H.4 Referral

H.4.1 Organisational models and referral pathways for triage, diagnosis, ongoing treatment and follow-up of people with suspected and confirmed age-related macular degeneration

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)?

RQ24: How soon should people with neovascular AMD be diagnosed and treated after becoming symptomatic?

Models of care

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Diagnosis agreement between optometrist and ophthalmologist								
Rapid access referral form (history finding (reduction in vision, distortion, central scotoma)								
1 (Muen 2011)	Prospective cohort	Serious[1]	N/A	Not serious	Serious[2]	54 (referrals)	57.4% (n=31) (44.2 to 70.6%)	VERY LOW
Rapid access referral form (accuracy in detecting Exudative AMD)								
1 (Muen 2011)	Prospective cohort	Serious[1]	N/A	Not serious	Serious[2]	54 (referrals)	37.0% (n=20) (24.1 to 50.0%)	VERY LOW
Vignette (no. of correctly classified nAMD)								
1 (Reeves 2016)	RCT	Serious[3]	N/A	Not serious	Not serious	2016 images	RR 1.01 (0.99 to 1.04)	MODERATE
Vignette (no. of correctly classified as reactivated)								
1 (Reeves	RCT	Serious[3]	N/A	Not serious	Not serious	994 images	RR 0.93	MODERATE

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
2016)							(0.88 to 0.97)	
Vignette (no. of error occurred that classified as reactivated)								
1 (Reeves 2016)	RCT	Serious[3]	N/A	Not serious	Very serious[4]	994 images	RR 1.09 (0.77 to 1.54)	VERY LOW
Vignette (no. of correctly classified as quiescent/suspicious)								
1(Reeves 2016)	RCT	Serious[3]	N/A	Not serious	Not serious	1022 images	RR 1.09 (1.06 to 1.11)	MODERATE
Number of patients referred								
Routine eye examination (patients with no symptoms being referred for AMD)								
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	1084	2.7% (n=30) (1.7 to 3.7%)	VERY LOW
Routine eye examination (patients with symptoms being referred for AMD)								
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	2992	5.1% (n=153) (4.3 to 6.0%)	VERY LOW
Routine eye examination (number of patients without symptoms vs no. of patients with symptoms being referred for AMD)								
1 (Dobbelsteyn 2015)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	4,076	RR 0.54 (0.37 to 0.80)	VERY LOW
Teleretinal screening								
1 (Chasan 2014)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	1935	24.0% (n=465) (22.1 to 25.9%)	VERY LOW
Electronically referrals resulting in a hospital appointment (with vs without attached images)								
1 (Goudie 2014)	Retrospective cohort	Serious[7]	N/A	Serious[6]	Not serious	1152 (referrals)	RR 0.73 (0.73 to 0.79)	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Anti-VEGF injection administration								
% of injection cycles were uninterrupted injection (by retinal specialist)								
1 (Engman 2011)	Chart review	Serious[7]	N/A	Not serious	Not serious	175 injection cycles	76.5% (70.2 to 82.8%)	VERY LOW
Visual acuity								
Community vs hospital follow-up								
% of people had a gain of 15 ETDRS letters								
1 (Tschuor 2013)	Prospective cohort	Serious[8]	N/A	Not serious	Serious[5]	62 people (72 eyes)	RR 9.00 (1.17 to 68.92)	VERY LOW
% of eyes had a loss of 15 letters								
1 (Tschuor 2013)	Prospective cohort	Serious[8]	N/A	Not serious	Very serious[4]	62 people (72 eyes)	RR 0.43 (0.12 to 1.59)	VERY LOW
Visual change over 6 visits, ETDRS letters (higher values better)								
1 (Tschuor 2013)	Prospective cohort	Serious[8]	N/A	Not serious	Serious[5]	62 people (72 eyes)	MD 1.20 (-4.00 to 6.40)	VERY LOW
Improvement in service provision (after vs before)								
% of patients had a gain of 15 letter or more								
1 (Ghazala 2013)	Audit study	Serious[7,8]	N/A	Not serious	Serious[5]	113	RR 3.53 (1.05 to 11.85)	VERY LOW
% patients maintained vision								
1 (Ghazala 2013)	Audit study	Serious[7,8]	N/A	Not serious	Serious[5]	113	RR 1.11 (0.94 to 1.45)	VERY LOW
Chronic model of care vs usual care								
VA at the end of follow-up (12 months) (ETDRS letters; higher scores indicate better vision)								
1 (Markun	RCT	Serious[10]	N/A	Not serious	Serious[5]	169	MD -4.80 letters	LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
2015)							(-11.31 to 1.71)	
Teleconsultation network vs usual care								
VA after treatment (logMAR; lower scores indicate better vision)								
Azzolini 2013	Prospective cohort	Serious[8]	n/a	Not serious	Very serious[11]	360	MD -0.05	VERY LOW
Time interval (diagnosis interval, treatment interval)								
Improvement in service provision (after vs before)								
% of patients being referred to 1st assessment within 1 week								
1 (Ghazala 2013)	Audit study	Serious[7]	n/a	Not serious	Not serious	120	RR 2.14 (1.33 to 3.45)	VERY LOW
Teleophthalmology vs routine								
Time from referral to diagnosis (diagnostic image), days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Serious[13]	106	MD 4.5 (-2.80 to 11.80)	LOW
Time from referral to treatment, days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Serious[13]	106	MD 8.7 (-5.29 to 22.69)	LOW
Time to recurrence, days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Serious[13]	63	MD -4.2 (-47.77 to 39.15)	LOW
Recurrence to treatment, days								
1 (Li 2015)	RCT	Serious[12]	N/A	Not serious	Not serious	63	MD 13.5 (9.0 to 18.2)	MODERATE
Teleconsultation network vs usual care (time from first visit to treatment), days								
1 (Azzolini	Prospective	Serious[8]	N/A	Not serious	Not serious	360	MD=-23.20	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
2013)	cohort						(-23.66 to -22.74)	

1. Downgraded one level for study population (a selection of patients being referred through eye causality, GPs, or other ophthalmologists' clinics, and some patients may be seen by other ophthalmologists).
2. Downgraded one level for wide 95%CI
3. Downgraded one level for selection and assessment bias (different experience and training in using vignettes)
4.Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
5. Downgraded one level for confidence interval crossing 1 lines of a defined minimal important difference
6. Downgraded one level for conditions included in the study not AMD specific
7. Downgraded one level for retrospective study design
8. Downgraded one level for study design (audit study; before-after)
9. Downgraded one level for Injection by nurse practitioners, no head-to-head comparison
10.Downgraded one level for risk of bias due to open label study
11. Downgraded two levels for 95%CI of the effect cannot be estimated
12. Downgraded one level for risk of bias due to masking of study participants being unclear
13. Downgraded one level for non-significant effect estimate (mean difference crosses 0)

Evidence on association between diagnosis/treatment time and visual acuity

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Time interval and visual acuity								
Visual acuity score change (longest vs shortest time to treatment)								
1 (Arias 2009)	Retrospective cohort	Serious[1]	N/A	Serious[2]	Not serious	100	Correlation r 0.3534 (p=0.0004)	VERY LOW
Visual acuity change treatment and baseline, BCVA decimal (higher values better)								
1 (Rauch	Case series	Serious[1]	N/A	Serious[2]	Not serious	22	MD 0.09	VERY LOW

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
2012) (symptoms duration <1m)							(-0.03 to 0.21)	
1 (Rauch 2012) (symptoms duration 1-6m)	Case series	Serious[1]	N/A	Serious[2]	Not serious	17	MD 0.07 (-0.04 to 0.18)	VERY LOW
1 (Rauch 2012) (symptoms duration >6m)	Case series	Serious[1]	N/A	Serious[2]	Not serious	6	MD 0.06 (-0.05 to 0.19)	VERY LOW
VA change between diagnosis and treatment (longer vs shorter treatment waiting time) (ETDRS letters; higher scores indicate better vision)								
1 (Real 2013)	Case series	Serious[1]	N/A	Serious[2]	Serious[3]	78	MD -7.55[5] (-12.94 to -2.16)	VERY LOW
1 (Rasmussen 2015)	Case series	Serious[1]	N/A	Serious[2]	Serious[3]	1185	MD -4.24[6] (-5.93 to -2.55)	VERY LOW
% of people had a gain of more than 2 lines (10 letters)								
Longer (>21 w) vs shorter (<7 w) delay from symptom to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[3]	109	RR 0.53 (0.29 to 1.00)	VERY LOW
Longer (>3w) vs shorter (<1w) delay from diagnosis to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[5]	134	RR 0.77 (0.41 to 1.43)	VERY LOW
% of people had a loss of more than 2 lines (10 letters)								

[5] Time difference=long waiting time (averge 153.80)-short waiting time (average 36.06)=117.74 days, so about 1 letter loss in 15 days more waiting to treatment.
[6] Time difference=long time to treatment (average 13.5) – short time to treatment (average 1.5)=12 days, so about 1 letter loss in 3 days more to treatment.

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Longer (>21w) vs shorter (7w) delay from symptom to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[5]	109	RR 1.19 (0.43 to 3.31)	VERY LOW
Longer (>3w) vs shorter (<1w) delay from diagnosis to treatment								
1 (Lim 2012)	Case series	Serious[4]	N/A	Serious[2]	Serious[5]	134	RR 0.84 (0.34 to 2.10)	VERY LOW
Vison loss during latency (ETDRS letters; higher scores indicate better vision)								
1 (Muether 2013)	Non-randomised trial	Serious[6]	N/A	Serious[2]	Not serious	83	MD -1.79 (-3.71 to 0.13)	VERY LOW
Vision loss with time delay (between initial referral and assessment and treatment								
1 (Oliver-Fermandez 2005)	Case series	Serious[8]	N/A	Serious[2]	Not serious	38	Coefficient -0.00674 (a decrease of 0.00674 logMAR with every one day delay) (-0.010 to -0.003)	VERY LOW
Time delay in first treatment, days								
People with visual loss vs no visual loss								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Not serious	69	MD 7.6 (1.07 to 14.13)	VERY LOW
People had a loss of more than 1 line vs no visual loss more than 1 line								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Serious[7]	69	MD 11.0 (-0.27 to 22.27)	VERY LOW
Time days in recurrent treatment, days								

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
People with visual loss vs no visual loss								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Serious[7]	21	MD 5.4 (-3.54 to 14.34)	VERY LOW
People had a loss of more than 1 line vs no visual loss more than 1 line								
1 (Muether 2011)	Non-randomised trial	Serious [6]	N/A	Serious[2]	Not serious	21	MD 32.0 (10.05 to 53.93)	VERY LOW

1. Downgraded one level for retrospective study design
2. Downgraded one level for no head-to-head comparisons and outcomes differed from primary interest-for instance.
3. Downgraded one level for confidence interval crossing 1 lines of a defined minimal important difference
4. Downgraded one level for self-reported time delay (questionnaire collected information)
5. Downgraded two levels for confidence interval crossing 2 lines of a defined minimal important difference
6. Downgraded one level for study design (interventional case series/non-randomised trial)
7. Downgraded one level for non-significant effect estimate (mean difference crosses 0)
8. Downgraded one level for study population (selected from a review of letters from referring doctors)

Vision related quality of life (NEI VFQ25)

Number of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Sample size	Effect (95%CI)	Quality
Vision-related quality of life (NEI-VFQ-25) (higher values better)								
Chronic model of care vs usual care								
Markun 2015	RCT	Serious[1]	N/A	Not serious	Serious[2]	169	MD 2.10 (-0.96 to 5.16)	LOW

1.Downgraded one level for open label study
2. Downgraded oned level for confidence interal crossing 1 line of a defined minimal important difference.