HTA 15.09.10. Systematic review of treatment of dry age-related macular degeneration and Stargardt disease.

Supplementary file 2. Physical interventions for AMD

To save space, rows in tables have been deleted if no data were provided in the study.

Acupuncture

Krenn et al

Study details	**Participant details**
Krenn H. Acupuncture may improve vision in patients with age-related macular degeneration (AMD): An observational study. Deutsche Zeitschrift fur Akupunktur 2008;51:25-8. *Country:* Austria *Design:* Before and After study *Number of centres:* one *Funding:* none *Trial ID:* not reported	*Number of Participants*: total 328 of 344 willing participants (16 were not eligible, see below) *Number of eyes* 656 *Sample attrition/dropout*: none *Sample crossovers:* not applicable *Inclusion criteria:* consecutive patients with dry AMD diagnosed by their ophthalmologist, given one acupuncture treatment and enrolled if vision improved. *Exclusion criteria:* After one acupuncture treatment, the eye test was repeated. Participants whose vision had not improved were classified as nonresponders and were not eligible for enrolment.
Intervention details	**Outcomes**
Intervention *1.* Acupuncture *Dose details:* two times per day, 5 days per week, minimum time of 60 minutes between treatments, each participant was acupunctured at the same points. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 2 weeks	*Outcomes (state if primary)* Visual acuity score (0% no letter correctly read to 100 % (all letters correctly read). *Length of follow-up:* 2 weeks

Participant characteristics, %			
	Acupuncture, n=328	**Intervention 2, n=**	**P value**
Age, years mean (SD)	77.4 (8.6)		
Sex, % male	30.8		
Ethnic origin *% White*	100		
Classification			
Smoking history			
Median (IQR) visual acuity reading from 3m distance, % lines correctly read	22 (0, 55)[a]		
Median (IQR) visual acuity reading from 40cm distance, % lines correctly read	45 (20, 67)[a]		

[a]estimated from figure			
Results			
	Acupuncture, n=328	**Intervention 2, n=**	**P Value**
Median (IQR) visual acuity reading from 3m distance, % lines correctly read at 2 weeks	33 (0, 66)[a]		
Median (IQR) visual acuity reading from 40cm distance, % lines correctly read at 2 weeks	66 (50, 82)[a]		
[a]estimated from figure			
Vision at 3m, % *Improved* *Stable* *Worsened*	 44.2 51.5 4.3		
Vision at 40cm, % *Improved* *Stable* *Worsened*	 88.4 8.8 2.7		
Comments			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?		x	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?		x	
5. Was the sample size sufficiently large to provide confidence in the findings?	x		
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?		x	
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?	x		
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?		x	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			N/A

Quality Rating: Poor
Exclusion of non-responders after 1 treatment, few details of outcome measures and no blinding of outcome assessor

*CD, cannot determine; NA, not applicable; NR, not reported

Blue light filters

Pipis et al

Study details	Participant details
Pipis A, Touliou E, Pillunat LE, Augustin AJ. Effect of the blue filter intraocular lens on the progression of geographic atrophy. European Journal of Ophthalmology 2015;25:128-33. *Country:* Germany *Design:* retrospective cohort study *Number of centres:* one *Funding:* States none. *Trial ID:* Not reported	*Number of Participants*: Total 40 *Number of eyes:* Total 66 1. Blue-light filter, n=39 2. No colour filter, n=27 6 patients had a blue light filter in one eye and no colour filter on the other eye. *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* pseudophakic AMD (following an uncomplicated extracapsular cataract extraction with phacoemulsification and in-the-bag implantation of a posterior chamber intraocular lens) with GA. *Exclusion criteria:* OCT scans to monitor 1-year progression of GA unavailable or of low quality (signal strength under 6/10), history of any other ocular disease, wet AMD, and following vitreoretinal surgery including intravitreal injections

Intervention details	Outcomes
Intervention *1.* blue light–filtering, UV-blocking intraocular lens *2.* no colour filter, UV-blocking intraocular lens Mean time between cataract surgery and baseline measurement for the sample was 31.8 (29.8) months. *Dose details:* Not applicable *Dose modifications:* Not applicable *Concurrent treatment:* Not reported *Duration of treatment:* Not reported	*Outcomes (state if primary)* GA progression *Length of follow-up:* one year

AMD: Age-related macular degeneration; GA: Geographic atrophy; OCT: Optical coherence tomography; UV: Ultra-violet

Participant characteristics, %			
	Blue-light filter, n=39 eyes	**No colour filter, n=27 eyes**	**P value**
Area of GA, mm^2, mean (SD)	5.95 (5.00)	4.96 (4.32)	
[a]Mean age of whole sample 82.3 years (range 71-94), 27.5% male			
Results			
	Blue-light filter, n=39 eyes	**No colour filter, n=27 eyes**	**P Value**
GA progression in 1 year mm^2, mean (SD)	0.72 (0.39)	1.48 (0.88)	P=0.0002
No correlation between size of the baseline GA lesion or time following cataract extraction and progression rate of GA for the whole sample or the separate groups.			
Adverse events			
Not reported			
Subgroups			

States in the subgroup of patients having a blue filter in one eye and a no colour filter in the other, a faster lesion growth in the non–blue filter eye was observed in 5 out of 6 cases.

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	X		
2. Was the study population clearly specified and defined?	X		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			CD
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			N/A
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?			N/A
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating: Poor

*CD, cannot determine; NA, not applicable; NR, not reported

Lavric & Pompe

Study details	**Participant details**
Lavric A, Pompe MT. Do blue-light filtering intraocular lenses affect visual function? Optom Vis Sci 2014;91:1348-54 *Country:* Slovenia *Design:* cohort study *Number of centres:* one *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: total 30 *Number of eyes* total 60 *Sample attrition/dropout*: not reported *Sample crossovers:* none *Inclusion criteria:* uncomplicated age-related cataract, phacoemulsification, intraocular lens implantation at least 2 years before. Interval between first and contralateral cataract operation ≤3 months. *Exclusion criteria:* any known ocular pathology (other than cataract) such as corneal disease, inflammation, glaucoma, amblyopia, diabetic retinopathy.
Intervention details	**Outcomes**

Intervention	*Outcomes (state if primary)*
1. Intraocular lens (IOL) after cataract extraction with UV-light and blue-light filter (study eye) *2.*IOL UV-light filter (fellow eye) *Dose details:* not applicable *Dose modifications:* not applicable *Concurrent treatment:* not reported *Duration of treatment:* at least up to follow-up	BCVA (ETDRS, converted to logMAR) Colour discrimination (not extracted) Contrast Sensitivity Macular findings Visual impression (subjective, not validated, not extracted) QOL (NEI-VFQ-25, score 0-100) *Length of follow-up:* mean 31.93 (SD 8.11) months blue light filter, 33.75 (8.4) months UV filter.

Participant characteristics, %			
	All participants, n=30		**P value**
Age, years mean (SD)	74.83 (8.04)		
Sex, % male	36.7		
Results			
	Blue light filter IOL, n=30 eyes	**UV filter IOL, n=30 eyes**	**P Value**
BCVA logMAR, mean (SD)	0.14 (0.15)	0.18 (0.18)	0.05
Comments			
Contrast sensitivity FACT log score, mean (SD) 1.5 cpd 3 cpd 6 cpd 12 cpd 18 cpd	 1.41 (0.13) 1.59 (0.17) 1.59 (0.18) 1.37 (0.18) 1.09 (0.19)	 1.41 (0.14) 1.55 (0.16) 1.57 (0.13) 1.29 (0.19) 1.00 (0.15)	 0.947 0.23 0.45 0.08 0.07
Signs of early DRAMD (e.g. drusen or RPE changes), n (%)	5 (17%)	5 (17%)	
Signs of potential choroidal neovascular membrane	0	0	
Comments			
NEI-VFQ-25, mean (SD) General health General vision Ocular pain Near activities Distance activities Social functioning Mental health Role difficulties Dependency Driving Colour vision Peripheral vision	**All participants, n=30** 48.15 (20.72) 78.52 (13.50) 77.31 (20.23) 89.79 (13.74) 93.52 (11.63) 93.98 (13.14) 92.82 (12.10) 94.91 (12.14) 96.61 (9.32) 85.62 (17.12), n=12 97.22 (10.59) 96.30 (11.40)		
Adverse events	NR		

Cohort and Cross-Sectional Studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?	x		

2. Was the study population clearly specified and defined?		x	
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?			CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating:Poor
Study population definition, participation rate, sample size, blinding of outcome assessors

*CD, cannot determine; NA, not applicable; NR, not reported

Nagai et al

Study details	**Participant details**
Nagai H, Hirano Y, Yasukawa T, Morita H, Nozaki M, Wolf-Schnurrbusch U, et al. Prevention of increased abnormal fundus autofluorescence with blue light-filtering intraocular lenses Presented at the 12th Congress of the European Society of Retina Specialists, Milan, Italy, September 2012. Journal of Cataract and Refractive Surgery 2015;41:1855-9. *Country:* Japan and Switzerland *Design:* cohort study *Number of centres:* 2 *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: total 131; 52 blue-light; 79 colourless *Number of eyes* total 131; 52 blue-light; 79 colourless *Sample attrition/dropout*: Of 174 eyes enrolled, total 43 eyes (blue-light IOL 22; colourless IOL 21) either no images obtained at follow-up; patient did not complete the visit or posterior capsule opacification *Sample crossovers:* not applicable *Inclusion criteria:* had uneventful cataract surgery with implantation of a blue-light IOL or colourless IOL and whose fundus autofluorescence images were obtainable immediately after surgery. If bilateral surgery, the first eye was included *Exclusion criteria:* presence of AMD, diabetic retinopathy, glaucoma or high myopia of -6.0 diopters or more.

Intervention details	**Outcomes**
Intervention *1.* blue-light filtering intraocular lens (IOL) (yellow-tinted) at cataract extraction *2.* colourless IOL at cataract extraction	*Outcomes* Development, progression or decrease in abnormal fundus autofluorescence (FAF) Presence or absence of drusen Development of wet AMD

Dose details: not applicable *Dose modifications:* not applicable *Concurrent treatment:* not reported *Duration of treatment:* at least 2 years	Development of GA *Length of follow-up:* 2 years

Participant characteristics, %			
	Blue-light filter, n=52	**Colourless lens, n=79**	**P value**
Age, years mean (SD)	73.9 (8.9)	75.5 (6.9)	0.26
Sex, % male	36.5	34.2	0.61
Smoking history, % *Never* *Past* *Current* *Unknown*	 57.7 7.7 11.5 23.1	 45.6 36.7 11.4 6.3	0.51
Key comorbidities *Diabetes* *Hypertension*	 76.9 44.2	 74.7 49.4	 0.12 0.44
Results			
	Blue-light filter, n=52	**Colourless lens, n=79**	**P Value**
Abnormal FAF development or increase in size or density, n (%)	0	12 (15.2)	0.0016
Abnormal FAF decrease, n (%)	3 (5.8)	2 (2.5)	NR
Wet AMD or GA development	1 (1.9)	9 (11.4)	0.042
Comments: states the type of AMD was GA in the blue-light filter lens group, in the colourless group this was GA in 6 and wet AMD in 3.			
Drusen progression, n (%)	0	3 (3.8)	NS
Comments			
Adverse events	Not reported	Not reported	
Comments			
Subgroups			
Reports incidence of abnormal FAF and progression of AMD according to different patterns of FAF at baseline, not extracted.			

Cohort and Cross-Sectional Studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			CD
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or			NA

exposure measured as continuous variable)?			
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?	x		
13. Was loss to follow-up after baseline 20% or less?		x	
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Chong et al

Study details	**Participant details**
Chong CF, Pham T, Chew J, Lee KL, Chang A, Liu H. Progression of age-related macular degeneration after cataract surgery in patients with a blue blocking intraocular lens in one eye and a clear intraocular lens in the fellow eye. Clinical and Experimental Ophthalmology 2011;39:23. *Country:* Not reported *Design:* Prospective cohort study (pilot) *Number of centres:* one *Funding:* Not reported *Trial ID:* Not reported	*Number of Participants*: 128 *Number of eyes:* 256 (blue blocking intraocular lens (IOL): 128, clear IOL: 128) *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* patients undergoing consecutive bilateral cataract surgery with implantation of a clear IOL in one eye and a blue blocking IOL in the fellow eye within 1 year *Exclusion criteria:* Not reported

Intervention details	**Outcomes**
Intervention *1.* Blue blocking IOL *2.* Clear UV-filter IOL *Dose details:* N/A *Dose modifications:* N/A *Concurrent treatment:* Not reported *Duration of treatment:* up to 2 years, mean duration between consecutive cataract surgeries was 307 days	*Outcomes (state if primary)* Progression of AMD, graded by clinical age-related maculopathy staging system (CARMS) *Length of follow-up:* mean 25.9 months

Participant characteristics, %			
	All patients, n=128		
Age, years mean (SD)	74		
Comments: States mean CARMS grade for eyes implanted with clear IOL and blue blocking IOL were similar pre-operatively (grade 2a)			
Results			

	Blue blocking IOL, n=128 eyes	Clear IOL, n=128 eyes	P Value
Progression of AMD	NR	NR	p=0.45
Adverse events	NR	NR	

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?		x	
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			CD
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NA
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?			CD
13. Was loss to follow-up after baseline 20% or less?			CD
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating: Poor due to limited details reported in abstract

*CD, cannot determine; NA, not applicable; NR, not reported

Rheopheresis

Koss et al

Study details	Participant details
Koss MJ, Kurz P, Tsobanelis T, Lehmacher W, Fassbender C, Klingel R, et al. Prospective, randomized, controlled clinical study evaluating the efficacy of Rheopheresis for dry age-related macular degeneration. Dry AMD treatment with Rheopheresis Trial-ART. Graefes Archive for Clinical & Experimental Ophthalmology 2009;247:1297-306. *Country:* Germany *Design:* RCT *Number of centres:* one *Funding:* commercial funding	*Number of Participants*: 52 (26 treatment, 26 control) *Number of eyes* 43 (22 treatment, 21 control) *Sample attrition/dropout*: 9 (4 treatment, 5 control) *Sample crossovers:* none *Inclusion criteria:* between 45 and 85 years; diagnosis of bilateral AMD, and dry AMD in the study eye confirmed by the use of fluorescein angiography and fundus photography; BCVA in study eyes 0.1-0.8 (by Early Treatment Diabetic Retinopathy Study (ETDRS) charts); peripheral veins allowing vascular access to establish the extracorporeal circuit. *Exclusion criteria:* other retinal or choroidal, optic nerve disease, glaucoma, conditions that limit the view of the fundus, acute bleeding

Trial ID: not reported	in any eye, anaemia, haemorrhagic diathesis or coagulopathy, diabetes, serious acute or chronic kidney or liver failure, hypotension, chronic viral infection, epilepsy, psychosis or dementia, malignant disease or any other condition with life expectancy <12 months, known history of alcohol or drug abuse and long-term serious nicotine abuse.

Intervention details	**Outcomes**
Intervention *1.* Rheopheresis *2.* Control (no treatment) *Dose details:* 10 treatments, treatments 1 and 2 were in the first week, with a 2–3 day interval, treatments 3-10 were performed as single therapies with a 1-week therapy-free interval between treatments. The target was to treat 100% of patient's plasma volume per treatment, estimated using the formula 40 ml x body weight (kg) of the patient. 99% (SE 0.08) of patients´ plasma volume was reached in 236 treatments of 25 patients. *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* within 17 weeks	*Outcomes (state if primary)* mean logMar change in BCVA by ETDRS (primary outcome) Proportion of eyes with loss or gain of BCVA Safety Tolerability (un-validated, not extracted) Post-hoc analysis of long-term visual acuity (in a small proportion only, not data extracted) *Length of follow-up:* 7.5 months

Participant characteristics, %			
	Rheopheresis, n=22	**Control, n=21**	**P value**
Age, years mean (SD)	70	73	
Sex, % male	23	33	
BCVA study eyes, mean	0.58	0.66	P=0.19
Results			
	Rheopheresis, n=22	**Control, n=21**	**P Value**
Change in BCVA, 7.5 months, ETDRS lines, mean (95% CI)	0.63 (0.28, 0.99)	-0.31 (-0.64, 0.02)	Difference 0.9 (0.2, 1.7), p=0.014
Comments: at week 18, the mean change was +0.6 ETDRS lines in the Rheopheresis group (95% CI: 0.43 to 0.77) and +0.18 ETDRS lines in the control group (95% CI: –0.09 to 0.45) (p=0.19).			
Improvement in BCVA ≥ 1 line, % at 7.5 months	31.8	23.8	Not calculated
Improvement in BCVA ≥ 2 lines, % at 7.5 months	9.1	0	Not calculated
Deterioration in BCVA ≥ 1 line, % at 7.5 months	0	23.8	Not calculated
Deterioration in BCVA ≥ 2 lines, % at 7.5 months	0	19.0	Not calculated
Deterioration in BCVA ≥ 3 lines, % at 7.5 months	0	9.5	Not calculated
Development of CNV	0	0	
Comments			
Adverse events, %	**Rheopheresis, n=25**	**Control, n=22**	
Any AE *AE requiring treatment* *Serious AE*	2.1 0.8 0	 4.5 (not treatment-related)	
Comments AEs were hypotension, hematoma/bleeding, dizziness			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement

Random sequence generation (selection bias)	Low	randomization list was computer-generated
Allocation concealment (selection bias)	Low	Used envelopes that were opened off site (central allocation).
Blinding participants and personnel (performance bias), Objective outcomes	High	Says patients and investigators were not blinded
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	High	Investigators not blinded.
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	Similar drop out between groups. Says used ITT analysis with last observation carried forward for missing data but the numbers reported do not reflect this. For safety was on all randomised who received at least one treatment.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes stated are reported.
Other biases	Low	No other biases

Pulido et al

Study details	**Participant details**
Pulido JS, Winters JL, Boyer D. Preliminary analysis of the final multicenter investigation of rheopheresis for age related macular degeneration (AMD) trial (MIRA-1) results. Transactions of the American Ophthalmological Society 2006;104:221-31. Linked publication of interim data Pulido J, Sanders D, Winters JL, Klingel R. Clinical outcomes and mechanism of action for rheopheresis treatment of age-related macular degeneration (AMD). *Journal of Clinical Apheresis* 2005;**20**:185-94. *Country:* USA *Design:* RCT *Number of centres:* 13 *Funding:* not stated *Trial ID:* not stated	*Number of Participants*: 216 randomised, 198 treated (rheopheresis 129; placebo 69) *Number of eyes* 198 (rheopheresis 129; placebo 69) *Sample attrition/dropout*: 18 did not complete 1 treatment and were not included in the analysis. No details of which group these were allocated to. 15 others were excluded from the rheopheresis group because of poor venous access (n=13) and no post baseline measurement (n=2). At 12 months, 10 rheopheresis and 6 placebo patients did not have follow-up. *Sample crossovers:* not reported assume none *Inclusion criteria:* between 50-85 years, weigh at least 50kg, study eye diagnosed with dry AMD with ≥10 large, soft, semisoft, and/or confluent drusen within 3,000 nm of the foveal centre, BCVA (ETDRS) between 20/32 and 20/125, geographic atrophy allowed if N 3 disc diameters outside of 3,000 nm foveal centre, serous pigment epithelial detachment allowed if no neovascularisation present, a score of no more than 75 on the VFQ-25 Visual Functioning Questionnaire, no conditions that limit the view of the fundus. If both eyes qualified, one eye was randomized to the study eye. *Exclusion criteria:* study eye with concomitant retinal or choroidal disorder other than AMD, significant central lens opacities, wet AMD, other ocular disease. Patient in poor health (various conditions stated but not extracted)
Intervention details	**Outcomes**

Intervention *1.* rheopheresis *2.* Placebo (sham treatment) *Dose details:* 8 treatments as paired sessions (1 plasma volume per session with a 2-day recovery interval between them) *Dose modifications:* those who experienced an "improvement" at 3-months but then later showed a decrease at 9-months were eligible to receive two additional treatments (either rheopheresis or placebo) 2 weeks after the 9-month post baseline visit. *Concurrent treatment:* Oral supplements of zinc, high-dose vitamins and antioxidants. *Duration of treatment:* 10 weeks	*Outcomes (state if primary)* BCVA change (primary outcome) Decrease in drusen Development of choroidal neovascularisation Adverse events Haematology outcomes (not extracted) BCVA in fellow eye Pepper Visual Skills for Reading Test National Eye Institute's Visual Functional Questionnaire (VFQ)-25. *Length of follow-up:* 12 months (initial data analysis of final data)

Participant characteristics, %			
	Rheopheresis, n=129	**Placebo, n=69**	**P value**
Age, years mean (SD)	75.0 (6.51)	74.2 (5.79)	
Sex, % male	48.1	52.2	
Ethnic origin *% White*	96.1	100	
Mean logMAR ETDRS visual acuity (SD)	-0.4 (0.16)[a], n=114	-0.4 (0.16), n=69[a]	P=0.95
[a]from the population described as the intention to treat population. Comments: also reports proportions within BCVA categories, not extracted. Also reports baseline characteristics for the efficacy outcome assessment populations and a modified per protocol population.			
Results			
	Rheopheresis, n=104	**Placebo, n=69**	**P Value**
Mean logMAR ETDRS visual acuity at 12 months	0.02 (0.213)	0.02 (0.20)	P=0.977
Comments			
Adverse events, %	**Rheopheresis, n=129**	**Placebo, n=69**	
Any AE during day of treatment	38.8	13.0	
AE requiring intervention during day of treatment	24.0	5.8	
AE resulting in treatment suspension during day of treatment	9.3	2.9	
AE during treatment phase not on treatment day	15.1	21.7	
AE requiring intervention during treatment phase not on treatment day	7.1	15.9	
AE during follow-up (after treatment phase)	34.4	27.5	
AE requiring intervention during follow-up (after treatment phase)	30.3	27.5	
Comments: also reports percentage of treatments with at least one report, not data extracted. No participants experienced an AE resulting in study discontinuation.			
Serious adverse events during day of treatment	2		
Serious adverse events during treatment phase	1		
Serious adverse events during follow-up	24		

Subgroups			
Interim data for BCVA at least 20/40 and below 20/40 reported for 43 participants only, not extracted.			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Used a computer-generated random number
Allocation concealment (selection bias)	Unclear	Sequentially numbered sealed envelopes were used, but no details of whether opaque
Blinding participants and personnel (performance bias), Objective outcomes	Low	Double masked by covering participants with an opaque shroud to stop observation of the treatment, pumps were activated for all participants, venipunctures were undertaken for all.
Blinding participants and personnel (performance bias), Subjective outcomes	NA	
Blinding outcome assessors (detection bias), Objective outcomes	Low	States ophthalmologic investigators masked as treatments were performed at separate location.
Blinding outcome assessors (detection bias), Subjective outcomes	NA	
Incomplete outcome data (attrition bias), Objective outcomes	High	States patients were analysed within the group to which they were randomly assigned on an intent to treat basis. Patients had to be able to complete at least 75% of the initial plasma volume treatment to be included as an 'intent to treat' patient. If they failed to complete the first treatment they were removed from the study. The analysis was not an ITT analysis for efficacy and withdrawals were unbalanced between groups.
Incomplete outcome data (attrition bias), Subjective outcomes	NA	
Selective reporting (reporting bias)	High	Outcomes stated in preliminary publication not reported in the 2006 publication
Other biases	Low	No other apparent biases

Brunner et al

Study details	Participant details
Brunner R, Widder RA, Walter P, Luke C, Godehardt E, Bartz-Schmidt KU, *et al.* Influence of membrane differential filtration on the natural course of age-related macular degeneration: A randomized trial. *Retina* 2000;**20**:483-91. Widder RA, Farvili E, Reis RJ, Luke C, Walter P, Kirchhof B, et al. The Treatment of Age-Related Macular Degeneration (ARMD) with Etracorporeal Treatment Procedures. A Follow-up of Four Years. Investigative Ophthalmology & Visual Science 2002;43:2906. *Country:* Germany *Design:* RCT, Follow-up cohort study *Number of centres:* one *Funding:* Commercial support *Trial ID:* Not reported Cohort study (Widder et al) assumed by reviewers to be linked to Brunner, assumed that a subgroup from both groups who had Dry AMD.	*Number of Participants*: Total 40 (membrane differential filtration 20, control 20) Cohort study: 20 participants. *Number of eyes* 40 (membrane differential filtration 20, control 20) Cohort study: 20 eyes. *Sample attrition/dropout*: 3 after randomisation (membrane differential filtration 2, control 1) non treatment-related concomitant disease; replaced by 3 new patients. *Sample crossovers:* assume none, but controls had opportunity for treatment after 21 weeks which affected follow-up times. *Inclusion criteria:* Visual acuity between 20/160 and 20/32 in at least one eye, signs of AMD such as drusen, areolar atrophy, pigment clumping, pigment epithelium detachment or subretinal neovascularization (SRNV). If both eyes eligible, one eye was randomized by random numbers. Cohort study: dry AMD (pigment clumping, soft and hard drusen and retinal degeneration) *Exclusion criteria:* Dementia, severe cardiac disease, history of malignoma or infection with hepatitis, HIV or Treponema pallidum, suitability for laser coagulation.

Intervention details	Outcomes
Intervention *1.* Membrane differential filtration *2.* Control (no treatment) *Dose details:* Treated 5 times (every 5 weeks). One treatment cycle was 2 treatments with a 2 day interval while patients were admitted to hospital. 120% of plasma volume processed during first treatment and 80% during second treatment *Dose modifications:* Smaller volumes of plasma, down to 60%, could be processed if the plasma protein values at the end of the first treatment were subnormal. *Concurrent treatment:* Anticoagulation of 4500 units of heparin and acid citrate dextrose formula A infused at a ratio of 1:16 *Duration of treatment:* 21 weeks Cohort study: 6 treatments per year.	*Outcomes (state if primary)* Visual acuity, ETDRS charts, at 21 weeks (primary outcome) Light responses Macular visual evoked potentials (not extracted) Central visual field Rheologic and biochemical parameters (not extracted) Adverse events Cohort study: BCVA *Length of follow-up:* treatment: 11 months (range 7-24), control 12 months (range 6-29) Cohort study: 3 years (4 years for 12 participants)

Participant characteristics, %			
	Membrane differential filtration, n=20	**Control, n=20**	**P value**
Age, years mean (SD)	72 (6)	70 (8)	
Classification Subfoveal SRNV, %	45	45	
Smoking history			
visual acuity, logMAR, mean (SD)	0.47 (0.13)	0.39 (0.24)	P=0.2

Light rise % (Arden ratio), mean (SD)	189.2 (49.8)	204.6 (67.5)	
Results			
	Membrane differential filtration, n=20	**Control, n=20**	**P Value**
Change in visual acuity at 21 weeks, ETDRS lines, mean (SD)	0.63 (1.8)	-0.94 (1.7)	Difference 1.6, p<0.01
Change in visual acuity at follow-up, ETDRS lines, mean (SD)	-0.21 (2.4)	-1.83 (2.9)	Difference 1.6, p=0.06
Comments			
Light rise % (Arden ratio), mean (SD)	194.4 (57.8)	187.4 (55.2)	
Comments: States that the light rise of the electrooculogram remained stable in the treatment group and deteriorated in the control group, but changes were not statistically significant.			
Visual field			
Comments States no significant changes for global mean defect.			
Adverse events			
Serious side effects	0	0	
Fall in blood pressure, % of treatments (n=200)	6		
Haemolysis, % of treatments (n=200)	2.5		
Flow problems, % of treatments (n=200)	5		
Comments			
Subgroups			
Change in visual acuity at 21 weeks (ETDRS lines) remained significantly different between treatment and controls for the subgroups of patients without SRNV and patients with drusen, but not for the subgroups of patients with SRNV or patients without soft drusen (data presented, not extracted)			
Cohort study (n=20)			
Patients with improvement in BCVA at 2 and 3 years	15/20 (75%)		
Mean improvement in visual acuity, lines at 2 years	1.9 (n=20)		
Mean improvement in visual acuity, lines at 3 years	1.2 (n=20)		
Patients with improvement in BCVA at 4 years	7/12 (58.3%)		
Mean improvement in visual acuity, lines at 4 years	0.8 (n=12)		
Comments: reports p-values for lines improvement at 2 years and 3 years: p<0.05; at 4 years: p=0.77			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	3 patients were withdrawn after randomisation and replaced with new patients – assume these were not randomised. States randomisation carried out my random numbers in closed envelopes, no further details
Allocation concealment (selection bias)	Unclear	States randomisation carried out my random numbers in closed envelopes, no further details
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Not reported
Blinding participants and personnel (performance bias), Subjective	N/A	N/A

outcomes		
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not reported
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Not reported, different follow-up times
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	Low	Outcomes reported as stated in methods, but no trial record
Other biases	Low	No other bias

Rencova et al

Study details	**Participant details**
Rencova E, Blaha M, Studnicka J, Blaha V, Lanska M, Renc O, et al. Preservation of the Photoreceptor Inner/Outer Segment Junction in Dry Age-Related Macular Degeneration Treated by Rheohemapheresis. Journal of ophthalmology 2015;2015:359747. *Country:* Czech Republic *Design:* RCT *Number of centres:* one *Funding:* Public body *Trial ID:* Not reported Possible overlap of participants from Blaha et al., 2013 and Studnička et al 2013, see below for citation details.	*Number of Participants*: Total 24: Rheohemapheresis (RHF) 12; Control 12 *Number of eyes:* Total 40 (RHF 22, control 18) *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* high-risk, preangiogenic form of AMD (dry) with soft drusen, reticular drusen, confluent soft drusen, and drusenoid pigment epithelium detachment (DPED) *Exclusion criteria:* any retinal or choroidal disorders other than AMD, optic nerve disorders, glaucoma, conditions limiting the examination of the fundus, and acute bleeding in the studied eye; extracorporeal circulation or therapeutic haemapheresis and the absence of peripheral veins suitable for establishing an extracorporeal circuit.

Intervention details	**Outcomes**
Intervention *1.* RHF *2.* Control (not specified) *Dose details:* 8 procedures (says standardised) *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* 10 weeks	*Outcomes (state if primary)* BCVA (ETDRS letters) DPED area morphological changes in the photoreceptor inner and outer segment (IS/OS) junction retinal layer (not extracted) *Length of follow-up:* 2.5 years

Participant characteristics, %			
	RHF , n=12	**Control, n=12**	**P value**
Age, years mean (range)	64.3 (64-93)	65.6 (64-83)	
Sex, % male			
BCVA, ETDRS letters, median (95% CI)	74.0 (56.2, 81.3)	74.0 (25.2, 82.6)	0.46
DPED, mm^2, mean (SD)	3.68 (4.45)	4.12 (6.64)	0.605
Results			
	RHF , n=12	**Control, n=12**	**P Value**

BCVA, ETDRS letters, median (95% CI)	79.0 (57.3, 83.4)	72.5 (23.4, 83.1)	0.021
Comments			
DPED, mm^2, mean (SD)	0.71 (1.27)	9.19 (9.51)	<0.001
Comments			
Reduction in DPED area, n/N (%)	19/22 (86.4) eyes	3/18 (16.7) eyes	
Enlargement of DPED area, n/N (%)	3/22 (13.6) eyes	15/18 (83.3) eyes	
Transition into the Wet Form of AMD	0	6/18 eyes with detachment of the IS/OS junction at baseline	
Adverse events	NR	NR	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Details not reported, possibly not a randomised study
Allocation concealment (selection bias)	Unclear	Details not reported
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Details not reported
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Details not reported
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Details not reported
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	Unclear	Results as reported in methods, no trial record
Other biases	Low	No other bias

Swartz et al

Study details	**Participant details**
Swartz M, Rabetoy G. Treatment of non-exudative agerelated macular degeneration using membrane differential filtration apheresis [meeting abstract from the Association for Research in Vision and Ophthalmology annual meeting. Fort Lauderdale, Florida, USA. May 9-14, 1999]. Invest Ophthalmol Vis Sci 1999;40:S319. *Country:* USA *Design:* RCT (pilot study) *Number of centres:* assumed one *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: total 30: Aphersis 10; treatment without filtration 10; no treatment 10 *Number of eyes* total 30: Apheresis 10; treatment without filtration 10; no treatment 10 *Sample attrition/dropout*: not stated *Sample crossovers:* not stated *Inclusion criteria:* non-exudative AMD characterised by large soft drusen and visual acuity 20/40 – 20/100 in one eye. *Exclusion criteria:* no details

Intervention details	**Outcomes**
Intervention *1.* Membrane Differential Filtration Apheresis *2.* Treatment without filtration *3.* No treatment *Dose details:* apheresis 10 treatments, no other details *Dose modifications:* no details *Concurrent treatment:* no details *Duration of treatment:* 20 weeks	*Outcomes (state if primary)* BCVA (distance) (ETDRS) (primary) Reading speed (Pepper Visual Skills for Reading Test, PVSRT) (primary) Haematological analysis, urinalysis and vital signs (not extracted) *Length of follow-up:* 20 weeks assumed

Participant characteristics, %				
	Apheresis, n=10	**No filtration, n=10**	**No treatment, n=10**	**P value**
Comments				
Results				
	Apheresis, n=10	**No filtration, n=10**	**No treatment, n=10**	**P Value**
BCVA mean change (logMAR) ETDRS chart lines	1.9	1.3	0.6	
Comments				
Median % change in PVSRT	27	-18	-20	
Comments				

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Says randomised, no further details
Allocation concealment (selection bias)	Unclear	As above
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Says double masked, no further details
Blinding participants and personnel (performance bias), Subjective	NA	

outcomes		
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not described
Blinding outcome assessors (detection bias), Subjective outcomes	NA	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Unclear if any attrition.
Incomplete outcome data (attrition bias), Subjective outcomes	NA	
Selective reporting (reporting bias)	High	No data presented for Haematological analysis, urinalysis and vital signs
Other biases	Unclear	Not enough information to assess.

Blaha et al

Study details	**Participant details**
Blaha M, Rencova E, Langrova H, Studnicka J, Blaha V, Rozsival P, et al. Rheohaemapheresis in the treatment of nonvascular age-related macular degeneration. Atherosclerosis Supplements 2013;14:179-84. Linked publication: Blaha M, Rencova E, Langrova H, Lanska M, Blaha V, Studnicka J, Rozsıval P et al. The importance of rheological parameters in the therapy of the dry form of age-related macular degeneration with rheohaemapheresis. Clinical Hemorheology and Microcirculation 50 (2012) 245–255 (adverse events and rheohaemapheresis and haematological outcomes) *Country:* Czech Republic *Design:* CCT (incorrectly described as randomised) *Number of centres:* one *Funding:* non-commercial grant *Trial ID:* not reported Possible overlap of participants from Studnilka et al 2013 and Rencová et al., 2015 see above and below for citation details	*Number of Participants*: total 72: 38 rheohaemapheresis; 34 controls. Of these 12 and 13 patients had DPED *Number of eyes*: unclear for total group, for subgroup with DPED this was 22 eyes in the rheohaemapheresis group and 18 in the control group. *Sample attrition/dropout*: 1 rheohaemapheresis participants withdrew after 2 treatments *Sample crossovers:* none *Inclusion criteria:* diagnosis of AMD in both eyes, including dry AMD in one or both eyes confirmed by fluorescein angiography and fundus photography, subgroup with late-stage, high-risk, preangiogenic form of AMD with soft drusen, confluent soft drusen and drusenoid retinal pigment epithelium detachment (DPED) *Exclusion criteria:* retinal or choroidal disorders other than AMD, optic nerve disorders, glaucoma, conditions limiting the examination of the fundus, and acute bleeding in the studied eye, extracorporeal circulation or therapeutic haemapheresis and the absence of peripheral veins suitable to establish an extracorporeal circuit.

Intervention details	**Outcomes**
Intervention *1.* rheohaemapheresis *2.* control *Dose details:* 8 procedures, 2 weekly with a 14-day pause, procedure repeated 4 times. *Dose modifications:* 1-2 procedures added after one year follow up if needed (if suspicion or symptoms of disease progression discovered).	*Outcomes (state if primary)* BCVA (ETDRS) Electroretinography measures of rod response, maximal response, oscillatory potentials, cone response and 30-Hz flicker (not extracted) Progression to wet AMD DPED area. Adverse events Laboratory examinations (not extracted) *Length of follow-up:* 2.5 years

Concurrent treatment: not reported *Duration of treatment:* 10 weeks	

Participant characteristics, %			
	Rheohaemapheresis, n=38	**Control, n=34**	**P value**
Age, years mean (SD)	66 (range 54-85)	76 (range 65-83)	
Sex, % male	36.8	13.4[a]	
Ethnic origin *% White*			
Classification			
Smoking history			
BCVA	0.61 (0.06 – 1.00)	0.60 (0.05 – 1.00)	P=0.95
lesion size			
previous treatments			
Key comorbidities			
Family history			
DPED area, mm²	3.68 (4.45)	4.12 (6.64)	0.61
Comments [a] states 11.8 in Blaha 2013			
Results			
	Rheohaemapheresis, n=37	**Control, n=34**	**P Value**
BCVA at 2.5 years	0.68 (0.35 – 1.00)	0.52 (0.25 – 0.80)	p=0.09
BCVA at 2.5 years, % of eyes: *Same as baseline* *Improved by 1 row* *Improved by ≥ 2 rows* *Decreased by 1 row* *Decreased by 2 rows*	(n=22 eyes) 36 27 23[a] 9 5[a]	(n=18 eyes) 44 0 6[a] 28[a] 22	
Comments [a]Calculated by reviewer, percentages reported in paper incorrect. Appears to be a subgroup but no details, possibly the DPED subgroup.			
Progression to wet AMD	0	NR	
Central retinal thickness	NR	NR	
Comments: states statistically significant differences did not appear in the central retinal thickness.			
Adverse events, %	**Rheohaemapheresis, n=37**	**Control, n=34**	
Any AE *Transient hypotension* *Faintness* *Fatigue, anxiety* *Paraesthesia*	5.4 1.3 1.3 0.7 2.0		
Any AE requiring intervention *Transient hypotension* *Faintness* *Fatigue, anxiety* *Paraesthesia*	1.0 0 0.3 0.3 0.3		
AE resulting in treatment termination *Transient hypotension* *Faintness* *Fatigue, anxiety* *Paraesthesia*	0 0 0 0 0		
Comments: also reports vascular access problems and technical problems, not extracted			
Subgroups	**22 eyes (12 patients) with DPED**	**18 eyes (13 patients) with DPED**	**P-value**
DPED area, mm² at 2.5 years	0.71 (1.27)	9.19 (9.51)	p<0.001
Comments: also states difference in DPED area p<0.0005			

Cochrane Risk of bias for RCTs

	Risk of bias (high,	Support for statement

	unclear, low)	
Random sequence generation (selection bias)	High	Described as randomised, but states that for those who met the criteria, one was assigned to treatment arm and the next to the control group, therefore not random assignment.
Allocation concealment (selection bias)	High	No concealment of allocation
Blinding participants and personnel (performance bias), Objective outcomes	High	Says is an open study
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Low	An experienced eye specialist evaluated all eye findings without knowledge of treatment assignment.
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	High	One participant withdrew and was not included in the analysis.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	Outcomes reported as stated.
Other biases	Low	No other apparent biases

Studnicka et al

Study details	**Participant details**
Studnicka J, Rencova E, Blaha M, Rozsival P, Lanska M, Blaha V, et al. Long-term outcomes of rheohaemapheresis in the treatment of dry form of age-related macular degeneration. Journal of ophthalmology 2013;2013:135798. *Country:* Czech Republic *Design:* CCT *Number of centres:* one *Funding:* non-commercial grant *Trial ID:* not reported Possible overlap of participants from Blaha et al., 2013 and Rencova 2015, see above for citation details	*Number of Participants*: Total 37: 19 rheohaemapheresis; 18 controls. Of these 17 and 17 patients had drusenoid pigment epithelium detachment (DPED) *Number of eyes* rheohaemapheresis 35, control 27. For subgroup with DPED rheohaemapheresis 30; control 20 *Sample attrition/dropout*: not reported *Sample crossovers:* assume none *Inclusion criteria:* dry AMD, latestage, high-risk, preangiogenic form of AMD with soft drusen, confluent soft drusen, and DPED *Exclusion criteria:* retinal or choroidal disorders other than AMD, optic nerve disorders, glaucoma, conditions limiting the examination of the fundus, and acute bleeding in the studied eye, general exclusion criteria for rheohaemapheresis. Eyes that had neovascular AMD and/or developed neovascular AMD during the follow up were not included in the subsequent evaluation.

Intervention details	**Outcomes**
Intervention *1.* rheohaemapheresis *2.* control *Dose details:* 8 procedures of 1.5 plasma volumes	*Outcomes (state if primary)* BCVA (ETDRS) Occurrence of wet AMD Occurrence of DPED Electroretinography measures (not extracted) Rheological and laboratory examinations (not extracted)

Dose modifications: not stated *Concurrent treatment:* not stated *Duration of treatment:* 10 weeks	*Length of follow-up:* minimum 3.5 years (between 42 and 84 months)

Participant characteristics, %			
	Rheohaemapheresis, n=19	**Control, n=18**	**P value**
Age, years mean (SD)	67.6 (range 55-76)	72.8 (range 64–81)	
Sex, % male	21.1	11.1	
Classification, % *Bilateral soft drusen* *Neovascular AMD in 1 eye*	 100 5.3	 16.7	
Smoking history			
Mean BCVA (95% CI)	0.74 (0.36, 1.0)	0.71 (0.15, 1.0)	
Mean (SD) DPED, mm^2	6.78 (3.79)	4.09 (3.48)	P=0.012
Results			
	Rheohaemapheresis, n=19	**Control, n=18**	**P Value**
Mean BCVA (95% CI) at 3.5 years	0.79 (0.41, 1.0)	0.7 (0.32, 0.87)	0.125[a]
[a]at 2 years follow-up there was a significant difference between groups p=0.028			
Mean (SD) DPED, mm^2	4.13 (3.84)	6.69 (4.2)	P=0.015
CNV development, n (eyes)	2	6	P=ns
Adverse events	0	NR	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	High	Not randomised. States that patients…were recruited so that one patient was always assigned to rheohaemapheresis therapy and the second one joined the control group
Allocation concealment (selection bias)	High	No concealment of allocation to groups
Blinding participants and personnel (performance bias), Objective outcomes	High	Says not double blind
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Low	States that an experienced eye specialist evaluated all eye findings of the study without knowledge of treatment group.
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Unclear if any participants were excluded from the analysis, states that eyes that suffered from neovascular AMD and/or developed neovascular AMD occurring during the follow up were not included in the subsequent evaluation, but no numbers analysed given.
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Low	All outcomes reported
Other biases	Low	

Klingel et al

Study details	**Participant details**
Klingel R, Fassbender C, Heibges A, Koch F, Nasemann J, Engelmann K, et al. RheoNet registry analysis of rheopheresis for microcirculatory disorders with a focus on age-related macular degeneration. Therapeutic Apheresis & Dialysis: Official Peer-Reviewed Journal of the International Society for Apheresis, the Japanese Society for Apheresis, the Japanese Society for Dialysis Therapy 2010;14:276-86. *Country:* Germany *Design:* Retrospective cohort study *Number of centres:* 65 *Funding:* Commercial funding *Trial ID:* not applicable	*Number of Participants*: 1110 with microcirculatory disorders for safety, total with Dry AMD 833. Total Dry AMD for efficacy 334 (279 treated; 55 controls) *Number of eyes* for efficacy assessments 513 (428 treated, 85 controls) *Sample attrition/dropout*: efficacy data only available for 33% of AMD patients *Sample crossovers:* none *Inclusion criteria:* patients having actually received a rheopheresis treatment were eligible for the data set. Dry AMD, soft drusen, pigmentary abnormalities or minor atrophy, visual acuity 0.1–0.63, or subjective or objective progression of vision loss with psychological strain. Dry AMD and drusen was the criteria of highest importance. Control patients met the criteria but were not treated for different reasons, including unwilling to receive treatment. *Exclusion criteria:* not reported

Intervention details	**Outcomes**
Intervention *1.* Rheopheresis (double filtration plasmapheresis (DFPP)) *2.* Control (no treatment) *Dose details:* 8–10 rheopheresis treatments (average 8.1, SD 1.6) within a period of 10–17 (average 15, SD 14) weeks. *Dose modifications:* Patients with sudden sensorineural hearing loss, as an example of acute therapy, were treated twice within one week. *Concurrent treatment:* not reported *Duration of treatment:* not reported	*Outcomes (state if primary)* Adverse events (of treatments for variety of microcirculatory disorders) Tolerability of treatment (not validated, not extracted) BCVA (various methods across the registry, transformed into log(Mar)) *Length of follow-up:* mean of 6.75 (SD 5.25) months

Participant characteristics, %			
	AMD, n=279	**Controls, n=55**	**P value**
Age, years mean (SD)			
Sex, % male	39.5	NR	
Results			
	AMD, eyes, n=428	**Controls, eyes, n=85**	**P Value**
% of eyes with improvement in visual acuity (difference of ≥0.1 log(Mar))	42	26	P<0.01
% of eyes with loss in visual acuity (difference of ≥0.1 log(Mar))	17	40	P<0.01
% of eyes with stable visual acuity	41	NR	
Comments			
Adverse events, %	**Any condition, n=1110, analysed by number of treatments (n=7722)**		

Uneventful Irreversible or long-lasting Any AE AE requiring intervention AE leading to treatment cessation	86.7 0 5.67 2.19 0.48		
Comments: states 3 serious adverse events occurred within 24 hours of treatment, one of these was in a patient with AMD. Reports specific AEs but not extracted as not in AMD group only.			
AE in AMD cases	**AMD, n=833**		
Retinal bleeding, %	0.24		

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			CD
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?	x		
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?		x	
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating: Poor
Unclear selection, consistency of treatment unclear, consistency of outcome measurement unclear, no blinding of outcome assessors, high rates of participants not analysed)

*CD, cannot determine; NA, not applicable; NR, not reported

Microcurrent stimulation

Anastassio et al

Study details	Participant details
Anastassiou G, Schneegans AL, Selbach M, Kremmer S. Transpalpebral electrotherapy for dry age-related macular degeneration (AMD): an exploratory trial. Restorative Neurology & Neuroscience 2013;31:571-8. *Country:* Germany *Design:* RCT *Number of centres:* 1 *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: 22 total (microstimulation: 12, placebo:10) of a total 31 eligible *Number of eyes:* not reported *Sample attrition/dropout*: 9 of 31 eligible refused. 3 (1 microstimulation [capsulotomy]: 2 placebo [refused]) at the 6 month evaluation *Sample crossovers:* not reported *Inclusion criteria:* Dry AMD, no history or signs of neovascular disease in either eye, visual acuity between 25 and 45 ETDRS letters. *Exclusion criteria:* current smoking or history of heavy smoking, living with an electrical implant such as a pacemaker, ocular comorbidities with significant influence on visual acuity like glaucoma or diabetic retinopathy, progressive corneal dystrophy or cataracts grade 3 or 4, amblyopia, seizure disorder, severe general disease, any previous brain damage, aged under 50 years.

Intervention details	Outcomes
Intervention *1.* Transpalpebral electrotherapy (microstimulation, TheraMac™) *2.* Placebo (sham treatment) *Dose details:* 2 sessions of 40 seconds on 5 consecutive days, *Dose modifications:* current varied between 150 and 220 µA. 8 contact points. Frequencies 5Hz to 80Hz in a pre-defined pattern. *Concurrent treatment:* not reported *Duration of treatment:* 5 days	*Outcomes (state if primary)* Change in visual acuity (ETDRS letters, distance 3.9 metres) at 4 weeks (primary outcome); change in contrast sensitivity; macular sensitivity; fixation stability; adverse events. *Length of follow-up:* 6 months

ETDRS: Early Treatment Diabetic Retinopathy Study

Participant characteristics, %			
	Microstimulation, n=12	**Placebo, n=10**	**P value**
Age, years mean (SD)	76.2	76.5	p=0.9
Classification, AREDs, % *Stage 2* *Stage 3* *Stage 4*	 33.3 50 16.7	 0 90 10	
Smoking history			
visual acuity, letters, mean (SD)	36.0 (7.5)	37.3 (4.2)	p=0.6
Contrast sensitivity, no. of optotypes[a]	7.5	6	
Macular sensitivity, dB[a]	21.8	21.3	
[a]estimated from figure			
Results			
	Microstimulation, n=12	**Placebo, n=10**	**P Value**

Visual acuity, change letters at 4 weeks (primary outcome)	5.7	-0.3[a]	p=0.1
Visual acuity, change letters at 6-months	4.1	-1.0[a]	p=0.3
[a]estimated from figure			
Contrast sensitivity change, no, of optotypes at 4 weeks	4.2[a]	1.0[a]	p=0.01
Contrast sensitivity change, no, of optotypes at 6 months	1.5	0[a]	p=0.9
[a]estimated from figure			
Macular sensitivity change, dB at 4 weeks	1.2	0[a]	P=ns
Macular sensitivity, change dB at 6 months	0.1[b]	-0.8[a]	p=0.4
[a]estimated from figure [b]text states 0.1 increase, figure appears to demonstrate approximately -0.4 change Comments: states fixation stability and central retinal thickness showed no significant changes,data not presented.			
Adverse events	0	0	
Comments States no adverse events were seen or reported during the study.			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	States 'random' no other details
Allocation concealment (selection bias)	Unclear	No description
Blinding participants and personnel (performance bias), Objective outcomes	Low	Participants were blinded but investigator was aware of intervention status.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	High	Only participants were blinded
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Low	Numbers and reasons provided, similar (low) drop out rates
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Unclear	Not enough information to assess
Other biases	Low	No other obvious risks of bias.

Shinoda et al

Study details	Participant details
Shinoda K, Imamura Y, Matsuda S, Seki M, Uchida A, Grossman T, et al. Transcutaneous electrical retinal stimulation therapy for age-related macular degeneration. The Open Ophthalmology Journal 2008;2:132-6. *Country:* Japan *Design:* Prospective before and after study *Number of centres:* one *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: 21 (5 Dry AMD; 16 Wet AMD [not extracted]) *Number of eyes:* 34 (7 dry AMD; 27 wet AMD) *Sample attrition/dropout*: not reported *Sample crossovers:* not applicable *Inclusion criteria:* Eyes with a wet-type or dry-type AMD lesion, which involved the geometric centre of the foveal avascular zone *Exclusion criteria:* any significant ocular disease affecting visual acuity (except subfoveal CNV or geographic atrophy), history of intraocular or laser surgery within 6 months, any medication used for AMD (e.g vitamins or lutein) in the 6 months, met the criteria of photodynamic therapy or antiVEGF therapy of intravitreal pegaptanib injection, with pathologic myopia (defined as requiring a distance correction of ≥ -6.0 diopters or eyes with an axial length of > 26.5 mm).

Intervention details	Outcomes
Intervention *1.* Transcutaneous Electrical Retinal Stimulation (microcurrent 800 μA transpalpebrally applied to both eyes) *Dose details:* each sessions 20 minutes (a monophasic pulse with a frequency of 290 Hz for 1 minute, 31 Hz for 2 minutes, 8.9 Hz for 10 minutes, and 0.28 Hz for 7 minutes), 4 times each day for up to 1 month *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* up to 4 weeks	*Outcomes (state if primary)* Best-corrected visual acuity; Early Treatment Diabetic Retinopathy Study (ETDRS) score; Mean deviation of the automated perimetry, Subjective treatment effect (not validated measure) *Length of follow-up:* 4 weeks

Participant characteristics, %			
	Dry AMD, n=5		**P value**
Age, years mean (SD)	75.7 (9.2)		
Sex, % male	100		
Snellen visual acuity, median (range)	Eyes, n=7 20/160 (20/1000 - 20/50)		
Mean (SE) ETDRS	39.8 (4.7)		
Mean deviation of the automated perimetry, db (SE)	-9.3 (3.2)		
Results			
	Dry AMD, eyes n=7		**P Value**
Snellen visual acuity, median (range)	20/200 (20/100 – 20/40)		
Mean (SE) ETDRS *p-value change from baseline*	42.9 (4.9) p=0.0401		
Comments			
Mean deviation of the automated perimetry, db (SE) *p-value change from baseline*	-9.3 (2.8) p>0.05		

Comments States No obvious change was observed by slit-lamp or funduscopy.			
Subjective visual function change (rated poor to very good), % of participants	Poor: 0 Fair: 20 Good: 80 Very good: 0		
Comments: states "Generally patients were satisfied and preferred to continue the treatment. However, it showed no significant correlation with the other parameters, such as visual acuity and the averaged mean deviation."			
Adverse events			
Comments: No ocular and systemic complications except in one participant who developed contact dermatitis on both superior lids and treatment was stopped as investigators considered this as serious adverse event. No details of which group participant belonged to.			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	x		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?			CD
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?	x		
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			CD
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			N/A

Quality Rating; Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Chaikin et al

Study details	Participant details
Chaikin L, Kashiwa K, Bennet M, Papastergiou G, Gregory W. Microcurrent stimulation in the treatment of dry and wet macular degeneration. Clinical Ophthalmology 2015;9:2345-53.	*Number of Participants*: 17 *Number of eyes* 31 (25 with dry AMD; 6 wet AMD [not extracted]) *Sample attrition/dropout*: not reported

Country: USA *Design:* Prospective before and after study *Number of centres:* 2 *Funding:* not reported *Trial ID:* NCT01790958.	*Sample crossovers: not applicable* *Inclusion criteria:* ≥50 years, history of retinal disease involvement, no antivascular endothelial growth factor treatments (for ≤ 3 months), no new antioxidant/vitamin supplementation (for ≤6 months). Those with wet AMD only after medically cleared as having no active bleeding *Exclusion criteria:* history of noncompliance with regular medical visits, significant media opacities that might interfere with assessing visual acuity, presence of pigment epithelial tears or rips, diabetic retinopathy, any known serious allergies to fluorescein dye, presence of retinal neovascularization, treatment with investigation agents in the past 30 days.

Intervention details	**Outcomes**
Intervention *1.* Frequency-specific microcurrent stimulation applied in a transpalpebral manner. *Dose details:* states the number of treatments was determined by condition severity and patient response, each session 35 minutes, microcurrent was 150 μA. Frequency (Hz) was used in pairs and selected depending on disease process. *Dose modifications:* no details *Concurrent treatment:* no details *Duration of treatment:* ranged between 2-10, mean 4.8 sessions.	*Outcomes (state if primary)* Best corrected visual acuity (BCVA); retinal thickness, microperimetry. *Length of follow-up:* varied, up to 3 months

Participant characteristics, %			
	FSM stimulation, n=17		**P value**
Age, years mean (SD)	82.9 years (range 67-95)		
visual acuity	No mean value given		
Results			
	Dry AMD, eyes = 25		**P Value**
Visual acuity, logMAR, mean (95% CI)	At 90 days (n=7) -0.1 (-0.2, -0.01)		
Comments: estimated by reviewer from figure. Assumptions were made by the authors about the pattern of logMAR results beyond the longest follow-up time for each patient. States mean letter changes from baseline to final visit by eye showed a significant change in dry AMD (p=0.012), although figure suggests not significant (p=0.059). Also states that in dry AMD 13 of 25 eyes (52%) showed improvement and 7 of 25 eyes (26%, calculated by reviewer to be 28%) showed deterioration.			
Retinal sensitivity			
Comments: states of the patients who had microperimetry testing, there was an overall increased retinal sensitivity across the board following microcurrent stimulation. There were no changes in retinal thickness seen.			
Adverse events			
Comments Not reported			

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	x		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD

4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?		x	
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	x		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			CD
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Poor
Sample size, consistency of intervention, lack of blinding

*CD, cannot determine; NA, not applicable; NR, not reported

Kondrot 2002

Study details	**Participant details**
Kondrot EC. Initial results of microcurrent stimulation in the treatment of age related macular degeneration. Townsend Letter for Doctors and Patients 2002;231:65-7. *Country:* USA *Design:* Before-and-after study (also reports pilot study) *Number of centres:* one *Funding:* Not reported *Trial ID:* Not reported	*Number of Participants*: Total 28 (n=10 pilot study) *Number of eyes* 56 *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* Dry AMD. No further details *Exclusion criteria:* glaucoma and previous retinal laser surgery

Intervention details	**Outcomes**
Intervention *1.* Microcurrent stimulation *Dose details:* Microstim 400 unit used for initial 8 treatments, then microstim 100 unit twice a day for 5/7 days a week. 4 points above and 4 points below eye each treated with 4 frequency settings (292 HZ, 30 Hz, 9.1 Hz and 0.3 Hz) for 12 seconds each. The current was slowly turned up until a sensation was produced and then it was turned down until all sensation of electricity subsided. All treatments were conducted at this sub-threshold level. *Dose modifications:* Not reported *Concurrent treatment:* vitamin and nutritional supplementation consisting of Pure Focus sublingual spray (Biomax) and the Macular Degeneration Formula (Nutritional Research)	*Outcomes (state if primary)* Visual acuity *Length of follow-up:* 3 months – 1 year

Duration of treatment: minimum 3 months (unclear) also states 'every' three months for a year	

Participant characteristics, %			
	Intervention 1, n=28		**P value**
visual acuity, range	20/25 to 1/400		
No patient characteristics reported			
Results			
	Intervention 1, n=28		**P Value**
Visual acuity, range	20/20 to 3/800		
Mean (range) improvement, lines of visual acuity	0.48 (0 to 2.5)		
Percent of eyes with improvement of acuity	66%		
Range of improvement, lines of visual acuity	0 to 2.5 lines		
States no loss of vision, change in amsler grid or change in intraocular pressure was noted in the first group of 10 patients (pilot study). No further details reported.			
Adverse events			
Not reported			

States there is a data sheet, not in file.

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?		x	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?		x	
6. Was the test/service/intervention clearly described and delivered consistently across the study population?		x	
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?		x	
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?			NR
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			CD
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?		x	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Poor
Additional Comments: population not predefined or described; sample size small; few details of intervention or outcomes; no statistical analysis.

*CD, cannot determine; NA, not applicable; NR, not reported

Kondrot 2015

Study details	Participant details
Kondrot EC. Improvement in Vision Parameters for Participants Treated With Alternative Therapies in a 3-day Program. Alternative Therapies in Health & Medicine 2015;21:22-35. *Country:* USA *Design:* retrospective before-and-after study (data collected over 10 years) *Number of centres:* one *Funding:* No external funding. Participants paid $3000 each. *Trial ID:* Not reported	*Number of Participants*: Total 152. Dry AMD 70, Stargardt's disease 3 (79 with other eye diseases, not extracted) *Number of eyes:* Total 290. Dry AMD 140, Stargardt's disease 6 (144 with other eye diseases, not extracted) *Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* eye disease not responsive to traditional treatments, patients wanted to avoid surgery or side effects of medication, paid $3000 for 3-day treatment programme. *Exclusion criteria:* Not reported

Intervention details	Outcomes
Intervention 1. Customised, Intravenous nutrition (Myer's cocktail), oxidative therapy, microcurrent stimulation, syntonic light therapy (all provided at least one to each participant) *Dose details:* Myer's cocktail: accorbic acid 600 mg/ml, 1cc; pyridoxine 100mg/ml 2cc; hydroxocobalamin 1000 ug/ml 1cc; B complex 100, 1cc; calcium gluconate 10% 1 cc; dexpanthenol 250 mg/ml, 1 cc; magnesium chloride 200 mg/ml, 1 cc; multitrave-5 concentrate 1cc; selenium 40 ug/ml 5cc; taurine 50 mg/ml 2cc; zinc 1 mg/ml 5cc; lidocaine 2% 5cc; sterile water 200cc; folic acid 1 mg. Oxidative therapy: minimum of 2 intravenous therapies. Ozone was mixed with blood and injected into body and provided as eye drops (no further details) Intravenous hydrogen peroxide given to some patients. Microcurrent stimulation: no details of frequency or duration of application Syntonic light therapy: 2 treatments per day *Dose modifications:* Not reported *Concurrent treatment:* Information about diet, nutrition, hydration and creation of balance in autonomic nervous system. Homeopathy prescribed but not started during 3 day programme. *Duration of treatment:* 3 days programme (microcurrent therapy initiated on day 2)	*Outcomes (state if primary)* Visual acuity (ETDRS), contrast sensitivity, campimetry, pursuits, saccade and fixation tests, pupillary examination, external examination of eye, anterior segment examination, intra-occular pressure, dilated examination of eye. Selected outcomes for some participants: ocular coherence tomography, infrared thermography, heavy-metal toxicity in urine, oxygen saturation at night *Length of follow-up:* 3-days (not clear)

ETDRS: Early Treatment Diabetic Retinopathy Study

Participant characteristics, %	Not reported per eye disease. For the total 152 participants:		
Age, years range	15-95		
Sex, % male	48		
Results			
	Dry AMD, n=70 (140 eyes)	**Stargardt's disease, n=3 (6 eyes)**	**P Value**

Acuity improvement, ETDRS chart, mean; n (%) *> 2 lines (10 letters)* *1-2 lines (5 letters)* *< 1 line* *No change*	Mean 5.5 letters 22 eyes (15.7) 53 eyes (37.9) 50 eyes (35.7) 15 eyes (10.7)	Mean 6.6 letters (range 2-13)	
Contrast improvement mean; n (%) *>6 letters* *3-5 letters* *1-2 letters* *No change*	Mean 3.8 letters 35 eyes (25.0) 38 eyes (27.1) 54 eyes (38.6) 13 eyes (9.3)	Mean 3.67 letters (range 0-10)	
Visual field expansion, n (%) *Marked* *Moderate no change or minimal*	76 eyes (54.3) 41 eyes (29.3) 23 eyes (16.4)	6 eyes (100) 0 eyes 0 eyes	

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?		x	
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?		x	
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?	x	x	(yes For Dry AMD)
6. Was the test/service/intervention clearly described and delivered consistently across the study population?		x	
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?			CD
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			CD
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?		x	
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Poor
Additional Comments: population not predefined or described; few details of intervention or outcomes; no statistical analysis; unclear duration of follow-up

*CD, cannot determine; NA, not applicable; NR, not reported

Lasers

Huang et al

Study details	Participant details
Huang YX, Xiang LN, Wang YL, Li MM,	*Number of Participants*: Total 10: laser 10 (same 10); control 10 (same

Hu YX. Long-term effect of prophylactic laser treatment for bilateral soft drusen. *Chinese Medical Journal* 2011;**124**:541-5. *Country:* China *Design:* non-random controlled trial (pilot) – eye unit of allocation *Number of centres:* one *Funding:* Not reported *Trial ID:* ChiCTR-TNRC-00000221	10) *Number of eyes* Total 20 *Sample attrition/dropout*: mean follow-up period of 98.5 months *Sample crossovers:* Not reported *Inclusion criteria:* patients with bilateral soft drusen *Exclusion criteria:* exudative macular degeneration in either eye and macular or retinal diseases that would interfere with vision (central serous choroidopathy, optic atrophy, macular pucker, macular hole, retinal vascular disease (diabetic retinopathy and retinal vein occlusion), active uveitis, other sight-threatening retinopathies and retinal degeneration)

Intervention details	**Outcomes**
Intervention *1.* Prophylactic laser treatment *2.* control *Dose details:* argon green laser, 514 nm. Approximately 100 laser spots with 0.1 second in duration and 200 μm in spot size with lowest intensity (55 mW–100 mW) to produce a barely visible lesion. The laser spots were placed in a temporal horseshoe-shaped area more than 750 μm from the foveal centre, extending to the vascular arcades *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* single application (assumed)	*Outcomes (state if primary)* Number of soft drusen BCVA Retinal contrast sensitivity Macular thickness Complications (CNV) pattern reversal visual evoked potentials – not extracted *Length of follow-up:* >8 years, mean 98.5 months

BCVA: Best Corrected Visual Acuity; CNV: choroidal neovascularization

Participant characteristics, %			
	All patients, n=10		
Age, years mean (range)	70.1 (55.0-80.0)		
BVCA	≥ 20/25		
lesion size			
Each eye had more than 10 soft drusen (>125 mm) from the macular foveal center extending to the vascular arcades. No reduced vision in either eye was observed. No choroidal neovascularization (CNV) or geographic atrophy			
Results			
	Laser, n=10 eyes	**Control, n=10 eyes**	
Soft drusen			
States 'soft drusen in the treatment group was dramatically reduced, although new drusen appeared. Mild depigmentation and no obvious pigment proliferation were observed. The soft drusen in the untreated eyes increased significantly' . Figures presented but no data reported.			
BCVA			
Comments States 'The BCVA in both the treated eye and the contralateral eye remained more than 20/25, which did not reduce significantly. The results of the Amsler tests were normal.'			
Retinal contrast sensitivity			
States two years after treatment, microperimetry tests showed no significant difference between the two groups			
Macular thickness, μ *RPE elevation* *Full retinal thickness*	 6.67 (13.32) 228.33 (13.59)	 13.17 (16.39) 235.00 (20.95)	 P=0.006 P=0.141

Adverse events *CNV*	0		

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	High	Not randomised
Allocation concealment (selection bias)	High	Not randomised
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Not reported
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	N/A
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not reported
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	N/A
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Not reported
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	N/A
Selective reporting (reporting bias)	High	No data reported, narrative only, unable to locate trial registration details on Chinese Clinical Trials Registry
Other biases	Low	No other biases

Prahs et al

Study details	**Participant details**
Prahs P, Walter A, Regler R, Theisen-Kunde D, Birngruber R, Brinkmann R, et al. Selective retina therapy (SRT) in patients with geographic atrophy due to age-related macular degeneration. Graefes Archive for Clinical & Experimental Ophthalmology 2010;248:651-8. *Country:* Germany *Design:* Non-randomised controlled study (pilot) *Number of centres:* 1 *Funding:* non-commercial funding *Trial ID:* not reported	*Number of Participants*: total: 6 *Number of eyes:*12 (6 intervention; 6 control) *Sample attrition/dropout*: none *Sample crossovers:* none *Inclusion criteria:* bilateral equally pronounced geographic atropy; eye with inferior visual acuity treated. *Exclusion criteria:* Not reported

Intervention details	**Outcomes**
Intervention *1.* Selective retina therapy laser (prototype) *2.* Control *Dose details:* short laser pulses, wavelength 527 nm. Duration of pulse adjusted from 200 ns up to 3 µs with 30 repetitive pulses at	*Outcomes (state if primary)* Progression of atrophic area (mean geographic area) Adverse events *Length of follow-up:* 1 year

100 Hz applied on each retinal spot. The treatment energies applied were 140–160µJ (200 ns) and 200–300µJ (1.7µs). *Dose modifications:* each patient received 5-16 test exposures with increasing energies up to the level where lesions became ophthalmoscopically visible or maximal laser energy was reached. *Concurrent treatment:* not reported *Duration of treatment:* not reported	

Participant characteristics, %			
	All participants, n=6		**P value**
Age, years mean (SD)	72 (6)		
Number of lesions, range	8-21		
	Treated eyes, n=6	**Untreated eyes, n=6**	
lesion size *mean atrophic area size, mm^2 (range)*	6.3 (1.5 - 14.9)	6.4 (0.9 - 15.4)	NR
Results			
	Treated eyes, n=6	**Untreated eyes, n=6**	**P Value**
Mean geographic area, mm^2 (range)	9.2 (3.1-16.4)	8.3 (1.4-16.8)	
Mean (SD) progression rate, mm^2 per year	3.0 (2.8)	1.9 (1.6)	
Comments: In two out of the six patients, a faster progression of the treated eye compared to the fellow eye was noted; however, statistical significance was not reached (p=0.134). In four patients progression rates were nearly the same between both eyes, with slightly enhanced progression of the treated eye			
Adverse events	0	NA	
Comments			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	High	Not a randomised study
Allocation concealment (selection bias)	High	No concealment of allocation
Blinding participants and personnel (performance bias), Objective outcomes	High	Not reported but unlikely
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	High	Not reported but unlikely
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Low	No withdrawal or drop out
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Unclear	Not enough information to assess
Other biases	Low	No other bias

Guymer et al

Study details	Participant details
Guymer RH, Brassington KH, Dimitrov P, Makeyeva G, Plunkett M, Xia W, et al. Nanosecond-laser application in intermediate AMD: 12-month results of fundus appearance and macular function. Clinical & Experimental Ophthalmology 2014;42:466-79. *Country:* Australia *Design:* Prospective cohort study (pilot), within participant controls *Number of centres:* 1 *Funding:* non-commercial grant and from Ellex R&D Pty Ltd. *Trial ID:* ACTRN12609001056280	*Number of Participants*: total: 52 *Number of eyes*: 52 treated; 52 control eyes. *Sample attrition/dropout*: 1 participant did not receive the intervention (unable to complete all tests required); 1 was lost to follow-up (died) *Sample crossovers:* not applicable *Inclusion criteria:* bilateral intermediate AMD (multiple drusen >125 μm in both maculae), aged over 49 years, BCVA (Early Treatment Diabetic Retinopathy Study logMAR chart) of at least 6/18 (60 letters). *Exclusion criteria:* evidence of GA on colour fundus photographic grading, presence of CNV, any past treatment for CNV in either eye or signs of any other ocular disease.

Intervention details	Outcomes
Intervention *1.* Ultra-low energy laser therapy *Dose details:* pulses to 12 spots around the macula of one eye (0.15–0.45 mJ), using 400 μm diameter spot, 3 nanosecond pulse length, 532 nm wavelength and energy titrated to each patient. The average laser energy at each treatment spot was 0.24 mJ (with a range of 0.15–0.45 mJ) with an average radiant exposure of 0.19 J/cm^2 (ranged 0.12–0.36). *Dose modifications:* at time unspecified the protocol was altered and treatment spots were moved out slightly further from the foveal centre (approximately 2000 μm), to just inside the arcades *Concurrent treatment:* not reported *Duration of treatment:* not reported	*Outcomes (state if primary)* AMD risk factor questionnaire, BCVA, macular sensitivity (flicker perimetry age-corrected), presence of geographic atropy or choroidal neovascularization, drusen area (in a subgroup who had baseline perimetry results worst point of >10 dB deviation in either eye (from aged-matched controls), 'high risk' group). *Length of follow-up:* 12 months

BCVA: best corrected visual acuity

Participant characteristics, %			
	Laser, n=52		**P value**
Age, years mean (range)	68 (49-86)		
Sex, % male	30.1		
BCVA, range of letters	93 (6/4.8) to 60 (6/18)		
Flicker sensitivity (average of worst point sensitivity defect at 1 degree visual angle)	-4.5dB treated eyes[a]	-5.5 dB fellow eyes[a]	
Comments: [a]estimated from figure 3 participants were found to have evidence of atrophy on review of images from baseline, therefore already had signs of advanced geographic atrophy. These participants were included in the analysis but not the high-risk subgroup.			
Results			
	Laser, n=50 eyes	**No laser, n=50 eyes**	**P Value**
BCVA mean change from baseline in range of letters. Improved by ≥5 letters, n (%) Lost ≥5 letters, n (%)	-0.1 8 (16) 7 (14)	0.8 4 (8) 4 (8)	Not reported

Comments: states that drusen and retinal function improved in the untreated fellow-eye which meant that the fellow eye could not be considered as a control eye.			
Reduction in drusen area, % Increase in drusen area, %	44 24	22 18	
Comments:			
Worst point analysis of flicker sensitivity, dB, change from baseline 1 degree (ring 1) 3 degree (ring 2) 6 degree (ring 3)	 4[a] -0.5[a] 2[a]	 1[a] 5[a] 1[a]	
Comments: states that reduced flicker sensitivities were often limited to small areas, with relatively normal function in other areas, therefore data for the worst point were analysed (presented). States that in the treated eye, the improvement was maximal between 3 and 6 months with a gradual decline after 6 months but not back to pre-treatment levels [a]Estimated from figure			
Development of CNV	0		
Adverse events *Dot haemorrhage*	 1		
Comments: states that no evidence of photoreceptor or inner retinal damage on optical coherence tomography was seen.			
High risk subgroup worst point analysis of flicker sensitivity, dB 1 degree (ring 1) 3 degree 6 degree	**N=23** 7[a] -0.5[a] 2[a]	**N=23** 2.5[a] 7[a] 3.5[a]	
[a]Estimated from figure			

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?	x		
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			CD
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
10. Was the exposure(s) assessed more than once over time?	x		
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
12. Were the outcome assessors blinded to the exposure status of participants?	x		
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating:Fair

*CD, cannot determine; NA, not applicable; NR, not reported

Ivandic et al

Study details	**Participant details**
Ivandic BT, Ivandic T. Low-level laser therapy improves vision in patients with age-related macular degeneration. Photomedicine and Laser Surgery 2008;26:241-5. *Country:* Germany *Design:* prospective cohort study (described as a case series) *Number of centres:* 1 *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: 203 total. 193 laser, 10 control *Number of eyes:* total 348 (laser group 328, control 20) *Sample attrition/dropout*: none *Sample crossovers:* not reported *Inclusion criteria:* AMD at all stages (dry to wet exudative forms with or without cataracts); visual acuity ≤20/20. *Exclusion criteria:* concomitant diseases that would impair vision except for new cataracts, or received any prior treatment that could have affected vision.

Intervention details	**Outcomes**
Intervention *1*. low-level laser therapy 2. control (mock treatment) *Dose details:* continuous emission at 780nm (7.5 mW, 292 Hz) fitted with collimating optics (spot diameter 3 mm) applied transconjunctivally to the macula for 40 sec (0.3 J/cm^2). *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* Four treatments (2 per week), total dose 1.2 J/cm^2.	*Outcomes (state if primary)* Visual acuity (Snellen); colour vision, central scotomas, safety. *Length of follow-up:* not reported ('after therapy')

Participant characteristics, %			
	Laser, n=193	**Control, n=10**	**P value**
Age, years mean (SD)	64.6 (4.3)	62.3 (6.4)	
Sex, % male	44.6	40	
Classification, % eyes *Cataract* *Drusen or depigmented* *Geographic atrophy* *Progressive, exudative AMD*	N=328 55 70.1 3.7 26.2	N=20 Not reported States 'all stages of AMD'	
Results			
	Laser, n=193	**Control, n=10**	**P Value**
Visual acuity, logMAR			
Comments: no aggregate results shown. States there was a statistically significant increase in visual acuity ($p<0.00001$, end of study versus baseline) for both patients with and those without cataracts. The improvement in visual acuity was maintained for 3–36 mo. By contrast, visual acuity remained unchanged in all patients in the control group.			
Concomittant eye disorders			
Comments: states most cases had a decrease in metamorphopsias, scotomas, and acquired dyschromatopsia. In patients with wet AMD, oedema and bleeding were reduced.			
Adverse events	none		

Subgroups			
Visual acuity in those without cataracts, % *Improved overall* *By one row optotype* *By two rows* *By three rows* *By four or five rows* *By six rows* *By seven rows* *Unchanged*	 97.3[a] 19.8 37.0 19.2 8.2 4.1 0.7 2.7		
Comments: [a]p<0.00001 from baseline			
Visual acuity in those with cataracts, % *Improved overall* *By one row optotype* *By two rows* *By three rows* *By four* *By five rows* *By six rows* *By seven rows* *Unchanged*	 94.5[a] 24.7 41.2 13.7 8.8 3.8 1.6 0.5 5.5		
Comments: [a]p<0.00001 from baseline			

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	X		
2. Was the study population clearly specified and defined?	X		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?			CD
5. Was a sample size justification, power description, or variance and effect estimates provided?		X	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	X		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			CD
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?			NR
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating:Fair/ Poor
Selection of participants, unclear timeframe, blinding of outcome assessors, confounding variables

*CD, cannot determine; NA, not applicable; NR, not reported

Luttrull et al

Study details	**Participant details**
Luttrull JK, Margolis BW. Functionally Guided Retinal Protective Therapy for Dry Age-Related Macular and Inherited Retinal Degenerations: A Pilot Study. Investigative Ophthalmology & Visual Science 2016;57:265-75. *Country:* USA *Design:* retrospective cohort study (pilot) *Number of centres:* 1 *Funding:* not reported *Trial ID:* not reported	*Number of Participants*: total 116: 108 AMD; 8 inherited photoreceptor degeneration (IPD) *Number of eyes* total 168: 158 AMD; 10 IPD *Sample attrition/dropout*: none *Sample crossovers:* not applicable *Inclusion criteria:* high-risk AMD (multiple large, diffuse, or bilateral macular drusen; macular pigment disturbance; extrafoveal or subfoveal geographic pigment atrophy; and/or choroidal neovascularization in the fellow eye) and IRDs, tested by pattern electroretinography (PERG) before and after SDM. *Exclusion criteria:* other obfuscating ocular disease, diabetic retinopathy, macular edema, current or prior macular retinal vascular occlusion, prior macular choroidal neovascular membrane, optic atrophy or advanced glaucomatous nerve damage, poor PERG test quality and/or reliability, subfoveal choroidal neovascular membrane in the treated eye, active choroidal neovascular membrane in the fellow eye requiring anti-VEGF treatment (<1 month of treatment or between treatment and follow-up), loss to follow-up before follow-up.

Intervention details	**Outcomes**
Intervention *1.* Panmacular subthreshold diode micropulse laser (SDM) *Dose details:* entire posterior retina circumscribed by the major vascular arcades was ‘‘painted’’ with 1800 to 3000 confluent spot applications of SDM (‘‘panmacular’’ treatment). *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* 0.15 second duration	*Outcomes (state if primary)* Visual function improvement (by PERG[a]); Snellen visual acuity; adverse events. [a]many eyes with AMD also tested with automated microperimetry (percentage-reduced thresholds, average threshold, and percent initial and final fixation preferences) and central vision analyzer as well. *Length of follow-up:* within 1 month of treatment

Participant characteristics, %			
	SDM for AMD, n=108		**P value**
Results			
	SDM for AMD, n=158 eyes		**P Value**
Improved by PERG	139/158 (88.0)		
Comments: In the overall group, 149/168 eyes were improved by PERG after SDM. Snellen VAs, ranging from 20/20 to count fingers preoperatively, were unchanged (P=0.75, SD pre-versus postoperative = -0.016). Results also reported for IRDs (not extracted) Also reports signal strength / signal latencies / frequency responses (various ‘magnitude’ indices) - data not extracted. Linear regression analyses revealed significant negative correlations for all testing measures in both AMD and IRDs, indicating that the worse the preoperative measure, the greater the likelihood of postoperative improvement State 28/33 eyes improved by PERG at 1-month post SDM remained improved by PERG at 6 to 9 months post SDM. No details of which group these 33 eyes relate to is given.			
Improved by automated microperimetry	**N= unclear**		
Comments: states that of the preoperative automated microperimetry measures, only the average thresholds were improved after SDM (P =0.0439).			

Adverse events	0		

Cohort and Cross-Sectional Studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the research question or objective in this paper clearly stated?	x		
2. Was the study population clearly specified and defined?	x		
3. Was the participation rate of eligible persons at least 50%?			CD
4. Were all the subjects selected or recruited from the same or similar populations (including the same time period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?	x		
5. Was a sample size justification, power description, or variance and effect estimates provided?		x	
6. For the analyses in this paper, were the exposure(s) of interest measured prior to the outcome(s) being measured?	x		
7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?			CD
8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g., categories of exposure, or exposure measured as continuous variable)?		x	
9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
10. Was the exposure(s) assessed more than once over time?		x	
11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?			CD
12. Were the outcome assessors blinded to the exposure status of participants?		x	
13. Was loss to follow-up after baseline 20% or less?	x		
14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?		x	

Quality Rating Poor

*CD, cannot determine; NA, not applicable; NR, not reported

Merry et al

Study details	**Participant details**
Merry GF, Munk MR, Dotson RS, Walker MG, Devenyi RG. Photobiomodulation reduces drusen volume and improves visual acuity and contrast sensitivity in dry age-related macular degeneration. Acta Ophthalmol 2016; 10.1111/aos.13354 *Country:* Canada *Design:* Before and after study (one group) *Number of centres:* Two *Funding:* Not reported *Trial ID:* Not reported	*Number of Participants*: Total 24 *Number of eyes:* 42 *Sample attrition/dropout*: Not reported *Sample crossovers:* not applicable *Inclusion criteria:* ≥50 years of age with dry AMD, AREDS grades (according to the American Academy of Ophthalmology) 2-4 [geographic atrophy no choroidal neovascularization (CNV)] and a BCVA of letter score 50 (logMAR 1.0, Snellen 20/200) or better. *Exclusion criteria:* previous/active wet AMD, a history of epilepsy, other retinal diseases, significant media opacity and cataracts worse than grade 2 (LOCS III)

Intervention details	**Outcomes**
Intervention *1.* Photobiomodulation (PBM) *Dose details:* Multiwavelength light emitting diode (LED) light comprising of yellow (590 nm), red (670 nm) and near-	*Outcomes (state if primary)* BCVA (primary outcome) Contrast sensitivity (CS) (primary outcome) Drusen volume Central drusen thickness

infrared (790 nm) bandwidths. Two separate devices were required to provide the multiple wavelengths. All subjects were treated in both eyes with the two devices used sequentially at each treatment visit. 3 sessions per week, total 9 sessions. *Dose modifications:* Not reported *Concurrent treatment:* All subjects had been taking AREDS supplementation prior to the intervention, and no changes were made to their current dosing regimen during the observational period. *Duration of treatment:* 3 weeks	Geographic atrophy area Retinal volume New CNV or geographic atrophy *Length of follow-up:* 3 months

Participant characteristics, %			
	Photobiomodulation, n=24, 42 eyes		
Age, years mean (SD)	78 (7.83)		
Sex, % male	37.5		
Classification, % of eyes *AREDS 2* *AREDS 3* *AREDS 4* *Geographic atrophy* *Reticular pseudodrusen,*	 21 48 31 31 67		
Smoking history			
visual acuity, ETDRS letters, mean (SD)	86.29 (11.36)		
CS 1.5 cycles per degree (log CS), mean (SD)	1.36 (0.17)		
CS 3.0 cycles per degree (log CS), mean (SD)	1.50 (0.23)		
CS 6.0 cycles per degree (log CS), mean (SD)	1.54 (0.20)		
Drusen volume (mm^3), mean (SD)	0.46 (0.14)		
Central drusen thickness (µm), mean (SD)	35.12 (36.58)		
Geographic atrophy area (mm^2), mean (SD)	7.01 (5.22)		
Central retinal thickness, (µm), mean (SD)	278.67 (47.60)		
Retinal volume (mm^3), mean (SD)	8.04 (0.78)		
Results			
	Photobiomodulation, n=24, 42 eyes		**P value change from baseline**
Change in BCVA letter score at 3 months	+5.14		p<0.001
Comments			
Change in CS 1.5 cycles per degree (log CS) at 3 months	+0.080		0.056
Change in CS 3.0 cycles per degree (log CS) at 3 months	+0.166		0.016
Change in CS 6.0 cycles per degree (log CS) at 3 months	+0.10		0.036
Change in drusen volume (mm^3) at 3 months	-0.029		0.021

Change in central drusen thickness (µm) at 3 months	-0.34		0.878
Change in central retinal thickness, (µm) at 3 months	+3.39		0.142
Change in geographic area square root, mm, at 3 months	+0.026		0.162
Change in retinal volume (mm^3) at 3 months	-0.049		0.464
% developing new wet AMD or geographic atrophy during study	0		
Adverse events	NR		

Before-After (Pre-Post) Studies With No Control Group

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Were eligibility/selection criteria for the study population prespecified and clearly described?	x		
3. Were the participants in the study representative of those who would be eligible for the test/service/intervention in the general or clinical population of interest?			CD
4. Were all eligible participants that met the prespecified entry criteria enrolled?			CD
5. Was the sample size sufficiently large to provide confidence in the findings?			CD
6. Was the test/service/intervention clearly described and delivered consistently across the study population?	x		
7. Were the outcome measures prespecified, clearly defined, valid, reliable, and assessed consistently across all study participants?	x		
8. Were the people assessing the outcomes blinded to the participants' exposures/interventions?		x	
9. Was the loss to follow-up after baseline 20% or less? Were those lost to follow-up accounted for in the analysis?			CD
10. Did the statistical methods examine changes in outcome measures from before to after the intervention? Were statistical tests done that provided p values for the pre-to-post changes?	x		
11. Were outcome measures of interest taken multiple times before the intervention and multiple times after the intervention (i.e., did they use an interrupted time-series design)?		x	
12. If the intervention was conducted at a group level (e.g., a whole hospital, a community, etc.) did the statistical analysis take into account the use of individual-level data to determine effects at the group level?			NA

Quality Rating: Fair
Borderline but unclear if all eligible pts met criteria, small sample, no blinding, unclear loss to follow-up

*CD, cannot determine; NA, not applicable; NR, not reported

Figueroa et al

Study details	Participant details
Figueroa MS, Regueras A, Bertrand J, Aparicio MJ, Manrique MG. Laser photocoagulation for macular soft drusen. Updated results. Retina 1997;17:378-84. *Country:* Spain *Design:* Case series and RCT	*Number of Participants*: Total n=46 Cohort 1, n=30 Cohort 2, n=16 *Number of eyes* Cohort 1, 60 eyes (one eye per patient assigned to intervention, n=30 and one eye assigned to control, n=30) Cohort 2, 16 eyes (drusen eyes received intervention)

Number of centres: One *Funding:* Not reported *Trial ID:* Not reported	*Sample attrition/dropout*: Not reported *Sample crossovers:* Not reported *Inclusion criteria:* Cohort 1: Bilateral confluent soft drusen and pigmentary changes. Group 2: High-risk drusen in one eye and choroidal neovascular membrane in fellow eye. *Exclusion criteria:* Not reported

Intervention details	**Outcomes**
Intervention Cohort 1: *1.* Laser photocoagulation *2.* Control Cohort 2: 1. Laser photocoagulation *Dose details:* Green argon laser applied a minimum of 500 microns from centre of the foveal avascular zone for 0.1 seconds with a spot size of 100 microns. Energy was sent at the minimum level to obtain a gray-white reaction. Average of 39 (range 18-47) laser spots applied. *Dose modifications:* Not reported *Concurrent treatment:* Not reported *Duration of treatment:* One application	*Outcomes (state if primary)* Drusen disappearance Visual acuity *Length of follow-up:* average 3 years (range 1.5 to 5 years)

Participant characteristics, %			
	All patients, n=46		
Age, years (range)	69 (62-74)		
Results			
	Cohort 1, n=30 Intervention, 30 eyes	**Cohort 1, n=30 control, 30 eyes**	**Cohort 2, n= 16 (16 eyes)**
Choroidal neovascular membrane developed, n/N (%)	0/30 eyes	1/30 (3.3) eyes P=0.5 vs intervention cohort 1	3/16 (18) patients
Drusen disappeared in all patients except 1 of 46 patients (cohort not stated), average time 3.5 months. Untreated drusen (located far from laser scars) disappeared in 43 of 46 patients (cohort not stated), average time 8.6 months,			
Improvement in Snellen visual acuity of one or more lines, after subfoveal drusen disappearance	10/30 (33.2) patients		5/16 (31.25) patients
Improvement in Snellen visual acuity of one or more lines, after mean follow-up of 3 years	5/30 (16.6) eyes	0/30 eyes	5/16 (31.25) patients
No change in Snellen visual acuity, after mean follow-up of 3 years	10 (33.3) eyes	15 (50) eyes	-

Deterioration in Snellen visual acuity of one or more lines, after mean follow-up of 3 years (caused by cataract progression)	15 (50) eyes	15 (50) eyes	-
Cohort 1: 5 of the 10 patients who showed initial improvement in visual acuity, lost this improvement after mean 3 years follow-up. Cohort 2: The 5 patients with initial improvement retained at least one line of improvement after mean 3 years follow-up, but the level of improvement diminished.			
Adverse events			
Not reported			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Unclear	Not reported
Allocation concealment (selection bias)	Unclear	Not reported
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	Not reported
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not reported
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Not reported
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	Unclear	Not reported
Other biases	Unclear	Not reported

Case series studies

Criteria	**Yes**	**No**	**Other (CD, NR, NA)***
1. Was the study question or objective clearly stated?	y		
2. Was the study population clearly and fully described, including a case definition?		n	
3. Were the cases consecutive?			NR
4. Were the subjects comparable?			NR
5. Was the intervention clearly described?	y		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	y		
7. Was the length of follow-up adequate?	y		
8. Were the statistical methods well-described?		n	
9. Were the results well-described?		n	

Quality Rating: Poor
Limited details of participants, generalisability unclear, poor reporting of outcomes

*CD, cannot determine; NA, not applicable; NR, not reported

Ozone

Borrelli et al

Study details	Participant details
Borrelli E, Diadori A, Zalaffi A, Bocci V. Effects of major ozonated autohemotherapy in the treatment of dry age related macular degeneration: a randomized controlled clinical study. International Journal of Ophthalmology 2012;5:708-13. *Country:* Italy *Design:* RCT *Number of centres:* one *Funding:* not stated *Trial ID:* not stated	*Number of Participants*: 140 (70 Oxygen Ozonetherapy (O_3-AHT); 70 control (multivitamins) *Number of eyes* 140 as state 1 study eye per participant (worst eye) *Sample attrition/dropout*: not reported *Sample crossovers:* not reported *Inclusion criteria:* between 59 and 82 years, diagnosis of AMD in both eyes, with dry AMD in the study eye confirmed by fluorescein angiography and fundus photography diagnosis of non-exudative dry AMD with > 10 large, soft, semisoft and/or confluent drusen within 3mm of the foveal centre and a best corrected visual acuity (BCVA) with the Early Treatment Diabetic Retinopathy Study (ETDRS) chart between 20/32 and 20/125 and no conditions limiting the view of the fundus. *Exclusion criteria:* study eye with concomitant retinal or choroidal disorder other than AMD, optic nerve pathology, glaucoma and bleeding.

Intervention details	Outcomes
Intervention *1.* Oxygen Ozonetherapy (O_3-AHT) *2.* Control (oral supplementation of zinc and a high dose of vitamins and antioxidants) *Dose details:* O_3-AHT blood 225ml withdrawn from participant, missed with anticoagulant and ozone added which was mixed and then infused over 15-20 minutes. The entire procedure took approximately 40 minutes. Control: refers to a secondary publication for details of the supplements. *Dose modifications:* not stated *Concurrent treatment:* not stated *Duration of treatment:* O_3-AHT treatment was twice weekly for 7 weeks, twice monthly for 3 months and then monthly until the 12th month. Control not stated, assume for 12 months.	*Outcomes:* mean change in log-MAR BCVA in study eyes (primary outcome); proportioning of eyes with best-corrected ETDRS acuity loss or gain; laboratory measures (not extracted here); adverse events; National Eye Visual Function Questionnaire (NEI-VFQ) (data not presented) recorded at baseline and after 6 and 12 months. *Length of follow-up:* 12 months

Participant characteristics, %			
	O_3-AHT, n=70	**Control, n=70**	**P value**
Age, years mean (SD)	70.6 (6.4)	71.4 (7)	>0.05
Sex, % male	76	84	>0.05
Visual acuity, mean	20/46	20/48	>0.05
LogMAR, mean (SD)	0.36 (0.12)	0.38 (0.18)	>0.05
Results			
	O_3-AHT, n=70	**Control, n=70**	**P Value**

LogMAR change from baseline at 12 months, mean (SD)	-0.2 (0.01)	0.3 (0.01)	p>0.05[a]
Comments: Also reports change at 6 months but no different pattern of results was seen, not data extracted [a]p-value is for all intergroup and intragroup (6 months, 12 months, interventions vs control).			
BCVA, change from baseline at 12 months, % *Loss > 2 Lines* *Loss > 3 Lines* *Gain > 1 Line*	 0 0 25	 40 38 0	 p<0.05[b] p<0.05[b]
Comments: Also reports change at 6 months, but no different pattern of results seen, not data extracted. [b]p-value is for intergroup and intragroup comparison, 6 months and 12 months.			
Adverse events temporary face redness	 3%	 -	

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	Low	Randomisation list was computer-generated and kept by a physician who had no involvement in the study.
Allocation concealment (selection bias)	Low	As above, also states that neither the investigator or the participant knew beforehand which study group the participant would be randomized.
Blinding participants and personnel (performance bias), Objective outcomes	Low	Open trial, participants and investigators were not blinded, however, objective outcomes unlikely to be at risk of performance bias.
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not discussed
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Low	Not stated but assume no attrition from the study
Incomplete outcome data (attrition bias), Subjective outcomes	N/A	
Selective reporting (reporting bias)	High	Minimal detail on adverse events and no detail from the NEI-VFQ.
Other biases	Low	No other apparent biases

Bocci et al

Study details	**Participant details**
Bocci V. The Clinical Application of Ozonetherapy. In: Ozone : a new medical drug. 2nd ed; 2011: 97-232. *Country:* Italy *Design:* controlled clinical trial *Number of centres:* one	*Number of Participants*: total 77: ozone 54; control 23 *Number of eyes:* not stated *Sample attrition/dropout*: not stated *Sample crossovers:* not stated *Inclusion criteria:* not specified as such, states all presented with dry AMD, most commonly with soft confluent drusen followed by the

Funding: not reported (assume none) *Trial ID:* none	geographic atrophy form *Exclusion criteria:* not stated

Intervention details	**Outcomes**
Intervention *1.* Ozonated AHT (undefined, assume autohaemotherapy) *2.* Oxygenated AHT (control) *Dose details:* ozonated AHT, a cycle of 12-13 treatments (elsewhere states 14-16) within 6.5-7.5 weeks *Dose modifications:* not reported *Concurrent treatment:* not reported *Duration of treatment:* not reported	*Outcomes (state if primary)* Best corrected visual acuity (Snellen chart) Haematological parameters (not data extracted) Adverse events Compliance *Length of follow-up:* 18 months

Participant characteristics, %			
	Ozonated AHT, n=54	**Oxygenated AHT, n=23**	**P value**
Age, years mean (SD)	63-81 years		
Sex, % male	States slight prevalence of males		
visual acuity (logMAR), mean (SD)	1.27 (0.49)	0.95 (0.5)	
Results			
	Ozonated AHT, n=54	**Oxygenated AHT, n=23**	**P Value**
Visual acuity logMAR, change from baseline at 18 months	0.15	-0.2	NR
Comments: estimated from a figure			
Visual acuity, % with: *improvement (>2 ETDRS lines)* *equal (≤ 2 ETDRS lines)*	 66.6 33.3	 30.4 68.5	
Comments states differences were statistically significant (no p-value reported)			
Adverse events	0		
States compliance was excellent			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	High	No discussion, unlikely a randomised comparison, groups unequal n's at baseline
Allocation concealment (selection bias)	High	As above
Blinding participants and personnel (performance bias), Objective outcomes	Unclear	No discussion of blinding
Blinding participants and personnel (performance bias), Subjective outcomes	N/A	
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	No discussion of blinding
Blinding outcome assessors (detection bias), Subjective outcomes	N/A	
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	Attrition rates not reported
Incomplete outcome data (attrition	N/A	

bias), Subjective outcomes		
Selective reporting (reporting bias)	Unclear	No detail on which to assess
Other biases	Low	No other bias identified.

Telescopes

Hudson et al

Study details	**Participant details**
Hudson HL, Lane SS, Heier JS, Stulting RD, Singerman L, Lichter PR, et al. Implantable miniature telescope for the treatment of visual acuity loss resulting from end-stage age-related macular degeneration: 1-year results. Ophthalmology 2006;113:1987-2001. Linked publications: Boyer D, Freund KB, Regillo C, Levy MH, Garg S. Long-term (60-month) results for the implantable miniature telescope: efficacy and safety outcomes stratified by age in patients with end-stage age-related macular degeneration. Clinical Ophthalmology 2015;9:1099-107 Hudson HL, Stulting RD, Heier JS, Lane SS, Chang DF, Singerman LJ, et al. Implantable telescope for end-stage age-related macular degeneration: long-term visual acuity and safety outcomes. American Journal of Ophthalmology 2008;146:664-73. Lane SS, Kuppermann BD. The Implantable Miniature Telescope for macular degeneration. Current Opinion in Ophthalmology 2006;17:94-8. *Country:* USA *Design:* CCT *Number of centres:* 28 *Funding:* commercial funding *Trial ID:* NCT00976235 (for 5 year follow-up study).	*Number of Participants*: total 217 enrolled; 206 implanted. *Number of eyes* total 434 (study eye 217; fellow eye 217) *Sample attrition/dropout*: 11 had aborted procedures (reasons provided); 2 required removal 1 month after implantation (condensation in the telescopic cylinder). At 12 months 14 were unavailable for analysis (10 discontinued, reasons provided; 4 missing or lost to follow-up). At 24 months an additional 18 dropped out (numbers stated add to 32 assume double counting between 12 and 24 months: 10 died, 8 device removed [2 device failures, 2 cases of corneal oedema, 4 patient request], 13 lost to follow-up, 1 missed the two-year visit) At 60 months there were 63 participants with follow-up. Those aged 55–65 years (n=20) were excluded from the analysis. No other reasons for losses were reported. *Sample crossovers:* not applicable *Inclusion criteria:* aged ≥55 years, bilateral, stable, central visual acuity loss by untreatable end-stage AMD (GA, disciform scar or both), phakic with evidence of cataract in the study eye, BCVA (distance) 20/80-20/800 (ETDRS), no ophthalmic pathologic features that could compromise functional peripheral vision in the fellow eye, at least a 5 letter improvement on ETDRS with an external telescope used for 3 days. If one or both eyes had better than 20/200 BCVA (distance) device was placed in the eye with the poorer visual acuity. If both had worse than 20/200 BCVA (distance) selection of which eye to implant was a choice based on experience with the external telescopes. *Exclusion criteria:* active CNV, treatment of CNV, intraocular or corneal surgery in the study eye, endothelial cell density <1600 cells/mm^2 and narrow angle.

Intervention details	**Outcomes**
Intervention *1.* implantable miniature telescope *2.* non-implanted fellow eye *Dose details:* fixed-focus telescopic optical device, surgically implanted into the capsular bag, protruding through the pupil by 0.1-0.5mm. Two models implanted which differ in image enlargement only. Central visual field is enlarged 2.2 – 3 times that of an image normally projected by the cornea and lens, and the nominal forward field of view is 24° or 20°.	*Outcomes (state if primary)* Gain of ≥ 2 lines of distance or near BCVA by ETDRS at 12 months (primary outcome) ≥3 line improvement in BCVA (distance and near) National Eye Institute Visual Function Questionnaire 25-item survey (NEI VFQ-25) Activities of daily living scale. Ocular complications from surgery Adverse events (primary outcome) Change in endothelial cell density (not extracted) Vision loss

Dose modifications: not reported *Concurrent treatment:* not reported *Duration of treatment:* up to 60 months	Telescope removal / malfunction *Length of follow-up:* up to 60 months (extension study Boyer, subgroup analyses only). Longest follow-up for whole population was 24 months (Hudson et al paper)

Participant characteristics, %			
	All patients, n=217		**P value**
Age, years mean (SD)	75.6 (7.3)		
Sex, % male	52.5		
Ethnic origin *% White*	95.9		
Classification visual impairment (ICD-9-CM), % *Moderate (<20/60 to ≥20/160)* *Severe (<20/160 to ≥20/400)* *Profound (<20/400 to ≥20/1000)*	 9.7 57.6 32.7		
Smoking history			
	Implanted eye, n=217	**Fellow eyes, n=217**	
BCVA (distance), mean SD logMAR; Snellen	1.20 (0.22); 20/316	1.07 (0.24); 20/233	
BCVA (near[a]), mean SD logMAR; Snellen	1.10 (0.23); 20/250	1.00 (0.26); 20/200	
[a]better of 8 inches or 16 inches distance.			
Results			
	Implanted eye, n=192	**Fellow eyes, n=192**	**P Value**
BCVA (distance) mean lines improvement at 12 months, logMAR	3.47	0.76	P<0.0001
BCVA (near) mean lines improvement at 12 months, logMAR	3.18	1.78	P<0.0001
BCVA (distance) gain of ≥ 3 lines at 12 months, %	66.7	12.5	P<0.0001
BCVA (near) gain of ≥ 3 lines at 12 months, %	67.7	33.3	P<0.0001
BCVA (distance <u>and</u> near) gain of ≥ 3 lines at 12 months, %[b]	53.1	10.4	P<0.0001
BCVA (distance <u>and</u> near) gain of ≥ 2 lines at 12 months, %[c]	73.4	29.2	P<0.0001
BCVA (distance) loss of ≥ 2 lines at 12 months, %	2.1	8.9	p=0.005
BCVA gain of ≥ 3 lines at 24 months, %	N=173 59.5	N=174 10.35	P<0.0001
BCVA loss of ≥ 3 lines at 24 months, %	N=173 0.6	N=174 7.5	0.013
Comments: figures show % with various lines of gains and losses (from ≥ 6 lines to ≤ -3 lines), at 12 and 24 months. At 12 months all but gain of ≥0 and loss of ≤3 lines for BCVA distance and gain of ≥0 and loss of ≤1; 2 and 3 lines for BCVA near were statistically significant between eyes in favour of the study eye (data not estimated from figures). At 24 months all but gain of ≥ 6 lines for BCVA were statistically significant between eyes in favour of the study eye (data not estimated from figure) [b]also reports 87% gained ≥ 3 lines at 12 months for BCVA (distance <u>or</u> near) in implanted eyes [c]Reports in the text that BCVA (distance <u>or</u> near) gain of ≥ 2 lines at 12 months, was 90% in implanted eyes			
Mean BCVA line change from baseline at 24 months[a]	N=173 3.2	N=174 0.4	P<0.0001

[a]estimated from figure Comments: Boyer 2015 long-term extension study gives results stratified by age groups only (not extracted)			
NEI VFQ-25 (mean SD) *Baseline* *Change at 12 months*	 43.9 (13.3) N=206 +6.1 (14.4), N=192 P<0.0001		
Comments: Individual subscales reported but not extracted. Paper states that statistically and clinically significant mean improvement was seen in 7 of 8 subscales			
ADL, mean (SD) *Baseline* *Change at 12 months*	 41.4 (15.7) N=206 +14.1, N=192 P<0.0001		
Comments: Individual subscales reported but not extracted			
Adverse events			
Ocular adverse events in ≥5% at 12 months, % *Inflammatory deposits* *Pigment deposits* *Guttae* *Posterior synechiae*	N=206 21 10 8 6		
Ocular complications in >5% at 12 months, % *Increased intraocular pressure (7 days)* *Corneal oedema (30 days)* *Iris prolapse* *Corneal abrasion*	N=206 28 7 6 5		
Corneal decompensation at 12 months, %	1		
Intraoperative iris prolapse	0.5		
Ocular adverse events in ≥ 5% at 24 months, % *Inflammatory deposits* *Pigment deposits* *Guttae* *Posterior synechiae* *Iris transillumination (>21 days)* *Iritis (>30 days)*	N=206 25 11 8 7 5 6		
Overview in 24 month follow-up study states: 1 CNV at 6 months (treated successfully). No retinal detachments, CNV, or visually significant cases of posterior capsule opacification during the two-year follow-up. 2 corneal oedema in eyes with operative complications that required grafts between 9 - 12 months. There were no cases of corneal decompensation 1-2 years after surgery.			
Comments			
Subgroups			
Lesion type GA, BCVA distance, mean (SD) *Baseline* *12 months* *change*	 N=80 1.18 (0.22) 0.86 (0.26) -0.32		
Not extracted: Subgroups at 60 months for age categories only Subgroups at 24 months for those who had cataract removal and intraocular lens implantation in the fellow eye versus their telescope implanted eye. Subgroups at 12 and 24 months for those implanted with model 3X and those implanted with model 2.2X. Subgroups at 12 months by lesion type (disciform scar, mixed)			

Cochrane Risk of bias for RCTs

	Risk of bias (high, unclear, low)	Support for statement
Random sequence generation (selection bias)	High	No randomisation between eyes
Allocation concealment (selection bias)	High	No randomisation between eyes
Blinding participants and personnel (performance bias), Objective outcomes	High	Unlikely masking would be possible
Blinding participants and personnel (performance bias), Subjective outcomes	High	Unlikely masking would be possible
Blinding outcome assessors (detection bias), Objective outcomes	Unclear	Not reported
Blinding outcome assessors (detection bias), Subjective outcomes	Unclear	Not reported
Incomplete outcome data (attrition bias), Objective outcomes	Unclear	At 12 months states the last available BCVA (distance) measure was used for the 14 participants without available data, however, the N's provided do not include these participants. Numbers and reasons for drop outs reported.
Incomplete outcome data (attrition bias), Subjective outcomes	Unclear	As above
Selective reporting (reporting bias)	Low	All outcomes stated were reported
Other biases	Low	No other apparent biases

Qureshi et al

Study details	**Participant details**
Qureshi MA, Robbie SJ, Tabernero J, Artal P. Injectable intraocular telescope: Pilot study. Journal of Cataract & Refractive Surgery 2015;41:2125-35. *Country:* UK *Design:* Case series *Number of centres:* one *Funding:* commercial funding *Trial ID:* not reported	*Number of Participants*: total 12 *Number of eyes* total 18 *Sample attrition/dropout*: not reported *Sample crossovers:* not applicable *Inclusion criteria:* bilateral, intermediate or advanced dry AMD with central scotomata, minimal cataract or pseudophakia, Snellen corrected distance visual acuity (CDVA) of <0.25, improvement with extraocular simulation of the intervention *Exclusion criteria:* active CNV treated within 6 months, phacodonesis or corneal guttata, axial length of >24.5mm or <20.5mm, history of angle closure or pigment dispersion syndrome, retinal detachment, retinitis pigmentosa, optic neuropathy, uncontrolled glaucoma, intraocular surgery within 6 months.

Intervention details	**Outcomes**
Intervention *1.* injectable telescopic intraocular lens (IOL) *Dose details:* consists of 2 soft hydrophobic acrylic IOLs, injected through a 3.0mm corneal incision, sits in the capsular bag and ciliary sulcus, provide a theoretical retical magnification of x1.25 to x1.3 with or without a prismatic effect.	*Outcomes (state if primary)* Subjective refraction (not extracted) CDVA (Snellen equivalent) Corrected near visual acuity (CNVA), Snellen equivalent Safety Intraocular pressure Microperimetry (not extracted) Endothelial cell density (not extracted)

Dose modifications: not reported *Concurrent treatment:* post-operative intracameral antibiotics, topical steroid and antibiotic for 1 month *Duration of treatment:* up to 4 months	*Length of follow-up:* 4 months

Participant characteristics, %			
	Telescope n=12		**P value**
Age, years mean (range)	77 (65-85)		
Sex, % male	33.3		
Ethnic origin *% White*			
Classification, WHO definition of visual impairment *Moderate* *Severe* *Profound*	 8 eyes 7 eyes 3 eyes		
Smoking history			
CNVA, decimalised Snellen equivalent, mean (assume SE)	N=18 eyes <0.14 (0.08)		
CDVA, decimalised Snellen equivalent mean (assume SE)	N=18 eyes 0.120 (0.08)		
Results			
	Telescope n=18 eyes		**P Value**
Mean CDVA (assume SE)	0.20 (0.13)		
Mean CDVA % improvement	67		
Mean CNVA (assume SE)	0.21 (0.11)		
Mean CNVA % improvement	50		
Reports rates of improvement of visual impairment classification in 11 eyes, 5 improved from moderate (to mild), 3 improved from severe (to moderate), 1 improved from severe (to mild), 1 improved from profound (to severe). One eye deteriorated from severe to profound. The remainder were unchanged in terms of classification.			
Comments			
Adverse events *Replacement IOL* *Raised intraocular pressure*	 1 1		
Comments States no cases of clinical corneal decompensation, no signs of cystoid macular oedema or active CNV			
Subgroups			
Reports mean improvement in CDVA by severity, not extracted.			

Case series studies

Criteria	Yes	No	Other (CD, NR, NA)*
1. Was the study question or objective clearly stated?	x		
2. Was the study population clearly and fully described, including a case definition?	x		
3. Were the cases consecutive?			CD
4. Were the subjects comparable?			CD
5. Was the intervention clearly described?	x		
6. Were the outcome measures clearly defined, valid, reliable, and implemented consistently across all study participants?	x		
7. Was the length of follow-up adequate?			CD
8. Were the statistical methods well-described?			N/A
9. Were the results well-described?	x		

Quality Rating: Fair

*CD, cannot determine; NA, not applicable; NR, not reported