

**Update of Systematic Review by M van der Reis et al.
(Interventions for neovascular age-related macular
degeneration)**



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1. METHODS

1.1 LITERATURE SEARCHES

The following searches acted as an update to the original review by Van der Reis “Interventions for neovascular age-related macular degeneration”¹. Searches were limited to date July 2011-Dec 2012 (date of update searches) in order to retrieve only new papers published since the Van der Reis searches.

The following databases were searched from July 2011-Dec 2012:

- Embase (OvidSP) (1974-2012/wk 48)
- Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley) (2011-2012/Issue 11:2012) <http://www.thecochranelibrary.com/>
- Database of Abstracts of Reviews of Effects (DARE) (Wiley) (2011-2012/Issue 11: 2012)
- Health Technology Assessment Database (HTA) (Wiley) (2011-2012/Issue 11: 2012)
- NHS Economic Evaluation Database (NHSEED) (Wiley) (2011-2012/Issue 11: 2012)
- Cochrane Database of Systematic Reviews (CDSR) (Wiley) (2011-2012/Issue 11:2012)
- PubMed (NLM) (up to 6/12/2012) <http://www.ncbi.nlm.nih.gov/pubmed/>

Searches were not limited by language. Identified references were downloaded in Endnote X6 software for further assessment and handling. Details of the search strategies are listed in Appendix 1. The bibliographies of identified systematic reviews and guidelines were checked for additional references.

1.2 METHODS OF DATA EXTRACTION

For each included analysis, data were extracted into specifically developed templates and tables in Microsoft Word 2007. Data extractions were carried out by one reviewer and checked by a second. Each included study has been identified by its main publication, using the surname of the first author or specific trial name. Multiple publications of the same patient population were considered together only if there were data for different follow-up times. Papers presenting duplicate data were not included. Any relevant additional information presented in the related papers, was added where appropriate.

1.3 DATA SYNTHESIS (NETWORK META-ANALYSIS METHODS)

The network meta-analysis followed the methods used in van der Reis¹.

Two main analyses were performed. The first one compared different drugs, regardless of doses or regimens; and the second compared doses and regimens within each drug type. In both cases the same network meta-analysis method was used. The primary outcome measure was a continuous measure of the change in the numbers of letters (measured with visual acuity charts) which was calculated as the mean value at follow-up minus the mean value at baseline. The mean and standard deviation (SD) or standard error (SE) of the change in number of letters was extracted for each treatment group in each study. To perform the meta-analysis the original individual patient dataset was recreated using simulation by sampling from a normal distribution with the mean and SD of the corresponding treatment group within each study. Due to chance, the means and SD of these simulated values will be slightly different to those reported by the study and so they were corrected using a simple linear transformation. A linear regression model was used with the outcome variable being the mean change in the number of letters at six months (using the simulated individual patient data) and the independent variables were the drug and an indicator variable for study (to adjust for differences between patient characteristics and study methods between studies by preserving randomisation). This analysis was repeated for the outcome of mean change in the number of letters at 12 months. The analyses comparing all drugs to placebo are presented in the main report, to enable ranking of the drugs.

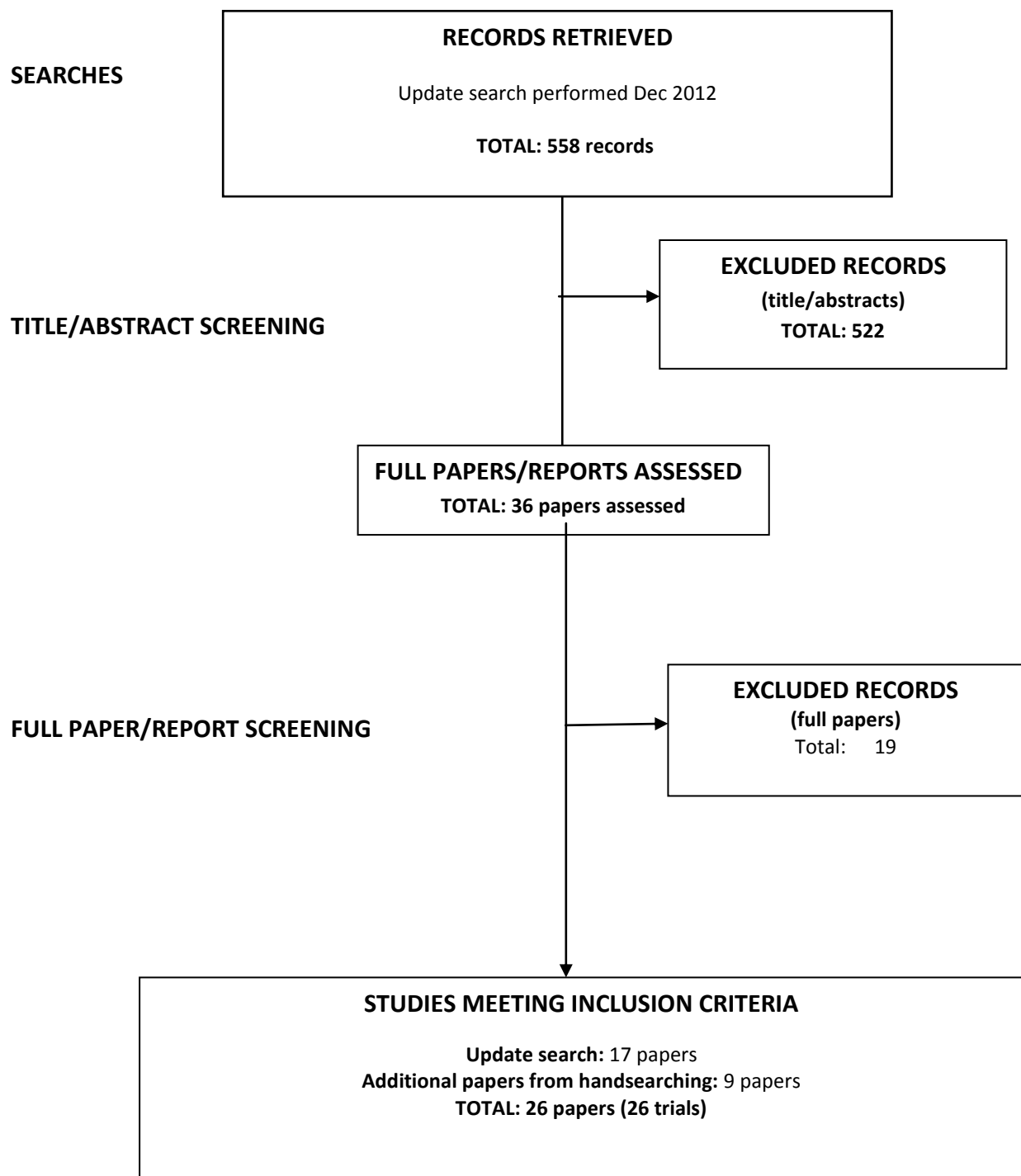
For the comparison of drug doses and regimens the analysis methods were similar. All data from all drugs were included in the analyses but the comparisons concentrated on different doses (or regimens) of the same drug. For example all the different doses of ranibizumab were compared to a reference dose (0.3 mg). Statistical analyses were performed using STATA version 10.1 (STATA corporation, College Station, Texas, US). The primary outcome used in the analysis was the mean change in the number of ETDRS letters from baseline; STATA codes are given in Appendices 2 and 3.

2. RESULTS

2.1 LITERATURE SEARCHES AND INCLUSION ASSESSMENT

Update searches were performed using a specific update search and by handsearching an existing systematic review of wet AMD. This identified 17 papers from the update search and seven papers from handsearching (Figure 1). Twenty-five new trials were identified (Table 2) and newly published 24 month trial data was found for the CATT trial (total of 26 trials), identified in the previous van der Reis review (Table 1). HORIZON (Table 2) was an open extension trial for patients completing MARINA, ANCHOR or FOCUS (Table1). Rouvas 2012 was a 36 month follow-up of the Rouvas 2009, these are included separately since the patient numbers for analysis differ.

Figure 1: Summary of update searches



2.2 OVERVIEW OF INCLUDED STUDIES

Table 1: Main Characteristics of the Original Included Studies

Study	Interventions	Year	Follow-up (months)	No. patients	Mean age (years)	Male / female	No. interventions	Lesion type on FA					Baseline VA (logMAR)	Delphi score
								C	MC	PC	O	Other		
CLEAR-IT 2 ^{2,3}	VEGF Trap (0.5 mg) monthly + PRN VEGF Trap (2 mg) monthly + PRN VEGF Trap (0.5 mg) 3-monthly + PRN VEGF Trap (2 mg) 3-monthly + PRN VEGF Trap (4 mg) 3-monthly + PRN	2011	12	157	78	60/97	757	-	37	60	60	-	0.58	4
CLEAR AMD1 ⁴	Placebo VEGF Trap (0.3 mg/kg) VEGF Trap (1 mg/kg) VEGF Trap (3 mg/kg)	2006	2	25	77	11/14	100	8	7	-	8	2*	0.83	4
CATT ^{5,6}	IVR (0.5 mg) monthly IVR (0.5 mg) PRN IVB (1.25 mg) monthly IVB (1.25 mg) PRN	2011	12 24	1185	79	453/732	11291	-	154	263	539	229†	0.49	8
Biswas ⁷	IVR (0.5 mg) PRN IVB (1.25 mg) PRN	2011	18	104	64	50/54	517	-	-	-	46	58*	0.55	6
Subramanian ⁸	IVR (0.5 mg) PRN IVB (1.25 mg) PRN	2009	12	22	79	21/1	141	4	-	-	15	3‡	0.72	7
Chen ⁹	IVR (0.5 mg) + placebo IVR (0.5 mg) + PDT§ IVR (0.5 mg) + PDT ¶	2010	12	7	76	7/0	49	-	-	-	-	-	0.27	2
Vallance ¹⁰	IVR (0.5 mg) + sPDT IVR (0.5 mg) + placebo	2010	12	18	-	-	24	-	-	8	-	10**	0.65	6
FOCUS ^{11,12}	IVR (0.5 mg) + sPDT sPDT + placebo	2008	24	162	74	76/86	2768	-	47	106	6	3*	0.77	7
ANCHOR ^{13,14}	IVR (0.5 mg) + placebo IVR (0.3 mg) + placebo sPDT + placebo	2009	24	423	77	212/211	6535	-	12	410	1	-	0.77	7

Study	Interventions	Year	Follow-up (months)	No. patients	Mean age (years)	Male / female	No. interventions	Lesion type on FA					Baseline VA (logMAR)	Delphi score
								C	MC	PC	O	Other		
Heier ¹⁵	IVR (0,3 mg) IVR (0,3 mg and 0,5 mg) Usual care ^{††}	2006	6	64	77	31/33	212	-	25	20	18	1*	0.75	5
MARINA ¹⁶	IVR (0.3 mg) monthly IVR (0.5 mg) monthly Placebo monthly	2006	24	716	77	252/464	-	-	264	1	451	-	0.63	8
PIER ¹⁷	IVR (0.3 mg) monthly then quarterly IVR (0.5 mg) monthly then quarterly Placebo monthly then quarterly	2008	12	184	79	74/110	1104	-	69	35	79	1*	0.60	7
EXCITE ¹⁸	IVR (0.3 mg) monthly then quarterly IVR (0.5 mg) monthly then quarterly IVR (0.3 mg) monthly	2011	12	353	75	144/209	2644	-	142	73	138	-	0.57	6
SAILOR ¹⁹	IVR (0.3 mg) IVR (0.5 mg)	2009	12	2378	79	975/1403	10939	-	544	736	1013	84*	0.66	6
Rosenfeld ²⁰	IVR 3 escalating dosing schedules	2006	0.5	32	80	12/20	-	-	7	10	14	1*	0.82	5
Bekkering ²¹	IVB (1.25 mg) IVB (1.25 mg) + IVTA (2 mg)	2011	6	115	71	46/69	396	-	22	42	32	19 ^{††}	0.66	6
Costagliola ²²	IVB (1.25 mg) IVB (1.25 mg) + rPDT	2010	12	85	64	38/47	319	-	-	-	-	85 ^{§§}	0.65	4
VIA ²³	IVB (1.25 mg) + rPDT IVB (1.25 mg) + rPDT ^{¶¶} IVB (1.25 mg) + placebo	2010	6	35	81	11/24	122	-	7	10	18	-	0.67	8
Lazic ²⁴	IVB (1.25 mg) IVB (1.25 mg) + sPDT sPDT	2007	3	156	76	50/106	156	-	127	-	29	-	1.09	5
Bashshur ²⁵	IVB (2.5 mg) sPDT	2007	6	62	75	31/31	146	-	-	62	-	-	0.75	2
Sacu ^{26,27}	IVB (1 mg) sPDT + IVTA (4 mg)	2009	12	28	78	9/19	122	-	-	-	-	-	0.74	4

Study	Interventions	Year	Follow-up (months)	No. patients	Mean age (years)	Male / female	No. interventions	Lesion type on FA					Baseline VA (logMAR)	Delphi score
								C	MC	PC	O	Other		
Hahn ²⁸	IVB (1 mg) IVTA (4 mg) + sPDT IVTA (4 mg) + rPDT	2007	3	30	79	23/7	50	3	9	-	18	-	0.47	4
ABC ²⁹	IVB (1.25 mg) Usual care***	2010	12	131	80	51/80	1260	-	-	32	-	99**	0.67	8
BEAT AMD ³⁰	Systemic B (5 mg /kg) v Systemic placebo	2009	6	8	77	4/4	24	-	-	-	-	-	0.45	6
Lai ³¹	IVB (1.25 mg) IVB (2.5 mg)	2009	6	50	75	34/16	183	-	16	5	19	-	0.93	8
Modarres ³²	IVB (1.25 mg) IVB (2.5 mg)	2009	5	86	73	58/28	127	12	-	18	46	-	1.19	4
Gragoudas ³³	IVP (0.3 mg) IVP (1.0 mg) IVP (3.0 mg) Placebo	2004	12	1190	-	494/696	10139	-	426	306	458	-	0.67	5
Gamulescu ³⁴	IVTA (4 mg) + sPDT IVTA (4 mg) + sPDT sPDT	2009	6	92	76	40/52	175	36	17	-	38	1*	0.66	3
Maberley ³⁵	IVTA (4 mg) + sPDT sPDT + placebo	2009	12	100	77	44/56	167	-	7	93	-	-	0.66	7
Piermarocchi ³⁶	IVTA (4 mg) + sPDT sPDT	2008	24	84	72	26/58	205	-	-	14	-	70+++	0.69	3
Chaudhary ³⁷	IVTA (12 mg) + sPDT sPDT	2007	12	30	80	14/16	71	-	-	-	-	-	0.65	5
NAPP ³⁸	Periocular injection TA (40 mg) + sPDT sPDT	2007	6	67	77	31/36	172	-	2	23	24	18*	0.65	6
Arias ³⁹	IVTA (11 mg) + sPDT sPDT	2006	12	61	76	29/32	132	-	-	61	-	-	1.01	5
Arguto-Rivera ⁴⁰	IVTA (4 mg) + TTT TTT	2005	6	26	74	-	35	-	4	5	14	3*	1.37	3

Study	Interventions	Year	Follow-up (months)	No. patients	Mean age (years)	Male / female	No. interventions	Lesion type on FA					Baseline VA (logMAR)	Delphi score
								C	MC	PC	O	Other		
Danis ⁴¹	IVTA (4 mg) no treatment	2000	6	27	76	12/15	16	-	-	-	-	-	0.63	4
Lee ⁴²	IVTA (20-25 mg) IVD (500 ug)	2007	12	39	69	27/12	78	-	31	-	8	-	0.64	7
Slakter ⁴³	anecortave + placebo sPDT + placebo	2006	12	530	77	254/276	-	-	-	530	-	-	0.72	6
D'Amico ⁴⁴	Anecortave (30 mg) anecortave (15 mg) anecortave (3 mg) placebo	2003	12	128	77	59/69	-	-	-	-	-	-	0.76	7
Odergren ⁴⁵	PDT + placebo TTT TTT + placebo PDT	2008	12	98	75	39/59	262	-	-	-	98	-	0.50	5
Boyer ⁴⁶	sPDT + topical NSAID sPDT + topical placebo	2007	3	60	78	21/39	60	-	-	60	-	-	0.73	5
Scorolli ⁴⁷	sPDT + antioxidant sPDT	2002	2	35	72	21/14	35	-	-	-	-	-	0.33	3
Kaiser ⁴⁸	sPDT placebo	2009	24	364	79	136/228	1625	-	-	-	364	-	0.57	5
Bressler ⁴⁹	sPDT rPDT Placebo	2005	24	117	78	42/75	499	-	91	-	17	9*	0.61	5
TAP ^{50, 51}	sPDT placebo PDT	2001	24	609	75	265/344	3592	-	304	244	57	4*	0.65	9
Arnold ⁵²	sPDT placebo	2001	24	258	75	98/160	-	-	-	-	258	-	0.39	8
Schmidt-Erfurth ^{53,54}	sPDT 2-monthly sPDT 3-monthly	2008	24	203	74	-	856	-	-	203	-	-	0.72	4
VALIO ⁵⁵	sPDT delayed light PDT###	2007	12	60	78	25/35	151	-	-	-	60	-	0.60	4

Table 2: Main Characteristics of the Update Review Included Studies

Study	Interventions	Year	Follow-up (months)	No. patients ##	Mean age (years)	% Male	No. interventions#	Lesion type on FA					Baseline VA (mean ETDRS)	Delphi score
								C	MC	PC	O	Other		
VIEW 1 ⁵⁶	IVR (0.5 mg) monthly	2012	12	304	78	43	3952	-	101	82	115	-	54	8
	VEGF Trap (2.0 mg) monthly			304	78	36	3952		105	87	110	55.2		
	VEGF Trap (0.5 mg) monthly			301	78	45	3913		97	81	121	55.6		
	VEGF Trap (2.0 mg) monthly then bimonthly			301	78	41	2408		110	71	118	55.7		
VIEW 2 ⁵⁶	IVR (0.5 mg) monthly	2012	12	291	73	42	3783	-	104	70	116	-	53.8	8
	VEGF Trap (2.0 mg) monthly			309	74	43	4017		112	72	123	52.8		
	VEGF Trap (0.5 mg) monthly			296	75	50	3848		103	80	113	51.6		
	VEGF Trap (2.0 mg) monthly then bimonthly			306	74	43	2448		106	88	110	51.6		
CLEAR -IT 1 ⁵⁷	VEGF Trap (0.15 mg) single dose	2012	2	14	75.6	57	14	1	2	-	11	-	49.7	3
	VEGF Trap (4 mg) single dose			14	76.9	50	14	5	3		6	51.8		
PARODI ⁵⁸	IVB (1.25mg) monthly then PRN	2011	12	26	73	42	120	-	-	-	-	12	0.59	4
	IVR (0.5 mg) monthly then PRN			24			94					0.66 (log MAR)		
Moon ⁵⁹	IVR (0.5 mg) monthly	2011	12	30	NR	NR	390	NR	NR	NR	NR	NR	NR	2
	IVR (2.0 mg) monthly + PRN			40			200							
Harbor {#3145}	IVR (0.5 mg) monthly	2012	12	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	3
	IVR (2.0 mg) monthly			NR	NR	NR	NR	NR	NR	NR	NR	NR		
	IVR (0.5 mg) monthly + PRN			NR	NR	NR	NR	NR	NR	NR	NR	NR		
	IVR (2.0 mg) monthly + PRN			NR	NR	NR	NR	NR	NR	NR	NR	NR		
EXTEND 1 ^{61, 62}	IVR (0.3 mg) monthly	2011	12	28	69.8	67.9	314	-	10	7	11	-	59.1	4
	IVR (0.5 mg) monthly			24	33	70.2	84.8	366		14	8	11	59.8	
	IVR (0.3 mg) monthly + PRN			28	28	69.8	67.9	428		10	7	11	59.1	
	IVR (0.5 mg) monthly + PRN			33	33	70.2	84.8	495		14	8	11	59.8	
El-Mollayess ⁶³	IVB (1.25mg) every 6wks	2012	12	60	76.8	35	570	NR	NR	NR	NR	NR	56.3	5
	IVB (1.25mg) PRN			60			228						53.3	
Jabbour 2008 ⁶⁴	IVR (0.3 mg) monthly + PRN	2008	6	21	79	38	223	NR	NR	NR	NR	NR	NR	1
	IVR (0.3 mg) +sPDT PRN			18	18	76	50	56						

Study	Interventions	Year	Follow-up (months)	No. patients ##	Mean age (years)	% Male	No. interventions#	Lesion type on FA					Baseline VA (mean ETDRS)	Delphi score
								C	MC	PC	O	Other		
DENALI ⁶⁵	IVR (0.5 mg) + sPDT + PRN	2012	12	103	77.5	38.5	536	-	32	29	38	-	53.8	5
	IVR (0.5 mg) + rPDT+ PRN			105	77.4	49.5	609		32	27	38	54.6		
	IVR (0.5 mg)+ sham PDT montly			110	77.2	33	1166		35	35	38	54.5		
Soderberg ⁶⁶	IVR (0.5 mg)+ TTT + PRN	2012	24	48	79.5	43	302	-	10	10	16	-	58.6	7
	IVR (0.5 mg)+ sham TTT + PRN			44	78.4	59	352		5	16	14	57.3		
Pruente ⁶⁷	IVR (0.3 mg) +sPDT + PRN	2011	6	19	79	NR	76	NR	NR	NR	NR	NR	52.1	5
	IVR (0.3 mg) +sham PDT + PRN			21	78		108					52.1		
ROUVAS 2009 ⁶⁸	IVR (0.5 mg) + PRN	2009	6	13	76.9	39	77	-	-	-	-	13	0.83	2
	IVR (0.5 mg) + PDT+ PRN			13	77.1	31	45					13	0.61	
	PDT+ IVTA (4mg) + PRN			11	76.5	46	-					11	0.92	
													(logMAR)	
ROUVAS 2012 ⁷⁴	IVR (0.5 mg) monthly then PRN	2012	36	12	77	39	148	-	-	-	-	36	0.83	3
	IVR (0.5 mg) +sPDT monthly then PRN			12	77	31	108					0.61		
	sPDT+ IVTA (4mg) fixed then PRN			9	77	46	-					0.92		
													(log MAR)	
MONET ⁶⁹	IVR (0.5 mg) single dose + siRNA PF-04523655 (1mg) monthly then PRN	2012	4	29	74.7	35	29	NR	NR	NR	NR	NR	52	3
	IVR (0.5 mg) single dose siRNA PF-04523655 (3mg) monthly then PRN			31	76	51	31					53		
	IVR (0.5 mg) single dose + siRNA PF-04523655 (3mg) biweekly then PRN			30	72.5	50	30					48.2		
	IVR (0.5 mg) + siRNA PF-04523655 (1mg) both monthly then PRN			30	74	40	120					49.5		
	IVR (0.5 mg) monthly then PRN			31	75.5	42	124					53.3		
FLAXEL ⁷⁰	IVR (0.5 mg) monthly then PRN	2012	4	10	77.5	NR	68		2	2		-	60.1	2
	IVR (0.5 mg)+ bromfenac/NSAID			20	85.5		143		4	4		52.8		
	monthly then PRN			12					(+OC)	(+cc)				
CABERNET ⁷¹	IVR (0.5 mg)+ epimacular brachytherapy + PRN	2013	12 24	302	76.4	29	1872	-	74	119	109	-	53.3	3

Study	Interventions	Year	Follow-up (months)	No. patients ##	Mean age (years)	% Male	No. interventions#	Lesion type on FA					Baseline VA (mean ETRS)	Delphi score
								C	MC	PC	O	Other		
	IVR (0.5 mg) + PRN			155	77.8	37	1612		41	61	53		53.6	
FUMI ⁷²	IVR (0.5 mg) + bromfenac/NSAID PRN IVR (0.5 mg) PRN	2012	6	NR	75 74	75 86	165 237	-	1 4	6 5	6 6	-	0.47 0.36 (log MAR)	7
LARSEN ⁷³	IVR (0.5 mg)+sPDT monthly then PRN IVR (0.5 mg)+sham PDT monthly then PRN	2012	12	121 132	77 76	36 44	581 673	-	20 25	50 57	51 51	1 0	56.5 56	5
Lim ⁷⁵	IVB (1.25mg) + PRN IVB (1.25mg) +sPDT + PRN	2012	12	18 23	70.9 66.5	72 65	60 74	NR	NR	NR	NR	NR	1.03 1.05 (logMAR)	2
Maam ⁷⁶	IVB (1mg) every 6wks IVB (1mg) + IVP (0.3mg) every 6wks IVP (0.3mg) every 6wks	2011	6	13 17 18	77 77 79 (median)	86 55 38	39 51 54	NR	NR	NR	NR	NR	23.5 31 24.5	5
Michels ⁷⁷	IVB (1mg) + PRN sPDT + IVTA (4mg) single dose	2007	3	NR	NR	NR	9 -	NR	NR	NR	NR	NR	49.6 40.5	1
SIN ⁷⁸	sPDT + nabumetone/NSAID (500mg) fixed then PRN sPDT + placebo fixed then PRN	2012	12	27 28	76 73	48 43	NR	NR	NR	NR	NR	NR	0.68 0.62 (log MAR)	5
Williams ⁷⁹	IVR fixed then PRN IVR+ PDT fixed then PRN	2012	12	27 29	79.1 79.3	NR	NR	NR	NR	NR	NR	NR	52.9 49.2	3
HORIZON ⁸⁰	IVR treated initial IVR cross over IVR naive	2012	24 ext. (48 from stdy baseline)	600 190 63	78 77 79	42 38 43	NR	- - -	68 51 10	14 18 15	251 73 18	18 2 0	60.5 42.3 41.6	7 ^{###}

B = bevacizumab; C = classic; IVB = intravitreal bevacizumab; IVD = intravitreal dexamethasone; IVP = intravitreal pegaptanib sodium; IVR = intravitreal ranibizumab; IVTA = intravitreal triamcinolone acetonide; FA = fluorescein angiography; logMAR = logarithm of the minimum angle of resolution; MC = minimally classic; NSAID = non-steroidal anti-inflammatory drugs; O = occult; PC = predominantly classic; PDT = photodynamic therapy; PRN = pro re nata (as needed); rPDT = reduced verteporfin photodynamic therapy (6 mg verteporfin per square m² of body surface area and 25 J/cm² at an intensity of 300 mW/cm² over 83 seconds); sPDT = standard verteporfin photodynamic therapy (6 mg verteporfin per m² of body surface area and 50 J/cm² at an intensity of 600 mW/cm² over 83 seconds); TA = triamcinolone acetonide; TTT = transpupillary therapy; VA = visual acuity; VEGF = vascular endothelial growth factor; ext=extension.

* Missing or cannot classify.
† Retinal angiomatous proliferans, lesion with more than 50% hemorrhage or cannot classify.
‡ Predominantly occult.
§ Photodynamic therapy with 10 J/cm² 120 mW/cm² with 20% fluence.
¶ Photodynamic therapy with 20 J/cm² 240 mW/cm² with 40% fluence.
** Minimally classic or non classic.
†† Usual care = verteporfin photodynamic therapy in predominantly classic lesions and observation in all other lesions.
‡‡ Retinal angiomatous proliferans.
§§ Classic or predominantly classic.
¶¶ Reduced photodynamic therapy with 12 J/cm².
*** Usual care = intravitreal pegaptanib injection or verteporfin photodynamic therapy.
††† Minimally classic, non classic or retinal angiomatous proliferans.
‡‡‡ delayed light = treatment with photodynamic therapy 30 minutes after the start of verteporfin infusion.
calculated from number of patients analysed x no. injections received or no of injections scheduled if 'received' was not reported.
number of patients analysed
###based on original trials

2.3 NETWORK OF INCLUDED STUDIES

Using the studies identified from the updated search (table 2), the network of Van der Reis was updated, and is illustrated in Figure 2. All newly identified trials were indicated in red. In line with the previous network the network included:

- Studies of all follow-up times
- Studies of all doses and regimens, systemic and intravitreal
- PDT included both standard and reduced fluency.

The previous analysis did not consider trials which could not connect to the overall network (Danis⁴¹ and Lee⁴²). Future networks should consider additional analyses based on treatment regimen (fixed or prn); the two regimens often lead to differences in the number of received injections which has implications for the patients quality of life and cost.

2.4 EFFECTIVENESS OF INTERVENTIONS

Results of the network meta-analysis in mean VA change (ETDRS letters) with the placebo group as reference are presented in Table 3. At six months the highest ranked and statistically significant interventions are ranibizumab (with or without PDT or NSAID), bevacizumab (with or without PDT or triamcinolone acetonide), triamcinolone acetonide plus PDT.

At 12 months the the highest ranked and statistically significant interventions are ranibizumab (with or without PDT or NSAID or brachytherapy), bevacizumab (with or without PDT), VEGF trap eye and triamcinolone acetonide plus PDT. These results are very similar to those of the original review by van der Reis and none of the conclusions have changed.

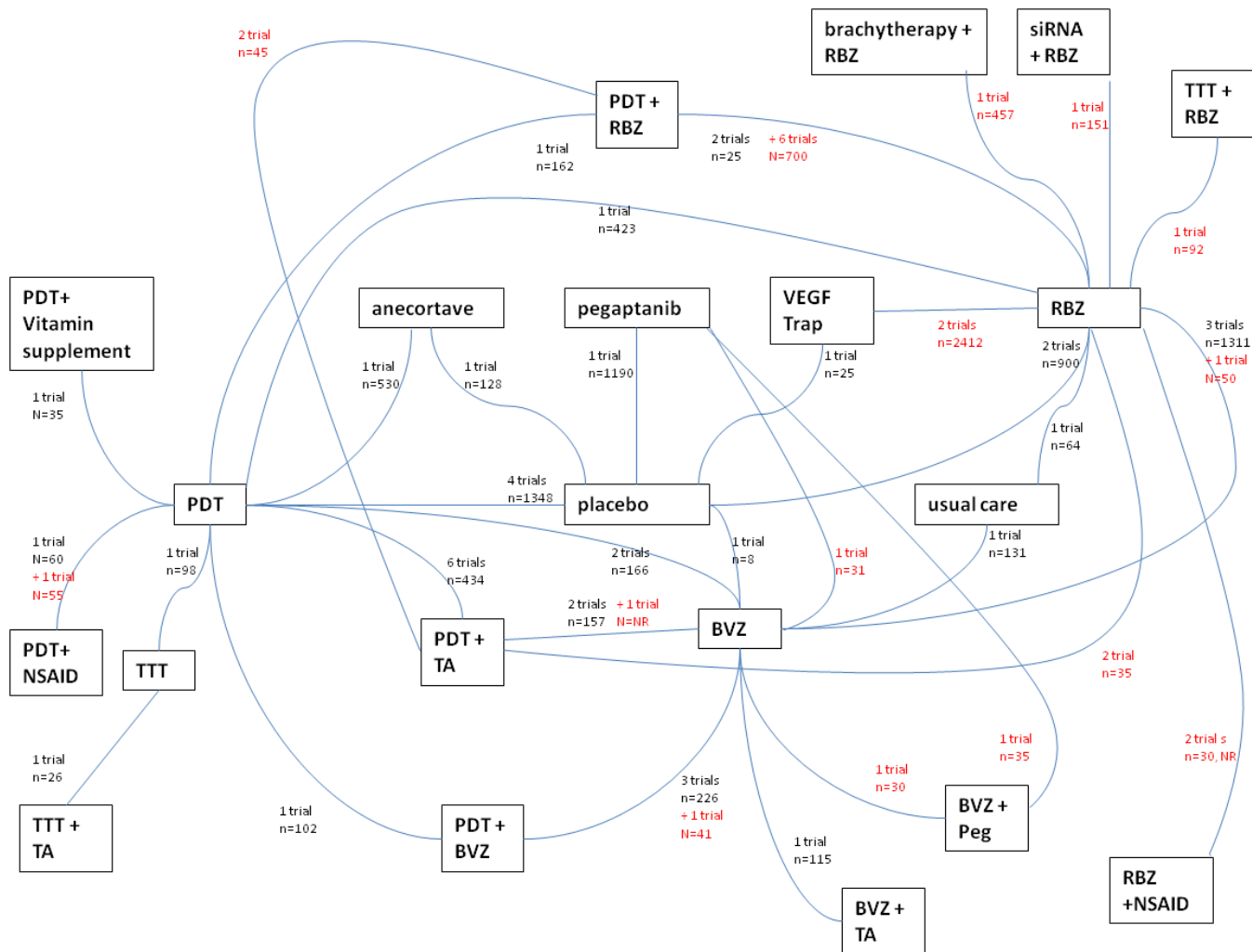
Results showing the effectiveness of each intervention compared to each other are presented in Appendices 4 (for six month results) and 5 (for 12 month results).

2.5 EFFECTIVENESS BETWEEN REGIMEN, DOSAGE OR APLLIANCE DIFFERENCES

The results of the network meta-analysis to assess the differences between regimen, dosage or appliance of a single intervention are presented in Table 4. Most of the comparisons were not statistically significant. The only statistically significant results were seen for the comparison of the dose and regimen of ranibizumab. Comparing 0.3 and 0.5 mg doses of ranibizumab there was a statistically significant difference in the mean number of letters at

six months of 1.35 (95% CI 0.38 to 2.32), but not at 12 months. This result favoured 0.5 mg ranibizumab for the improvement of visual acuity indicating that the mean number of letters was higher. We found a statistically significant difference of -3.99 (95% CI -7.35 to -0.63) letters at 12 months which showed that ranibizumab injections every three months were less effective than monthly ranibizumab injections. We found no other statistically significant differences between regimen, dosage or appliances.

Figure 2: Updated network (based on Figure 2 of van der Reis review)



BVZ = bevacizumab; RBZ = ranibizumab; TA = triamcinolone acetonide; Peg = pegaptanib; PDT = photodynamic therapy; TTT = transpupillary therapy; VA = visual acuity; VEGF = vascular endothelial growth factor; NSAID = nonsteroidal anti inflammatory drug.

Table 3: Effectiveness of interventions for neovascular AMD (all compared to placebo)

Intervention	Mean change in number of letters 6 months	95% CI	p-value	Mean change in numbers of letters 12 months	95% CI	p-value
Ranibizumab	14.31	(12.45, 16.16)	<0.001	19.16	(17.02, 21.31)	<0.001
Pegaptanib	5.12	(3.10, 7.15)	<0.001	6.67	(4.22, 9.13)	<0.001
Anecortave	-0.73	(-3.79, 2.34)	0.64	1.46	(-1.87, 4.79)	0.39
PDT	1.53	(-0.60, 3.66)	0.16	3.93	(2.10, 5.76)	<0.001
Usual care	2.25	(-3.64, 8.13)	0.45	2.09	(-4.94, 9.12)	0.56
Bevacizumab	14.95	(12.55, 17.34)	<0.001	18.49	(15.60, 21.38)	<0.001
Bevacizumab + Triamcinolone acetonide	17.55	(11.32, 23.77)	<0.001			
Bevacizumab + PDT	14.51	(3.30, 25.73)	0.01	16.44	(9.01, 23.87)	<0.001
Ranibizumab + PDT	9.94	(5.89, 13.98)	<0.001	16.66	(13.37, 19.96)	<0.001
Triamcinolone acetonide + PDT	8.29	(4.85, 11.73)	<0.001	14.81	(10.25, 19.38)	<0.001
Triamcinolone acetonide + laser	4.89	(-8.88, 18.66)	0.49			
PDT + NSAID				-3.07	(-13.13, 7.00)	0.55
Ranibizumab + NSAID	16.46	(8.50, 24.35)	<0.001	19.26	(4.89, 33.63)	0.009
Ranibizumab + epimacular brachytherapy				12.66	(8.45, 16.87)	<0.001
Bevacizumab + pegaptanib	8.53	(-0.88, 17.95)	0.076			

Key: AMD = age-related macular degeneration, CI = confidence interval, NSAID = non-steroidal anti-inflammatory drug, PDT = verteporfin photodynamic therapy, VA = visual acuity, VEGF = vascular endothelial growth factor.

Table 4: Results of the network meta-analysis: Differences in drug regimens, doses or appliances.

Intervention	Mean change in number of letters 6 months	95% CI	p-value	Mean change in numbers of letters 12 months	95% CI	p-value
Ranibizumab dose 0.3 mg IVI (reference) 0.5 mg IVI	1.35	(0.38, 2.32)	0.006	1.00	(-0.08, 2.09)	0.07
Ranibizumab regimen Monthly (reference) 3 monthly then monthly PRN 3 monthly then quarterly PRN Monthly PRN	0.13 -1.63 -0.46	(-4.37, 4.62) (-4.41, 1.14) (-2.88, 1.95)	0.96 0.25 0.71	-0.14 -3.99 -1.56	(-4.21, 3.93) (-7.35, -0.63) (-4.47, 1.35)	0.95 0.02 0.29
Bevacizumab dose 2.5 mg IVI (reference) 1.25 mg IVI 1 mg IVI 5 mg/kg systemic	-2.28 -18.36	(-6.78, 2.21) (-40.80, 4.08)	0.32 0.11			
Bevacizumab regimen Monthly (reference) 3 monthly then monthly PRN 3 every 6 weeks then monthly PRN Monthly PRN 3 every 2 weeks 3 every 6 weeks	-0.53 -2.60 -1.22 -17.01 5.83	(-6.02, 4.96) (-8.33, 3.13) (-3.73, 1.30) (-38.91, 4.89) (-5.89, 17.55)	0.85 0.37 0.34 0.13 0.33	-0.69	(-6.54, 5.15)	0.14
Pegaptanib dose 0.3 mg IVI (reference) 1.0 mg IVI 3.0 mg IVI	0.17 -1.83	(-2.33, 2.67) (-4.34, 0.68)	0.89 0.15	1.00 -2.00	(-2.01, 4.01) (-5.02, 1.02)	0.51 0.19
PDT regimen 2 monthly (reference) 3 monthly	2.00	(-2.32, 6.32)	0.36	-2.02	(-5.11, 1.07)	0.20

Intervention	Mean change in number of letters 6 months	95% CI	p-value	Mean change in numbers of letters 12 months	95% CI	p-value
PDT appliance						
Standard* (reference)						
Reduced**	3.37	(-2.80, 9.54)	0.28	6.15	(-1.83, 14.12)	0.13
Delayed light***	4.80	(-3.21, 12.80)	0.24	4.30	(-6.19, 14.79)	0.42
Anecortave dose						
3 mg juxtascleral (reference)						
15 mg juxtascleral	1.04	(-5.79, 7.87)	0.77	1.03	(-7.89, 9.94)	0.82
30 mg juxtascleral	0.50	(-7.11, 8.11)	0.90	-2.5	(-12.48, 7.48)	0.62

Reference – the reference category to which other doses (regimens) were compared within each drug category

*Standard PDT= 6 mg verteporfin/m² of body surface area and 50 J/cm² at an intensity of 600 mW/cm² over 83 seconds.

**Reduced PDT= 6 mg verteporfin/m² of body surface area and 25 J/cm² at an intensity of 600 mW/cm² over 83 seconds.

***Delayed light PDT= treatment with photodynamic therapy 30 minutes after the start of verteporfin infusion.

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APPENDIX 1: UPDATE SEARCHES

Embase (OvidSP): 1974-2012/wk 48

Searched 5.12.12

- 1 (Retina macula lutea or macula* or retina macula degeneration or macular degeneration or AMD).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (55528)
- 2 (Bevacizumab or avastin or ranibizumab or lucentis or pegaptanib or macugen or prednisolone or triamcinolone or photodynamic therapy or photodynamic therap\$ or photodynamic or verteporfin or PDT or VEGF trap-eye or VEGF trap or aflibercept or vascular endothelial growth factor trap or vascular endothelial growth factor trap-eye).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (161803)
- 3 (Clinical article or clinical study or clinical trial or controlled study or randomized controlled trial or major clinical study or double blind procedure or multicenter study or single blind procedure or phase 3 clinical study or phase 4 clinical study or crossover procedure or placebo or allocate\$ or assign\$ or blind\$ or (clinic\$ adj25 (study or trial)) or compar\$ or control\$ or cross?over or factorial\$ or follow?up or prospective\$ or random\$ or ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj25 (blind\$ or mask\$)) or trial or (versus or vs)).ti,ab. (6999838)
- 4 human/ (13922957)
- 5 (nonhuman or animal or animal experiment).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (6226392)
- 6 ((#3 not #5) or (#3 and (#4 and #5))).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (2923712)
- 7 1 and 2 and 6 (1263)
- 8 (201107\$ or 201108\$ or 201109\$ or 201110\$ or 201111\$ or 201112\$ or 2012\$).dd. (1816713)
- 9 7 and 8 (215)
- 10 limit 9 to embase (195)
- 11 remove duplicates from 10 (195)**

Update of searches undertaken by:

Van der Reis (2011) "Interventions for neovascular age-related macular degeneration: a systematic review and network meta-analysis"

Cochrane Central Register of Controlled Trials (CENTRAL) (Wiley): 2011-2012/Issue 11

Database of Abstracts of Reviews of Effects (DARE) (Wiley): 2011-2012/Issue 11

Health Technology Assessment Database (HTAD) (Wiley): 2011-2012/Issue 11

NHS Economic Evaluation Database (NHSEED) (Wiley): 2011-2012/Issue 11

Cochrane Database of Systematic Reviews (CDSR) (Wiley): 2011-2012/Issue 11

<http://cochranelibrary.com/>

Searched 5.12.12

- #1 Macula* or macular degeneration or AMD 2969
- #2 Bevacizumab or ranibizumab or pegaptanib or prednisolon or triamcinolon or photodynamic therapy or photodynamic or verteporfin or VEGF trap-eye or VEGF trap 1742
- #3 #1 and #2 from 2011 to 2012 64

CENTRAL search retrieved 42 records.

DARE search retrieved 3 records.

HTA search retrieved 1 record.

NHSEED search retrieved 4 records.

CDSR search retrieved 14 records.

Update of searches undertaken by:

Van der Reis (2011) "Interventions for neovascular age-related macular degeneration: a systematic review and network meta-analysis"

Pubmed (NLM): up to 2012/12/06

<http://www.ncbi.nlm.nih.gov/pubmed/>

Searched 6.12.12

History

[Clear history](#)

Search	Add to builder	Query	Items found	Time
#9	Add	Search (#6) OR #8	397	09:00:41
#8	Add	Search (#4) AND #7	382	08:58:24
#7	Add	Search ("2011/07/01"[Date - Publication] : "3000"[Date - Publication])	1384855	08:57:59
#6	Add	Search (#4) AND #5	337	08:57:36
#5	Add	Search ("2011/07/01"[Date - Entrez] : "3000"[Date - Entrez])	1299922	08:47:43
#4	Add	Search ((#1) AND #2) AND #3	2380	08:47:20
#3	Add	Search ((randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] OR double-blind method [mh] OR single-blind method [mh] OR clinical trial [pt] OR clinical trials [mh] OR "clinical trial" [tw] OR ((singl* [tw] or doubl* [tw] or trebl* [tw] or tripl* [tw]) AND (mask* [tw] or blind* [tw])) OR placebos [mh] OR placebo* [tw] OR random* [tw] OR research design [mh:noexp] OR comparative study [pt] OR evaluation studies as Topic [mh] OR evaluation studies [pt] OR follow up studies [mh] OR prospective studies [mh] OR control* [tw] OR prospectiv* [tw] OR volunteer* [tw]) NOT (animals [mh] NOT humans [mh]))	4668303	08:29:28
#2	Add	Search (Becavizumab [nm] OR bevacizumab OR avastin OR ranibizumab [nm] OR ranibizumab OR lucentis OR pegaptanib [nm] OR pegaptanib OR macugen OR prednisolone [mh] OR prednisolone OR triamcinolone [mh] OR triamcinolone OR photochemotherapy [mh] OR photochemotherap* OR photodynamic therap* OR photodynamic OR verteporfin [nm] OR verteporfin OR VEGF trap-eye OR VEGF trap OR aflibercept OR vascular endothelial growth factor trap OR vascular endothelial growth factor trap-eye)	83599	08:29:17
#1	Add	Search (Macula* OR macula lutea [mh] OR macular degeneration [mh] OR macular degeneration OR macular degenerations OR age-related maculopathy OR age related maculopathy OR age-related maculopathies OR age related maculopathies OR AMD)	41937	08:28:54

Searches were limited by both date of publication and date of entry to ensure all preprints from 2011/7-present date range included. Both limits retrieved unique records.

Update of searches undertaken by:

Van der Reis (2011) "Interventions for neovascular age-related macular degeneration: a systematic review and network meta-analysis"

APPENDIX 2: SIX MONTH STATA CODE

```
**use the 12 mth program first if you need to read in the data and create
the dataset**

clear
use stata612

**6 months change in mean number of letters**

drop if change_letters_6==.
drop if patients==0
drop if sd_letters_6==.
generate meanq=change_letters_6
generate sdq=sd_letters_6
generate nq=patients
gen recordq=_n
expand nq
gen xq=rnormal(meanq,sdq)
bysort recordq: egen meqq=mean(xq)
bysort recordq: egen sdqq=sd(xq)
gen sampleq=(xq-meqq)* sdq/sdqq+ meanq
drop nq sdq meanq xq

bysort record: sum sampleq change_letters_6 sd_letters_6
bysort interv_group: sum sampleq change_letters_6 sd_letters_6

**All compared with placebo treatment 1 to redo table 3**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\placebo", text replace
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with RBZ 2**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\RBZ", text replace
    char interv_group [omit] 2
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with pegaptanib 3**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\pegaptanib", text replace
    char interv_group [omit] 3
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with anecortave 5**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\anecortave", text replace
    char interv_group [omit] 5
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with PDT 6**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\PDT", text replace
```

```

        char interv_group [omit] 6
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with usual care 10**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\usual care", text replace
        char interv_group [omit] 10
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with BVZ 11**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\BVZ", text replace
        char interv_group [omit] 11
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with BVZ+TA 13**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\BVZ_TA", text replace
        char interv_group [omit] 13
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with BVZ+PDT 14**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\BVZ_PDT", text replace
        char interv_group [omit] 14
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with RBZ+PDT 15**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\RBZ_PDT", text replace
        char interv_group [omit] 15
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with TA+PDT 17**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\TA_PDT", text replace
        char interv_group [omit] 17
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with TA+laser 18**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\TA_laser", text replace
        char interv_group [omit] 18
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with PDT+NSAID 19**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\PDT_NSAID", text replace
        char interv_group [omit] 19
        xi: regress sampleq i.interv_group i.studyid
log close

```

```
**All compared with PDT+vitamin 20**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\PDT_vitamin", text replace
    char interv_group [omit] 20
    xi: regress sampleq i.interv_group i.studyid
log close
```

```
**All compared with RBZ+NSAID 31**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\RBZ_NSAID", text replace
    char interv_group [omit] 31
    xi: regress sampleq i.interv_group i.studyid
log close
```

```
**All compared with BVZ+pegaptanib 33**
log using "\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\6
mth by drug\BVZ_pegaptanib", text replace
    char interv_group [omit] 33
    xi: regress sampleq i.interv_group i.studyid
log close
```

```
**Comparing doses of ranibizumab Coded as Ran_dose 0.3mg=21 (reference),
0.5mg=22, 0.3+0.5mg=2**
```

```
log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Ran_dose6",
text replace
    char ran_dose [omit] 21
    xi: regress sampleq i.ran_dose i.studyid
log close
```

```
**Comparing doses of bevacizumab Coded as Bev_dose 2.5mg=24 (reference),
1.25mg=11, 1mg=23, 5mg/kg=22**
```

```
log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Bev_dose6",
text replace
    char bev_dose [omit] 24
    xi: regress sampleq i.bev_dose i.studyid
log close
```

```
**Comparing doses of pegaptanib Coded as Peg_dose 0.3mg=21 (reference)
1mg=22 3mg=23**
```

```
log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Peg_dose6",
text replace
    char pegdose [omit] 21
    xi: regress sampleq i.pegdose i.studyid
log close
```

```
**Comparing regimens of ranibizumab Coded as Ran_regimen PRN=21, IV
monthly=22 (reference),
    3 monthly then monthly PRN=23, 3 monthly then quarterly PRN=24 **
```

```

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Ran_reg6",
text replace
    char ran_regimen[omit] 22
    xi: regress sampleq i.ran_regimen i.studyid
log close

**Comparing regimens of bevacizumab Coded as Bev_regimen PRN=21, IV
monthly=22 (reference),
    3 monthly then monthly PRN=23, 6 wkly then monthly PRN=24, 3 IV 2
wkly=25, 3 IVI 6 wkly=27 **

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Bev_reg6",
text replace
    char bev_regimen[omit] 22
    xi: regress sampleq i.bev_regimen i.studyid
log close

**Comparing PDT regimens 21=2 monthly (reference) 6=3 monthly**

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Pdt_regimen
6", text replace
    char pdt_regimen [omit] 21
    xi: regress sampleq i.pdt_regimen i.studyid
log close

**Comparing PDT appliances 6=standard(reference) 21=reduced 22=delayed
light**

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Pdt_applian
ce6", text replace
    char pdt_appliance [omit] 6
    xi: regress sampleq i.pdt_appliance i.studyid
log close

**Comparing doses of anecortave Coded as Anec_dose 30mg=21 (reference)
15mg=22 3mg=23**
**No extra studies from our update so just using the original Dutch review
data**

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Anec_dose6"
, text
    char anec_dose [omit] 23
    xi: regress sampleq i.anec_dose i.studyid if studyid<79
log close

```

APPENDIX 3: 12 MONTH STATA CODE

```
**Reading in the data and analysing change in VA (letters) at 12 mths**

clear

insheet using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\stata
612.csv", comma

save stata612, replace

**12 months change in mean number of letters**

drop if change_letters_12==.
drop if patients==0
drop if sd_letters_12==.
generate meanq=change_letters_12
generate sdq=sd_letters_12
generate nq=patients
gen recordq=_n
expand nq
gen xq=rnormal(meanq,sdq)
bysort recordq: egen meqq=mean(xq)
bysort recordq: egen sdqq=sd(xq)
gen sampleq=(xq-meqq)* sdq/sdqq+ meanq
drop nq sdq meanq xq

bysort record: sum sampleq change_letters_12 sd_letters_12
bysort interv_group: sum sampleq change_letters_12 sd_letters_12

**All compared with placebo treatment 1 to redo table 3**

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Letters12",
text replace
xi: regress sampleq i.interv_group i.studyid
log close

**All compared with RBZ 2**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\RBZ", text replace
char interv_group [omit] 2
xi: regress sampleq i.interv_group i.studyid
log close

**All compared with pegaptanib 3**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\pegaptanib", text replace
char interv_group [omit] 3
xi: regress sampleq i.interv_group i.studyid
log close

**All compared with anecortave 5**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\anecortave", text replace
```

```

        char interv_group [omit] 5
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with PDT 6**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\PDT", text replace
        char interv_group [omit] 6
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with VEGF trap 8**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\VEGF", text replace
        char interv_group [omit] 8
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with usual care 10**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\usual care", text replace
        char interv_group [omit] 10
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with BVZ 11**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\BVZ", text replace
        char interv_group [omit] 11
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with BVZ+TA 13**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\BVZ_TA", text replace
        char interv_group [omit] 13
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with BVZ+PDT 14**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\BVZ_PDT", text replace
        char interv_group [omit] 14
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with RBZ+PDT 15**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\RBZ_PDT", text replace
        char interv_group [omit] 15
        xi: regress sampleq i.interv_group i.studyid
log close

**All compared with TA+PDT 17**

```

```

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\TA_PDT", text replace
    char interv_group [omit] 17
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with TA+laser 18**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\TA_laser", text replace
    char interv_group [omit] 18
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with PDT+NSAID 19**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\PDT_NSAID", text replace
    char interv_group [omit] 19
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with PDT+vitamin 20**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\PDT_vitamin", text replace
    char interv_group [omit] 20
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with RBZ+NSAID 31**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\RBZ_NSAID", text replace
    char interv_group [omit] 31
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with RBZ+epimacular brachytherapy 32**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\RBZ_epimacular", text replace
    char interv_group [omit] 32
    xi: regress sampleq i.interv_group i.studyid
log close

**All compared with BVZ+pegaptanib 33**
log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\12 mth by
drug\BVZ_pegaptanib", text replace
    char interv_group [omit] 33
    xi: regress sampleq i.interv_group i.studyid
log close

**Comparing doses of ranibizumab Coded as Ran_dose 0.3mg=21 (reference)
0.5mg=22 0.3+0.5mg=23**

log using
"\\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Ran_dose12"
, text replace

```

```

        char ran_dose [omit] 21
        xi: regress sampleq i.ran_dose i.studyid
log close

**Comparing regimens of ranibizumab Coded as Ran_regimen PRN=21, IV
monthly=22 (reference),
    3 monthly then monthly PRN=23, 3 monthly then quarterly PRN=24 **

log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Ran_reg12",
text replace
    char ran_regimen[omit] 22
    xi: regress sampleq i.ran_regimen i.studyid
log close

**Comparing regimens of bevacizumab Coded as Bev_regimen PRN=21, IV
monthly=22 (reference),
    3 monthly then monthly PRN=23, 6 wkly then monthly PRN=24, 3 IV 2
wkly=25, 3 IVI 6 wkly=27 **

log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Bev_reg12",
text replace
    char bev_regimen[omit] 22
    xi: regress sampleq i.bev_regimen i.studyid
log close

**Comparing doses of pegaptanib Coded as Pegdose 0.3mg=21 (reference)
1mg=22 3mg=23**

log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Peg_dose12"
, text replace
    char pegdose [omit] 21
    xi: regress sampleq i.pegdose i.studyid
log close

**Comparing PDT regimens 21=2 monthly (reference) 6=3 monthly**

log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Pdt_regimen
12", text replace
    char pdt_regimen [omit] 21
    xi: regress sampleq i.pdt_regimen i.studyid
log close

**Comparing PDT appliances 6=standard(reference) 21=reduced 22=delayed
light**

log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Pdt_applian
cel2", text replace
    char pdt_appliance [omit] 6
    xi: regress sampleq i.pdt_appliance i.studyid if studyid<79
log close

```



```
**Comparing doses of anecortave Coded as Anec_dose 30mg=21 (reference)
15mg=22 3mg=23**
**No extra studies from our update so just using the original Dutch review
data**
```

```
log using
"\KSRSERVER01\ksr\Projects\2012\WAMD_Dutch_Guidelines\Analysis\Anec_dose12
", text replace
    char anec_dose [omit] 23
    xi: regress sampleq i.anec_dose i.studyid if studyid<79
log close
```

APPENDIX 4: SIX MONTH RESULTS FOR ALL INTERVENTION COMPARISONS

This shows the mean difference (95% CI) in the change in number of letters from baseline for the intervention in the row when compared with the intervention in the column.

Intervention	Ranibizumab	Pegaptanib	Anecortave	PDT	Usual care	Bevacizumab
Ranibizumab						
Pegaptanib	-9.18 (-11.88, -6.48)					
Anecortave	-15.03 (-18.15, -11.91)	-5.85 (-9.50, -2.20)				
PDT	-12.78 (-14.88, -10.70)	-3.60 (-6.51, -0.69)	2.25 (-0.23, 4.74)			
Usual care	-12.06 (-17.67, -6.46)	-2.88 (-9.06, 3.30)	2.97 (-3.40, 9.34)	0.72 (-5.41, 7.01)		
Bevacizumab	0.64 (-0.99, 2.27)	9.82 (6.75, 12.88)	15.67 (12.23, 19.11)	13.42 (10.88, 15.95)	12.7 (7.34, 18.06)	
Bevacizumab + TA	3.24 (-2.72, 9.20)	12.42 (5.92, 18.92)	18.27 (11.59, 24.95)	16.02 (9.75, 22.28)	15.3 (7.45, 23.14)	2.6 (-3.13, 8.33)
Bevacizumab + PDT	0.21 (-10.84, 11.26)	9.39 (-1.97, 20.74)	15.24 (3.78, 26.70)	12.98 (1.76, 24.21)	12.27 (0.09, 24.44)	-0.43 (-11.36, 10.5)
Ranibizumab + PDT	-4.37 (-8.21, -0.53)	4.81 (0.31, 9.31)	10.66 (6.19, 15.13)	8.41 (4.64, 12.17)	7.69 (0.92, 14.46)	-5.01 (-9.14, -0.88)
TA + PDT	-6.01 (-9.38, -2.64)	3.16 (-0.80, 7.13)	9.02 (5.29, 12.75)	6.76 (3.97, 9.56)	6.05 (-0.43, 12.52)	-6.65 (-10.28, -3.03)
TA + laser	-9.42 (-23.16, 4.32)	-0.24 (-14.13, 13.65)	5.61 (-8.19, 19.42)	3.36 (-10.22, 16.94)	2.64 (-12.18, 17.47)	-10.06 (-23.87, 3.76)
Ranibizumab + NSAID	2.12 (-5.57, 9.81)	11.30 (3.15, 19.45)	17.15 (8.85, 25.45)	14.90 (6.92, 22.87)	14.18 (4.66, 23.70)	1.48 (-6.49, 8.85)
Bevacizumab + pegaptanib	-5.77 (-15.20, 3.66)	3.41 (-5.95, 12.76)	9.26 (-0.55, 19.07)	7.01 (-2.54, 16.55)	6.29 (-4.56, 17.14)	-6.41 (-15.84, 3.02)

Intervention	Bevacizumab + TA	Bevacizumab + PDT	Ranibizumab + PDT	TA+ PDT	TA + laser	Ranibizumab + NSAID
Ranibizumab						
Pegaptanib						
Anecortave						
PDT						
Usual care						
Bevacizumab						
Bevacizumab + TA						
Bevacizumab + PDT	-3.03 (-15.27, 9.31)					
Ranibizumab + PDT	-7.61 (-14.67, -0.54)	-4.58 (-16.26, 7.11)				
TA + PDT	-9.25 (-16.03, -2.47)	-6.22 (-17.74, 5.30)	-1.64 (-6.20, 2.91)			
TA + laser	-12.66 (-27.61, 2.30)	-9.63, (-27.24, 7.99)	-5.05, (-19.14, 9.05)	-3.40 (-17.27, 10.46)		
PDT + NSAID						
Ranibizumab + NSAID	-1.12 (-10.84, 8.61)	1.91 (-11.55, 15.38)	6.49 (-2.11, 15.08)	8.13 (-0.26, 16.53)	11.54 (-4.21, 27.29)	
Ranibizumab + epimacular brachytherapy						
Bevacizumab + pegaptanib	-9.01 (-20.05, 2.03)	-5.98 (-20.42, 8.46)	-1.40 (-11.52, 8.72)	0.24 (-9.67, 10.15)	3.65 (-12.96, 20.25)	-7.89 (-20.06, 4.28)

TA=triamcinolone acetonide

APPENDIX 5: 12 MONTH RESULTS FOR ALL INTERVENTION COMPARISONS

This shows the mean difference (95% CI) in the change in number of letters from baseline for the intervention in the row when compared with the intervention in the column.

Intervention	Ranibizumab	Pegaptanib	Anecortave	PDT	VEGF trap	Usual care
Ranibizumab						
Pegaptanib	-12.49 (-15.75, -9.23)					
Anecortave	-17.70 (-21.37, -14.04)	-5.21 (-9.35, -1.08)				
PDT	-15.23 (-17.53, -12.93)	-2.74 (-5.80, 0.32)	2.47 (-0.48, 5.43)			
VEGF trap	-0.09 (-1.83, 1.64)	12.40 (8.70, 16.09)	17.61 (13.55, 21.66)	15.14 (12.25, 18.02)		
Usual care	-17.07 (-23.78, -10.37)	-4.58 (-12.03, 2.86)	0.63 (-7.00, 8.26)	-1.84 (-8.92, 5.23)	-16.98 (-23.91, -10.05)	
Bevacizumab	-0.67 (-2.65, 1.30)	11.82 (8.02, 15.61)	17.03 (12.89, 21.17)	14.56 (11.56, 17.56)	-0.58 (-3.21, 2.05)	16.4 (9.99, 22.81)
Bevacizumab + PDT	-2.73 (-9.85, 4.40)	9.76 (1.94, 17.59)	14.98 (6.98, 22.98)	12.50 (5.03, 19.98)	-2.63 (-9.96, 4.70)	14.35 (4.97, 23.73)
Ranibizumab + PDT	-2.50 (-5.25, 0.25)	9.99 (5.88, 14.10)	15.20 (10.84, 19.56)	12.73 (9.45, 16.01)	-2.41 (-5.66, 0.85)	14.57 (7.33, 21.82)
TA + PDT	-4.35 (-9.06, 0.36)	8.14 (2.96, 13.32)	13.35 (8.20, 18.50)	10.88 (6.65, 15.10)	-4.26 (-9.28, 0.76)	12.72 (4.58, 20.86)
PDT + NSAID	-22.23 (-32.39, -12.07)	-9.74 (-20.10, 0.62)	-4.53 (-14.85, 5.80)	-7.00 (-16.90, 2.90)	-22.14 (-32.44, -11.83)	-5.16 (-17.32, 7.01)
Ranibizumab + NSAID	0.10 (-14.11, 14.31)	12.59 (-1.99, 27.17)	17.80 (3.13, 32.48)	15.33 (0.94, 29.72)	0.19 (-14.12, 14.51)	17.17 (1.46, 32.89)
Ranibizumab + epimacular brachytherapy	-6.5 (-10.12, -2.88)	5.99 (1.12, 10.86)	11.2 (6.05, 16.36)	8.73 (4.44, 13.03)	-6.41 (-10.42, -2.39)	10.57 (2.95, 18.20)

Intervention	Bevacizumab	Bevacizumab + PDT	Ranibizumab + PDT	TA + PDT	PDT + NSAID	Ranibizumab + NSAID
Ranibizumab						
Pegaptanib						
Anecortave						
PDT						
VEGF trap						
Usual care						
Bevacizumab						
Bevacizumab + PDT	-2.05 (-8.90, 4.79)					
Ranibizumab + PDT	-1.83 (-5.21, 1.55)	0.23 (-7.41, 7.86)				
TA + PDT	-3.68 (-8.70, 1.34)	-1.63 (-10.11, 6.86)	-1.85 (-7.13, 3.42)			
PDT + NSAID	-21.56 (-8.70, 1.34)	-19.50 (-31.91, -7.10)	-19.73 (-30.15, -9.31)	-17.88 (-28.64, -7.12)		
Ranibizumab + NSAID	0.77 (-13.57, 15.12)	2.83 (-13.07, 18.72)	2.60 (-11.87, 17.07)	4.45 (-10.52, 19.42)	22.33 (4.86, 39.80)	
Ranibizumab + epimacular brachytherapy	-5.83 (-9.95, -1.70)	-3.77 (-11.77, 4.22)	-4.00 (-8.55, 0.55)	-2.15 (-8.09, 3.80)	15.73 (4.94, 26.52)	-6.60 (-21.26, 8.06)

TA=triamcinolone acetonide