Annex 1:

Photochemical Corneal Collagen Cross-Linkage (CXL) using Riboflavin and ultraviolet A (UVA) for Management of Keratoconus

Meta-Analysis

Quantics Consulting Limited

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Table of contents

Summary

This document present the results of a meta-analysis of results from studies collected in a systematic review of the literature on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UVA) for management of keratoconus.

Five outcome measures are presented: Change in Visual Acuity, Change in Topography, Change in Refraction and Astigmatism, Change in Intraocular Pressure and Change in Central Corneal Thickness. Results were available to justify meta-analysis of changes from baseline for treated patients at some or all of 6, 12 and 24 months. Table A shows the analyses that were carried out and indicates the significance of the result.

Table A: Summary of all meta-analyses

Number of studies		6 months	12 months	24 months
Visual Acuity	Uncorrected	12	18	6
	Corrected	15	22	7
Topography	Max K	10	18	6
	Mean K	7	12	
	Min K	4	8	
Refraction and Astigmatism	Astigmatism grouped	7	13	5
	Spherical equivalent grouped	8	10	
Central Corneal Thickness		6	6	
Intra ocular pressure		2		

Green: Significant
White: Not significant
Grey: Not done

A small minority of the studies found were randomized, controlled trials. Results were available to justify meta-analysis of comparisons of changes from baseline between treated and control treated patients at 12 months for Change in Visual Acuity and Refraction and Astigmatism only as shown in Table B.

Table B: Summary of meta analyses for randomized controlled trials

Number of studies		6 months	12 months	24 months
Visual Acuity	Uncorrected		2	
	Corrected		3	
Refraction and Astigmatism	Astigmatism grouped		2	
	Spherical equivalent grouped			

Green: Significant
White: Not significant
Grey: Not done

1. Introduction

Keratoconus is a degeneration of the structure of the cornea, the clear tissue covering the front of the eye. Keratectasia is an infrequent but serious complication of laser-assisted in situ keratomileusis (LASIK) surgery where the cornea bulges forward in an irregular fashion.

The National Institute for Health and Clinical Excellence (NICE) has commissioned a systematic review of the literature on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UVA) for management of keratoconus. The agreed research question was:

> 'What is the current evidence base for the effectiveness and safety of photochemical corneal cross-linkage using riboflavin and ultraviolet A for keratoconus and keratectasia, alone or in combination with therapies that are designed to improve visual acuity?'

The York Health Economics Consortium (YHEC) carried out the systematic review and provided outcome data to Quantics for meta-analysis. Quantics reviewed these results and provided a preliminary report of the suitability of outcomes for meta-analysis. Following feedback from clinicians, Quantics have carried out a series of meta-analyses. The report presents the findings.

2. Data

Data extracted from 46 publications, reporting results from 40 studies, four of which are described as randomized, controlled trials, was received from YHEC as two ACCESS files. See Appendix 1. We have focused on the data availability for the following five variables:

- Change in Visual Acuity
- Change in Topography
- Change in Refraction and Astigmatism
- Change in Intraocular Pressure
- Change in Central Corneal Thickness

The first three variables have each been measured in a range of different ways. Change in Visual Acuity has been measured on several different scales.

The impact of treatment is analysed by examining the difference between post-treatment and pre-treatment measurements (change from baseline). For randomized controlled trials, the change from baseline was compared between the treated and untreated patients. For single arm studies, the change from baseline was compared with zero.

3. *Available Data for Meta-Analysis*

The studies reported endpoints in different ways and at different timepoints. Not all the studies reported all the information required to be included in a meta-analysis study for the difference from baseline.

3.1 *Change in Visual Acuity*

Table 1 contains a summary of the visual acuity measures for which results were reported in the literature review.

Table 1 - Visual Acuity Measures

Acronym	Meaning
UCVA	Uncorrected visual acuity
UDVA	Uncorrected distant visual acuity
UVA	Uncorrected visual acuity
CDVA	Corrected distant visual acuity
BSCVA	Best Spectacle-Corrected Visual Acuity
BCVA	Best Corrected Visual Acuity

Following expert advice we have assumed the following:

- BSCVA (Best Spectacle-Corrected Visual Acuity) and BCVA (Best Corrected Visual Acuity) are equivalent.
- If the distance at which visual acuity was measured is not stated we will assume a distant measure. Hence for example, UVA and UDVA will be considered equivalent.

The uncorrected measures reported, highlighted in blue in Table 1, were pooled for the meta-analysis. The corrected measures, highlighted in green, were pooled for a separate meta-analysis.

3.1.1 Data availability for change in visual acuity

The number of studies with enough information to support meta-analysis on the mean difference from baseline for visual acuity can be found in Table 2.

Table 2 - Change in Visual Acuity - Available data

	Corrected VA	Uncorrected VA
1 Week	1	0
1 Month	5	3
3 Months	5	3
6 Months	15	12
12 Months *†	22	18
18 Months	1	1
24 Months *	7	6
36 Months	4	3
48 Months	4	3
60 Months	1	0
72 Months	1	0

* Caporossi (Study ref 11) reported its findings for three age groups at 12, 24, 36 and 48 months; these are counted as separate studies in the table.
† Both Greenstein (Study ref 38) and Hersh (Study ref 52) reported results on the same study. Hersh at 1 month, 3 months, 6 months and 12 months and Greenstein at 12 months only. Because Greenstein provided more information its results were used instead of Hersh's at the 12 month point.

Meta-analysis was carried out for uncorrected and corrected visual acuity at 6, 12 and 24 months as highlighted in Table 2.

3.2 *Change in Topography*

Topography can be measured in several ways. Table 3 contains a summary of the topography measures for which results were reported in the literature review.

Table 3 - Topography Measures

Measurement	Measurement group
Max k, maximum k, Kmax	Max k
Steepest k	Max k
Min k, kmin	Min k
Flattest k	Min k
Mean k	Mean k
Central k	Mean k
Mean sim k, sim k	Mean k

Following expert advice we have assumed the following:

- Steepest K and max k are equivalent.
- Flattest K and min k are equivalent. However we note that Vinciguerra, P (Study ref 114), reported values for both these measures, which were similar but not identical.

The maximum measures reported, highlighted in blue in Table 3, were pooled for the meta-analysis. The minimum measures, highlighted in green, were pooled for a separate meta-analysis. The mean measures, highlighted in purple, were pooled for a third meta-analysis.

3.2.1 Data Availability for change in topography

The number of studies with enough information to do meta-analysis on the mean difference from baseline for topography can be found in Table 4.

Table 4 - Change in Topography - Available data

	Max K	Mean K	Min K
1 Month	2	1	1
3 Months	2	1	1
6 Months	10	7	4
9 Months	1	0	0
12 Months*	18	12	8
18 Months	0	0	0
24 Months*	6	2	1
36 Months	4	1	0
48 Months	4	1	0
60 Months	1	0	0
72 Months	1	0	0

* Caporossi (Study ref 11) reported its findings for three age groups at 12, 24, 36 and 48 months; these are counted as separate studies in the table.

Meta-analysis was carried out at 6, 12 and 24 months for Max K, and at 6 and 12 months for Mean K and Min K, as highlighted in Table 4.

3.3 Change in Refraction and Astigmatism

Change in Refraction and Astigmatism can be measured in several ways. Table 5 contains a summary of the topography measures for which results were reported in the literature review.

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Table 5 - Refraction and Astigmatism Measures

Measurement	Measurement group
Astigmatism	Astigmatism grouped
Manifest Astigmatism	Astigmatism grouped
Residual astigmatism	Astigmatism grouped
Cylinder	Astigmatism grouped
Cylinder refraction	Astigmatism grouped
Refractive astigmatism cylinder	Astigmatism grouped
Refractive cylinder	Astigmatism grouped
Mean astigmatism	Mean astigmatism grouped
Mean cylinder	Mean astigmatism grouped
Corneal astigmatism	Corneal astigmatism grouped
Topographic astigmatism	Corneal astigmatism grouped
Mean spherical equivalent	Spherical equivalent grouped
Spherical equivalent	Spherical equivalent grouped
Manifest Refraction Spherical Equivalent (MRSE)	Spherical equivalent grouped
Sphere	Spherical equivalent grouped
Spherical equivalent refractive error	Spherical equivalent grouped

Following expert advice we have assumed the following:

- Astigmatism and cylinder are different names for the same measure.
- Corneal and topographic astigmatism relate to corneal shape only, as opposed to the lens required for optical correction of astigmatism which is a product of corneal and intraocular astigmatism.
- The mean refraction spherical equivalent (MRSE) is an estimate of total myopia/hypermetropia based on the spherical and cylindrical components in the spectacle prescription (all of the spherical error + half the astigmatism).
- Mean cylinder and astigmatism are the mean values for these indices.

Based on the above, corneal astigmatism and topographic astigmatism measures were pooled together (in purple in Table 5). Mean astigmatism and mean cylinder were pooled together in a different group (in green in Table 5). The rest of the measures relating to either cylinder or astigmatism were considered equivalent: rows shaded in blue in Table 5. Finally, measures relating to a spherical measurement were considered separately (in orange in Table 5).

Note that the same amount of astigmatism can be expressed using a positive or, more commonly, a negative value. To avoid confusion we have used the absolute value of the reported astigmatism measure.

3.3.1 Data Availability for change in refraction and astigmatism

The number of studies with enough information to do meta-analysis on the mean difference from baseline for topography can be found in Table 6.

Three studies reported on two measures assumed to be equivalent (see Table 5). In order not to repeat results from the same study, only results from one of the measures were included in the meta-analysis:

- Pinero DP (Study ref 97): astigmatism and cylinder measurements available. Cylinder measurements were chosen due to smaller reported SDs.
- Vinciguerra P (Study ref 114): sphere and mean spherical equivalent measurements available. Sphere measurements were chosen, due to smaller reported SDs.
- Saffarian L (Study ref 106): sphere and mean spherical equivalent available. Sphere measurements were chosen, due to smaller reported SDs.

Table 6 - Data Availability for change in topography

	Astigmatism grouped	Mean astigmatism grouped	Corneal astigmatism grouped	Spherical equivalent grouped
1 Week	0	0	0	1
1 Month	3	0	1	5
3 Months	3	0	1	4
6 Months	7	1	2	8
9 Months	1	0	0	1
12 Months	13	1	2	10
18 Months	2	0	0	2
24 Months	5	0	0	3
36 Months	2	0	0	0
48 Months	2	0	0	0
60 Months	1	0	0	0
72 Months	1	0	0	0

Meta-analysis was carried out at 6, 12 and 24 months for the grouped astigmatism measure, and at 6 and 12 months for the grouped spherical equivalent measure, as highlighted in Table 6.

3.4 *Change in Intraocular Pressure*

Intraocular pressure (IOP) can be measured in several ways. Table 7 contains a summary of the measures used in the studies on the literature review (some studies did not report how IOP was measured).

Table 7 - IOP Measures

Acronym	Meaning
CRF	Corneal resistance factor
CH	Corneal hysteresis
(no acronym)	Goldman correlated
(no acronym)	Corneal compensated

Following clinical advice, only studies reporting the Goldman correlated and Corneal compensated results were included in the meta-analysis.

3.4.1 Data Availability for IOP

Table 8 - Change in IOP Available Data

	Goldman correlated	Corneal compensated	TOTAL
6 Months	1	1	2
9 Months	0	0	0
12 Months	0	1	1
24 Months	0	0	0

Meta-analysis was carried out at 6 months only for studies reporting Goldman correlated or Corneal compensated results, as highlighted in Table 8.

3.5 Change in Central Corneal Thickness

Central corneal thickness (CCT) can be measured in several ways, depending on the measurement technique and where in the eye it is measured. Table 9 contains a summary of the measures used in the studies on the literature review. (Some studies did not report how CCT was measured.)

Table 9 - CCT Measures

	Acronym	Meaning
Techniques	US	Ultrasonic pachymetery
	SST	Scanning –slit tomography
	RST	Rotating Schelmpflug tomography
	OCT	Optical coherence tomography
	(no acronym)	Optical pachy
Eye location	(no acronym)	Pupil centre thickness
	(no acronym)	Apex
	(no acronym)	Thinnest point

Following clinical advice, studies which reported only SST were excluded. Meta-analysis was carried out for the remaining studies at 6 and 12 months, with the exception of those where no indication was provided of either the method or the location.

3.5.1 Data Availability for change on central corneal thickness

Table 10 - Change in CCT available data

	US	SST	RST	OCT	Pentacam imaging	Optical	Pupil centre thickness	Thinnest point	Apex	TOTAL meta-analysis
1 Week	0	0	0	0	0	0	0	0	0	0
1 Month	0	0	0	0	1	0	0	0	0	1
3 Months	0	0	0	0	1	0	0	0	0	1
6 Months	2	1	2	1	1	0	0	0	0	6
9 Months	0	0	0	0	0	0	0	0	0	1
12 Months	0	1	2	0	1	0	1	1	1	6
18 Months	1	0	0	0	0	1	0	0	0	2
24 Months	0	0	0	0	0	0	1	0	0	1

Meta-analysis was carried out at 6 and 12 months, as highlighted in Table 10.

4. Statistical Methodology

4.1 Calculation of the standard deviation of the change from baseline

Meta-analysis requires both the mean and a variability measure (standard deviation) for the change from baseline in each study. The majority of studies in this review focussed on final values rather than the change from baseline. In such cases, where statistical analyses comparing the changes themselves are presented (confidence intervals, standard errors, t-values, p-values, F values) then the techniques described in (1) section 7.7.3.3 were used to calculate the relevant SD. Where p-values were reported we have assumed that this corresponded to a one-sided test. Otherwise, and assuming the values measured at baseline and at the follow up timepoint are independent, the standard deviations at pre and post treatment were used to estimate the SD of the change from baseline. (The independence assumption is unlikely to hold as the measurements are for the same patients and therefore assuming independence will correspond to an overestimate of the variance and a down-weighting of the evidence from these studies.)

When a p-value was reported for the difference between two treatments, this has been assumed to relate to a two-sided test.

4.2 Visual acuity scales of measurement

For Visual Acuity, measurements are given in two different scales: Decimal and logMAR. Measurements in the decimal scale can be converted to logMAR using the formula below, see (2):

$$logMAR = -\log_{10} Decimal.$$

For studies where visual acuity was reported in the decimal scale, we have converted results to the logMAR scale using the approximation described as method 3 in (3).

Where the scale of measurement was not reported, the data were excluded from the meta-analysis.

Caporossi (Study ref 10) reported changes from baseline for several follow up periods in Snellen lines. However, the term 'Snellen chart' has never been standardized (4), and for this reason it was not clear how these results should be transformed into either the decimal equivalent or the logMAR scale. The results from this study were therefore excluded from the meta-analysis.

4.3 Some Comments on Meta-analysis

4.3.1 Fixed Effects versus Random Effects

According to (5), see page 83-84, a fixed effects model is appropriate in meta-analysis if the following two conditions are met:

- all studies included in the analysis are functionally identical
- the goal of the meta-analysis is to compute the common effect size for the identified populations and not to generalize to other populations.

By contrast, for a series of studies by researchers operating independently, it is unlikely for all the studies to be functionally equivalent and therefore a random effects model should be assumed for the meta-analysis. However if the number of studies is very small there may not be enough information available for the random effects model to be applied correctly. In this case the reviewer may choose to use the fixed effects model instead.

Results for both the fixed effects and random effects models will be reported. For meta-analysis studies where the results of the fixed effects and the random effects models do not agree we will discuss which model gives the most reliable results.

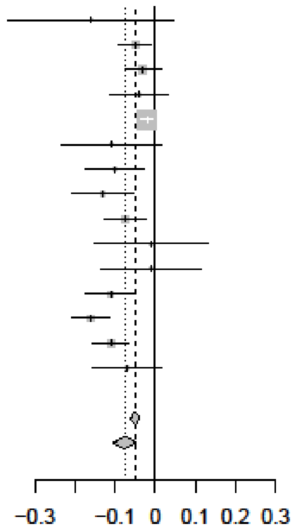
4.3.2 Heterogeneity

Heterogeneity is related to how similar the studies in a meta-analysis are. This can be measured using the I^2 index. Benchmarks have been suggested for I^2 (5) : values of the order of 25% should be considered *low*, 50% *moderate* and 75% *high*. In this report we have flagged I^2 between 50% and 70% as moderate and above 70% as high.

4.3.3 Interpretation of a Forest Plot

The aim of forest plots is to provide a graphical summary of a meta-analysis. We will describe in detail the forest plot for corrected visual acuity at 6 months, see Figure M4 in section 5.1. This plot is also reproduced below for ease of reference:

Study	TE (post–pre)	standard error		95%–CI	W(fixed)	W(random)
4. Arbelaez MC	−0.16	0.1051	−0.16	[−0.37; 0.05]	0.3%	1.8%
6. Asri D	−0.05	0.0212	−0.05	[−0.09; −0.01]	7.6%	9.1%
26. Doors M	−0.03	0.0223	−0.03	[−0.07; 0.01]	6.8%	8.9%
34. Goldich Y	−0.04	0.0378	−0.04	[−0.11; 0.03]	2.4%	6.6%
43. Grewal DS	−0.02	0.0080	−0.02	[−0.04; 0.00]	53.3%	10.7%
50. Henriquez MA	−0.11	0.0636	−0.11	[−0.23; 0.01]	0.8%	3.8%
52. Hersh PS	−0.10	0.0378	−0.10	[−0.17; −0.03]	2.4%	6.6%
53. Holopainen JM	−0.13	0.0400	−0.13	[−0.21; −0.05]	2.1%	6.3%
87. Mazzotta	−0.08	0.0261	−0.08	[−0.13; −0.02]	5.0%	8.3%
97. Pinero DP	−0.01	0.0730	−0.01	[−0.15; 0.13]	0.6%	3.1%
107. Salgado JP	−0.01	0.0633	−0.01	[−0.13; 0.11]	0.8%	3.8%
108. Sedaghat	−0.11	0.0317	−0.11	[−0.17; −0.05]	3.4%	7.5%
114. Vinciguerra P	−0.16	0.0235	−0.16	[−0.21; −0.11]	6.1%	8.8%
116. Vinciguerra P	−0.11	0.0228	−0.11	[−0.15; −0.07]	6.6%	8.9%
117. Wittig-Silva C	−0.07	0.0438	−0.07	[−0.16; 0.02]	1.8%	5.8%
Fixed effect model			**−0.05**	**[−0.06; −0.04]**	**100%**	**--**
Random effects model			**−0.08**	**[−0.11; −0.05]**	**--**	**100%**
Heterogeneity: I-squared=75.4%						



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed). Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

The table on the left side of the plot summarises the data on the studies used in this meta-analysis.

- 'Study' provides for each study the reference number and the name of first author, as per Appendix 1.
- 'TE (post-pre)' stands for treatment effect. The mean value before the treatment (pre) is subtracted from the mean value obtained after the treatment (post).
- 'standard error' is the standard error of the treatment effect (TE (post-pre)) and is defined as the standard deviation of the treatment effect divided by the square root of the sample size. In this case the sample size is the number of eyes for which uncorrected visual acuity was measured at 6 months. The smaller the standard error, the more accurate the estimate of treatment effect.

The table on the right summarises the meta-analysis results.

- '95%-CI' provides the 95% confidence interval for the treatment effect for each study (whose TE value is repeated from the left side table). This confidence interval assumes that treatment effect is normally distributed.

  If zero is included in the confidence interval, the reported treatment effect is said to be not statistically significant. In this example that would mean that there is no evidence of a change in corrected visual acuity before and after the treatment. In other words the

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treatment had no significant effect on corrected visual acuity in the study's patients. This is the case for example for study 4. Arbelaez MC.

If zero is not included in the confidence interval, the reported treatment effect is said to be statistically significant. In this example that would mean that there is evidence of a change in corrected visual acuity before and after the treatment. In other words the treatment had a significant effect on the corrected visual acuity in the study's patients. Because higher corrected visual acuity (logMAR scale) corresponds to poorer vision, a negative treatment effect would correspond to an improvement in vision. This is the case for example, for the 6. Asri D study.

- 'W (fixed)' and 'W (random)' give the weights assigned to each study by of the fixed and random effects models, respectively. The weights for the fixed effects model are proportional to the inverse of the variability of each study, while those for the random effects model also take into account the variability between studies. If this variability is high the weights will be more equally spread between studies; if it is small the weights will be similar to the fixed effects weights.
- **The bottom values correspond to the results for the fixed and random effects model and they summarise the results of the meta-analysis. If the confidence intervals include zero we conclude that the meta-analysis found no significant evidence of a treatment effect. If however the confidence intervals do not include zero (as is the case in this example) we may conclude that there is evidence of a significant treatment effect.**

Finally, the heterogeneity of the studies in the meta-analysis is reported at the bottom of the left hand side of the table (heterogeneity was discussed in section 4.3.2). In this example, I^2=75.4%, which corresponds to high heterogeneity.

If heterogeneity is low the fixed-effect results will tend to agree with the mixed-effect results. However, if this is not the case they can be quite different. In this example although heterogeneity is high both models estimated a significant improvement of between 0.05 and 0.08 logMAR in corrected visual acuity at 6 months. If the results of the two models had not been in agreement, those given by the random effects model would be more reliable, as the way this model allocates weights to the studies takes into account the overall variability.

The plot provides a graphical interpretation of the meta-analysis results.

- The small vertical line for each study corresponds to the treatment effect value (this can be read on the bottom x-axis).
- The horizontal line for each study represents the confidence interval (values can be read on the x-axis).
- The grey boxes are proportional in size to the study weights (fixed).
- The dashed and dotted lines correspond to the mean treatment effect estimated by the fixed and random effects models respectively.
- The grey diamonds represent the confidence intervals for the corresponding meta-analysis models as indicated on the left.

In this example most of the data is on the left hand side of the plot as all studies reported a post-treatment improvement, although not all are significant. The 43. Grewal DS study stands out from the plot as it has by far the biggest weight (over 53%) in the fixed-effects model. The fixed and random effects models estimated similar treatment effects, clearly seen in the plot as the dotted and dashed lines have been plotted very closely together. Because the random-effects model takes into account the between studies variability its confidence interval, represented by the bottom diamond, is wider than that of the fixed effects model. Finally, because neither 'diamonds' cross the zero line, both models estimate a significant improvement in visual acuity post-treatment.

Please note that we have opted not to report the p-values for the meta-analysis results. It was felt that this would be inappropriate due to the poor quality of the studies. Moreover the information on whether the results are or not significant can be easily extracted from the confidence interval (as discussed above).

4.4 Statistical analysis

All analyses were carried out based on the number of eyes treated.

For each endpoint, meta-analyses were carried out for the time points previously identified in section 3. A forest plot and a summary table were provided in each case. A table summarising the meta-analysis results across the time points and different measurements was also provided for each variable.

Statistical software used: R version 2.15.1 (2012-06-22). Meta-analysis was performed using the meta package.

5. Results – treated group only

5.1 Visual Acuity

Table M1: Change in uncorrected visual acuity (LogMAR) at 6 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	1.18	0.63	-0.55	0.54	0.17	-0.88	-0.22	1.31	3.66
6. Asri D	142	142	0.9	0.78	-0.12	0.52	0.05	-0.22	-0.02	14.72	12.64
34. Goldich Y	14	14	0.62	1.02	0.40	0.55	0.21	-0.01	0.81	0.87	2.62
50. Henriquez MA	10	10	1.18	0.56	-0.62	0.65	0.29	-1.19	-0.05	0.46	1.48
52. Hersh PS	58	71	0.84	0.81	-0.03	0.36	0.06	-0.15	0.09	10.67	11.58
53. Holopainen JM	30	30	0.83	0.72	-0.11	0.24	0.04	-0.20	-0.02	19.72	13.46
87. Mazzotta	44	44	0.33	0.49	-0.17	0.39	0.06	-0.28	-0.05	10.95	11.67
97. Pinero DP	12	16	0.84	0.56	-0.28	0.35	0.12	-0.52	-0.04	2.46	5.75
107. Salgado JP	15	22	0.53	0.53	0.00	0.37	0.11	-0.22	0.22	3.13	6.69
108. Sedaghat	51	56	1.1	0.76	-0.34	0.78	0.15	-0.63	-0.05	1.77	4.58
114. Vinciguerra P	40	40	0.79	0.66	-0.13	0.19	0.04	-0.21	-0.05	20.79	13.59
116. Vinciguerra P	28	28	0.77	0.51	-0.26	0.20	0.05	-0.37	-0.15	13.15	12.29
Fixed effects model					-0.14			-0.18	-0.10	100	
Random effects model					-0.15			-0.23	-0.08		100
Heterogeneity I^2	62.50										

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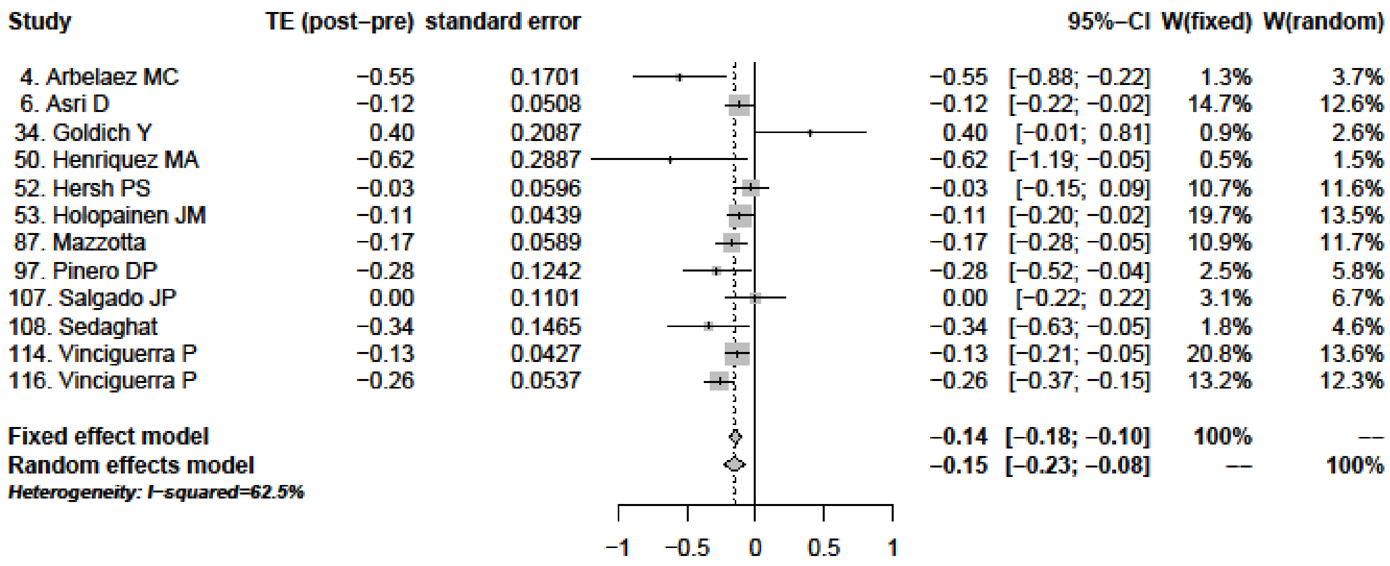
Figure M1: Change in uncorrected visual acuity (LogMAR) at 6 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

Most studies reported a significant improvement in visual acuity. The exceptions were 34. GoldichY, 52. Hersh PS and 107. Salgado JP.

Although there is moderate heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of around -0.15 in LogMAR.

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Table M2: Change in uncorrected visual acuity (LogMAR) at 12 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	1.18	0.55	-0.63	0.54	0.17	-0.96	-0.30	0.33	1.46
6. Asri D	142	142	0.9	0.9	0.00	0.50	0.08	-0.15	0.15	1.68	4.73
11. Caporossi A I	105	152	0.42	0.56	-0.15	0.51	0.05	-0.25	-0.04	3.28	6.43
11. Caporossi A II	243	286	0.34	0.47	-0.14	0.52	0.05	-0.23	-0.04	3.85	6.82
11. Caporossi A III	65	78	0.48	0.56	-0.08	0.17	0.03	-0.14	-0.03	10.92	8.76
34. Goldich Y	14	14	0.62	0.78	0.16	1.33	0.36	-0.54	0.86	0.08	0.37
38. Greenstein SA	76	99	0.8	0.71	-0.09	0.28	0.03	-0.15	-0.03	11.81	8.86
50. Henriquez MA	10	10	1.18	0.46	-0.72	0.62	0.28	-1.26	-0.18	0.12	0.60
68. Kranitz K	22	25	0.23	0.31	-0.08	0.26	0.07	-0.23	0.06	1.71	4.77
71. Kymionis GD	12	14	0.25	0.27	-0.02	0.17	0.06	-0.15	0.10	2.33	5.57
84. Li G	11	20	0.77	*	-0.07	0.07	0.02	-0.10	-0.04	38.74	9.85
87. Mazzotta	44	44	0.33	0.51	-0.19	0.31	0.05	-0.28	-0.10	4.24	7.04
97. Pinero DP	12	16	0.84	0.65	-0.19	0.40	0.14	-0.46	0.08	0.49	2.02
100. Raiskup F	114	149	0.75	0.63	-0.12	0.39	0.05	-0.21	-0.03	4.65	7.24
106. Saffarian L	53	92	0.61	0.31	-0.30	0.28	0.04	-0.38	-0.22	5.51	7.60
107. Salgado JP	15	22	0.53	0.4	-0.13	0.33	0.10	-0.32	0.06	0.96	3.36
114. Vinciguerra P	40	40	0.79	0.62	-0.17	0.20	0.04	-0.26	-0.08	4.73	7.28
116. Vinciguerra P	28	28	0.77	0.57	-0.20	0.17	0.05	-0.29	-0.11	4.58	7.21
Fixed effects model					-0.11			-0.13	-0.09	100	
Random effects model					-0.14			-0.18	-0.10		100
Heterogeneity I^2	70.39										

*Value not reported in the study

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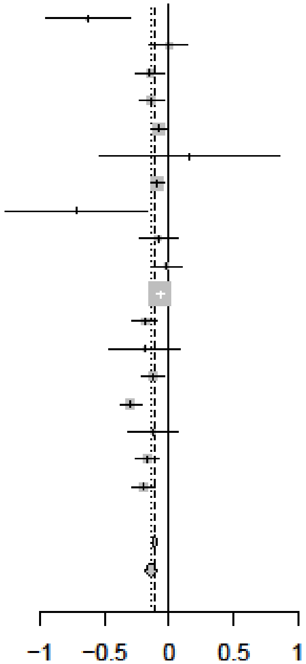
Figure M2: Change in uncorrected visual acuity (LogMAR) at 12 months

Study	TE (post–pre)	standard error	TE	95%–CI	W(fixed)	W(random)
4. Arbelaez MC	−0.63	0.1701	−0.63	[−0.96; −0.30]	0.3%	1.5%
6. Asri D	0.00	0.0752	0.00	[−0.15; 0.15]	1.7%	4.7%
11. Caporossi A I	−0.15	0.0538	−0.15	[−0.25; −0.04]	3.3%	6.4%
11. Caporossi A II	−0.14	0.0496	−0.14	[−0.23; −0.04]	3.9%	6.8%
11. Caporossi A III	−0.08	0.0295	−0.08	[−0.14; −0.03]	10.9%	8.8%
34. Goldich Y	0.16	0.3554	0.16	[−0.54; 0.86]	0.1%	0.4%
38. Greenstein SA	−0.09	0.0283	−0.09	[−0.15; −0.03]	11.8%	8.9%
50. Henriquez MA	−0.72	0.2774	−0.72	[−1.26; −0.18]	0.1%	0.6%
68. Kranitz K	−0.08	0.0745	−0.08	[−0.23; 0.06]	1.7%	4.8%
71. Kymionis GD	−0.02	0.0638	−0.02	[−0.15; 0.10]	2.3%	5.6%
84. Li G	−0.07	0.0157	−0.07	[−0.10; −0.04]	38.7%	9.9%
87. Mazzotta	−0.19	0.0473	−0.19	[−0.28; −0.10]	4.2%	7.0%
97. Pinero DP	−0.19	0.1398	−0.19	[−0.46; 0.08]	0.5%	2.0%
100. Raiskup F	−0.12	0.0452	−0.12	[−0.21; −0.03]	4.6%	7.2%
106. Saffarian L	−0.30	0.0415	−0.30	[−0.38; −0.22]	5.5%	7.6%
107. Salgado JP	−0.13	0.0994	−0.13	[−0.32; 0.06]	1.0%	3.4%
114. Vinciguerra P	−0.17	0.0448	−0.17	[−0.26; −0.08]	4.7%	7.3%
116. Vinciguerra P	−0.20	0.0455	−0.20	[−0.29; −0.11]	4.6%	7.2%
Fixed effect model			**−0.11**	**[−0.13; −0.09]**	**100%**	**--**
Random effects model			**−0.14**	**[−0.18; −0.10]**	**--**	**100%**
Heterogeneity: I-squared=70.4%						



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

Most studies reported a significant improvement in visual acuity. The exceptions were 34. GoldichY, 68. Kranitz K, 71. Kymionis GD, 97. Pinero DP and 107. Salgado JP. Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of around -0.12.

Table M3: Change in uncorrected visual acuity (LogMAR) at 24 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
11. Caporossi A I	105	152	0.42	0.59	-0.17	0.55	0.06	-0.30	-0.05	13.61	13.61
11. Caporossi A II	243	286	0.34	0.5	-0.16	0.55	0.06	-0.28	-0.04	15.47	15.47
11. Caporossi A III	65	78	0.48	0.59	-0.11	0.20	0.04	-0.19	-0.03	34.86	34.86
97. Pinero DP	12	16	0.84	0.7	-0.14	0.33	0.12	-0.37	0.09	4.10	4.10
114. Vinciguerra P	40	40	0.79	0.58	-0.21	0.20	0.04	-0.30	-0.12	29.09	29.09
116. Vinciguerra P	28	28	0.77	0.53	-0.24	0.74	0.14	-0.51	0.03	2.87	2.87
Fixed effects model					-0.16			-0.21	-0.12	100	
Random effects model					-0.16			-0.21	-0.12		100
Heterogeneity I^2	0.00										

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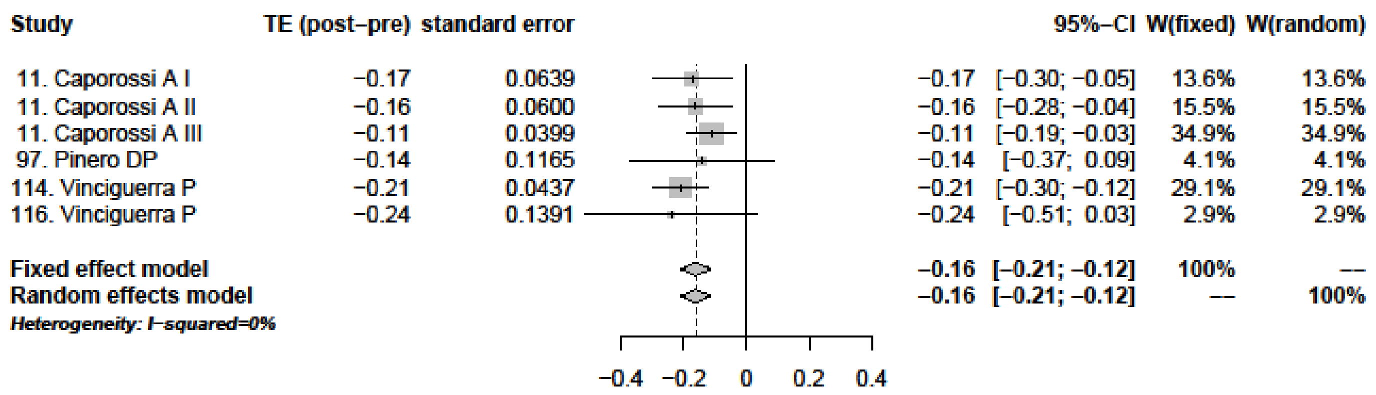
Figure M3: Change in uncorrected visual acuity (LogMAR) at 24 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

The majority of studies reported a significant improvement in visual acuity. The exceptions were 97. Pinero DP and 116. Vinciguerra P.

There is very low heterogeneity between the studies; both the fixed effect and the random effects models estimated a significant mean improvement of around -0.16.

QUANTICS

Table M4: Change in corrected visual acuity (LogMAR) at 6 months

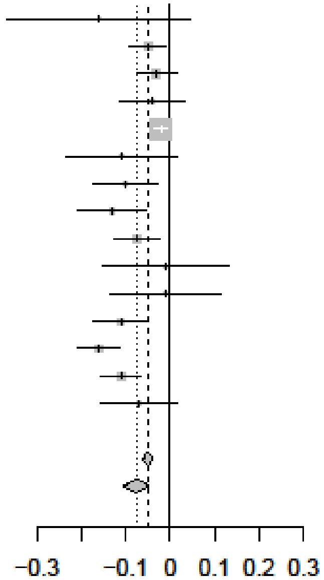
Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	0.4	0.24	-0.16	0.33	0.11	-0.37	0.05	0.31	1.77
6. Asri D	142	142	0.34	0.29	-0.05	0.22	0.02	-0.09	-0.01	7.58	9.12
26. Doors M	29	29	0.17	*	-0.03	0.12	0.02	-0.07	0.01	6.84	8.95
34. Goldich Y	14	14	0.21	0.17	-0.04	0.10	0.04	-0.11	0.03	2.38	6.59
43. Grewal DS	102	102	0.22	0.2	-0.02	0.06	0.01	-0.04	0.00	53.27	10.73
50. Henriquez MA	10	10	0.2	0.09	-0.11	0.14	0.06	-0.23	0.01	0.84	3.79
52. Hersh PS	58	71	0.35	0.25	-0.1	0.23	0.04	-0.17	-0.03	2.37	6.58
53. Holopainen JM	30	30	0.31	0.18	-0.13	0.16	0.04	-0.21	-0.05	2.12	6.28
87. Mazzotta	44	44	0.58	0.69	-0.08	0.17	0.03	-0.13	-0.02	4.97	8.35
97. Pinero DP	12	16	0.32	0.31	-0.01	0.21	0.07	-0.15	0.13	0.64	3.13
107. Salgado JP	15	22	0.19	0.18	-0.01	0.21	0.06	-0.13	0.11	0.85	3.81
108. Sedaghat	51	56	0.19	0.08	-0.11	0.17	0.03	-0.17	-0.05	3.38	7.49
114. Vinciguerra P	40	40	0.39	0.23	-0.16	0.11	0.02	-0.21	-0.11	6.14	8.76
116. Vinciguerra P	28	28	0.28	0.17	-0.11	0.09	0.02	-0.15	-0.07	6.56	8.87
117. Wittig-Silva C	49	33	*	*	-0.07	0.25	0.04	-0.16	0.02	1.77	5.79
Fixed effects model					-0.05			-0.06	-0.04	100	
Random effects model					-0.08			-0.11	-0.05		100
Heterogeneity I^2	75.44										

*Value not reported in the study

Figure M4: Change in corrected visual acuity (LogMAR) at 6 months

Study	TE (post–pre)	standard error		95%–CI	W(fixed)	W(random)
4. Arbelaez MC	−0.16	0.1051	−0.16	[−0.37; 0.05]	0.3%	1.8%
6. Asri D	−0.05	0.0212	−0.05	[−0.09; −0.01]	7.6%	9.1%
26. Doors M	−0.03	0.0223	−0.03	[−0.07; 0.01]	6.8%	8.9%
34. Goldich Y	−0.04	0.0378	−0.04	[−0.11; 0.03]	2.4%	6.6%
43. Grewal DS	−0.02	0.0080	−0.02	[−0.04; 0.00]	53.3%	10.7%
50. Henriquez MA	−0.11	0.0636	−0.11	[−0.23; 0.01]	0.8%	3.8%
52. Hersh PS	−0.10	0.0378	−0.10	[−0.17; −0.03]	2.4%	6.6%
53. Holopainen JM	−0.13	0.0400	−0.13	[−0.21; −0.05]	2.1%	6.3%
87. Mazzotta	−0.08	0.0261	−0.08	[−0.13; −0.02]	5.0%	8.3%
97. Pinero DP	−0.01	0.0730	−0.01	[−0.15; 0.13]	0.6%	3.1%
107. Salgado JP	−0.01	0.0633	−0.01	[−0.13; 0.11]	0.8%	3.8%
108. Sedaghat	−0.11	0.0317	−0.11	[−0.17; −0.05]	3.4%	7.5%
114. Vinciguerra P	−0.16	0.0235	−0.16	[−0.21; −0.11]	6.1%	8.8%
116. Vinciguerra P	−0.11	0.0228	−0.11	[−0.15; −0.07]	6.6%	8.9%
117. Wittig–Silva C	−0.07	0.0438	−0.07	[−0.16; 0.02]	1.8%	5.8%
Fixed effect model			**−0.05**	**[−0.06; −0.04]**	**100%**	**--**
Random effects model			**−0.08**	**[−0.11; −0.05]**	**--**	**100%**

Heterogeneity: I–squared=75.4%



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

Most studies reported a significant improvement in visual acuity.

Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of between -0.05 and -0.08.

Table M5: Change in corrected visual acuity (LogMAR) at 12 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	0.4	0.22	-0.18	0.25	0.05	-0.29	-0.07	0.51	2.94
6. Asri D	142	142	0.34	0.33	-0.01	0.05	0.01	-0.02	0.00	45.29	6.55
11. Caporossi A I	105	152	0.7	0.85	-0.09	0.35	0.04	-0.16	-0.02	1.17	4.30
11. Caporossi A II	243	286	0.66	0.76	-0.06	0.25	0.02	-0.11	-0.02	2.67	5.36
11. Caporossi A III	65	78	0.64	0.71	-0.04	0.10	0.02	-0.08	-0.01	5.82	5.99
26. Doors M	29	29	0.17	*	-0.02	0.08	0.01	-0.05	0.01	6.92	6.08
34. Goldich Y	14	14	0.21	0.11	-0.10	0.10	0.04	-0.17	-0.03	1.07	4.16
38. Greenstein SA	76	99	0.33	0.23	-0.10	0.23	0.03	-0.16	-0.04	1.49	4.65
43. Grewal DS	102	102	0.22	0.2	-0.02	0.16	0.02	-0.05	0.01	5.82	5.99
50. Henriquez MA	10	10	0.2	0.09	-0.11	0.14	0.06	-0.23	0.01	0.38	2.47
68. Kranitz K	22	25	0.58	0.89	-0.19	0.14	0.04	-0.27	-0.12	0.97	4.01
71. Kymionis GD	12	14	0.4	0.49	-0.06	0.12	0.05	-0.15	0.04	0.69	3.44
84. Li G	11	20	0.36	*	-0.13	0.17	0.04	-0.20	-0.06	1.06	4.14
87. Mazzotta	44	44	0.58	0.75	-0.11	0.19	0.03	-0.16	-0.05	1.95	5.01
97. Pinero DP	12	16	0.32	0.27	-0.05	0.18	0.06	-0.17	0.07	0.40	2.56
100. Raiskup F	114	149	0.41	0.3	-0.11	0.30	0.03	-0.18	-0.04	1.26	4.41
101. Raiskup-Wolf F	130	241	*	*	-0.08	0.24	0.02	-0.11	-0.05	6.39	6.04
106. Saffarian L	53	92	0.06	0	-0.06	0.09	0.01	-0.08	-0.04	9.69	6.23
107. Salgado JP	15	22	0.19	0.15	-0.04	0.18	0.05	-0.15	0.07	0.53	3.01
114. Vinciguerra P	40	40	0.39	0.21	-0.18	0.11	0.02	-0.23	-0.13	2.76	5.40
116. Vinciguerra P	28	28	0.28	0.14	-0.14	0.09	0.02	-0.18	-0.10	2.95	5.46
117. Wittig-Silva C	49	33	*	*	-0.12	0.45	0.08	-0.28	0.04	0.24	1.83
Fixed effects model					-0.04			-0.05	-0.04	100	
Random effects model					-0.09			-0.11	-0.06		100
Heterogeneity I^2	85.12										

*Value not reported in the study

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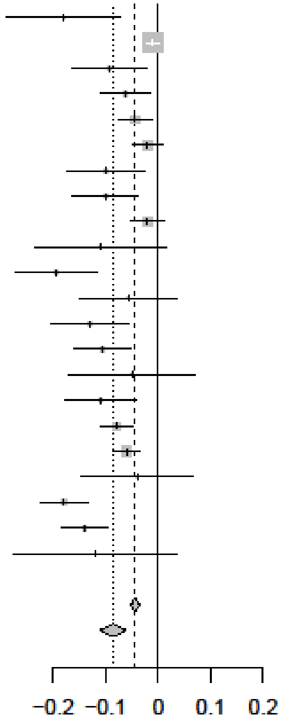
Figure M5: Change in corrected visual acuity (LogMAR) at 12 months

Study	TE (post–pre)	standard error	95%–CI		W(fixed)	W(random)
4. Arbelaez MC	−0.18	0.0550	−0.18	[−0.29; −0.07]	0.5%	2.9%
6. Asri D	−0.01	0.0058	−0.01	[−0.02; 0.00]	45.3%	6.5%
11. Caporossi A I	−0.09	0.0362	−0.09	[−0.16; −0.02]	1.2%	4.3%
11. Caporossi A II	−0.06	0.0239	−0.06	[−0.11; −0.02]	2.7%	5.4%
11. Caporossi A III	−0.04	0.0162	−0.04	[−0.08; −0.01]	5.8%	6.0%
26. Doors M	−0.02	0.0149	−0.02	[−0.05; 0.01]	6.9%	6.1%
34. Goldich Y	−0.10	0.0378	−0.10	[−0.17; −0.03]	1.1%	4.2%
38. Greenstein SA	−0.10	0.0321	−0.10	[−0.16; −0.04]	1.5%	4.6%
43. Grewal DS	−0.02	0.0162	−0.02	[−0.05; 0.01]	5.8%	6.0%
50. Henriquez MA	−0.11	0.0636	−0.11	[−0.23; 0.01]	0.4%	2.5%
68. Kranitz K	−0.19	0.0397	−0.19	[−0.27; −0.12]	1.0%	4.0%
71. Kymionis GD	−0.06	0.0472	−0.06	[−0.15; 0.04]	0.7%	3.4%
84. Li G	−0.13	0.0380	−0.13	[−0.20; −0.06]	1.1%	4.1%
87. Mazzotta	−0.11	0.0280	−0.11	[−0.16; −0.05]	2.0%	5.0%
97. Pinero DP	−0.05	0.0619	−0.05	[−0.17; 0.07]	0.4%	2.6%
100. Raiskup F	−0.11	0.0348	−0.11	[−0.18; −0.04]	1.3%	4.4%
101. Raiskup−Wolf F	−0.08	0.0155	−0.08	[−0.11; −0.05]	6.4%	6.0%
106. Saffarian L	−0.06	0.0126	−0.06	[−0.08; −0.04]	9.7%	6.2%
107. Salgado JP	−0.04	0.0538	−0.04	[−0.15; 0.07]	0.5%	3.0%
114. Vinciguerra P	−0.18	0.0235	−0.18	[−0.23; −0.13]	2.8%	5.4%
116. Vinciguerra P	−0.14	0.0228	−0.14	[−0.18; −0.10]	2.9%	5.5%
117. Wittig−Silva C	−0.12	0.0793	−0.12	[−0.28; 0.04]	0.2%	1.8%
Fixed effect model			**−0.04**	**[−0.05; −0.04]**	**100%**	**--**
Random effects model			**−0.09**	**[−0.11; −0.06]**	**--**	**100%**

Heterogeneity: I−squared=85.1%



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

The majority of studies reported a significant improvement in visual acuity. Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of between -0.04 and -0.09.

Table M6: Change in corrected visual acuity (LogMAR) at 24 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
11. Caporossi A I	105	152	0.7	0.89	-0.12	0.36	0.04	-0.20	-0.04	3.80	11.96
11. Caporossi A II	243	286	0.66	0.78	-0.07	0.25	0.03	-0.13	-0.02	8.59	14.78
11. Caporossi A III	65	78	0.64	0.7	-0.04	0.07	0.01	-0.06	-0.01	34.22	17.20
97. Pinero DP	12	16	0.32	0.31	-0.01	0.19	0.07	-0.14	0.12	1.53	7.91
101. Raiskup-Wolf F	130	241	*	*	-0.09	0.24	0.02	-0.12	-0.06	27.32	16.96
114. Vinciguerra P	40	40	0.39	0.2	-0.19	0.10	0.02	-0.23	-0.15	14.43	15.99
116. Vinciguerra P	28	28	0.28	0.13	-0.15	0.10	0.03	-0.20	-0.10	10.10	15.21
Fixed effects model					-0.09			-0.11	-0.07	100	
Random effects model					-0.10			-0.15	-0.05		100
Heterogeneity I^2	86.58										

*Value not reported in the study

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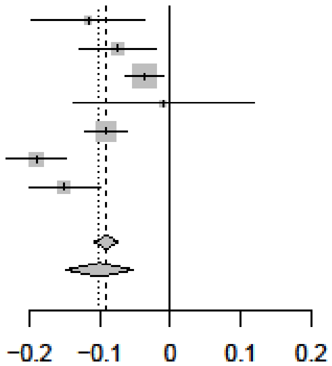
Figure M6: Change in corrected visual acuity (LogMAR) at 24 months

Study	TE (post–pre)	standard error		95%–CI	W(fixed)	W(random)
11. Caporossi A I	−0.12	0.0414	−0.12	[−0.20; −0.04]	3.8%	12.0%
11. Caporossi A II	−0.07	0.0276	−0.07	[−0.13; −0.02]	8.6%	14.8%
11. Caporossi A III	−0.04	0.0138	−0.04	[−0.06; −0.01]	34.2%	17.2%
97. Pinero DP	−0.01	0.0654	−0.01	[−0.14; 0.12]	1.5%	7.9%
101. Raiskup−Wolf F	−0.09	0.0155	−0.09	[−0.12; −0.06]	27.3%	17.0%
114. Vinciguerra P	−0.19	0.0213	−0.19	[−0.23; −0.15]	14.4%	16.0%
116. Vinciguerra P	−0.15	0.0254	−0.15	[−0.20; −0.10]	10.1%	15.2%
Fixed effect model			**−0.09**	**[−0.11; −0.07]**	**100%**	**--**
Random effects model			**−0.10**	**[−0.15; −0.05]**	**--**	**100%**

Heterogeneity: I−squared=86.6%



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

Most studies reported a significant improvement in visual acuity. The exception was 97. Pinero DP.

Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of around -0.10.

Table M7: Summary of meta-analysis results for change in visual acuity (logMAR)

		Uncorrected			Corrected		
	Period	Mean Difference	95% lcl	95% ucl	Mean Difference	95% lcl	95% ucl
Fixed effects model	6M	-0.14	-0.18	-0.10	-0.05	-0.06	-0.04
Random effects model		-0.15	-0.23	-0.08	-0.08	-0.11	-0.05
Heterogeneity I^2		62.50			75.44		
Fixed effects model	12M	-0.11	-0.13	-0.09	-0.04	-0.05	-0.04
Random effects model		-0.14	-0.18	-0.10	-0.09	-0.11	-0.06
Heterogeneity I^2		70.39			85.12		
Fixed effects model	24M	-0.16	-0.21	-0.12	-0.09	-0.11	-0.07
Random effects model		-0.16	-0.21	-0.12	-0.10	-0.15	-0.05
Heterogeneity I^2		0.00			86.58		

Red text endpoint not significant. **Shading** green: $I^2 < 50\%$; orange: $50\% \leq I^2 < 70\%$; red: $I^2 \geq 70\%$.

The meta-analyses reported in Table M7 show reductions compared with baseline in both uncorrected and corrected visual acuity at 6, 12 and 24 months. The estimated difference in means for both fixed and random effects models is negative and the 95% upper confidence limit is negative for both models in all cases.

QUANTICS

5.2 *Topography*

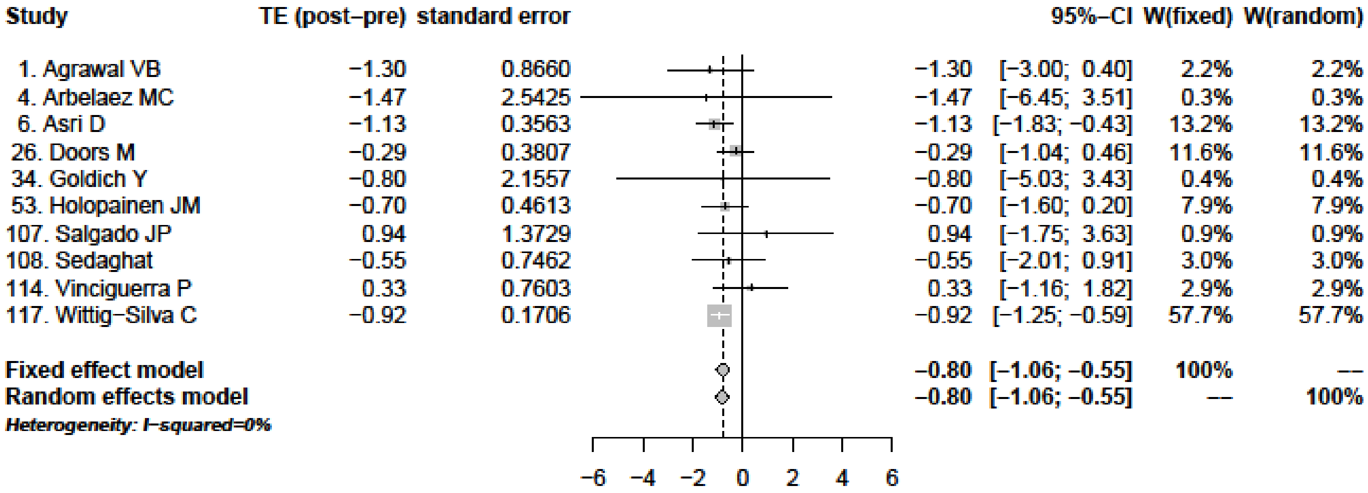
Table M8: Change in Max K (diopters) at 6 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
1. Agrawal VB	68	41	53.26	*	-1.3	4.33	0.87	-3.00	0.40	2.24	2.24
4. Arbelaez MC	19	20	51.89	50.42	-1.47	8.04	2.54	-6.45	3.51	0.26	0.26
6. Asri D	142	142	54.09	52.96	-1.13	3.63	0.36	-1.83	-0.43	13.22	13.22
26. Doors M	29	29	48.66	*	-0.29	2.05	0.38	-1.04	0.46	11.58	11.58
34. Goldich Y	14	14	53.9	53.1	-0.8	5.70	2.16	-5.03	3.43	0.36	0.36
53. Holopainen JM	30	30	48.9	48.2	-0.7	2.53	0.46	-1.60	0.20	7.88	7.88
107. Salgado JP	15	22	44.12	45.06	0.94	4.55	1.37	-1.75	3.63	0.89	0.89
108. Sedaghat	51	56	50.16	49.61	-0.55	3.95	0.75	-2.01	0.91	3.01	3.01
114. Vinciguerra P	40	40	51.48	51.81	0.33	3.40	0.76	-1.16	1.82	2.90	2.90
117. Wittig-Silva C	33	33	*	*	-0.92	0.98	0.17	-1.25	-0.59	57.66	57.66
Fixed effects model					-0.80			-1.06	-0.55	100	
Random effects model					-0.80			-1.06	-0.55		100
Heterogeneity I^2	0										

*Value not reported in the study

QUANTICS

Figure M8: Change in Max K (diopters) at 6 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

Most studies did not report a significant improvement in topography (although in most cases a non-significant improved was observed). The two studies with the smallest standard error and therefore the biggest weight (117. Wittig-Silva C and 6. Asri D.) did report significant improvements.

There is very low heterogeneity between the studies; hence both the fixed effect and the random effects models estimated a significant mean improvement of around -0.8.

QUANTICS

Table M9: Change in Max K (diopters) at 12 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
1. Agrawal VB	68	41	53.26	*	-2.47	3.89	0.78	-3.99	-0.95	0.69	3.01
4. Arbelaez MC	19	20	51.89	50.49	-1.4	2.47	0.55	-2.48	-0.32	1.38	4.59
6. Asri D	142	142	54.09	53.6	-0.49	2.28	0.28	-1.05	0.07	5.17	7.55
11. Caporossi A I	105	152	50.22	49.53	-0.69	2.57	0.27	-1.22	-0.16	5.78	7.74
11. Caporossi A II	243	286	51.72	51.12	-0.6	2.40	0.23	-1.05	-0.15	7.87	8.20
11. Caporossi A III	65	78	51.88	51.43	-0.45	1.02	0.17	-0.79	-0.11	14.21	8.86
26. Doors M	29	29	48.66	*	-0.08	1.56	0.29	-0.65	0.49	4.99	7.48
34. Goldich Y	14	14	53.9	52.1	-1.8	2.31	0.62	-3.01	-0.59	1.10	4.05
50. Henriquez MA	10	10	*	*	-2.66	4.05	1.35	-5.30	-0.02	0.23	1.26
52. Hersh PS	58	71	*	*	-1.7	3.90	0.46	-2.61	-0.79	1.95	5.45
64. Koller T	192	192	*	*	-0.89	1.49	0.12	-1.13	-0.65	28.48	9.33
68. Kranitz K	22	25	48.39	46.71	-1.68	5.52	1.56	-4.74	1.38	0.17	0.97
84. Li G	11	20	45.37		-2.14	1.23	0.28	-2.68	-1.60	5.53	7.66
100. Raiskup F	114	149	53.7	52.9	-0.8	7.85	0.91	-2.58	0.98	0.51	2.39
101. Raiskup-Wolf F	130	241	*	*	-1.46	3.76	0.24	-1.93	-0.99	7.14	8.06
107. Salgado JP	15	22	44.12	44.43	0.31	4.02	1.21	-2.06	2.68	0.29	1.51
114. Vinciguerra P	40	40	51.48	52.16	0.68	3.45	0.77	-0.83	2.19	0.70	3.04
117. Wittig-Silva C	33	33	*	*	-1.45	1.00	0.17	-1.79	-1.11	13.82	8.84
Fixed effects model					-0.95			-1.08	-0.83	100	
Random effects model					-1.03			-1.34	-0.71		100
Heterogeneity I^2	76.19										

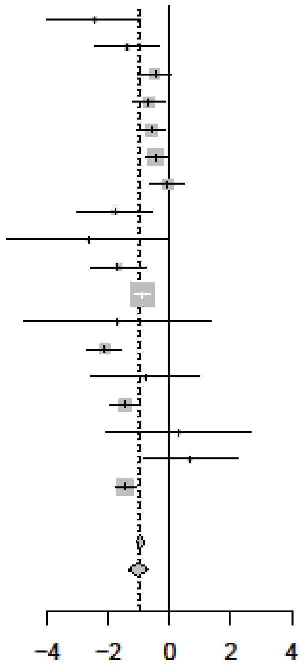
*Value not reported in the study

QUANTICS

Figure M9: Change in Max K (diopters) at 12 months

Study	TE (post–pre)	standard error	95%–CI		W(fixed)	W(random)
1. Agrawal VB	−2.47	0.7780	−2.47	[−3.99; −0.95]	0.7%	3.0%
4. Arbelaez MC	−1.40	0.5513	−1.40	[−2.48; −0.32]	1.4%	4.6%
6. Asri D	−0.49	0.2846	−0.49	[−1.05; 0.07]	5.2%	7.5%
11. Caporossi A I	−0.69	0.2691	−0.69	[−1.22; −0.16]	5.8%	7.7%
11. Caporossi A II	−0.60	0.2307	−0.60	[−1.05; −0.15]	7.9%	8.2%
11. Caporossi A III	−0.45	0.1717	−0.45	[−0.79; −0.11]	14.2%	8.9%
26. Doors M	−0.08	0.2897	−0.08	[−0.65; 0.49]	5.0%	7.5%
34. Goldich Y	−1.80	0.6170	−1.80	[−3.01; −0.59]	1.1%	4.0%
50. Henriquez MA	−2.66	1.3484	−2.66	[−5.30; −0.02]	0.2%	1.3%
52. Hersh PS	−1.70	0.4628	−1.70	[−2.61; −0.79]	2.0%	5.5%
64. Koller T	−0.89	0.1213	−0.89	[−1.13; −0.65]	28.5%	9.3%
68. Kranitz K	−1.68	1.5602	−1.68	[−4.74; 1.38]	0.2%	1.0%
84. Li G	−2.14	0.2750	−2.14	[−2.68; −1.60]	5.5%	7.7%
100. Raiskup F	−0.80	0.9099	−0.80	[−2.58; 0.98]	0.5%	2.4%
101. Raiskup−Wolf F	−1.46	0.2422	−1.46	[−1.93; −0.99]	7.1%	8.1%
107. Salgado JP	0.31	1.2106	0.31	[−2.06; 2.68]	0.3%	1.5%
114. Vinciguerra P	0.68	0.7715	0.68	[−0.83; 2.19]	0.7%	3.0%
117. Wittig−Silva C	−1.45	0.1741	−1.45	[−1.79; −1.11]	13.8%	8.8%
Fixed effect model			**−0.95**	**[−1.08; −0.83]**	**100%**	**--**
Random effects model			**−1.03**	**[−1.34; −0.71]**	**--**	**100%**

Heterogeneity: I−squared=76.2%



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

The majority of studies reported a significant improvement in topography.

Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of around -1.0.

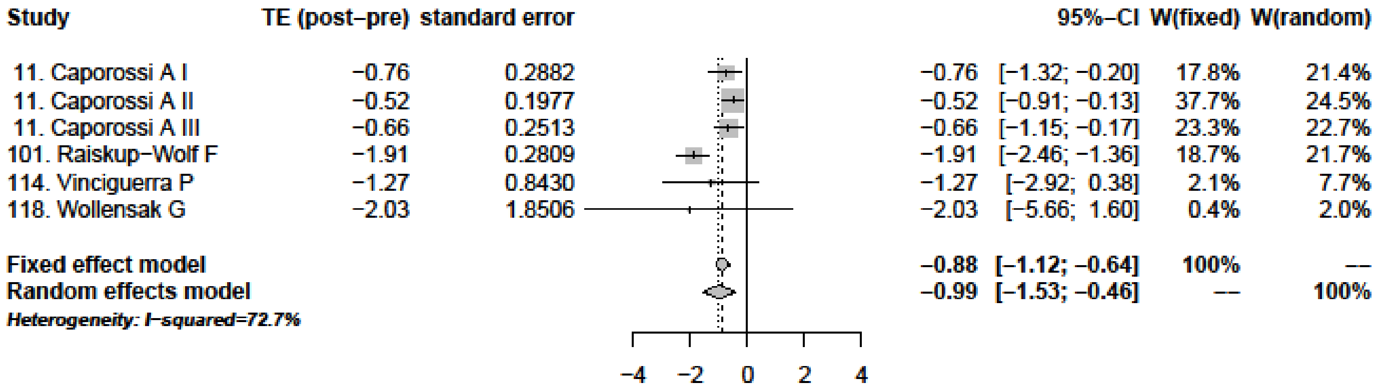
Table M10: Change in Max K (diopters) at 24 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
11. Caporossi A I	105	152	50.22	49.46	-0.76	2.48	0.29	-1.32	-0.20	17.76	21.42
11. Caporossi A II	243	286	51.72	51.2	-0.52	1.80	0.20	-0.91	-0.13	37.71	24.50
11. Caporossi A III	65	78	51.88	51.22	-0.66	1.26	0.25	-1.15	-0.17	23.34	22.71
101. Raiskup-Wolf F	130	241	*	*	-1.91	4.36	0.28	-2.46	-1.36	18.69	21.68
114. Vinciguerra P	40	40	51.48	50.21	-1.27	5.33	0.84	-2.92	0.38	2.07	7.66
118. Wollensak G	22	23	54.18	52.15	-2.03	6.28	1.85	-5.66	1.60	0.43	2.03
Fixed effects model					-0.88			-1.12	-0.64	100	
Random effects model					-0.99			-1.53	-0.46		100
Heterogeneity I^2	72.68										

*Value not reported in the study

QUANTICS

Figure M10: Change in Max K (diopters) at 24 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

The majority of studies reported a significant improvement in topography. The exceptions were 114. Vinciguerra P and 118. Wollensak G.

Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of between -0.88 and -0.99.

Table M11: Change in Mean K (diopters) at 6 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	49.93	48.68	-1.25	4.82	1.52	-4.24	1.74	1.56	4.62
6. Asri D	142	142	50.76	49.81	-0.95	4.76	0.61	-2.16	0.26	9.58	15.39
26. Doors M	29	29	47.49	*	0.64	1.73	0.32	0.01	1.27	35.10	22.94
33. Gkika M	30	50	49.2	48.6	-0.6	2.52	0.36	-1.30	0.10	28.63	22.03
34. Goldich Y	14	14	46.2	46.3	0.1	3.06	1.16	-2.17	2.37	2.71	7.16
87. Mazzotta	44	44	51.4	50.2	-1.2	2.87	0.43	-2.05	-0.35	19.31	19.94
97. Pinero DP	12	16	47.46	46.68	-0.78	3.05	1.08	-2.89	1.33	3.11	7.93
Fixed effects model					-0.31			-0.68	0.06	100	
Random effects model					-0.48			-1.19	0.22		100
Heterogeneity I^2	61.06										

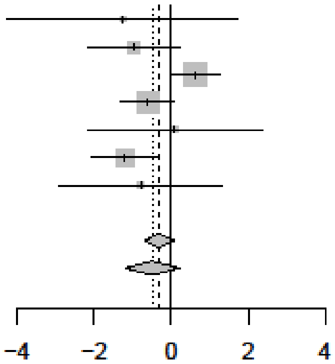
*Value not reported in the study

QUANTICS

Figure M11: Change in Mean K (diopters) at 6 months

Study	TE (post–pre)	standard error	95%–CI	W(fixed)	W(random)
4. Arbelaez MC	−1.25	1.5240	−1.25 [−4.24; 1.74]	1.6%	4.6%
6. Asri D	−0.95	0.6149	−0.95 [−2.16; 0.26]	9.6%	15.4%
26. Doors M	0.64	0.3213	0.64 [0.01; 1.27]	35.1%	22.9%
33. Gkika M	−0.60	0.3557	−0.60 [−1.30; 0.10]	28.6%	22.0%
34. Goldich Y	0.10	1.1567	0.10 [−2.17; 2.37]	2.7%	7.2%
87. Mazzotta	−1.20	0.4332	−1.20 [−2.05; −0.35]	19.3%	19.9%
97. Pinero DP	−0.78	1.0787	−0.78 [−2.89; 1.33]	3.1%	7.9%
Fixed effect model			**−0.31 [−0.68; 0.06]**	**100%**	**--**
Random effects model			**−0.48 [−1.19; 0.22]**	**--**	**100%**

Heterogeneity: I–squared=61.1%



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

87. Mazzota was the only study that reported a significant improvement in topography, whereas the results were found to be significantly worse for 26. Doors M (both studies have big weights in both models). None of the results for the other studies were significant although most reported improvements.

There is moderate heterogeneity between the studies and both the fixed effect and the random effects models estimate a non-significant mean improvement.

QUANTICS

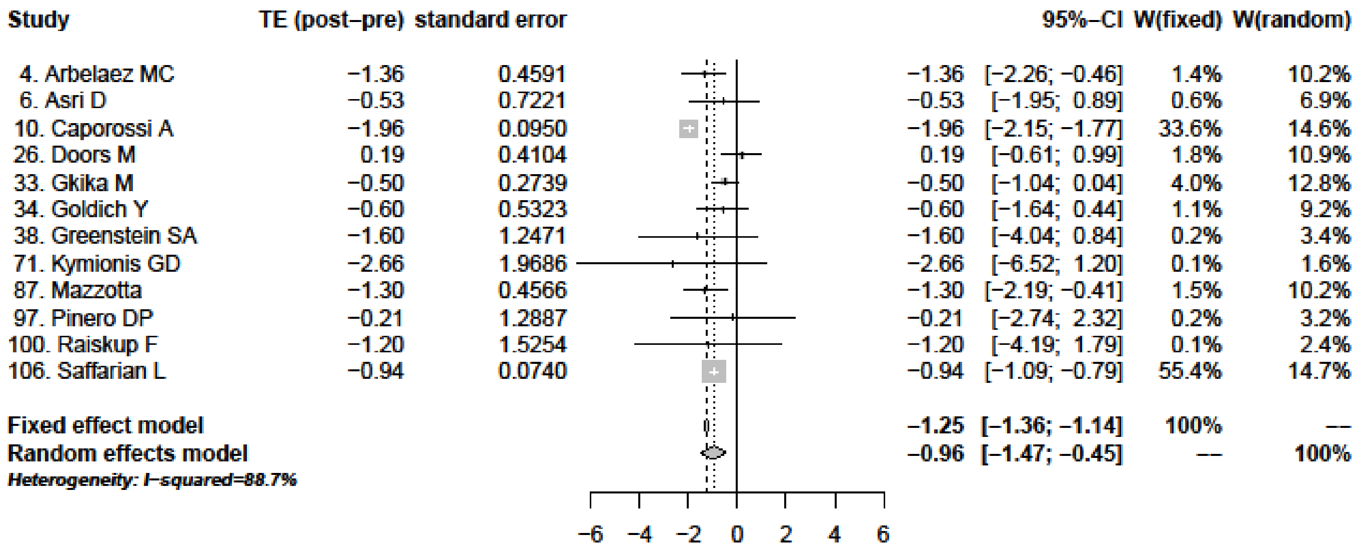
Table M12: Change in Mean K (diopters) at 12 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	49.93	48.57	-1.36	2.05	0.46	-2.26	-0.46	1.44	10.17
6. Asri D	142	142	50.76	50.23	-0.53	4.80	0.72	-1.95	0.89	0.58	6.92
10. Caporossi A	44	44	*	*	-1.96	0.63	0.09	-2.15	-1.77	33.64	14.62
26. Doors M	29	29	47.49	*	0.19	2.21	0.41	-0.61	0.99	1.80	10.86
33. Gkika M	30	50	49.2	48.7	-0.5	1.94	0.27	-1.04	0.04	4.05	12.79
34. Goldich Y	14	14	46.2	45.6	-0.6	1.99	0.53	-1.64	0.44	1.07	9.17
38. Greenstein SA	76	99	58	56.4	-1.6	8.77	1.25	-4.04	0.84	0.20	3.36
71. Kymionis GD	12	14	51.99	49.33	-2.66	5.21	1.97	-6.52	1.20	0.08	1.56
87. Mazzotta	44	44	51.4	50.1	-1.3	3.03	0.46	-2.19	-0.41	1.46	10.20
97. Pinero DP	12	16	47.46	47.25	-0.21	3.64	1.29	-2.74	2.32	0.18	3.19
100. Raiskup F	114	149	62.1	60.9	-1.2	13.17	1.53	-4.19	1.79	0.13	2.43
106. Saffarian L	53	92	46.94	*	-0.94	0.71	0.07	-1.09	-0.79	55.38	14.73
Fixed effects model					-1.25			-1.36	-1.14	100	
Random effects model					-0.96			-1.47	-0.45		100
Heterogeneity I^2	88.66										

*Value not reported in the study

QUANTICS

Figure M12: Change in Mean K (diopters) at 12 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

Most studies reported improvements in topography although this was only significant for three studies: 10. Caporossi A, 87. Mazzota and 106. Saffarian. The only study to report worse results was 26. Doors M (although these were not significant).

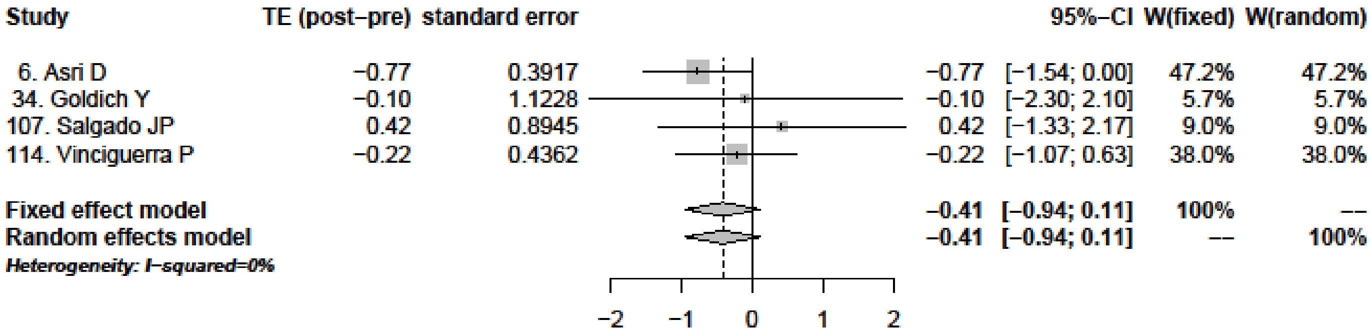
Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant mean improvement of between -0.96 and -1.25.

Table M13: Change in Min K (diopters) at 6 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
6. Asri D	142	142	47.43	46.66	-0.77	3.99	0.39	-1.54	0.00	47.18	47.18
34. Goldich Y	14	14	44.3	44.2	-0.1	2.97	1.12	-2.30	2.10	5.74	5.74
107. Salgado JP	15	22	41.78	42.2	0.42	2.97	0.89	-1.33	2.17	9.04	9.04
114. Vinciguerra P	40	40	42.95	42.73	-0.22	1.95	0.44	-1.07	0.63	38.04	38.04
Fixed effects model					-0.41			-0.94	0.11	100	
Random effects model					-0.41			-0.94	0.11		100
Heterogeneity I^2	0										

QUANTICS

Figure M13: Change in Min K (diopters) at 6 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

There were very few studies in this meta-analysis. Most studies reported an improvement in topography (with the exception of 107. Salgado JP) although none was significant.

There is very low heterogeneity between the studies and both the fixed effect and the random effects models estimate a non-significant mean improvement.

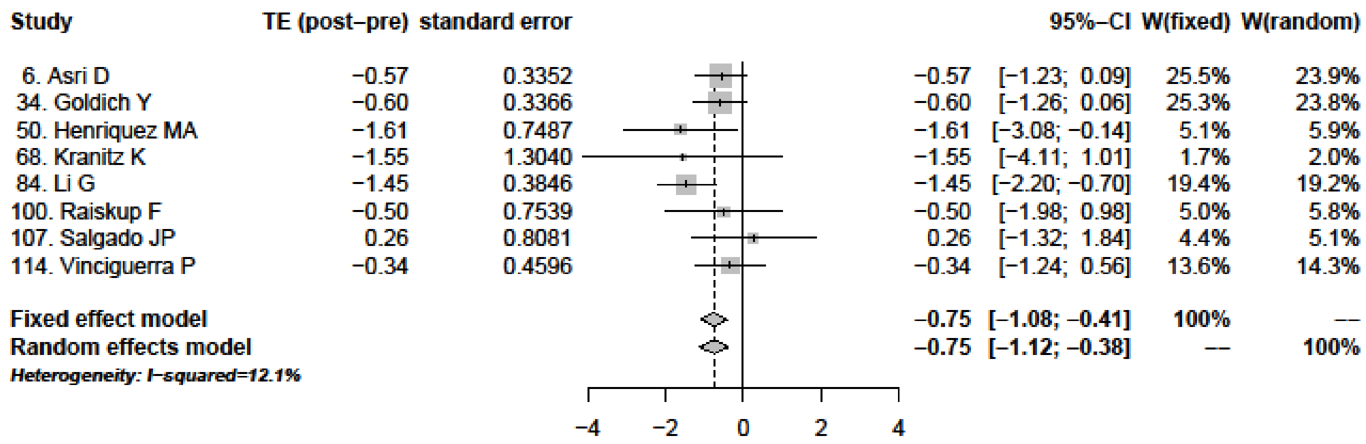
Table M14: Change in Min K (diopters) at 12 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
6. Asri D	142	142	47.43	46.86	-0.57	2.68	0.34	-1.23	0.09	25.51	23.90
34. Goldich Y	14	14	44.3	43.7	-0.6	1.26	0.34	-1.26	0.06	25.31	23.76
50. Henriquez MA	10	10	*	*	-1.61	2.25	0.75	-3.08	-0.14	5.11	5.89
68. Kranitz K	22	25	45.06	43.51	-1.55	4.61	1.30	-4.11	1.01	1.69	2.02
84. Li G	11	20	43.01	*	-1.45	1.72	0.38	-2.20	-0.70	19.38	19.24
100. Raiskup F	114	149	46.6	46.1	-0.5	6.51	0.75	-1.98	0.98	5.04	5.81
107. Salgado JP	15	22	41.78	42.04	0.26	2.68	0.81	-1.32	1.84	4.39	5.10
114. Vinciguerra P	40	40	42.95	42.61	-0.34	2.06	0.46	-1.24	0.56	13.57	14.27
Fixed effects model					-0.75			-1.08	-0.41	100	
Random effects model					-0.75			-1.12	-0.38		100
Heterogeneity I^2	12.09										

*Value not reported in the study

QUANTICS

Figure M14: Change in Min K (diopters) at 12 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

The majority of studies reported an improvement in topography, although this was only significant for 50. Henriquez MA and 84. Li G . The exception was 107. Salgado JP for which worse (though non-significant) results after treatment were reported.

There is low heterogeneity between the studies and both the fixed effect and the random effects models estimate a significant mean improvement of -0.75.

Table M15: Summary of meta-analysis results for change in topography

	Period	Max K (diopters) Mean Difference	95% lcl	95% ucl	Mean K (diopters) Mean Difference	95% lcl	95% ucl	Min K (diopters) Mean Difference	95% lcl	95% ucl
Fixed effects model	6M	-0.80	-1.06	-0.55	-0.31	-0.68	0.06	-0.37	-0.86	0.11
Random effects model		-0.80	-1.06	-0.55	-0.48	-1.19	0.22	-0.37	-0.86	0.11
Heterogeneity I^2		0.00			61.06			0.00		
Fixed effects model	12M	-0.95	-1.08	-0.83	-1.25	-1.36	-1.14	-0.70	-1.02	-0.38
Random effects model		-1.03	-1.34	-0.71	-0.96	-1.47	-0.45	-0.69	-1.05	-0.34
Heterogeneity I^2		76.19			88.66			12.21		
Fixed effects model	24M	-0.88	-1.12	-0.64						
Random effects model		-0.99	-1.53	-0.46						
Heterogeneity I I^2		72.68								

Red text endpoint not significant. **Shading** green: $I^2 < 50\%$; orange: $50\% \le I^2 < 70\%$; red: $I^2 \ge 70\%$.

The meta-analyses reported in Table M15 show reductions compared with baseline in Max K at 6, 12 and 24 months. The estimated difference in means for both fixed and random effects models is negative and 95% upper confidence limit is negative for both models in all cases.

For Min K and Mean K the results were significant at 12 months, though not at 6 months.

5.3 Refraction and Astigmatism (grouped measures)

As per section 3.3, the astigmatism values used in the meta-analysis are the absolute values reported in the studies at baseline and post-treatment. This was done for consistency reasons as some studies reported astigmatism as a positive number while others as negative.

Spherical equivalent measures were reported consistently as negative values.

Table M16: Change in Astigmatism grouped (diopters) at 6 months

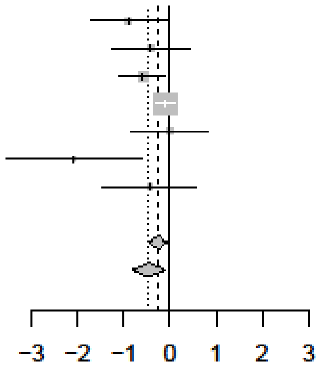
Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	4.04	3.15	-0.89	1.36	0.43	-1.73	-0.05	4.72	12.02
6. Asri D	142	142	6.6	6.19	-0.41	3.33	0.43	-1.25	0.43	4.69	11.98
26. Doors M	29	57	4.84	*	-0.59	1.96	0.26	-1.10	-0.08	12.87	20.03
33. Gkika M	30	50	1.5	1.4	-0.1	0.80	0.11	-0.32	0.12	68.07	29.12
52. Hersh PS	58	71	4.76	4.76	0	2.51	0.42	-0.83	0.83	4.89	12.29
97. Pinero DP	12	16	3.9	1.83	-2.07	2.10	0.74	-3.52	-0.62	1.58	5.33
107. Salgado JP	15	22	2.59	2.15	-0.44	1.73	0.52	-1.46	0.58	3.19	9.23
Fixed effects model					-0.25			-0.43	-0.07	100	
Random effects model					-0.45			-0.82	-0.09		100
Heterogeneity I^2	51.42										

*Value not reported in the study

Figure M16: Change in Astigmatism grouped (diopters) at 6 months

Study	TE (post–pre)	standard error	95%–CI		W(fixed)	W(random)
4. Arbelaez MC	−0.89	0.4289	−0.89	[−1.73; −0.05]	4.7%	12.0%
6. Asri D	−0.41	0.4301	−0.41	[−1.25; 0.43]	4.7%	12.0%
26. Doors M	−0.59	0.2596	−0.59	[−1.10; −0.08]	12.9%	20.0%
33. Gkika M	−0.10	0.1129	−0.10	[−0.32; 0.12]	68.1%	29.1%
52. Hersh PS	0.00	0.4213	0.00	[−0.83; 0.83]	4.9%	12.3%
97. Pinero DP	−2.07	0.7418	−2.07	[−3.52; −0.62]	1.6%	5.3%
107. Salgado JP	−0.44	0.5217	−0.44	[−1.46; 0.58]	3.2%	9.2%
Fixed effect model			**−0.25**	**[−0.43; −0.07]**	**100%**	**--**
Random effects model			**−0.45**	**[−0.82; −0.09]**	**--**	**100%**

Heterogeneity: I-squared=51.4%



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

All studies reported and improvement in astigmatism with the exception of the 52. Hersh PS study (which reported no change on average).

There is moderate heterogeneity between the studies, however both the fixed and random effects models estimate a significant decrease in astigmatism of between -0.25 and -0.45.

QUANTICS

Table M17: Change in Astigmatism grouped (diopters) at 12 months

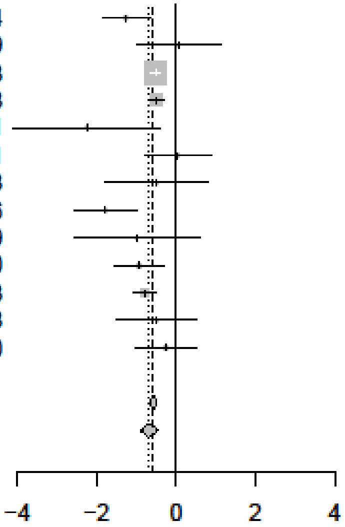
Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	4.04	2.79	-1.25	1.36	0.30	-1.85	-0.65	2.20	8.03
6. Asri D	142	142	6.6	6.67	0.07	3.59	0.54	-0.99	1.13	0.70	3.35
10. Caporossi A	44	44	3.9	*	-0.52	0.38	0.06	-0.63	-0.41	61.99	21.51
26. Doors M	29	57	4.84	*	-0.51	0.78	0.10	-0.71	-0.31	19.06	18.89
50. Henriquez MA	10	10	3.5	*	-2.25	2.81	0.94	-4.09	-0.41	0.23	1.23
52. Hersh PS	58	71	4.76	4.81	0.05	2.52	0.42	-0.78	0.88	1.14	5.02
68. Kranitz K	22	25	3.49	3	-0.49	2.35	0.67	-1.79	0.81	0.46	2.33
84. Li G	11	20	2.36	0.58	-1.78	1.27	0.40	-2.57	-0.99	1.25	5.40
97. Pinero DP	12	16	3.9	2.91	-0.99	2.30	0.81	-2.58	0.60	0.31	1.61
101. Raiskup-Wolf F	130	241	*	*	-0.93	3.67	0.31	-1.53	-0.33	2.14	7.91
106. Saffarian L	53	92	-3.93	*	-0.78	1.49	0.16	-1.08	-0.48	8.43	15.46
107. Salgado JP	15	22	2.59	2.1	-0.49	1.73	0.52	-1.51	0.53	0.75	3.57
115. Vinciguerra P	28	28	3.02	2.76	-0.26	1.46	0.39	-1.02	0.50	1.34	5.67
Fixed effects model					-0.57			-0.66	-0.48	100	
Random effects model					-0.68			-0.89	-0.47		100
Heterogeneity I^2	53.88										

*Value not reported in the study

QUANTICS

Figure M17: Change in Astigmatism grouped (diopters) at 12 months

Study	TE (post−pre)	standard error		95%−CI	W(fixed)	W(random)
4. Arbelaez MC	−1.25	0.3044	−1.25	[−1.85; −0.65]	2.2%	8.0%
6. Asri D	0.07	0.5399	0.07	[−0.99; 1.13]	0.7%	3.4%
10. Caporossi A	−0.52	0.0573	−0.52	[−0.63; −0.41]	62.0%	21.5%
26. Doors M	−0.51	0.1033	−0.51	[−0.71; −0.31]	19.1%	18.9%
50. Henriquez MA	−2.25	0.9381	−2.25	[−4.09; −0.41]	0.2%	1.2%
52. Hersh PS	0.05	0.4221	0.05	[−0.78; 0.88]	1.1%	5.0%
68. Kranitz K	−0.49	0.6653	−0.49	[−1.79; 0.81]	0.5%	2.3%
84. Li G	−1.78	0.4026	−1.78	[−2.57; −0.99]	1.3%	5.4%
97. Pinero DP	−0.99	0.8129	−0.99	[−2.58; 0.60]	0.3%	1.6%
101. Raiskup−Wolf F	−0.93	0.3080	−0.93	[−1.53; −0.33]	2.1%	7.9%
106. Saffarian L	−0.78	0.1553	−0.78	[−1.08; −0.48]	8.4%	15.5%
107. Salgado JP	−0.49	0.5203	−0.49	[−1.51; 0.53]	0.8%	3.6%
115. Vinciguerra P	−0.26	0.3900	−0.26	[−1.02; 0.50]	1.3%	5.7%
Fixed effect model			**−0.57**	**[−0.66; −0.48]**	**100%**	**--**
Random effects model			**−0.68**	**[−0.89; −0.47]**	**--**	**100%**
Heterogeneity: I−squared=53.9%						



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

All studies reported and improvement in astigmatism with the exception of the 6. Asri D and 52. Hersh PS studies that reported a small, non-significant increase.

There is moderate heterogeneity between the studies, however both the fixed and random effects models estimate a significant decrease in astigmatism of between -0.57 and -0.68.

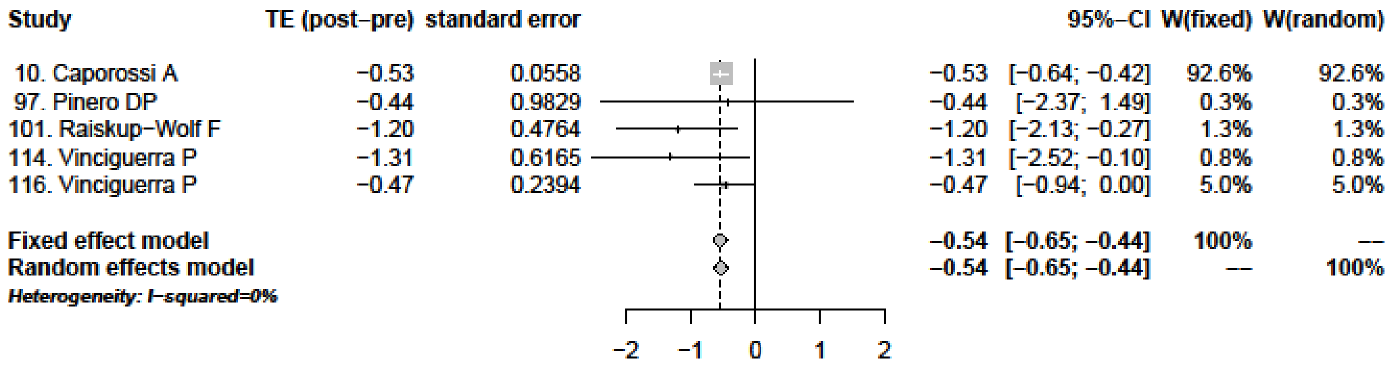
Table M18: Change in Astigmatism grouped (diopters) at 24 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
10. Caporossi A	44	44	3.9	*	-0.53	0.37	0.06	-0.64	-0.42	92.64	92.64
97. Pinero DP	12	16	3.9	3.46	-0.44	2.78	0.98	-2.37	1.49	0.30	0.30
101. Raiskup-Wolf F	130	241	*	*	-1.2	3.87	0.48	-2.13	-0.27	1.27	1.27
114. Vinciguerra P	40	40	2.87	1.56	-1.31	3.90	0.62	-2.52	-0.10	0.76	0.76
116. Vinciguerra P	28	28	4.27	3.8	-0.47	1.27	0.24	-0.94	0.00	5.03	5.03
Fixed effects model					-0.54			-0.65	-0.44	100	
Random effects model					-0.54			-0.65	-0.44		100
Heterogeneity I^2	0										

*Value not reported in the study

QUANTICS

Figure M18: Change in Astigmatism grouped (diopters) at 24 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

There were only a few studies in this meta-analysis, all of which reported an improvement in Astigmatism. 97. Pinero DP was the only study not to report a significant effect.

There is very low heterogeneity between the studies and both the fixed effect and the random effects models estimate a significant improvement of astigmatism of -0.54 diopters.

QUANTICS

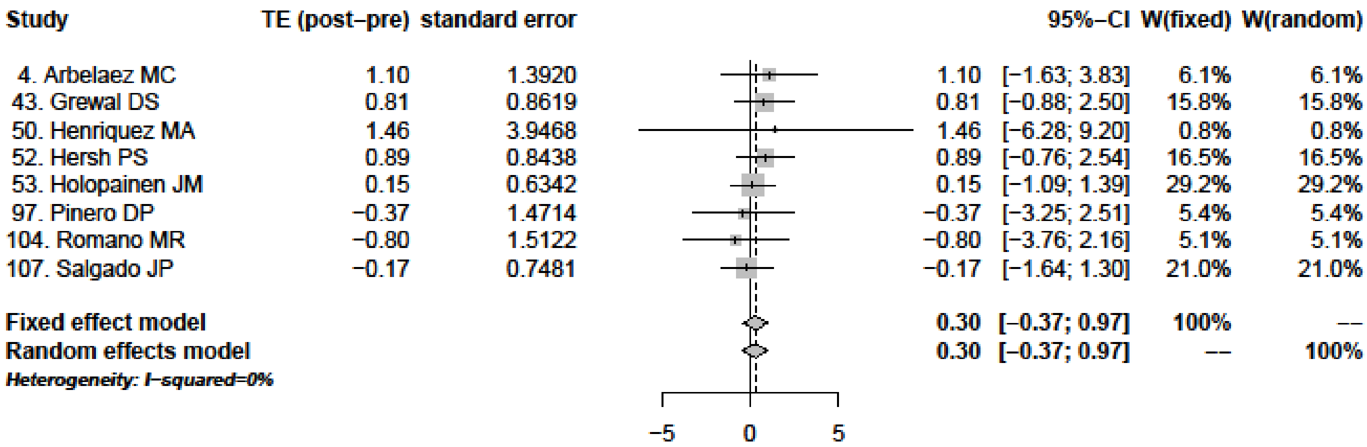
Table M19: Change in Spherical equivalent grouped (diopters) at 6 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	-3.84	-2.74	1.1	4.40	1.39	-1.63	3.83	6.07	6.07
43. Grewal DS	102	102	-6.32	-5.51	0.81	6.16	0.86	-0.88	2.50	15.83	15.83
50. Henriquez MA	10	10	-4.57	-3.11	1.46	12.48	3.95	-6.28	9.20	0.75	0.75
52. Hersh PS	58	71	-8.63	-7.74	0.89	5.03	0.84	-0.76	2.54	16.52	16.52
53. Holopainen JM	*	30	-1.37	-1.22	0.15	2.46	0.63	-1.09	1.39	29.24	29.24
97. Pinero DP	12	16	-2.3	-2.67	-0.37	4.16	1.47	-3.25	2.51	5.43	5.43
104. Romano MR	17	21	-4	-4.8	-0.8	4.90	1.51	-3.76	2.16	5.14	5.14
107. Salgado JP	15	22	-2.39	-2.56	-0.17	2.48	0.75	-1.64	1.30	21.01	21.01
Fixed effects model					0.30			-0.37	0.97	100	
Random effects model					0.30			-0.37	0.97		100
Heterogeneity I^2	0										

*Value not reported in the study

QUANTICS

Figure M19: Change in Spherical equivalent grouped (diopters) at 6 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

None of the studies in this meta-analysis reported significant changes in the spherical equivalent measure. Moreover, five studies reported an improvement while for the remaining three the results were worse after treatment. (Note that because spherical equivalent is reported as a negative value, a positive difference corresponds to an improvement.)

There is very low heterogeneity between the studies and both the fixed effect and the random effects models estimate a non-significant mean improvement.

Table M20: Change in Spherical equivalent grouped (diopters) at 12 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
4. Arbelaez MC	19	20	-3.84	-2.58	1.26	2.89	0.65	-0.01	2.53	1.38	6.83
43. Grewal DS	102	102	-6.32	0.2	6.52	84.94	8.41	-9.96	23.00	0.01	0.05
50. Henriquez MA	10	10	-4.57	-2.32	2.25	2.52	0.80	0.69	3.81	0.90	4.70
52. Hersh PS	58	71	-8.63	-7.77	0.86	5.35	0.90	-0.90	2.62	0.71	3.79
68. Kranitz K	22	25	-2.55	-1.48	1.07	2.83	0.80	-0.50	2.64	0.90	4.67
71. Kymionis GD	12	14	-5.6	-4.91	0.69	4.43	1.67	-2.59	3.97	0.21	1.15
97. Pinero DP	12	16	-2.3	-1.8	0.5	4.07	1.44	-2.32	3.32	0.28	1.54
106. Saffarian L	53	92	-1.06	*	0.18	0.79	0.08	0.02	0.34	84.72	44.83
107. Salgado JP	15	22	-2.39	-2.07	0.32	2.24	0.68	-1.00	1.64	1.26	6.32
115. Vinciguerra P	28	28	-6.73	-6.3	0.43	0.91	0.24	-0.05	0.91	9.64	26.12
Fixed effects model					0.25			0.11	0.40	100	
Random effects model					0.51			0.15	0.86		100
Heterogeneity I^2	26.07										

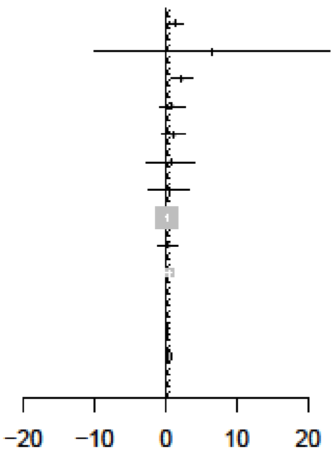
*Value not reported in the study

QUANTICS

Figure M20: Change in Spherical equivalent grouped (diopters) at 12 months

Study	TE (post−pre)	standard error	95%−CI	W(fixed)	W(random)
4. Arbelaez MC	1.26	0.6459	1.26 [−0.01; 2.53]	1.4%	6.8%
43. Grewal DS	6.52	8.4101	6.52 [−9.96; 23.00]	0.0%	0.0%
50. Henriquez MA	2.25	0.7975	2.25 [0.69; 3.81]	0.9%	4.7%
52. Hersh PS	0.86	0.8980	0.86 [−0.90; 2.62]	0.7%	3.8%
68. Kranitz K	1.07	0.8004	1.07 [−0.50; 2.64]	0.9%	4.7%
71. Kymionis GD	0.69	1.6737	0.69 [−2.59; 3.97]	0.2%	1.2%
97. Pinero DP	0.50	1.4402	0.50 [−2.32; 3.32]	0.3%	1.5%
106. Saffarian L	0.18	0.0824	0.18 [0.02; 0.34]	84.7%	44.8%
107. Salgado JP	0.32	0.6756	0.32 [−1.00; 1.64]	1.3%	6.3%
115. Vinciguerra P	0.43	0.2442	0.43 [−0.05; 0.91]	9.6%	26.1%
Fixed effect model			**0.25 [0.11; 0.40]**	**100%**	**--**
Random effects model			**0.51 [0.15; 0.86]**	**--**	**100%**

Heterogeneity: I−squared=26.1%



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

All studies reported a post-treatment improvement in the spherical equivalent measure although this only significant for two studies 50. Henriques MA and 106. Saffarian L.

There is low heterogeneity between the studies and hence both the fixed effects and the random effects model estimate a significant post-treatment increase of between 0.25 and 0.51 diopters.

QUANTICS

Table M21: Summary of meta-analysis results for change in topography

	Period	Astigmatism Grouped Mean Difference	95% lcl	95% ucl	Spherical equivalent grouped Mean Difference	95% lcl	95% ucl
Fixed effects model	6M	-0.25	-0.43	-0.07	0.30	-0.37	0.97
Random effects model		-0.45	-0.82	-0.09	0.30	-0.37	0.97
Heterogeneity I^2		51.42			0.00		
Fixed effects model	12M	-0.57	-0.66	-0.48	0.25	0.11	0.40
Random effects model		-0.68	-0.89	-0.47	0.51	0.15	0.86
Heterogeneity I^2		53.88			26.07		
Fixed effects model	24M	-0.54	-0.65	-0.44			
Random effects model		-0.54	-0.65	-0.44			
Heterogeneity I^2		0.00					

Red text endpoint not significant. **Shading** green: $I^2 < 50\%$; orange: $50\% \leq I^2 < 70\%$; red: $I^2 \geq 70\%$.

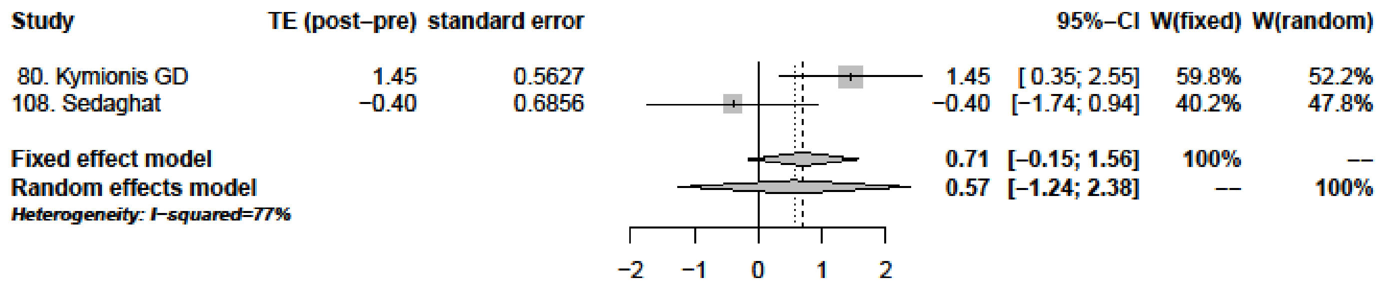
The meta-analyses reported in Table M21 show significant reductions in astigmatism when compared with baseline at 6, 12 and 24 months. For the spherical equivalent measure improvements were also reported but these were only significant at 12 months. (Note that as previously discussed in this section, because spherical equivalent is a negative measure an estimated positive difference corresponds to an improvement.)

5.4 IOP

Table M22: Change in IOP (mmHg) at 6 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
80. Kymionis GD	55	55	9.95	11.4	1.45	2.95	0.56	0.35	2.55	59.76	52.24
108. Sedaghat	51	56	10.47	10.07	-0.4	5.13	0.69	-1.74	0.94	40.24	47.76
Fixed effects model					0.71			-0.15	1.56	100	
Random effects model					0.57			-1.24	2.38		100
Heterogeneity I^2	77.02										

Figure M22: Change in IOP (mmHg) at 6 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

There is high heterogeneity between the two studies and both the fixed effect and the random effects models estimate a non-significant positive change in IOP.

QUANTICS

5.5 *CCT*

Table M23: Change in CCT (µm) at 6 months

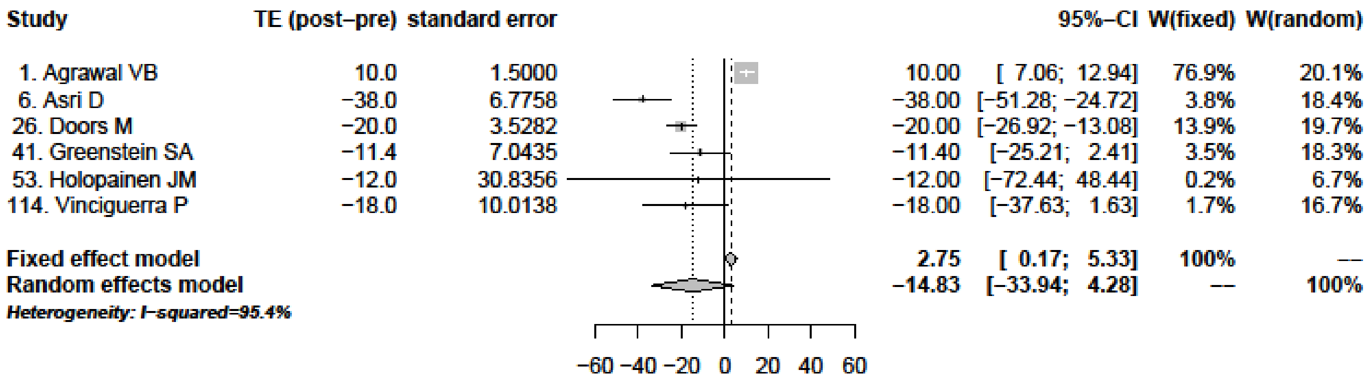
Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95 lcl	95 ucl	W fixed	W random
1. Agrawal VB	68	41	478	*	10	7.50	1.50	7.06	12.94	76.93	20.15
6. Asri D	142	142	482	444	-38	52.50	6.78	-51.28	-24.72	3.77	18.44
26. Doors M	29	29	495	*	-20	19.00	3.53	-26.92	-13.08	13.90	19.72
41. Greenstein SA	65	82	472	460.6	-11.4	45.10	7.04	-25.21	2.41	3.49	18.31
53. Holopainen JM	30	30	483	471	-12	168.89	30.84	-72.44	48.44	0.18	6.69
114. Vinciguerra P	40	40	489	471	-18	63.33	10.01	-37.63	1.63	1.73	16.68
Fixed effects model					2.75			0.17	5.33	100	
Random effects model					-14.83			-33.94	4.28		100
Heterogeneity I^2	95.44										

*Value not reported in the study

Note that the standard deviance for the 53. Holopainen JM study is very big when compared to the rest of the studies. In the 53. Holopainen JM study the p-value of the difference between the means was reported and this value was used to estimate the SD in table M23. As explained in section 4.1we have assumed p-values corresponded to one-sided tests (no information was provided on this). Had we assumed a one sided test the estimated SD would be smaller and more in line with the rest, see Appendix 2.

The 1. Agrawal VB study is unusual as it was the only study to report a positive mean difference. Note that in this case, a change from baseline and not values at baseline and post-treatment was reported. This also explains the small SD difference value which is more or less in line with that from the other study that reported changes from baseline (26. Doors M). As noted in section 4.1, where only the SD values at baseline and treatment are available, the SD of the difference is estimated assuming that the baseline and treatment values are independent. Because these results are from the same patients, this assumption is unlikely to hold hence and therefore we would expected the estimated SDs to be overestimated.

Figure M23: Change in CCT (µm) at 6 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

The majority of studies reported a negative change in CCT, although this was only significant for 6. Asri D and 26. Doors M. However the 1. Agrawal VB study reported a positive change in CCT which was found to be significant. Because this study has a very small standard error it is a very influential especially for the fixed effect model.

The heterogeneity between the studies is very high which explains the different results given by the fixed effect model, a significant increase in CCT, and the random effects model, a non-significant decrease in CCT. The fixed effect model is heavily reliant on the 1. Agrawal study which reported very different results from the other studies. Because the heterogeneity is so high, the random effects model would give more reliable results. Moreover, the meta-analysis results reported in Appendix 2 (which assume two-sided tests for the reported p-values) shows non-significant results for both the fixed and random effects models.

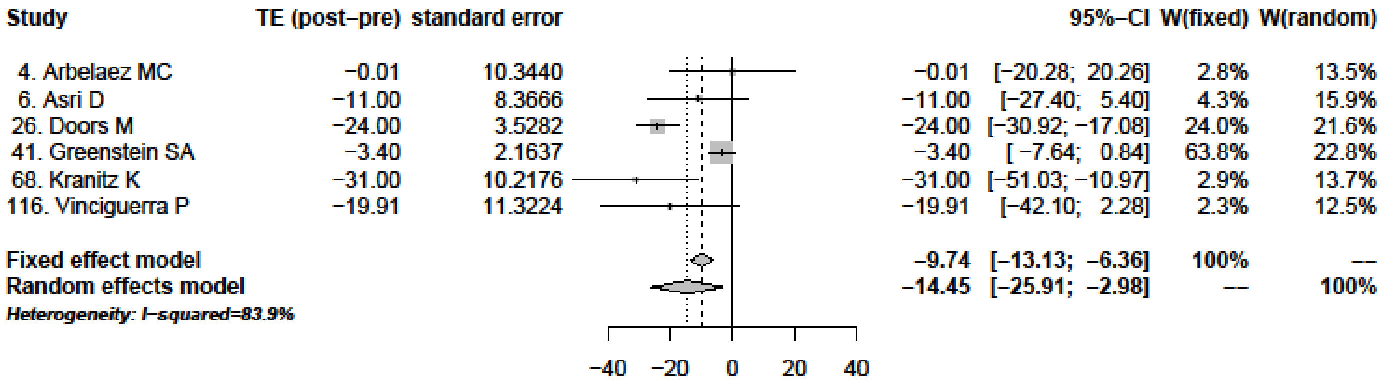
Table M24: Change in CCT (μm) at 12 months

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95 lcl	95 ucl	W fixed	W random
4. Arbelaez MC	19	20	463.96	463.95	-0.01	32.71	10.34	-20.28	20.26	2.79	13.55
6. Asri D	142	142	482	471	-11	55.57	8.37	-27.40	5.40	4.27	15.87
26. Doors M	29	29	495	*	-24	19.00	3.53	-30.92	-17.08	23.98	21.64
41. Greenstein SA	65	82	472	468.6	-3.4	19.59	2.16	-7.64	0.84	63.77	22.76
68. Kranitz K	22	25	472	441	-31	36.12	10.22	-51.03	-10.97	2.86	13.69
116. Vinciguerra P	28	28	490	470.09	-19.91	59.91	11.32	-42.10	2.28	2.33	12.50
Fixed effects model					-9.74			-13.13	-6.36	100	
Random effects model					-14.45			-25.91	-2.98		100
Heterogeneity I^2	83.85										

*Value not reported in the study

QUANTICS

Figure M24: Change in CCT (µm) at 12 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

All studies reported a decrease in CCT, although this was only significant for26. Doors M and 68. Krantitz K.

Although there is high heterogeneity between the studies, both the fixed effect and the random effects models estimate a significant decrease in CCT between -9.74 and -14.45.

QUANTICS

Table M25: Summary of meta-analysis results for change in CCT(µm)

	Period	Mean Difference	95% lcl	95% ucl
Fixed effects model	6M	2.75	0.17	5.33
Random effects model		-14.83	-33.94	4.28
Heterogeneity I^2		95.44		
Fixed effects model	12M	-9.74	-13.13	-6.36
Random effects model		-14.45	-25.91	-2.98
I^2		83.85		

Red text endpoint not significant. **Shading** green: $I^2 < 50\%$; orange: $50\% \leq I^2 < 70\%$; red: $I^2 \geq 70\%$.

The meta-analyses reported in Table M25 show reductions compared with baseline at 6 and 12 months (though as previously discussed the fixed effects model results at 6 months may be unreliable). However because the 95% upper confidence limit is positive for the 6 months meta-analysis, the results are only significant at 12 months.

QUANTICS

6. Results – comparisons between treated and control groups in RCTs

6.1 Meta-analysis results for Visual Acuity at 12 Months

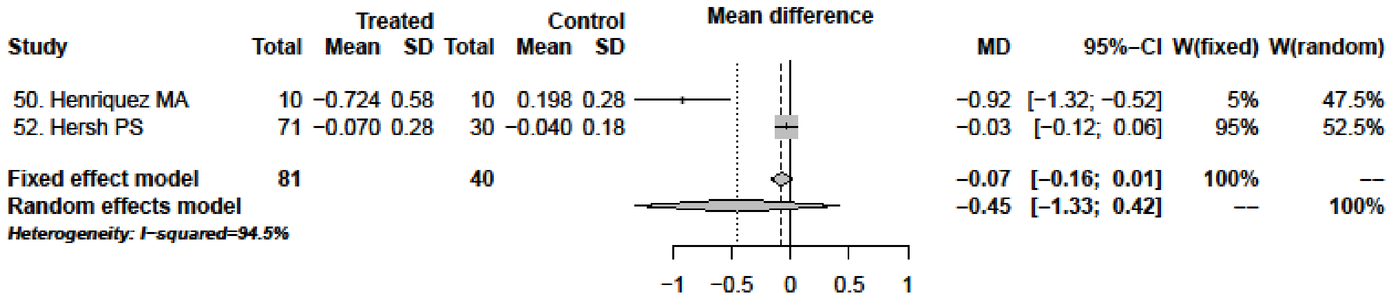
The four studies that were described as randomised, controlled trials only reported change in visual acuity at 12 months consistently and with enough data provided to allow meta-analysis.

Table M26: Difference between treated and control patients for change from baseline in uncorrected visual acuity (logMAR) at 12 months

Study	Patients n treated	Patients n control	Eyes N treated	Eyes N control	Mean Treated	SD Treated	Mean control	SD control	Mean Difference	95% lcl	95% ucl	W fixed	W random
50. Henriquez MA	10	10	10	10	-0.724	0.58	0.198	0.275	-0.92	-1.32	-0.52	5.0	47.5
52. Hersh PS	58	41	71	30	-0.07	0.28	-0.04	0.18	-0.03	-0.12	0.06	95.0	52.5
Fixed effects model									-0.07	-0.16	0.01	100	
Random effects model									-0.45	-1.33	0.42		100
Heterogeneity I^2	94.48												

QUANTICS

Figure M26: Difference between treated and control patients for change from baseline in uncorrected visual acuity (logMAR) at 12 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

Both studies reported an improvement in visual acuity. However this was only significant for the smaller 50. Henriquez MA study.

The heterogeneity between the studies is very high and this is reflected in the difference between the estimated mean differences between the fixed effect and the random effects model, -0.07 and -0.45. In both cases this improvement was not found to be significant.

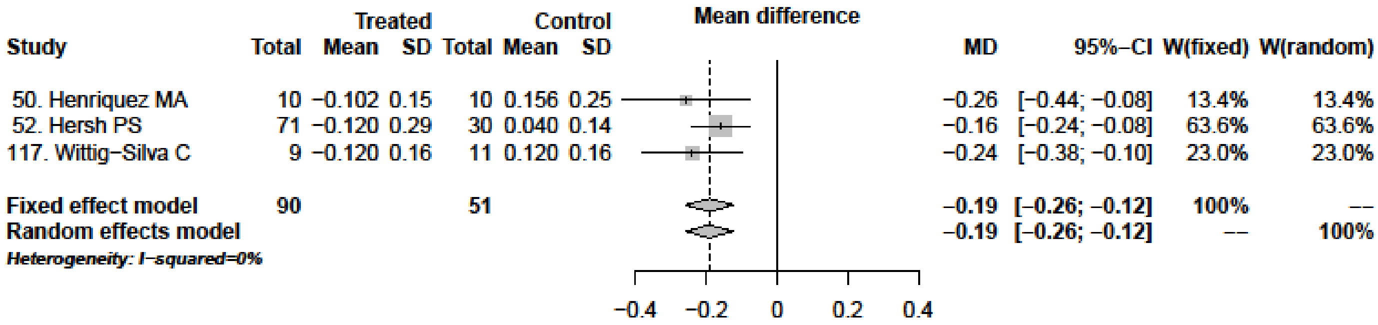
Table M27: Difference between treated and control patients for change from baseline in corrected visual acuity (logMAR) at 12 months

Study	Patients n treated	Patients n control	Eyes N treated	Eyes N control	Mean Treated	SD Treated	Mean control	SD control	Mean Difference	95% lcl	95% ucl	W fixed	W random
50. Henriquez MA	10	10	10	10	-0.10	0.15	0.16	0.25	-0.26	-0.44	-0.07	13.37	13.37
52. Hersh PS	58	41	71	30	-0.12	0.29	0.04	0.14	-0.16	-0.24	-0.08	63.62	63.62
117. Wittig-Silva C	49	*	9	11	-0.12	0.16	0.12	0.156	-0.24	-0.38	-0.10	23.01	23.01
Fixed effects model									-0.19	-0.26	-0.12	100	
Random effects model									-0.19	-0.26	-0.12		100
Heterogeneity I^2	0												

*Value not reported in the study

QUANTICS

Figure M27: Difference between treated and control patients for change from baseline in corrected visual acuity (logMAR) at 12 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

All studies reported a significant improvement in visual acuity.

The heterogeneity between the studies is very low and the estimated results for the fixed effect and the random effects model are equivalent. Both models estimated a significant improvement of about -0.19

Table M28: Summary of meta-analysis of RCTs: visual acuity (logMAR) at 12 months

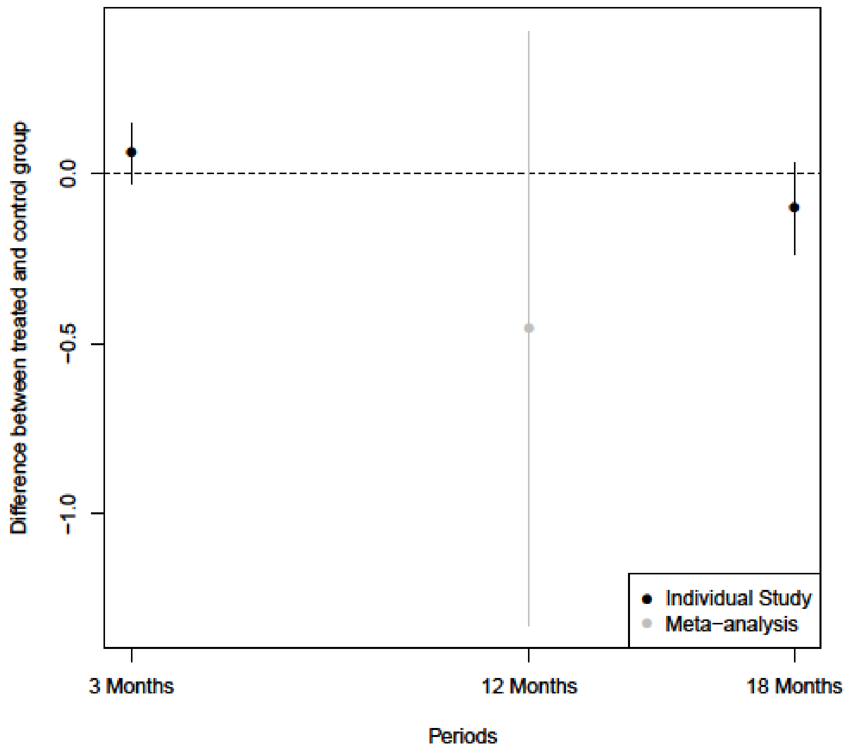
		Corrected			Uncorrected		
	Period	Mean Difference	95% lcl	95% ucl	Mean Difference	95% lcl	95% ucl
Fixed effects model		-0.19	-0.26	-0.12	-0.07	-0.16	0.01
Random effects model	12M	-0.19	-0.26	-0.12	-0.45	-1.33	0.42
Heterogeneity I^2		0.00			94.48		

Red text endpoint not significant. **Shading** green: $I^2 < 50\%$; orange: $50\% \leq I^2 < 70\%$; red: I2≥ 70%.

The meta-analyses reported in Table M28 show reductions between the treated and control groups for corrected visual at 12 months. However this difference was only found to be significant for corrected visual acuity.

6.2 Results for the RCT studies for Visual Acuity over time

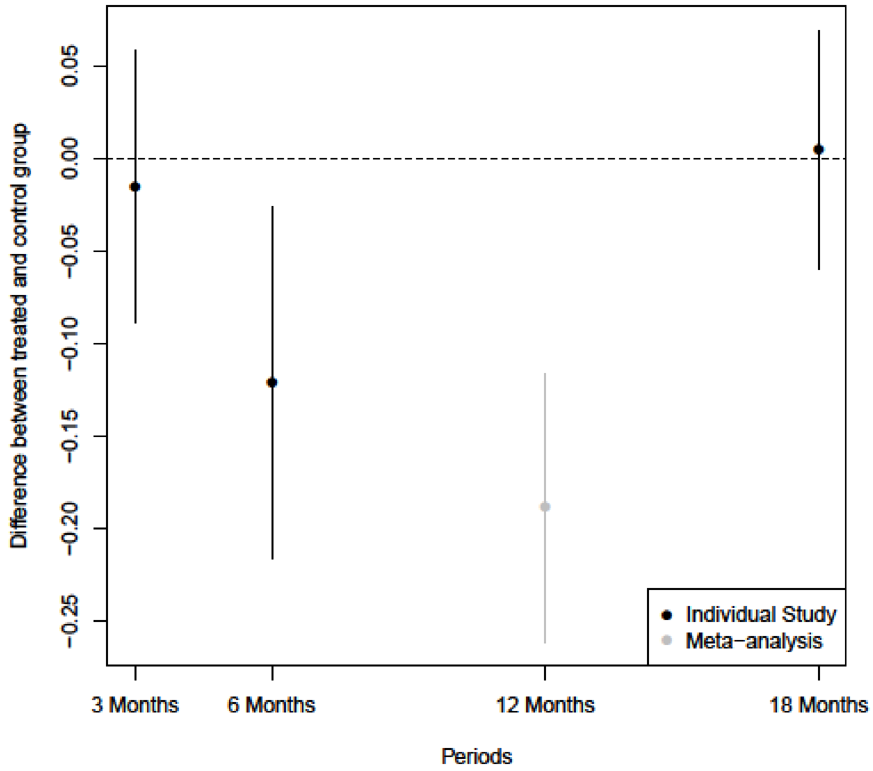
Figure M29: Change in uncorrected visual acuity over time: data from RCTs



As discussed in section 6.1meta-analysis results were only available at 12 months (highlighted in grey in Figure M29. The results at 3 months are from the 117. Wittig-Silva study and those at 18 months from the 96. O'Brart study.

No significant differences were found at any of the time-points.

Figure M30: Change in corrected visual acuity over time: data from RCTs



As discussed in section 6.1, meta-analysis results were only available at 12 months (highlighted in grey in Figure M30). The results at 3 and 6 months are from the 117. Wittig-Silva study and those at 18 months from the 96. O'Brart study.

The difference in corrected visual acuity between the treated and control groups seems to be increasing between 3 and 12 months. However, these differences are only significant at 6 and 12 months. The results at 18 months do not confirm the improvement of corrected visual acuity overtime. These were reported in the 96. O'Brart study and show no change between the control and treatment groups.

Both the results in Figures M29 and M30 are summarised in table M30.

Table M30: Summary of overtime results for RCTs: visual acuity (logMAR)

	Corrected			Uncorrected		
Period	Mean Difference	95% lcl	95% ucl	Mean Difference	95% lcl	95% ucl
3 Months	-0.02	-0.09	0.06	0.06	-0.03	0.15
6 Months	-0.12	-0.22	-0.03	-0.45	-1.33	0.42
12 Months	-0.19	-0.26	-0.12			
18 Months	0.005	-0.06	0.07	-0.10	-0.24	0.03

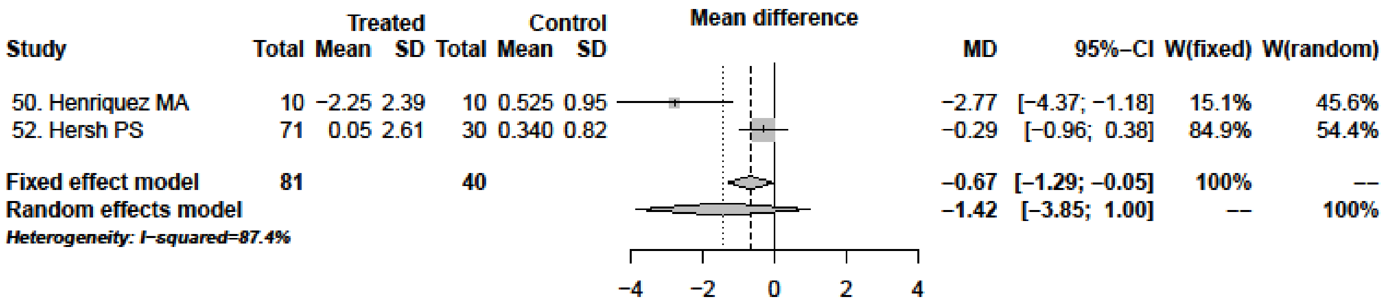
6.3 Meta-analysis results for Refraction and Astigmatism at 12 Months

Of the four studies that were described as randomised, controlled trials only two reported change in refraction and astigmatism at 12 months consistently and with enough data provided to allow meta-analysis.

Table M31: Difference between treated and control patients for change from baseline in astigmatism grouped (diopters) at 12 months

Study	Patients n treated	Patients n control	Eyes N treated	Eyes N control	Mean Treated	SD Treated	Mean control	SD control	Mean Difference	95% lcl	95% ucl	W fixed	W random
50. Henriquez MA	10	10	10	10	-2.25	2.39	0.525	0.953	-2.78	-4.37	-1.18	15.12	45.59
52. Hersh PS	58	41	71	30	0.05	2.61	0.34	0.82	-0.29	-0.96	0.38	84.88	54.41
Fixed effects model									-0.67	-1.29	-0.05	100	
Random effects model									-1.42	-3.85	1.00		100
Heterogeneity I^2	87.35												

Figure M31: Difference between treated and control patients for change from baseline in astigmatism grouped (diopters) at 12 months



The size of the grey box is proportional to the weight of the study under the fixed effect model: W(fixed).
Dashed line: mean fixed effect model. Dotted line: mean random effects model. Grey diamonds: confidence intervals for meta-analysis models.

QUANTICS

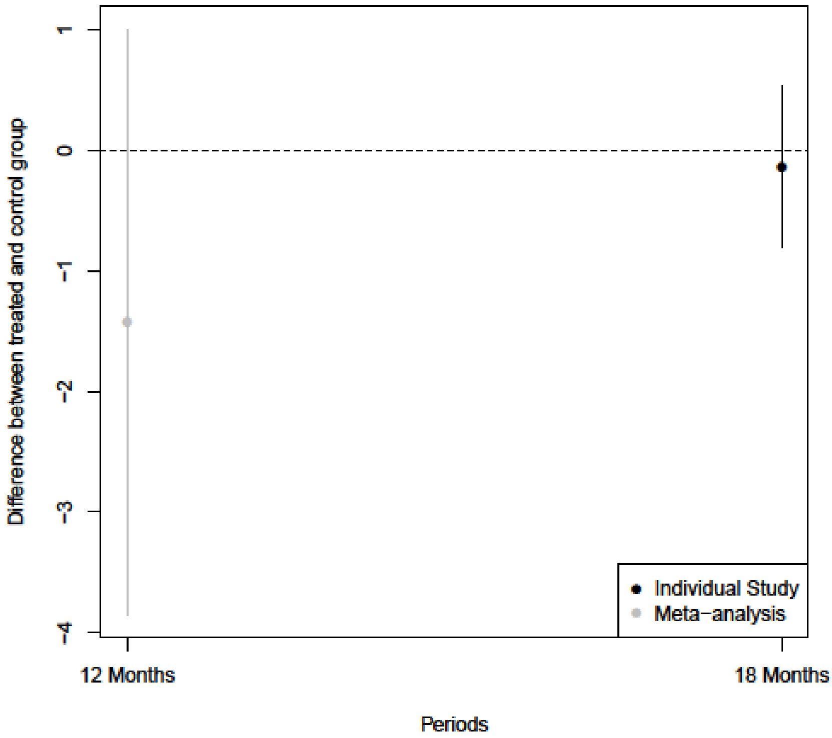
The 50. Henriquez MA study reported an improvement from baseline for the treatment group whereas results were worse for the control. When comparing the two groups there was a significant improvement for the treated group.

The 52. Hersh PS study reported very different results. Both groups showed an increased in astigmatism from baseline. However this increase was greater for the control group than for the treated group. The difference between the two groups was not found to be significant.

The heterogeneity between the studies is very high (for the reasons stated above). Both the fixed and random effects models estimate an improvement for the treated group with respect to the control group, although this is only significant for the fixed effects model. Because heterogeneity is so high the results for the random effects model are more reliable than those from the fixed effects model.

6.4 Results for the RCT studies for Refraction and Astigmatism over time

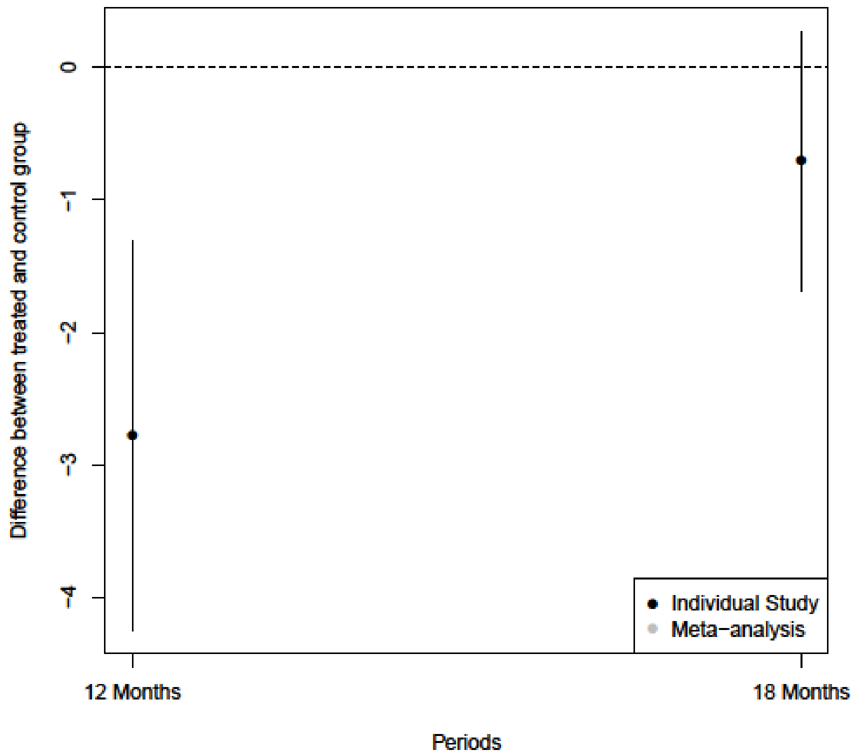
Figure M32: Change in Astigmatism grouped over time: data from RCTs



As discussed in section 6.3 meta-analysis results were only available at 12 months (highlighted in grey in Figure M32). The results at 18 months are from the 96. O'Brart study.

No significant differences were found at any of the time-points.

Figure M33: Change in spherical equivalent grouped over time: data from RCTs



Meta-analysis was not possible at any of the time-points. The results at 12 months are from the 50. Henriquez study whereas those at 18 months are from the 96. O'Brart study. In both cases there was an improvement when comparing the treated and control groups although this was only significant at 12 months for the 50. Henriquez study.

Both the results in Figures M32 and M33 are summarised in table M33.

Table M33: Summary of overtime results for RCTs: refraction and astigmatism

	Astigmatism grouped			Spherical equivalent grouped		
Period	Mean Difference	95% lcl	95% ucl	Mean Difference	95% lcl	95% ucl
12 Months	-1.42	-3.85	1.00	-2.78	-4.24	-1.31
18 Months	-0.140	-0.81	0.53	-0.71	-1.69	0.27

7. Conclusions

Two types of meta-analysis are reported. Firstly we analysed changes from baseline for topography, visual acuity, refraction and astigmatism, IOP (intra-ocular pressure) and CCT (central corneal thickness) for treated patients only, as few randomized control trials (RCT) were found. Secondly we looked at changes between the control and treated groups. However this was only possible for visual acuity and refraction and astigmatism at 12 months.

7.1 Change from Baseline

Below is a summary of the meta-analysis results for differences between post-treatment and baseline values for treated patients for each one of the variables under study.

- **Visual Acuity**: significant improvements for corrected and uncorrected visual acuity at 6, 12 and 24 months. The improvements on the logMAR scale were of around -0.15 for uncorrected visual acuity and of around -0.10 for corrected visual acuity across time-points. See section 5.1.
- **Topography**: significant improvements for max K at 6, 12 and 24 months, these improvements were of around -0.8D at 6 months and around -1.0D at 12 and 24 months respectively. For min K and mean K meta-analysis was only done at 6 and 12 months (as there was less data available for these two measurements). The meta-analysis results were only significant at 12 months; average changes of around -1.0D were found for mean K and around -0.7D for min K. See section 5.2.
- **Refraction and Astigmatism**: significant improvements for astigmatism at 6, 12 and 24 months, of around -0.4D at 6 months and around -0.6D at 12 and 24 months. For spherical equivalent, meta-analysis was only done at 6 and 12 months. The meta-analysis results were only significant at 12 months and these show a reduction of between 0.25 and 0.5D. See section 5.3.
- **IOP**: following clinical advice only two studies were included and the meta-analysis was done at 12 months only. No significant differences were found. See section 5.3
- **CCT**: only six studies were used for the meta-analysis and this was done at 6 and 12 months only. A significant decrease of between -10μm and -14μm in CCT was found at 12 months. No significant difference was found for the 6 months meta-analysis. The results for this meta-

analysis are very heavily influenced by the Agrawal study which reported unusual results when compared to the other studies. See section 5.5.

7.2 Change between Treated and Control Groups (RCT)

Due to lack of data meta-analysis was only done for visual acuity (corrected and uncorrected) and the grouped astigmatism measured both at 12 months.

- **Visual Acuity:** Only three studies contributed to the meta-analysis: 50. Henriquez, 52. Hersh and 117. Wittig-Silva. The difference between the treatment and control groups was analysed; for both groups the difference in visual acuity post-treatment and at baseline was used. No significant difference was found between the treatment and control groups for uncorrected visual acuity, whereas a significant difference of around -0.20 (logMAR) was found for corrected visual acuity. See section 6.1.

  We have also looked at the differences between treatment and control groups overtime, see section 6.2. Where no meta-analysis results were available results from individual studies were used instead. Results from the 96. O'Brart study were also used at 18 months. No significant differences were found for uncorrected visual acuity. For corrected visual acuity there seemed to be an improvement overtime, as the difference between the treatment and control groups was not significant at 3 months and significant at both 6 and 12 months (-0.12 and -0.19 (logMAR) respectively). However 96. O'Brart reported non-significant differences at 18 months between the treatment and control groups.

- **Refraction and Astigmatism:** Only two studies contributed to the meta-analysis: 50. Henriquez and 52. Hersh and the difference between the treatment and control groups was analysed (for both groups the difference in astigmatism post-treatment and at baseline was used). No significant difference was found between the treatment and control groups. See section 6.3.

  We have also looked at the differences between treatment and control groups overtime, see section 6.4. Where no meta-analysis results were available results from individual studies were used instead. In addition to astigmatism, the spherical equivalent measured was also analysed, as 50. Henriquez reported results for this measure at 12 months and 96. O'Brart at 18 months. No significant differences were found for astigmatism. For the spherical equivalent measured 50. Henriquez reported a significant difference between the two groups at 12 months.

However 96. O'Brart reported non-significant differences at 18 months between the treatment and control groups.

8. *Bibliography*

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3. *Meta-analysis of skewed data: Combining results reported on log-transformed or raw scales.* **Higgins, Julian P. T., White, Ian R. and Anzures-Cabrera, Judith.** s.l. : Statistics in Medicine, 2008, Vol. 27.

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5. **Borenstein, Michael, et al., et al.** *Introduction to Meta-Analysis.* s.l. : John Wiley & Sons, 2009.

Appendix 1: List of 46 studies with unique reference number

Study Reference	Author	Title	Country of research	Year of research
1	Agrawal VB	Corneal collagen cross-linking with riboflavin and ultraviolet-A light for keratoconus: Results in Indian eyes	India	NR
4	Arbelaez MC	Collagen cross linking with riboflavin and ultraviolet A light in keratoconus	Oman	
6	Asri D	Corneal collagen crosslinking in progressive keratoconus: Multicenter results from the French National Reference Center for Keratoconus	France	NR
7	Braun E	Riboflavin/Ultraviolet A-induced collagen cross-linking in the management of keratoconus	USA (LOA)	2005
10	Caporossi A	Long-term results of riboflavin ultraviolet A corneal cross-linking for keratoconus in Italy: The Siena Eye Cross Study	Italy	
11	Caporossi A	Age-related long-term functional results after riboflavin UVA corneal cross linking	Italy	
14	Charters L	Study: PRK, CXL for keratoconus	Argentina	2012
16	Coskunseven	Contralateral eye study of corneal collagen cross-linking with riboflavin and UVA irradiation in patients with keratoconus	Turkey	2009a
20	Croxatto JO	Sequential in vivo confocal microscopy study of corneal wound healing after cross-linking in patients with keratoconus	Argentina	2010
26	Doors M	Use of anterior segment optical coherence tomography to study corneal changes after collagen cross-linking	Netherlands	2009
33	Gkika M	Evaluation of corneal hysteresis and corneal resistance factor after corneal cross-linking for karatoconus	Greece	2012
34	Goldich Y	Safety of corneal collagen cross-linking with UV-A and riboflavin in progressive keratoconus	Israel	2010
35	Goldich Y	Clinical and Corneal Biomechanical Changes after collagen cross linking with riboflavin and UV irradiation in pateints with progressive keratocononus: Results after 2 years of follow-up	Israel	2012
38	Greenstein SA	Effect of topographic cone location on outcomes of corneal collagen cross linking for keratoconus and corneal ectasia	USA	
37	Greenstein SA	In Vivo Biomechanical Changes After Corneal Collagen Cross-linking for Keratoconus and Corneal Ectasia: 1 Year Analysis of a Randomized, Controlled, Clinical Trial	USA	
41	Greenstein SA	Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one year results	USA	
8	Brooks NO	Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia	USA	2012
52	Hersh PS	Corneal collagen crosslinking for keratoconus and corneal extasia: One year results.	USA	2011
43	Grewal DS	Corneal collagen crosslinking using riboflavin and ultraviolet-A light for keratoconus	India	2009
47	Hafezi F	Corneal collagen crosslinking with riboflavin and ultraviolet A to treat induced keratectasia after laser in situ keratomileusis	Switzerland and Greece	2007
49	Hasson M	Corneal cross-linking improves quality of life, refraction in patients with keratoconus	USA	
50	Henriquez MA	Riboflavin/ultraviolet A corneal collagen cross-linking for the treatment of keratoconus: Visual outcomes and Scheimpflug analysis	Peru	2011
53	Holopainen JM	Transient corneal thinning in eyes undergoing corneal cross-linking	Finland	2011
64	Koller T	Flattening of the cornea after collagen crosslinking for keratoconus	Switzerland	
64	Koller T	Flattening of the cornea after collagen crosslinking for keratoconus	Switzerland	2011
68	Kranitz K	Corneal changes in progressive keratoconus after corss-linking assessed by scheimpflug camera	Hungary	
80	Kymionis GD	Intraoperative pachymetric measurements during corneal collagen cross linking with riboflavin and ultraviolet A irradiation	Greece	
71	Kymionis GD	Corneal collagen crosslinking with riboflavin and ultraviolet A irradiation in patients with thin corneas	Greece	
84	Li G	Corneal collagen crosslinking for corneal ectasia of post-LASIK: one year results.	China	2010
87	Mazzotta	Morphological and functional correlations in riboflavin UVA corneal collagen cross-linking for keratoconus	Italy	
89	Mazzotta C	Stromal haze after combined riboflavin-UVA corneal collagen cross-linking in keratoconus: in vivo confocal microscopic evaluation	Italy	
90	Mazzotta C	Treatment of progressive keratoconus by riboflavin UVA induced crosslinking of corneal collagen	Italy	
96	O'Brart DP	A randomised, prospective study to investigate the efficacy of rioboflavin/ultraviolet A (370nm) corneal collagen cross-linkage to halt the progression of keratoconus	UK	
97	Pinero DP	Vectorial astigmatic changes after corneal collagen crosslinking in keratoconic corneas previously treated with intracorneal ring segments: a prelimanary study	Spain	
100	Raiskup F	Permanent corneal haze after riboflavin-UVA-induced cross-linking in keratoconus	Germany	2009
101	Raiskup-Wolf F	Collagen crosslinking with riboflavin and ultraviolet-A light in keratoconus: Long term results.	Germany	2008
104	Romano MR	No retinal morphology changes after use of riboflavin and long-wavelength ultraviolet light for treatment of keratoconus	Italy	2012
106	Saffarian L	Corneal crosslinking for keratoconus in Iranian patients: Outcomes at 1 year following treatment	Iran	2010
107	Salgado JP	Corneal collagen crosslinking in post-LASIK keratectasia	Germany (LOA)	2010
108	Sedaghat	Biomechanical parameters of the cornea after collagen crosslinking measured by waveform analysis	Iran	
114	Vinciguerra P	Two Year corneal cross linking results in patients younger than 18 years with documented progressive keratoconus	Italy and Switzerland	
116	Vinciguerra P	Intraoperative and postoperative effects of corneal collagen cross-linking on progressive keratoconus	Italy	
115	Vinciguerra P	Refractive, Topographic, Tomographic, and Aberrometric Analysis of Keratoconic Eyes Undergoing Corneal Cross-Linking	Italy	
117	Wittig-Silva C	A randomised controlled trial of corneal collagen cross-linking in progressive keratoconus: Preliminary results	Australia	2008
118	Wollensak G	Riboflavin/ultraviolet-A-induced collagen crosslinking for the treatment or keratoconus	Germany	2003

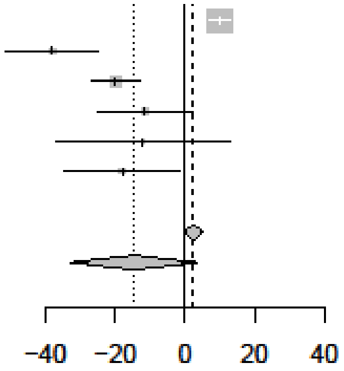
Appendix 2: Meta-analysis for Change in CCT (μm) at 6 months assuming two-sided tests

Study	Patients n	Eyes N	Mean Baseline	Mean Treatment	Mean Difference	SD Difference	SE difference	95% lcl	95% ucl	W fixed	W random
1. Agrawal VB	68	41	478	*	10	7.50	1.50	7.06	12.94	75.73	18.50
6. Asri D	142	142	482	444	-38	52.50	6.78	-51.28	-24.72	3.71	16.88
26. Doors M	29	29	495	*	-20	19.00	3.53	-26.92	-13.08	13.69	18.09
41. Greenstein SA	65	82	472	460.6	-11.4	45.10	7.04	-25.21	2.41	3.43	16.75
53. Holopainen JM	30	30	483	471	-12	69.19	12.63	-36.76	12.76	1.07	13.74
114. Vinciguerra P	40	40	489	471	-18	53.58	8.47	-34.60	-1.40	2.37	16.04
Fixed effects model					2.48			-0.08	5.04	100	
Random effects model					-14.63			-32.60	3.35		100
Heterogeneity I^2	95.55										

*Value not reported in the study

Study	TE (post–pre)	standard error		95%–CI	W(fixed)	W(random)
1. Agrawal VB	10.0	1.5000	10.00	[7.06; 12.94]	75.7%	18.5%
6. Asri D	−38.0	6.7758	−38.00	[−51.28; −24.72]	3.7%	16.9%
26. Doors M	−20.0	3.5282	−20.00	[−26.92; −13.08]	13.7%	18.1%
41. Greenstein SA	−11.4	7.0435	−11.40	[−25.21; 2.41]	3.4%	16.8%
53. Holopainen JM	−12.0	12.6326	−12.00	[−36.76; 12.76]	1.1%	13.7%
114. Vinciguerra P	−18.0	8.4716	−18.00	[−34.60; −1.40]	2.4%	16.0%
Fixed effect model			**2.48**	**[−0.08; 5.04]**	**100%**	**--**
Random effects model			**−14.63**	**[−32.60; 3.35]**	**--**	**100%**

Heterogeneity: I−squared=95.6%



QUANTICS