Blue-light filtering intraocular lenses (IOLs) for protecting macular health (Protocol)

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Blue-light filtering intraocular lenses (IOLs) for protecting macular health

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ABSTRACT

This is the protocol for a review and there is no abstract. The objectives are as follows:

To assess the effects of blue-light filtering intra-ocular lenses (IOLs) for providing protection to macular health and function.

BACKGROUND

Description of the condition

The macula is the specialised region of the human retina that mediates the central 15 to 20 degrees of vision (Holz 2013). Anatomically, the macula corresponds to an area of approximately five millimetres in diameter within the posterior pole (Snell 1998) and has a distinctive yellow pigmentation resulting from the presence of the carotenoid pigments, lutein and zeaxanthin (Beatty 1999; Wald 1945). The macular pigments are thought to protect against the hazards of short-wavelength visible light, which includes violet and blue light. Functionally, the macula enables high-resolution spatial vision and colour perception. The maintenance of macular health is essential to normal visual function. It follows that diseases adversely affecting the macula can lead to significant vision impairment. In 2010, 2.1 million people globally were blind and 6.0 million people were visually impaired due to macular diseases (Jonas 2014).

A common form of macular disease is age-related macular degeneration (AMD), which is a leading cause of blindness in developed countries (Congdon 2004; Pascolini 2012). AMD is a slowly progressive retinal degenerative condition that selectively affects the macula and, thereby, central vision. The prevalence of AMD increases dramatically with age (Owen 2003; Wong 2014). Approximately one-third of people aged 80 years or over are likely to show clinical signs of AMD (Klein 1992). Furthermore, about one in five people aged 65 or older have sight-threatening forms of AMD (Owen 2012). Established risks for AMD include increasing age, genetic factors (Klein 2005; Yang 2006) and smoking (Thornton 2005). It has been hypothesised, but remains unclear, whether other factors, including long-term exposure to environmental short-wavelength light, contribute to AMD (Beatty 1999). AMD is typically asymptomatic in its early stages. Clinically, a key retinal sign is the appearance of drusen, visible as amorphous yellow deposits between the retinal pigment epithelium (RPE) and Bruch's membrane, which result from the deposition of lipoproteinaceous material (Bressler 1994; Sarks 1999). The presence of

large drusen and hyper- and/or hypo-pigmentary changes within the macula, confers a higher risk of progression to late-stage AMD (Ferris 2005). Progressive disease may result in the development of geographic atrophy (GA) and/or choroidal neovascularisation (CNV); both of these forms of late-stage AMD pose a high risk of significant vision loss.

High-contrast visual acuity is currently the most consistently reported measure of visual function in studies of AMD, but is a relatively insensitive tool (Downie 2014a). A range of other functional measures have also been shown to be affected in AMD; these include static and flicker perimetry (Luu 2013), micropertimetry (Wu 2013), colour vision (Downie 2014b) and the multifocal electroretinogram (Gin 2011).

There is currently no intervention for preventing the development of AMD, nor a cure for AMD. Although treatments, in the form of intra-vitreous vascular endothelial growth factor inhibitors, exist for CNV, at present therapeutic treatments for early stages of AMD, or GA, are still considered to be experimental. In light of the enormous human and economic impact of AMD, there is great interest in interventions that can be used to prevent the development of AMD and/or delay progression to late-stage AMD.

Description of the intervention

Sunlight is composed of electromagnetic radiation that ranges from ultraviolet (UV) through to infrared (IR) light. UV radiation involves wavelengths in the 200 to 400 nanometre (nm) range (Youssef 2011). Visible light is in the 380 to 760nm range; short-wavelength visible light (400 to 500nm) corresponds to the violet (400 to 440nm) and blue (440 to 500nm) colours within the visible spectrum (Mainster 2005). Modern technological devices, such as light emitting diodes (LEDs) and compact fluorescent lamps (CFLs) also emit relatively high levels of blue light. Blue-light filtering, also termed 'blue-blocking', ophthalmic lenses are lenses that are designed to selectively attenuate the transmission of UV radiation and short-wavelength visible light (Mainster 2006). Two main categories of blue-light filtering ophthalmic lens products are currently commercially available, being intra-ocular lenses (IOLs) and spectacle lenses; this review focusses specifically on IOLs.

An IOL is a synthetic lens that is surgically implanted within the eye following removal of the natural crystalline lens, during cataract surgery. Blue-blocking IOLs typically contain yellow chromophores that attenuate the transmission of about half of incident short-wavelength light, depending upon their dioptric power (Brockmann 2008; Mainster 2006). Blue-blocking IOLs contrast with UV-blocking IOLs which are colourless and absorb most UV radiation and a small amount of violet light (Mainster 1986; Mainster 2006). A range of blue-blocking IOLs are currently available on the market; examples include the OptiBlue (AMO), AF-1 (Hoya), AcrySof Natural (Alcon) and PC 440Y Orange Series (Optech).

How the intervention might work

While light is essential to visual perception, it is also a potential ocular hazard. Fortunately, the natural absorbance characteristics of the anterior structures of the eye limit the amount of potentially damaging ultraviolet (UV) radiation that reaches the retina. The cornea absorbs UV radiation below 300nm (Boettner 1962) and the crystalline lens blocks most light between 300 and 400nm (Boettner 1962; Norren 1974). The crystalline lens becomes progressively less transparent and more yellowed with age; the result of this physiological process is a relative reduction in the transmittance of short-wavelength visible light to the retina (van Norren 2007). The aged crystalline lens therefore demonstrates blue-light filtering properties, whereas younger crystalline lenses allow more short-wavelength visible light to be transmitted to the retina. It has been suggested that following cataract surgery, the implantation of an IOL that enables relatively greater transmittance of short-wavelength visible light than the aged crystalline lens, could precipitate retinal dysfunction, in particular AMD; there are insufficient data currently to support this suggestion (Casparis 2012). The relative vulnerability of the younger eye to retinal damage due to the natural transmittance of blue light has also been raised.

Blue-light filtering ophthalmic lenses are proposed to protect against potential light-induced retinal damage, a phenomenon known as retinal phototoxicity which may arise from short-wavelength visible light. Laboratory studies have shown that retinal phototoxicity is commonly due to photochemical damage (Youssef 2011), which occurs when light is absorbed by a photosensitiser (a chromophore) and reactive oxygen species (ROS) are liberated (Boulton 2001). ROS can induce cytotoxic retinal damage through various processes, including lipid peroxidation, protein oxidation and mutagenesis (Boulton 2001). Although the retina has cellular defence mechanisms to combat ROS, for various reasons the efficiency of these compensatory processes typically decline with age (Margarin 2004). The highly oxygenated outer retinal layers, in particular the RPE and photoreceptors, are considered most vulnerable to photochemical damage. Under experimental conditions, short-wavelength visible light has been shown to induce cellular damage to the RPE (Ham 1978; Ham 1984); this region of the visible spectrum has the most potential for retinal phototoxicity (Ham 1976), which forms the basis for the commonly-adopted phrase, 'blue light hazard' (Boulton 2001). Although the precise intracellular chromophore(s) that mitigate the reported blue-light sensitivity of RPE cells is not certain, the lipofuscin component A2E has been proposed to be a likely candidate. This fluorophore is found specifically in RPE cells and accumulates with age (Parish 1998); the absorbance spectrum for lipofuscin also mirrors the action spectra for blue-light phototoxicity (Mainster 2010).

Based mostly on evidence from animal studies, it has been hypothesised that cumulative retinal damage in humans, due to phototoxicity from environmental light exposure (Mainster 1978), may contribute to the macular changes that occur in AMD. Based upon

this hypothesis, blue-light filtering ophthalmic lenses have been suggested to have a role in protecting the macula and possibly preventing the development and/or progression of AMD (Beatty 1999; Bernstein 2010). Concerns regarding the possible disruption of circadian rhythms by blue-light filtering ophthalmic lenses remain controversial (Mainster 2006).

Why it is important to do this review

While the rationale for blue-light filtering ophthalmic lenses is scientifically plausible, there is significant academic debate with regard to the merit, or otherwise, of these ophthalmic devices for protecting the macula (Lee 2012; Mainster 2011; Symes 2012). This is due, at least in part, to apparently contradictory evidence relating to their merit, and creates potential confusion for eye care practitioners seeking to provide best-practice care. Blue-blocking IOLs were first introduced into ophthalmologic practice in 1991 and are now routinely used for cataract surgery, recently accounting for approximately 25% of IOLs implanted worldwide (Mainster 2011). This is despite the relative paucity of epidemiological evidence to corroborate the postulated benefit of blue-blocking lenses for macular protection; 10 of the 12 major population-based studies that sought to determine whether there was a correlation between light exposure and AMD did not report a positive association (Mainster 2006). Similarly inconclusive are studies that have sought to determine whether cataract surgery is a risk factor for the development or progression of AMD; while some studies have reported positive associations (Klein 1998; Liu 1989), others have found no clear effects upon AMD progression (Batz 2008; Chew 2009). Importantly, observational studies have acknowledged methodological limitations, including the potential influences of bias and confounding, which can limit the interpretation of their findings.

Whether blue-light filtering lenses are protective to macular health is a major public health issue. AMD is a leading cause of blindness worldwide, and effective methods for preventing its development and/or progression would be expected to have immense benefits in reducing the individual and economic burden of this disease. The relevance of these potential gains is heightened in the context of global demographic shifts toward enhanced longevity. A systematic review, considering the best-available research evidence, is essential to objectively evaluating the relative appropriateness of current practices in relation to the prescription of blue-light filtering ophthalmic lenses. Such an evaluation considers both the relative benefits and potential harms of these devices. We consider this topic to be of significant interest to clinicians, researchers and the wider community. The undertaking of this systematic review may also identify areas of focus for future research in the field.

OBJECTIVES

To assess the effects of blue-light filtering intra-ocular lenses (IOLs) for providing protection to macular health and function.

METHODS

Criteria for considering studies for this review

Types of studies

We will consider randomised controlled trials (RCTs) only.

Types of participants

Participants in the RCTs will be adults, at least 18 years of age.

Types of interventions

We will include RCTs where a blue-light filtering IOL was compared with an equivalent type of non-blue-light filtering IOL. We will exclude studies where blue-light filtering IOLs were used in combination with any other potential intervention for age-related macular degeneration (e.g., antioxidant nutritional supplements).

Types of outcome measures

Primary outcomes

The primary outcome will be change in distance best-corrected visual acuity (BCVA), measured in logMAR and considered as a continuous outcome, between baseline and 12 months of follow-up. For this outcome, we will accept BCVA measures between 6 and 18 months of follow-up. If studies do not report the change in distance BCVA, we will utilise data reported at the end of the follow-up period.

Secondary outcomes

We will consider the following secondary outcomes:

1. proportion of eyes with late-stage AMD, being neovascular AMD or geographic atrophy, at three years of follow-up (with an acceptable follow-up range of between two and four years);
2. proportion of eyes with any stage of AMD, as defined by the study investigators, at 12 months (with an acceptable follow-up range of between six and 18 months);
3. proportion of eyes with a finding of pathological structural change at the macula, detected by clinical observation or optical coherence tomography (OCT) or retinal fundus photography, at 12 months (with an acceptable follow-up range of between six and 18 months);

4. effect on distance BCVA, measured in logMAR and considered as a dichotomous outcome (being the proportion of eyes that experience loss of 15 or more letters from baseline BCVA), at six months (with an acceptable follow-up range of three to nine months);

5. effect on contrast sensitivity function, measured in log Contrast Threshold (%), and considered as a continuous outcome using the mid-range of the available spatial frequencies (between six and 12 cycles per degree) as determined by various contrast acuity charts, at six months (with an acceptable follow-up range of three to nine months);

6. effect on colour discrimination, measured as the proportion of eyes that had a measurable loss of colour discrimination from baseline using the Farnsworth-Munsell 100-hue colour test score under photopic conditions, at six months (with an acceptable follow-up range of three to nine months);

7. effect on average retinal macular pigment optical density (MPOD), measured as the proportion of eyes that had a significant increase in MPOD at six months (with an acceptable follow-up range of three to nine months);

8. effect on daytime alertness, considered as the proportion of participants who had reduced daytime alertness when measured using the Epworth Sleepiness Scores, after six months (with an acceptable follow-up range of three to nine months);

9. effect on reaction time, as a cognitive outcome variable, considered as the proportion of participants who had reduced reaction times, after six months (with an acceptable follow-up range of three to nine months);

10. proportion of people who were overall satisfied with their visual outcome after six months (with an acceptable follow-up range of three to nine months).

Adverse effects

We will tabulate any ocular and systemic adverse effects, as reported in the included studies.

Search methods for identification of studies

Electronic searches

We will search CENTRAL (which contains the Cochrane Eyes and Vision Trials Register) (latest issue), Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid MEDLINE Daily, Ovid OLDMEDLINE (January 1946 to present), EMBASE (January 1980 to present), Latin American and Caribbean Health Sciences Literature Database (LILACS) (1982 to present), PubMed (January 1966 to present), the ISRCTN registry (www.isrctn.com/editAdvancedSearch), ClinicalTrials.gov (www.clinicaltrials.gov), and the World Health Organization (WHO) International Clinical Trials Registry Platform

(ICTRP) (www.who.int/ictcp/search/en). We will not use any date or language restrictions in the electronic search for trials.

See: Appendices for details of search strategies for CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), LILACS (Appendix 4), PubMed (Appendix 5), ISRCTN (Appendix 6), ClinicalTrials.gov (Appendix 7) and the ICTRP (Appendix 8).

Searching other resources

We will undertake additional searching using the bibliographies of included RCTs to identify other potentially relevant studies. We will not handsearch conference abstracts specifically for this review as Cochrane Eyes and Vision routinely conducts handsearching for RCTs from major ophthalmology meetings and incorporates the results into CENTRAL.

Data collection and analysis

Selection of studies

We will adopt a two-stage process to select studies for this review. First, two of the review authors will independently evaluate the title and abstract results from the electronic search strategies, in order to identify potentially suitable studies for inclusion in the review.

Next, full-text copies will be obtained for studies that are deemed relevant or possibly relevant to the review by at least one review author. Two review authors will independently assess each full-text article and classify the suitability for inclusion in the review, according to the [Criteria for considering studies for this review](#) into one of three categories: (i) definitely include, (ii) inclusion status unclear or (iii) definitely exclude.

Any discrepancies in classification will be resolved by discussion and consensus between the two review authors; a third review author will be consulted for final judgement if required. For cases where further information is considered necessary to determine the eligibility of a study for inclusion, we will contact the study authors for this information. If no response is received from the study authors within four weeks, or the requested information is not provided, the information within the full-text article will be used to decide upon the eligibility of the study. We will provide details relating to the reason for excluding studies that undergo full-text review in the 'Characteristics of excluded studies' table.

Data extraction and management

Two review authors will independently extract key study data (detailed in [Appendix 9](#)) using forms developed by Cochrane Eyes and Vision. We will collect details relating to the study design, participant characteristics, number of participants, outcomes, results

and any other relevant information (e.g., funding sources). Wherever possible, quantitative data will be extracted for outcomes. Any discrepancies will be resolved by discussion and consensus. Collated data will be entered into Cochrane's Review Manager software (RevMan 2014) by one review author and independently verified by a second review author.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in each of the included studies using the guidelines in Chapter 8 of the *Cochrane Handbook for Systematic Review of Interventions* (Higgins 2011). We will evaluate the risk of bias in the following domains:

- selection bias (random sequence generation and allocation concealment);
- performance bias (masking of participants and personnel);
- detection bias (masking of outcome assessment);
- attrition bias (incomplete outcome data);
- reporting bias (selective reporting of outcomes);
- other bias (funding source, other conflicts of interest).

Each review author will make a judgement regarding the estimated risk of each type of bias in each included study as: (i) low risk, (ii) unclear risk (due to either lack of information or uncertainty over the potential for bias) or (iii) high risk. Review authors will resolve disagreements in bias assessment by consensus; a third author will be consulted if necessary. For cases where further information is considered necessary to determine the risk of bias in a particular domain, we will contact the study authors for this information. If no response is received from the authors within four weeks, or the requested information is not provided, the information within the full-text article will be used to specify the risk of bias.

Measures of treatment effect

We will undertake the data analyses according to the methods described in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

For continuous outcomes, we will extract information on the change in means of the outcome measures for the intervention and comparator groups at the specified follow-up periods and standard deviations of change. Where no change scores are reported, we will extract information on means and standard deviation of the outcome for the intervention and comparator groups at the specified follow-up periods. Treatment effects will be expressed as mean difference (MD) with 95% confidence intervals (CIs) between the intervention and comparator groups.

For dichotomous outcomes (including progression to late-stage AMD and development of early stages of AMD), the proportion of eyes reaching defined categories of AMD (i.e., any AMD or late-stage AMD) will be compared between the intervention and

control groups at the nominated time points. Treatment effects will be presented as risk ratios (RRs) with 95% CIs.

Unit of analysis issues

For the purpose of this review, the unit of analysis will be the enrolled study eye of the participant.

It is possible that trials may randomise one or both eyes to the intervention or comparator. If people are randomly allocated to treatment but only one eye per person is included in the trial, then there will not be a unit of analysis issue. In these cases, we will document how the eye was selected. If people are randomly allocated to treatment but both eyes are included and reported, we will analyse this as 'clustered data' (i.e., adjust for within-person correlation). We may have to contact the trial investigators for further information about this. If the study is a within-person study (i.e., one eye is randomly allocated to intervention and the other eye receives the comparator), then we will analyse this as 'paired data'. We may have to contact the trial investigators for further information to do this.

Dealing with missing data

For any studies where missing outcome data (e.g., omitted standard deviations, standard errors) are identified, we will attempt to contact the study authors. If a response is not received from the study authors within four weeks or if the study authors are unable to provide this further information, we will proceed using the information that is available within the publication.

If possible, we will conduct an intention-to-treat (ITT) analysis. We will use imputed data if determined by the trial investigators using an appropriate method, but will not impute missing data ourselves.

If ITT data are not available, we will do an available case analysis. This assumes that data are missing at random. We will assess whether this assumption is reasonable by collecting data from each included trial on the number of participants excluded or lost to follow up and reasons for loss to follow up by treatment group, if reported.

Assessment of heterogeneity

We will assess studies for heterogeneity using the recommendations outlined in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Deeks 2011).

We will assess for clinical and methodological heterogeneity between studies by examining differences in trial design, participant characteristics at baseline (e.g., age, gender, eligibility criteria, etc.) and risk of bias. We will quantify statistical heterogeneity between studies using the I^2 statistic. We will interpret an I^2 statistic of 60% or more to be at risk of moderate heterogeneity (Ng 2014). In identifying and measuring heterogeneity, we will also examine the magnitude and direction of effects of individual studies as well as

the strength of evidence for heterogeneity (using a P value < 0.10, from the Chi² test) as an indication of significant heterogeneity.

Assessment of reporting biases

We will assess the risk of reporting bias (due to selective reporting of outcomes) by comparing the outcomes defined in the trial protocol with those in the publication(s). If available, we will review published protocols and methodological papers and clinical trial registries to clarify intended outcomes. Otherwise, we will compare outcomes measures, based on those described in the materials and methods sections, with the outcomes reported in the results section of the published reports. If at least ten studies are included in a meta-analysis, we will use a funnel plot to assess for any potential publication bias. We will interpret any asymmetries in the funnel plot in association with characteristics of the trial, considering factors such as sample size.

Data synthesis

If appropriate, we will perform a meta-analysis for primary and/or secondary outcomes using a random-effects model. If fewer than three RCTs are to be included in the meta-analysis, we will use a fixed-effect model.

If there is inconsistency between individual study results such that a pooled result may not provide a good summary of the trial findings (such as the effects being in different directions, or $I^2 > 60\%$, or a Chi² test P value < 0.10), we will not pool the data but will describe the pattern of the individual study results.

If there is statistical heterogeneity but all of the effect estimates are in the same direction, such that a pooled estimate would seem to provide a good summary of the individual trial results, we may pool the data.

If a meta-analysis is not deemed appropriate, a descriptive or tabulated results summary will be provided.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available, we will perform a subgroup analysis for prognostic factors at baseline for the primary outcome measure. Specifically, we will assess for the potential effects of participant gender (male versus female) and age (70 years or older versus less than 70 years of age), as these factors are potentially important in relation to the risk of developing AMD.

Sensitivity analysis

If there are sufficient studies included in the review, we will perform a sensitivity analysis on the primary outcome measure, to assess the effect of excluding studies that: (i) have a high risk of bias (due to lack of allocation concealment or incomplete outcome data or lack of masking), (ii) are unpublished and (iii) were industry-funded.

Summary of findings

Provided that sufficient data are available, we will present a 'Summary of findings' table for outcomes, using the formats described in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). We will follow the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) Working Group approach to grade the quality of evidence. Outcomes will include:

- mean change in number of letters of distance BCVA from baseline BCVA in intervention and control groups after 12 months of follow-up;
- proportion of participants who lost 15 or more letters of distance BCVA from baseline BCVA in intervention and control groups after six months of follow-up;
- mean change in contrast sensitivity from baseline in intervention and control groups after six months of follow-up;
- proportion of eyes with a measurable loss of colour discrimination from baseline in intervention and control groups after six months of follow-up;
- proportion of eyes that developed late-stage AMD in intervention and control groups after three years of follow-up;
- proportion of eyes that developed any AMD in intervention and control groups after one year of follow-up;
- proportion of participants with adverse events with a probably causal link with the study intervention after six months of follow-up.

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* Indicates the major publication for the study

APPENDICES

Appendix I. CENTRAL search strategy

- #1 MeSH descriptor: [Filtration] this term only
- #2 blue near/2 light* near/2 filter*
- #3 blue near/3 filter*
- #4 #1 or #2 or #3
- #5 MeSH descriptor: [Retina] explode all trees
- #6 MeSH descriptor: [Retinal Pigments] explode all trees
- #7 retina* near/3 (damage* or phototoxic* or photoprotect*)
- #8 MeSH descriptor: [Retinal Degeneration] explode all trees
- #9 MeSH descriptor: [Retinal Neovascularization] this term only
- #10 MeSH descriptor: [Choroidal Neovascularization] this term only
- #11 MeSH descriptor: [Macula Lutea] explode all trees
- #12 maculopath*
- #13 (macula* or retina* or choroid*) near/3 degener*
- #14 (macula* or retina* or choroid*) near/3 neovasc*
- #15 AMD or ARMD or CNV
- #16 #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15
- #17 #4 and #16

Appendix 2. MEDLINE (Ovid) search strategy

1. randomized controlled trial.pt.
2. (randomized or randomised).ab,ti.
3. placebo.ab,ti.
4. dt.fs.
5. randomly.ab,ti.
6. trial.ab,ti.
7. groups.ab,ti.
8. or/1-7
9. exp animals/
10. exp humans/
11. 9 not (9 and 10)
12. 8 not 11
13. Filtration/
14. (blue adj2 light\$ adj2 filter\$).tw.
15. (blue adj3 filter\$).tw.
16. or/13-15
17. exp Retina/
18. exp Retinal Pigments/
19. (retina\$ adj3 (damage\$ or phototoxic\$ or photoprotect\$)).tw.
20. (photochemical adj2 damage\$).tw.
21. exp retinal degeneration/
22. retinal neovascularization/
23. choroidal neovascularization/
24. exp macula lutea/
25. maculopath\$.tw.
26. ((macul\$ or retina\$ or choroid\$) adj3 degener\$).tw.
27. ((macul\$ or retina\$ or choroid\$) adj3 neovasc\$).tw.
28. (AMD or ARMD or CNV).tw.
29. or/17-28
30. 16 and 29
31. 12 and 30

The search filter for trials at the beginning of the MEDLINE strategy is from the published paper by Glanville et al ([Glanville 2006](#)).

Appendix 3. EMBASE (Ovid) search strategy

1. exp randomized controlled trial/
2. exp randomization/
3. exp double blind procedure/
4. exp single blind procedure/
5. random\$.tw.
6. or/1-5
7. (animal or animal experiment).sh.
8. human.sh.
9. 7 and 8
10. 7 not 9
11. 6 not 10
12. exp clinical trial/
13. (clin\$ adj3 trial\$).tw.
14. ((singl\$ or doubl\$ or trebl\$ or tripl\$) adj3 (blind\$ or mask\$)).tw.
15. exp placebo/
16. placebo\$.tw.

17. random\$.tw.
18. exp experimental design/
19. exp crossover procedure/
20. exp control group/
21. exp latin square design/
22. or/12-21
23. 22 not 10
24. 23 not 11
25. exp comparative study/
26. exp evaluation/
27. exp prospective study/
28. (control\$ or prospectiv\$ or volunteer\$).tw.
29. or/25-28
30. 29 not 10
31. 30 not (11 or 23)
32. 11 or 24 or 31
33. blue light/
34. (blue adj2 light\$ adj2 filter\$).tw.
35. (blue adj3 filter\$).tw.
36. or/33-35
37. exp Retina/
38. Visual Pigment/
39. (retina\$ adj3 (damage\$ or phototoxic\$ or photoprotect\$)).tw.
40. (photochemical adj2 damage\$).tw.
41. exp retina degeneration/
42. retina neovascularization/
43. subretinal neovascularization/
44. exp retina macula lutea/
45. maculopath\$.tw.
46. ((macul\$ or retina\$ or choroid\$) adj3 degener\$).tw.
47. ((macul\$ or retina\$ or choroid\$) adj3 neovasc\$).tw.
48. (AMD or ARMD or CNV).tw.
49. or/37-48
50. 36 and 49
51. 32 and 50

Appendix 4. LILACS search strategy

retina\$ or macular\$ or AMD or ARMD or CNV [Words] and blue or light [Words] and filter\$ [Words]

Appendix 5. PubMed search strategy

(((((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomized[tiab]) OR (placebo[tiab]) OR (drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh]))) AND ((blue light filter*[Text Word] OR blue filter*[Text Word])) AND (((((((((((Retina[MeSH Terms]) OR retinal pigments[MeSH Terms]) OR ((retina* AND damage*[Text Word] OR retina* AND phototoxic*[Text Word] OR retina* AND photoprotect*[Text Word])) OR photochemical damage*[Text Word]) OR retinal degeneration[MeSH Terms]) OR retinal degeneration[MeSH Terms]) OR retinal neovascularization[MeSH Terms]) OR choroidal neovascularization[MeSH Terms]) OR macula lutea[MeSH Terms]) OR maculopath*[Text Word])) AND ((macula* AND degener*[Text Word] OR retina* AND degener*[Text Word] OR choroid* AND degener*[Text Word] OR macula* AND neovasc*[Text Word] OR retina* AND neovasc*[Text Word] OR choroid* AND neovasc*[Text Word]))))

Appendix 6. ISRCTN search strategy

(light OR filter) AND blue within Condition: eye

Appendix 7. ClinicalTrials.gov search strategy

eye OR retina OR macula = Condition
(light OR blue) AND filter = Intervention

Appendix 8. ICTRP search strategy

eye OR retina OR macula = Condition AND blue OR light OR filter = Intervention

Appendix 9. Data on study characteristics

Primary items		Other items
Methods		
Study design	<ul style="list-style-type: none">· Parallel group RCT <i>i.e. people randomised to treatment</i>· Within-person RCT <i>i.e. eyes randomised to treatment</i>· Cluster RCT <i>i.e. communities randomised to treatment</i>· Cross-over RCT· Other	Exclusions after randomisation Losses to follow up Number randomised/analysed How missing data were handled <i>e.g., available case analysis, imputation methods</i> Reported power calculation (Y/N), <i>including sample size and power</i> Unusual study design/issues
Eyes <i>or</i> Unit of randomisation/ unit of analysis	<ul style="list-style-type: none">· One eye included in study, <i>including specifying how eye selected</i>· Two eyes included in study, both eyes received same treatment, <i>including specifying how analysed (best/worst/average/both and adjusted for within person correlation/ both and not adjusted for within person correlation) and specifying if mixture (one eye and two eyes)</i>· Two eyes included in study, eyes received different treatments, <i>including specifying if correct pair-matched analysis was performed</i>	
Participants		
Country		Setting Ethnic group Equivalence of baseline characteristics (Y/N)

(Continued)

Total number of participants		
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n=) Comparator (n=)	· Number of people randomised to each group · Intervention name	
Outcomes		
Primary and secondary outcomes <i>as defined in study reports</i>	List outcomes Adverse events reported (Y/N) Length of follow up and intervals at which outcomes assessed	Planned/actual length of follow up
Notes		
Date conducted	Specify dates of recruitment of participants mm/yr to mm/yr	Full study name: <i>(if applicable)</i> Reported subgroup analyses (Y/N) Were trial investigators contacted?
Sources of funding		
Declaration of interest		

CONTRIBUTIONS OF AUTHORS

LED drafted the initial protocol, with substantial input, discussion and editing from LB and PRK. All authors provided final approval of the protocol.

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Ljoudmila Busija: none known

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