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Femtosecond laser versus mechanical microkeratome use for laser-assisted in-situ keratomileusis (LASIK).
Cochrane Database of Systematic Reviews 2018, Issue 2. Art. No.: CD012946.
DOI: 10.1002/14651858.CD012946.

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TABLE OF CONTENTS

[Intervention Protocol]

Femtosecond laser versus mechanical microkeratome use for laser-assisted in-situ keratomileusis (LASIK)

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Editorial group: Cochrane Eyes and Vision Group.
Publication status and date: New, published in Issue 2, 2018.

Citation: Kahuam-López N, Navas A, Castillo-Salgado C, Graue-Hernandez EO, Jimenez-Corona A, Ibarra A. Femtosecond laser versus mechanical microkeratome use for laser-assisted in-situ keratomileusis (LASIK). *Cochrane Database of Systematic Reviews* 2018, Issue 2. Art. No.: CD012946. DOI: 10.1002/14651858.CD012946.

ABSTRACT

This is a protocol for a Cochrane Review (Intervention). The objectives are as follows:

To compare the effectiveness and safety of femtosecond laser versus mechanical microkeratome in LASIK for myopia.

BACKGROUND

Description of the condition

Refractive errors are an important cause of vision impairment and blindness in people (Holden 2016). Myopia (near-sightedness) is a type of refractive error that causes blurry vision at distance because abnormal structural conditions of the cornea, lens, or length of the eye prevent the images from focusing properly on the retina (Riordan-Eva 2011). Myopia affects 1950 million people worldwide based on estimates from 2010 (Holden 2016), with a higher prevalence in urban areas (Morgan 2012). The global economic burden generated by myopia has been estimated at USD 202 billion per annum (Smith 2009), and approximately USD 139 billion in the USA alone (NASEM 2016).

Description of the intervention

Refractive errors can be corrected through non-surgical (eyeglasses and contact lenses) and surgical methods. The surgical methods are long-lasting treatments that are used when a person becomes intolerant to contact lenses, encounters visual aberration from high-powered spectacles, or desires to eliminate or reduce their dependence on glasses or contact lenses (Azar 2002). The eye is an optical system with a refractive power that can be changed by altering the curvature of its refractive surface or the location of

elements of the system. Intraocular implants, such as intraocular lenses (IOLs), can be used to correct refractive errors; however, the most common refractive surgeries performed in the USA are keratorefractive techniques. Keratorefractive surgeries are a group of techniques that modify the refractive power of the cornea by changing its curvature. These techniques include photorefractive keratectomy (PRK), laser subepithelial keratomileusis, intrastromal lenticule extraction, and laser assisted in-situ keratomileusis (LASIK) (Bower 2001).

Due its safety and efficacy profile, LASIK is more popular compared with other surgeries. This technique creates a flap of the outermost parts of the cornea (epithelium, bowman layer, and anterior stroma) to expose the middle part of the cornea (stromal bed) and reshape it with excimer laser using photoablation (Ang 2009). LASIK includes the creation of a corneal flap with a diameter that ranges from 7.8 to 9.8 mm and a thickness of 90 to 180 µm. The flap can be achieved by a mechanical microkeratome or a femtosecond laser (Farjo 2013). The mechanical microkeratome uses an oscillating blade to create the corneal flap (Bower 2001), the while femtosecond laser creates the flap with a focusable photodisruptive laser that delivers ultrashort (10^{-15} seconds) pulses with a wavelength within the infrared spectrum in a preset pattern (Lubatschowski 2000). This laser ionizes the tissue, causing molecular disruption within the cornea. The beam is focused on a small spot, creating electrically charged particles through multiphotonic absorption which release electrons from the atoms by a process known as avalanche ionization (Azar 2006). The free electrons transfer their energy to the surrounding medium, evaporating the adjacent tissue and forming cavitation bubbles consisting of carbon dioxide (CO_2), nitrogen (N_2), and water (H_2O) (Bashir 2017). When the cavitation bubbles expand, they produce a regular and precise dissection of the corneal flap (Farjo 2013; Huhtala 2016; Sales 2016). The main differences between femtosecond and microkeratome flaps are the thickness and architecture. This Cochrane Review will focus on the use of femtosecond laser or mechanical microkeratome in LASIK to correct myopia.

How the intervention might work

The femtosecond laser has some theoretical advantages over the use of a mechanical microkeratome in LASIK. For instance, the thickness of flaps created with the mechanical microkeratome have a significant variation (25 to 250 µm) compared with the femtosecond laser (78 to 173 µm). The predictability of the procedure to create a flap could be an important factor in the biomechanical integrity of the cornea (Flanagan 2003). Free or incomplete flaps, buttonholes, and epithelial erosions are intraoperative flap complications associated to the mechanical microkeratome (Azar 2006). These complications are less common with the femtosecond laser, because it dissects in precise geometrical patterns that allow variation of flap width, depth, and diameter that may lead to better surgical results (Ang 2009; Gil-Cazorla 2011; Issa 2011; Medeiros 2011). Other proposed benefits of the femtosecond laser use in LASIK are better uncorrected visual acuity (Gil-Cazorla 2011), lower intraocular pressure during the procedure (Chaurasia 2010), and a lower incidence of dry eye (Salomão 2009). Some disadvantages of the femtosecond laser over the mechanical microkeratome include increased procedure duration and cost (the cornea needs time to recover its transparency due to the cavitation bubbles before excimer photoablation and the patient must be transferred to the excimer laser bed) (Azar 2006), corneal haze (Patel 2007), transient light sensitivity (Stonecipher 2006), diffuse lamellar keratitis (Moshirfar 2010), rainbow glare (Gatinel 2013), opaque bubble layer (Courtin 2015), and the cost of the device (Azar 2006).

Why it is important to do this review

The total number of people with myopia globally was estimated to be about 1950 million in 2010 and is projected to increase to 4758 million by 2050 (Holden 2016). The trend has important economic (Corcoran 2015) and public health implications (NASEM 2016).

LASIK is one of the most common surgical procedures used to correct refractive errors (Bower 2001). As previously stated, the femtosecond laser has some advantages and disadvantages over the mechanical microkeratome, some of which are controversial (Ang 2009; Azar 2006; Bashir 2017; Farjo 2013). Therefore, it is important to evaluate the current evidence to compare the use of femtosecond laser with the mechanical microkeratome in LASIK, to determine the better option in terms of effectiveness and safety, thus optimizing the value and impact of LASIK in eye and vision care (NASEM 2016).

OBJECTIVES

To compare the effectiveness and safety of femtosecond laser versus mechanical microkeratome in LASIK for myopia.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomized controlled trials. Study inclusion will not be restricted on the basis of language or publication status.

Types of participants

We will include trials where the study population comprises people 18 years old or older with more than 0.5 diopters of myopia or myopic astigmatism.

Types of interventions

We will include studies that compare femtosecond laser-assisted LASIK versus mechanical microkeratome-assisted LASIK.

Types of outcome measures

Primary outcomes

- Mean uncorrected visual acuity at 12 months after surgery. We will use logMAR for visual acuity analyses.

Secondary outcomes

- Mean uncorrected visual acuity at one and three months after surgery.
- Mean best corrected visual acuity at one, three, and 12 months after surgery.
- Proportion of eyes within ± 0.5 diopters of target refraction at one and 12 months after surgery.
- Proportion of eyes with loss of 2 or more lines of best corrected visual acuity at 12 months after surgery, from pre-operative visual acuity.
- Mean spherical equivalent of the refractive error, measured in diopters, at one and 12 months after surgery.
- Intraoperative and postoperative pain at one day and one week, assessed with any validated measurement scale.
- Quality of life measures assessed with any validated measurement scale at any point within follow-up.

Adverse outcomes

We will compare the proportion of adverse outcomes between treatment groups. We will consider adverse outcomes as reported by included studies up to 12 months after surgery. Specific adverse outcomes of interest will include the following.

- Corneal haze.
- Dry eye.
- Visual symptoms (double images, glares, halos, starburst).
- Flap displacement.
- Flap melt.
- Diffuse lamellar keratitis.
- Infectious keratitis.
- Epithelial ingrowth.
- Corneal ectasia.

Search methods for identification of studies

Electronic searches

The Cochrane Eyes and Vision (CEV) Information Specialist will search the following electronic databases for randomized controlled trials. There will be no language or publication year restrictions.

- Cochrane Central Register of Controlled Trials (CENTRAL) (which contains the CEV Trials Register) in the Cochrane Library (latest issue) (Appendix 1).
- MEDLINE Ovid (1946 to present) (Appendix 2).
- Embase (1947 to present) (Appendix 3).
- PubMed (1948 to present) (Appendix 4).
- LILACS (Latin American and Caribbean Health Science Information Database (1982 to present) (Appendix 5).
- US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (Appendix 6).
- World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP) (www.who.int/ictrp) (Appendix 7).

Searching other resources

We will search the reference lists of eligible studies identified from the electronic searches for additional relevant trials that may not have been identified from the electronic searches.

Data collection and analysis

Selection of studies

Pairs of review authors will assess the titles and abstracts of articles identified through the literature search against inclusion criteria (listed in the 'Criteria for considering studies for this review' section) and will independently classify these as either 'definitely relevant', 'possibly relevant', or 'definitely not relevant'. We will use Covidence software to manage the screening process (Covidence 2017). Any disagreement will be resolved by a third review author. We will obtain the full-text copies of all studies classified as 'definitely relevant' or 'possibly relevant'. Each review author will independently assess each study for inclusion and will label it as either 'include' or 'exclude'. We will contact the authors of the primary studies via email for clarification whenever necessary. If no response is received within three weeks, we will assess the study based on the information available. A third review author will resolve any disagreement. We will document the reason for exclusion of each study excluded after reviewing the full report in a 'Characteristics of excluded studies' table. We will use Google Translate to assess studies written in languages other than English

and Spanish. We will illustrate the study selection process in a PRISMA diagram.

Data extraction and management

Pairs of review authors will independently extract data from the included studies using data extraction forms developed by CEV and accessed via Covidence (Appendix 8). A third review author will resolve any disagreements. We will contact authors of the primary studies via email to obtain missing information or to clarify data. We will wait three weeks for a response; in the absence of a response, we will use the available information as provided in published reports. One review author will enter data into Review Manager 5 (RevMan 5) (Review Manager 2014), and a second review author will verify the data entered.

Assessment of risk of bias in included studies

Pairs of review authors will evaluate the risk of selection (random sequence generation and allocation concealment before randomization), performance (masking of study participants and personnel), detection (masking of outcome assessors), attrition (missing data and absence of an intention-to-treat analysis), reporting (selective outcome reporting), and other potential sources of bias using the Cochrane 'Risk of bias' assessment tool (Higgins 2011). We will classify the risk of bias as either 'low', 'high', or 'unclear' (insufficient information for assessment). We will contact authors of the primary studies when methods are unclear or when additional information about study design or methods is required to assess the risk of bias. We will wait three weeks for a response; in the absence of a response, we will assess the risk of bias on the basis of descriptions provided in published reports. A third review author will resolve any disagreement between review authors.

Measures of treatment effect

We will calculate mean difference (MDs) with 95% confidence intervals (CIs) for continuous measures (e.g. mean spherical equivalent) and risk ratios (RRs) with the corresponding 95% CIs for dichotomous outcomes (e.g. corneal haze) to estimate treatment effects. We will choose a cut-off for ordinal outcomes and measurement scales to handle them as binary data or treat them as continuous data, as appropriate.

Unit of analysis issues

The participant will be the primary unit of analysis whenever: a) only one eye per participant is enrolled in the trial; or b) two eyes of an individual are treated as a single unit after being administered the same treatment (e.g. mean values, binocular visual acuity). For studies that enrolled both eyes of participant and in which the eye was the unit of analysis, we will document whether the trial had a within-person (i.e. paired eye) design and analyzed the data appropriately.

Dealing with missing data

We will contact study authors to obtain missing data or data reported unclearly in the study reports. We will allow three weeks for study authors to respond and will use the available information whenever there is no response. We will not impute missing participant data for analysis.

Assessment of heterogeneity

We will compare the participant characteristics, study interventions, and outcomes across trials to assess for clinical and methodological heterogeneity. A visual inspection of forest plots and Chi^2 test statistics will be used to assess the statistical heterogeneity among estimates of effect size from the included studies. We will use the I^2 statistic, which estimates the proportion of variation in observed effects not due to chance, to identify inconsistency among trials; an I^2 statistic value of greater than 50% will represent substantial heterogeneity (Higgins 2011).

Assessment of reporting biases

If we conduct a meta-analysis with 10 or more studies, we will visually inspect funnel plots of the intervention effect estimates for evidence of asymmetry. An asymmetric funnel plot may suggest small study effects, which could be the result of reporting bias, heterogeneity, or differences in the methodological quality of studies. We will assess selective outcome reporting as part of the 'Risk of bias' assessment among individual studies.

Data synthesis

We will combine the effect estimates from individual studies using the random-effects model when there is no substantial clinical or methodological heterogeneity observed. If fewer than three trials are included in a meta-analysis, we will use a fixed-effect model. If we deem meta-analysis as inappropriate, we will document the reasons and report findings from the individual studies narratively.

Subgroup analysis and investigation of heterogeneity

If sufficient data are available from included studies, we will examine findings by the degree of myopia at baseline among the study participants: low to moderate myopia (less than 6.0 diopters) and high myopia (6.0 diopters or more).

Sensitivity analysis

Where possible, we will perform sensitivity analyses for primary and secondary outcomes to explore the effects of restricting our analyses to trials judged to have adequate allocation concealment, adequate masking of outcome assessors, and had at least 80% follow-up of participants in each group.

Summary of findings

When sufficient evidence is available, we will summarize the findings of the review using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach to assess the strengths and limitations of evidence for both primary and secondary outcomes. We will use GRADEpro Guideline Development Tool (GDT) software (GRADEpro 2015). We will include the following seven outcomes in 'Summary of findings' tables.

- Mean uncorrected visual acuity at 12 months after surgery.
- Proportion of eyes within ± 0.5 diopters of target refraction 12 months after surgery.
- Proportion of eyes with loss of 2 or more lines of best corrected visual acuity 12 months after surgery.
- Mean spherical equivalent of the refractive error 12 months after surgery.
- Postoperative pain within one week after surgery.
- Quality of life score 12 months after surgery.
- Proportion with adverse outcomes up to 12 months after surgery.

ACKNOWLEDGEMENTS

We thank Cochrane Eyes and Vision (CEV) for their support and guidance. We acknowledge Lori Rosman, CEV Information Specialist, for developing the search strategy.

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* *Indicates the major publication for the study*

APPENDICES

Appendix 1. CENTRAL search strategy

#1 MeSH descriptor: [Myopia] explode all trees
#2 myop*
#3 (short near/3 sight*) or ("near" near/3 sight*)
#4 nearsighted*
#5 MeSH descriptor: [Refractive Errors] this term only
#6 (Refract*) near/3 (error* or disorder*)
#7 {or #1-#6}
#8 MeSH descriptor: [Keratomileusis, Laser In Situ] explode all trees
#9 Keratomileus*
#10 LASIK
#11 Femto-lasik or Femtolasik
#12 (Femtosecond near/3 laser*)
#13 Microkeratom*
#14 (refract* near/3 surg*)
#15 corneal flap*
#16 MeSH descriptor: [Refractive Surgical Procedures] this term only
#17 MeSH descriptor: [Corneal Surgery, Laser] this term only
#18 MeSH descriptor: [Cornea] explode all trees and with qualifier(s): [Surgery - SU]
#19 {or #8-#18}
#20 #7 and #19

Appendix 2. MEDLINE Ovid search strategy

1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp myopia/
13. myop*.tw.
14. ((short or near) adj3 sight*).tw.
15. nearsighted*.tw.
16. Refractive Errors/
17. (Refract* adj3 (error* or disorder*)).tw.
18. or/12-17
19. exp Keratomileusis, Laser In Situ/
20. Keratomileus*.tw.
21. LASIK.tw.
22. (Femto-lasik or Femtolasik).tw.
23. (Femtosecond adj3 laser*).tw.
24. Microkeratom*.tw.
25. (refract* adj3 surg*).tw.

26. corneal flap*.tw.
27. Refractive Surgical Procedures/
28. Corneal Surgery, Laser/
29. exp Cornea/su [Surgery]
30. or/19-29
31. 18 and 30
32. 11 and 31

Appendix 3. Embase search strategy

#1 'randomized controlled trial'/exp
#2 'randomization'/exp
#3 'double blind procedure'/exp
#4 'single blind procedure'/exp
#5 random*:ab,ti
#6 #1 OR #2 OR #3 OR #4 OR #5
#7 'animal'/exp OR 'animal experiment'/exp
#8 'human'/exp
#9 #7 AND #8
#10 #7 NOT #9
#11 #6 NOT #10
#12 'clinical trial'/exp
#13 (clin* NEAR/3 trial*):ab,ti
#14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
#15 'placebo'/exp
#16 placebo*:ab,ti
#17 random*:ab,ti
#18 'experimental design'/exp
#19 'crossover procedure'/exp
#20 'control group'/exp
#21 'latin square design'/exp
#22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
#23 #22 NOT #10
#24 #23 NOT #11
#25 'comparative study'/exp
#26 'evaluation'/exp
#27 'prospective study'/exp
#28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
#29 #25 OR #26 OR #27 OR #28
#30 #29 NOT #10
#31 #30 NOT (#11 OR #23)
#32 #11 OR #24 OR #31
#33 'myopia'/exp
#34 'high myopia'/exp
#35 myop*:ab,ti
#36 ((short NEAR/3 sight*):ab,ti) OR ((near NEAR/3 sight*):ab,ti)
#37 nearsighted*:ab,ti
#38 'refraction error'/de
#39 (refract* NEAR/3 (error* OR disorder*)):ab,ti
#40 #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39
#41 'keratomileusis'/exp
#42 keratomileus*:ab,ti

#43 lasik:ab,ti
#44 'femto-lasik':ab,ti OR femtolasik:ab,ti
#45 (femtosecond NEAR/3 laser*):ab,ti
#46 microkeratom*:ab,ti
#47 (refract* NEAR/3 surg*):ab,ti
#48 'corneal flap*':ab,ti
#49 'refractive surgery'/de
#50 'laser refractive surgery'/de
#51 'cornea'/exp AND 'surgery'/lnk
#52 #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51
#53 #40 AND #52
#54 #32 AND #53

Appendix 4. PubMed search strategy

#1 ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] 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])
#2 myop*[tw]
#3 (short[tw] OR near[tw]) AND sight*[tw]
#4 nearsighted*[tw]
#5 (Refract*[tw]) AND (error*[tw] OR disorder*[tw])
#6 #2 OR #3 OR #4 OR #5
#7 Keratomileus*[tw]
#8 LASIK [tw]
#9 Femto-lasik[tw] OR Femtolasik[tw]
#10 Femtosecond[tw] AND laser*[tw]
#11 Microkeratom*[tw]
#12 refract*[tw] AND surg*[tw]
#13 corneal flap*[tw]
#14 #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13
#15 #1 AND #6 AND #14
#16 Medline[sb]
#17 #15 NOT #16

Appendix 5. LILACS search strategy

(Myop$ OR Miopía OR Miopia OR MH:C11.744.636 OR ((short or near) AND sight$) OR nearsighted$ OR (refract$ AND (error$ OR disorder$)) OR "Errores de Refracción" OR "Erros de Refração" OR MH: C11.744) AND (Keratomileus$ OR "Queratomileusis por Láser In Situ" OR "Ceratomileuse Assistida por Excimer Laser In Situ" OR LASIK OR MH:E02.594.480.750$ OR MH:E04.014.520.480.750$ OR MH:E04.540.825.437.374$ OR "Femto-lasik" OR Femtolasik OR (Femtosecond laser$) OR Microkeratom$ OR (refractive surg$) OR (corneal flap$) OR "Procedimientos Quirúrgicos Refractivos" OR "Procedimentos Cirúrgicos Refrativos" OR MH:E04.540.825 OR MH:E02.594.480 OR MH:E04.014.520.480 OR MH:E04.540.825.437 OR mh:("Cornea/SU"))

Appendix 6. ClinicalTrials.gov search strategy

(myopia OR refractive errors) AND (LASIK OR keratomileusis OR femtosecond laser OR microkeratome OR refractive surgery OR corneal flap OR corneal laser surgery)

Appendix 7. WHO ICTRP search strategy

myopia AND LASIK OR myopia AND keratomileusis OR myopia AND femtosecond laser OR myopia AND microkeratome OR myopia AND refractive surgery OR myopia AND corneal flap OR myopia AND corneal laser surgery OR refractive error AND LASIK OR refractive error AND keratomileusis OR refractive error AND femtosecond laser OR refractive error AND microkeratome OR refractive error AND refractive surgery OR refractive error AND corneal flap OR refractive error AND corneal laser surgery

Appendix 8. Data extraction form on study characteristics

Mandatory items		Optional items
Methods		
Study design	• Parallel group RCT i.e. people randomized to treatment • Within-person RCT i.e. eyes randomized to treatment • Cluster RCT i.e. communities randomized to treatment • Cross-over RCT • Other, specify	Exclusions after randomization Losses to follow-up Number randomized/analyzed How were missing data handled? e.g. available case analysis, imputation methods Reported power calculation (Y/N), if yes, sample size and power Unusual study design/issues
Eyes or unit of randomization/unit of analysis	• One eye included in study, specify how eye selected • Two eyes included in study, both eyes received same treatment, briefly specify how analyzed (best/worst/average/ both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye • Two eyes included in study, eyes received different treatments, specify if correct pair-matched analysis done	
Participants		
Country		Setting Ethnic group Equivalence of baseline characteristics (Y/N)

(*Continued*)

Total number of participants	This information should be collected for	
Number (%) of men and women		
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =) Comparator (n =) **See MECIR 65 and 70**	• Number of people randomized to this group • Drug (or intervention) name • Dose • Frequency • Route of administration	
Outcomes		
Primary and secondary outcomes as defined in study reports **See MECIR R70**	List outcomes Adverse events reported (Y/N) Length of follow-up and intervals at which outcomes assessed	Planned/actual length of follow-up

CONTRIBUTIONS OF AUTHORS

NKL developed and design the protocol with input from AN, CCS, EGH, AJC, and AI.

NKL, AN, CCS, EGH, AJC, and AI contributed to the content and writing of the protocol.

All authors approved the final protocol draft.

DECLARATIONS OF INTEREST

NKL has no known conflicts of interest.

AN has no known conflicts of interest.

CCS has no known conflicts of interest.

EGH has no known conflicts of interest.

AJC has no known conflicts of interest.

AI has no known conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- No sources of support supplied

External sources

- Cochrane Eyes and Vision (CEV) US Project, supported by grant 1 U01 EY020522, National Eye Institute, National Institutes of Health, USA.
- National Institute for Health Research (NIHR), UK.
- Richard Wormald, Co-ordinating Editor for Cochrane Eyes and Vision (CEV) acknowledges financial support for his CEV research sessions from the Department of Health through the award made by the National Institute for Health Research to Moorfields Eye Hospital NHS Foundation Trust and UCL Institute of Ophthalmology for a Specialist Biomedical Research Centre for Ophthalmology.
- This protocol was supported by the NIHR, via Cochrane Infrastructure funding to the CEV UK editorial base.

The views and opinions expressed therein are those of the authors and do not necessarily reflect those of the Systematic Reviews Programme, NIHR, NHS or the Department of Health.