degeneration. Retina 35 (7): 1331-38. 2015

	Mean administration delays (days)				
Starting point BCVA	0	7	14	28	56
VA logMAR 1 Sneller 20/200	0.55 (0.55, 0.56)	0.57 (0.53-0.62)	0.59 (0.55-0.64)	0.64 (0.60-0.68)	0.72 (0.66-0.77)
VA logMAR 0.4 Sneller 20/50	0.22 (0.19-0.24)	0.24 (0.22-0.26)	0.26 (0.24-0.28)	0.31 (0.28-0.33)	0.39 (0.35-0.42)
VA logMAR 0.1, Sneller 20.25	0.05 (0.03-0.08)	0.08 (0.05-0.10)	0.10 (0.07-0.12)	0.14 (0.11-0.16)	0.22 (0.18-0.26)