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Photochemical Corneal Collagen Cross-Linkage Using Riboflavin and Ultraviolet A for Keratoconus: A Systematic Review

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Annex A (separate document by Quantics Consulting Limited)
Photochemical Corneal Collagen Cross-Linkage using Riboflavin and Ultraviolet A for Management of Keratoconus.

Executive Summary

1. BACKGROUND

The systematic review is of two groups of patients, namely those with a diagnosis of keratoconus or keratectasia.

Keratoconus is a corneal thinning disorder occurring when the normally round dome-shaped cornea, the clear tissue covering the front of the eye, progressively changes shape to a conical bulge. Thinning occurs primarily in the stroma layers and one potential explanation for this a defect in the collagen process.

Keratoconus has a prevalence of under 0.05% (1 in 2,000) of the population, with an earlier onset than most chronic eye diseases with a patient median age of 25 years. Those with the disease suffer a loss in visual acuity, making tasks such as driving, reading and screen work difficult.

Keratoconus can also be secondary, resulting from an infrequent but serious complication of laser-assisted *in situ* keratomileusis (LASIK) surgery, and is then called keratectasia. If the cornea's structure is weakened during LASIK surgery, it can bulge forward in an irregular fashion, causing increasing astigmatism and distorted vision. This cannot be corrected with spectacles, contact lenses, or a LASIK enhancement procedure. Patients with thin corneas prior to LASIK have a higher risk of developing keratectasia. The treatment pathway is similar to that for keratoconus.

Diagnosis of keratoconus is often not straightforward and typically requires a review of family history, looking for clinical signs, and use of various instruments to measure corneal topography and central corneal thickness. The management of keratoconus depends on the stage of the disease. The stage can be identified using the Amsler-Krumeich classification which has 4 stages from mild (grade I) to severe (grade IV).

In mild to moderate keratoconus, clinical management to correct visual acuity is by spectacles or contact lenses. With disease progression, rigid gas permeable contact lenses may be fitted or corneal ring segment inserts used. However, if the corneal shape deteriorates further some form of corneal surgery may be required, including deep lamellar keratoplasty or penetrating keratoplasty for severe progressive keratoconus.

Prior to introduction of corneal collagen cross-linkage (CXL), no interventions were available to arrest or slow disease progression, with corneal transplantation required in up to 21% of keratoconic eyes. Visual acuity may not be fully restored after transplant and the disease may recur, requiring subsequent interventions.

CXL using riboflavin and ultraviolet A (UV A) radiation was piloted on patients in 2003. It increases corneal biomechanical stiffness thereby strengthening and stabilising the cornea. This is achieved by increasing the number of 'anchors' that bond collagen fibres together. The aim is to stop disease progression.

With 'epithelium-off cross-linkage', the epithelium is removed with a blunt spatula or laser. Riboflavin eye drops are applied to the corneal surface 5 minutes before the procedure to enable penetration into the corneal tissue and then every 3 to 5 minutes during the procedure. The corneal surface is exposed to the UV A radiation, usually for up to 30 minutes. Postoperatively, topical antibiotics and anti-inflammatory drops will normally be prescribed with topical steroids if necessary. In some cases, a bandage contact lens may

also be used for a few days. The outpatient procedure takes 60 to 90 minutes in most cases.

With transepithelial corneal cross-linkage (epithelium-on) the corneal epithelial surface is left intact, which requires a longer riboflavin loading time but may reduce the risk of infection.

CXL can be used in conjunction with various techniques designed to improve visual acuity. Adjunct procedures include:

- A range of corneal implants, also known as intracorneal ring segments (ICRS);
- Topography-guided and other forms of photorefractive keratectomy (PRK), a form of laser ablation;
- Phakic intraocular lens (PIOL).

The most common complications reported after the procedure are stromal haze, which usually resolves, and pain. More serious events include infection, corneal melting, perforation and ulceration, and stromal scarring.

2. OBJECTIVE

The objective of this systematic review is to examine evidence for the efficacy and safety of CXL using riboflavin and ultraviolet A for keratoconus and keratectasia, alone or in combination with interventions designed to improve visual acuity. These combination interventions are referred to as 'CXL-Plus'.

The evidence will allow the Interventional Procedures Advisory Committee to reassess guidance on the procedure. This was originally issued in November 2009 by the National Institute for Health and Clinical Excellence (NICE). This recommended that, given inadequate evidence, the procedure should only be used with special arrangements for clinical governance, consent and audit or research. Subsequently, new evidence has been published.

3. LITERATURE SEARCH AND SYNTHESIS OF PAPERS

The systematic review adopted a search strategy designed to identify all relevant published, unpublished and grey literature. A date limit of 2000 to 31 October 2012 was applied. The search returned 1,747 abstracts, after removal of duplicates. Inclusion criteria were:

- English-language reports and human studies;
- Patients with keratoconus or keratectasia;
- Reports with interventions using photochemical corneal collagen cross-linkage using riboflavin and ultraviolet alone, or in combination or sequence with other treatments;
- Original reports with defined study methodology;
- Reports including standardised measurements on outcome events such as technical access, safety, efficacy, durability, vision, quality of life or patient satisfaction;
- Systematic reviews, meta-analyses, randomised controlled trials, observational studies, retrospective analyses, case series, case studies, letters, comments and conference abstracts.

These eligibility criteria were applied to abstracts and titles to inform provisional study selection. Two researchers reviewed the retrieved abstracts and titles, for those with no abstract, and made their selections independently. Differences were reconciled by mutual

agreement. Two hundred and fifteen papers were selected by agreement, 17 were in a foreign language and not retrieved, and a further 8 papers could not be obtained. The remaining 190 papers were retrieved.

The inclusion and exclusion criteria were applied to the full papers to judge which should be included in this study. Seventy-one papers on efficacy and 26 on adverse events were selected for full data extraction, with 93 papers excluded. Of these, 19 were efficacy studies with fewer than 10 patients or less than 6 months follow-up; these were partially extracted and reported as an appendix, but not considered in the analysis. Full data extraction was undertaken on the 71 efficacy papers and a more limited extraction on the 26 papers on safety events.

Formal meta-analyses were undertaken on publications reporting results using the epithelium-off procedure. Extracted data showing effect sizes, study end points and time periods were reviewed and any inconsistencies or unexpected results checked by going back to original papers. The relevant end points agreed with NICE were:

- Change in visual acuity;
- Change in topography;
- Change in refraction and astigmatism;
- Change in intraocular pressure;
- Change in central corneal thickness.

Where sufficient data were available across common time periods they were synthesised using meta-analysis based on both random effects and fixed effects models. Heterogeneity was identified by using the I^2 statistic. Meta-analysis results were reported using forest plots.

For CXL-Plus interventions and the transepithelial corneal cross-linkage (epithelium-on) procedure, a narrative synthesis of the same end points was undertaken.

4. RESULTS

4.1 Evidence on epithelium-off CXL

Identified evidence comprised 49 papers on the efficacy of epithelium-off CXL and 26 on the safety of epithelium-off CXL. Of the 49 efficacy papers, 8 were randomised controlled trials (RCTs), reporting 4 unique studies with the main comparator being fellow-eyes; the exception was an Australian RCT which did randomise eyes matched for disease status. Only preliminary results have been reported from that study.

The remaining papers reported changes before and after the procedure, which limits the ability to draw conclusions on the causal nature of the effect presented. However, given the disease is progressive, evidence of halting progression or indeed reversing it is supportive of a beneficial effect.

Of the non-RCT papers, the majority (25) were prospective case series, usually with well-defined inclusion criteria and trial design. However, few papers reported drop-out rates or reasons for them, thereby limiting the strength of the evidence.

Seven of the remaining papers were retrospective reviews, often using patient records as the data source. Using such data has strengths including that of reflecting actual outcomes in settings which may be similar to those of the NHS and are, thus, representative of clinical practice. However, there was concern about potential for bias in patient selection.

Almost 60% of papers were set in European tertiary centres, with a further 15% set in the USA; all sites undertook very similar CXL procedures. These settings are anticipated to be comparable to NHS settings. Two papers explicitly excluded patients with Amsler-Krumeich scale grade IV; otherwise the main inclusion criterion was progressive keratoconus. Thuse, there were no major concerns about the external validity of the results to a UK setting.

Overall, 39 papers were graded as very low evidence, six as low and four moderate. Those graded moderate reported on 4 RCTs but, as noted, these do not provide comparative evidence in eyes with progressive keratoconus.

Summary of findings from epithelium-off CXL papers

As noted, meta-analyses were conducted when sufficient data were reported for consistent end-points and time periods. To enable results for papers which could not be formally synthesised to be captured, a simple arithmetic mean across time periods was calculated. The results were grouped into consistent end points and by time period: 6, 12 and 24 months. Papers reporting at 9 months were included under the 12-month period and those reporting at 18 months under the 24-month period to avoid removing evidence. Papers reporting end points where the units measured were unclear or used measures which could not be aggregated with others were not included. The remaining results were used to calculate the mean value of the change reported for each end point/time period combination.

These assumptions and methodology were adopted for all parameters. The estimates are not offered as a precise estimate of the change in measures as a result of CXL, rather they give an indication of the size effect and its direction. They are intended to display the trend in evidence for each group of similar parameters but do no more than that.

Many meta-analyses displayed moderate to high heterogeneity across papers, giving wide confidence intervals, which suggests the studies were not consistent in their conduct.

Topography

Due to a lack of data, no meta-analyses of change between treated and control groups could be undertaken for measures of topography. Meta-analysis results for differences between post-treatment and baseline values for treated patients reported significant improvements for Max K (maximum keratometry) at 6, 12 and 24 months; these improvements were -0.8 dioptres (D) at 6 months and around -1.0 D at 12 and 24 months. For Min (minimum) K and mean K, meta-analysis was only undertaken at 6 and 12 months. Meta-analysis results were only significant at 12 months; average changes of around -1.0 D and -0.7 D were found for mean K and Min K, respectively.

The number of papers synthesized was for:

- Max K: 10, 18 and 6 papers at 6, 12 and 24 months, respectively;
- Min K: 4 and 8 papers at 6 and 12 months, respectively;
- Mean K: 7 and 12 papers at 6 and 12 months, respectively.

In total, 38 papers reported 104 comparable measures of topography over the three time periods, with 41 (38%) reporting statistically significant improvements in K values. The improvement increased over time with 4 papers reporting statistically significant differences at 12 months but not at 6 months. Of the 8 papers reporting data at 12 and 24 months, the 24-month values showed an improvement or no change on the 12-month values in all cases but one. One paper reporting a longer follow-up showed the improvement continued into year 3 and was then maintained to year 6. However, the number of patients lost to follow-up was large, thereby limiting the weight attributed to these results.

No precise estimate of the benefit across all papers is possible. However, a simple arithmetic mean calculated from the 104 measures gave an improvement of 1.5 D for Max K, 1.4 D for mean K and 1.1 D for Min K at 12 months, which were slightly higher than the meta-analyses results.

Visual acuity

Due to a lack of data, a meta-analysis of change between treated and control groups was only undertaken for visual acuity at 12 months. Only 3 studies contributed to the meta-analysis of corrected visual acuity and only two to the meta-analysis of uncorrected visual acuity. No significant difference was found between treatment and control groups for uncorrected visual acuity, whereas a significant difference of around -0.20 (LogMAR) was found for corrected visual acuity.

Differences between treatment and control groups over time were not significant for uncorrected visual acuity. For corrected visual acuity, there seemed to be an improvement over time, as the difference between treatment and control groups was not significant at 3 months but was so at both 6 and 12 months (-0.12 and -0.19 LogMAR, respectively). However, non-significant differences were reported at 18 months between treatment and control groups.

Based on results for differences between post-treatment and baseline values for treated patients, significant improvements were reported for corrected and uncorrected visual acuity at 6, 12 and 24 months. These were calculated using data from 12, 18 and 6 papers for uncorrected visual acuity and 15, 22 and 7 papers for corrected visual acuity, at 6, 12, and 24 months, respectively. Improvements on the LogMAR scale were in the order of -0.15 for uncorrected visual acuity and -0.10 for corrected visual acuity across the various time points.

In total, 38 papers reported 104 usable results on visual acuity of which 52 (50%) reported significant improvements in visual acuity. Arithmetic means of the differences calculated from this larger data set were similar to those from the meta-analyses. For uncorrected and corrected visual acuity the estimated benefit at 12 months was 0.19 and 0.10, respectively, on the LogMAR scale.

Astigmatism and cylinder measures

Due to a lack of data, meta-analysis was only undertaken for grouped astigmatism measured at 12 months. Only 2 studies contributed and no significant differences between treatment and control groups were found from the random effects model.

Meta-analysis results for differences between post-treatment and baseline values for treated patients showed statistically significant improvements in astigmatism at 6, 12 and 24 months, in the order of -0.4 D at 6 months, -0.7 D at 12 months and -0.5 D at 24 months. For spherical equivalence, meta-analysis was only undertaken at 6 and 12 months. The meta-analysis results, which were only significant at 12 months, showed a reduction of between 0.3 and 0.5 D.

These analyses included 7, 13 and 5 papers on astigmatism at 6, 12 and 24 months, respectively, and 8 and 10 papers on spherical equivalence at 6 and 12 months, respectively.

In total, 31 papers provided 88 usable results of astigmatism and refraction measures, of which 21 (23%) were statistically significant. Eleven values reported in 8 papers were negative (increase in a negative value), showing deterioration in the measure, but none were statistically significant. Analysing the usable results from all papers provided estimates of the reduction at 12 months of:

- 0.9 D for astigmatism, somewhat higher than the value from meta-analysis;
- 1.0 D in spherical equivalence.

Central corneal thickness

Due to a lack of data, no meta-analyses of change between treated and control groups could be undertaken for central corneal thickness. Two meta-analyses of data from 6 papers estimated differences in central corneal thickness values between post-treatment and baseline values for treated patients at 6 and 12 months. A significant decrease of 14 µm in central corneal thickness was found at 12 months. No significant difference was found in the meta-analysis of 6-month results.

In total, 25 papers reported on central corneal thickness measurements, of which three noted no statistical differences at any time period and two reported statistically significant reductions at 12 months. The arithmetic means of the changes across 23 papers at 6 and 12 months were -12 µm and -8 µm respectively, which support the results of the meta-analyses.

One paper reported changes in central corneal thickness for patients with keratoconus and keratectasia. Patients with keratectasia regained the pre procedure level of central corneal thickness at 12 months, whilst patients with keratoconus had a reduced central corneal thickness of about 6 µm.

Intraocular pressure

No meta-analyses of change between treated and control groups could be undertaken for intraocular pressure. Following clinical advice, only 2 studies were included in an analysis of differences between post-treatment and baseline values for treated patients, and this was undertaken at 6 months only. No significant differences were found.

Four papers stated that intraocular pressure was unchanged over all time periods, and one reported a statistically significant increase in intraocular pressure at 12 months of 2.9 mmHg. This was the only statistically significant value reported. Overall, 3 negative values with a mean value of -0.3 mmHg were reported, compared with 11 positive values with a mean value of 0.8 mmHg.

Adverse events and complications

Table 1 summarises adverse events reported in the 49 efficacy studies and 26 safety papers. In total, 40 serious complications were reported in 39 patients. To address events which did not resolve, 4 patients had corneal transplants and one an unspecified procedure. Four patients suffered reduced visual acuity and 6 had unresolved corneal oedema. In the other patients there were no major long-term complications. Some adverse events may be due to poor after care compliance by the patient and others may be site specific. For example, the 4 transplants were reported in one paper which was set in multiple centres in France.

Several studies reported pain, corneal oedema and corneal haze as common side effects. Sterile keratitis was reported in 20 patients. Other minor complications included striae, Descemet, blepharitis, endothelial irregularities and mild photophobia. These resolved over time.

Table 1: Adverse events and complications in epithelium-off CXL papers

Complication	Status	Occurrence	Consequences
Infections	Serious	8 single case reports.	4 with no major long-term adverse impact; 1 with reduced visual acuity; 3 not reported.
Corneal melting and perforation	Serious	3 single case reports.	2 with no major long-term adverse impact; 1 further procedure.
Corneal ulcer or burn	Serious	3 single case reports.	1 with improved corrected visual acuity; 2 not reported.
Stromal scar	Serious	4 cases (3 in one study).	3 with improved uncorrected visual acuity despite scars; 1 with vision corrected with lens.
Repeat surgery	Serious	4 patients (2.8%) required deep anterior lamellar keratoplasty; 1 patient required surgery due to riboflavin intolerance.	Post-treatment vision reported as good for 4 patients. For the case study, the outcome was described as uneventful.
Sterile keratitis	Serious	5 cases (4 in one study).	2 had persistent decrease in visual acuity; 1 had scars at 2 months.
Sterile keratitis	Minor	20 cases.	Resolved with treatment; 2 had residual scarring.
Corneal haze	Serious	1 case.	Haze disappeared gradually.
Corneal haze	Minor	Rate 7% to 100% in 6 studies; 5 case studies plus 91 cases from RCT.	Haze disappeared over 12 months and no loss of visual acuity.
Corneal oedema	Serious	11 cases.	1 resolved, 4 improved, 6 unresolved, with 1 case left with very poor visual acuity.
Corneal oedema	Minor	Ranged from common to 70% of patients.	All resolved in 6 months.
Corneal erosion	Minor	1 case.	Settled.
Pain	Minor	Ranged from most to all patients.	Settled.
Other minor	Minor	Striae, Descemet; blepharitis, endothelial irregularities and photophobia.	Settled.

Papers with fewer than 10 patients were excluded, but still almost a third of papers reported on 20 or fewer 20 patients. The small study size has been partially addressed through meta-analyses which can add power to calculation of the end point. However, this cannot address the problem that the numbers in the studies are too small to measure rarer complications and safety-related events. Thus, these are likely to be under-reported.

Conclusions from consideration of epithelium-off CXL papers

The evidence from 49 papers on the efficacy of epithelium-off CXL and 26 on the safety of epithelium-off CXL for each parameter examined is:

- Improvements in measures of topography were found for Max K, mean K and Min K, respectively at 6, 12 months and 24 months. Benefit increased to 12 months and then stabilised. This evidence came from a comparison of baselines before and after procedure; no randomised control data were available.

- For measures of visual acuity, meta-analysis of change between treated and control groups at 12 months found no significant differences for uncorrected visual acuity but a significant difference of around -0.20 (LogMAR) for corrected visual acuity. One RCT reporting at 18 months only, however, found non-significant differences between the treatment and control groups in corrected visual acuity. The results for differences between post-treatment and baseline values for treated patients showed significant improvements for corrected and uncorrected visual acuity at 6, 12 and 24 months. Improvement was also indicated by the results from all papers reporting this outcome.

- No significant differences were found between the treatment and control groups for measures of astigmatism. Differences between post-treatment and baseline values for treated patients showed statistically significant improvements in astigmatism at 6, 12 and 24 months, and for spherical equivalence measures, significant differences at 12 months.

- A meta-analysis of 6 papers found a statistically significant reduction in central corneal thickness values between post-treatment and baseline values for treated patients at 12 months. Evidence from 25 papers was supportive of a reduction.

- Evidence on intraocular pressure is poor but suggestive of a tendency to higher intraocular pressure after procedure.

- The procedure is generally reported as safe but serious complications were reported, including the need for 4 patients to have corneal transplant, and a similar number suffering long-term loss in visual acuity. Cause of the events was seldom disclosed. For example, some infections may be due to the patient failing to comply with advice on after care, while other events may be due to operator error. Most events resolved over time with no major consequences for the patient.

4.2 Evidence on epithelium-off CXL with intrastromal corneal ring segments

Six studies provided evidence of epithelium-off CXL with intrastromal corneal ring segments (ICRS) implantation. Three papers reported findings from RCTs; two were retrospective case series and one a comparative case series. Three of the papers were graded very low quality evidence, 1 paper was classified as low quality, and the remaining two papers were classified as moderate quality.

One RCT randomised 48 eyes with keratoconus to receive CXL followed by ICRS implantation or ICRS implantation followed by CXL. The 2 treatments took place with a mean interval of 7 months. Postoperative follow-up outcomes are provided at a mean of 6 months.

A second RCT randomised 39 eyes to classic CXL or riboflavin eye drops for 1 month. After 3 months, all patients underwent insertion of ICRS.

The third RCT randomised 16 eyes to ICRS insertion followed by CXL either 6 months later or on the same day.

Summary of findings from epithelium-off CXL papers with intrastromal corneal ring segments

No meta-analyses were planned but rather a narrative synthesis of the papers is provided.

Topography

Both groups in the first RCT reported statistically significant improvement in mean K values with the group with CXL then ICRS reporting the greater change (3.3 D versus 1.1 D).

Results for the second RCT comparing ICRS insertion after drops of riboflavin with insertion after classic CXL reported no statistically significant changes in K values at 6, 12 or 24 months. All measures were improvement on baseline with the CXL group gaining the greater benefit.

The third RCT reported statistically significant improvements in mean K in each arm, with the same-day procedure arm having a greater benefit than delaying CXL for 6 months (5.2 K versus 3.1 K).

One other paper reported an improvement in mean K at 6 months of 4.5 D.

Visual acuity

For the first RCT, at 6 months post both procedures, each group gained 1 Snellen line in uncorrected visual acuity, with the group having CXL then ICRS gaining one line in corrected visual acuity but the ICRS then CXL group gaining only half a line. All results were statistically significant.

Results from the second RCT indicated that the CXL arm received the greater improvement in uncorrected visual acuity at 6 months, but the benefit from CXL tapered until at 24 months the 2 interventions were virtually equivalent. No statistically significant differences were reported.

The third RCT of sequential or simultaneous CXL and ICRS reported statistically significant and similar increases in uncorrected and corrected visual acuity for each arm at 6 months.

One other paper, the larger retrospective case series of CXL and ICRS performed on the same day, reported statistically significant improvements in uncorrected visual acuity (0.27 LogMAR) and corrected visual acuity (0.24 LogMAR) at 6 months.

The final paper reporting changes in visual acuity compared classic CXL with CXL using an intrastromal pocket for the riboflavin solution. Uncorrected measures improved by 0.14 and 0.23 LogMAR, respectively, and best corrected vision by 0.06 and 0.24 LogMAR, respectively. None of the results were statistically significant.

Astigmatism and refraction

Both groups in the first RCT reported statistically significant improvements in sphere values at 6 months. The CXL before ICRS group also reported a statistically significant improvement in cylinder measures.

Results for the second RCT were mixed and not significant. The third RCT reported statistically significant improvements in sphere or cylinder error in either arm.

The larger retrospective case series paper reported an improvement in sphere and cylinder values at 6 months of 2.6 D and 1.6 D, respectively, compared to baseline.

Central corneal thickness

Only 3 papers reported on this parameter and the evidence was inconclusive.

Intraocular pressure

Only 2 papers reported change in intraocular pressure. No values were statistically significant. In the first RCT, at 6 months, in group 1 (CXL then ICRS) there was a 'marginal change' in IOP compared to a 1-mmHg increase in the second group. In the second RCT, both arms reported increases in pressure at 6 and 12 months but these were lower in the CXL arm.

Complications reported in these papers were grouped with other CXL-Plus papers and are reported later.

Conclusions on epithelium-off CXL with ICRS

The evidence on visual acuity, topography and astigmatism/refraction comes from 3 RCTs and 3 case series, providing a mix of moderate and low quality evidence. It supports:

- Same-day procedures (CXL and ICRS) in preference to a delay of several months;
- CXL conducted before ICRS if a delay is necessary.

There is insufficient evidence to draw conclusions on the other interventions.

4.3 Evidence on epithelium-off CXL with photorefractive keratectomy

Nine studies, all case series, provided evidence of epithelium-off CXL with photorefractive keratectomy (PRK). These comprised 5 prospective case series, 1 retrospective comparative case series, 1 randomised comparative case series and 2 case series. The randomised comparative study compared CXL with an increased light fluence of 7 mW/cm^2 for 15 minutes (group A) with the standard UV A light fluence of 3 mW/cm^2 for 30 minutes (group B). The retrospective comparative case series compared PRK 6 months after CXL with same-day procedures. Seven papers were graded as very low evidence and two as low evidence.

Topography

Results from the randomised study of different light and time intensities at 24 months reported reductions of 3.4 D and 2.9 D in the Max K values. No p-values were provided.

The comparative study of CXL and PRK on the same day and with a 6-month gap found the simultaneous group had the bigger improvement in mean K (3.5 D versus 2.8 D); this was not significant.

At 12 months, 2 papers reported a mean improvement of 3.0 D in Max K and 1 paper reported a 2.1 D improvement in Min K. Two of the 3 values were statistically significant.

Longer term follow-up inm 1 paper showed a reduction in 'steep and flat keratometry' at 19.5 months of 2.4 D ($p<0.05$). At 24 months the reductions reported from a second paper were 2.4 D for Max K and 1.2 D for Min K, whilst a third paper reported a reduction in mean K of 0.8 D.

Visual acuity

The randomised study of different light and time intensities reported that at 24 months:

- Uncorrected visual acuity improved from 20/60 to 20/38 and corrected visual acuity from 20/30 to 20/25 Snellen lines in the increased light/shorter time arm;
- Uncorrected visual acuity improved from 20/62 to 20/40 and corrected visual acuity from 20/30 to 20/25 Snellen lines in the standard light/time (classic CXL) group. No p-values were provided.

The comparative study of CXL and PRK on the same day and with a 6-month gap found that the simultaneous group had bigger improvements in both uncorrected and corrected visual acuity, which were statistically significant.

At 12 months, 3 papers reported mean improvements of (all LogMAR):

- 1.3 in corrected visual acuity;
- 0.1 in best corrected vision;
- 0.04 in corrected visual acuity.

Results from 19.5 to 26 months showed a mean improvement in uncorrected visual acuity of 0.28, with a 0.27 improvement for corrected visual acuity (LogMAR). All results were statistically significant.

Astigmatism and refraction

Results from the randomised study of different light and time intensities showed reductions in spherical equivalence of 2.5 D and 2.3 D in the 2 groups. The reductions in refractive cylinder change were 2.9 D and 2.8 D, respectively. No p-values were provided.

The simultaneous group showed a greater improvement in spherical equivalence (3.2 D versus 2.5 D) compared with delaying PRK (i.e. the sequential group).

At 12 months, two papers reported reductions in spherical equivalence; the mean reduction was 1.9 D. The reduction at 24 months reported in another paper was 1.15 D, all values were statistically significant.

Intraocular pressure, central corneal thickness and adverse events

No results were reported for intraocular pressure.

The study of sequential versus simultaneous CXL and PRK reported identical reductions in central corneal thickness in both groups of 70 µm.

Complications reported in these papers were grouped with other CXL-Plus papers and are reported later.

Conclusions on epithelium-off CXL with PRK

The evidence from 9 studies, 7 graded as very low quality, suggests that CXL with PRK improves visual acuity, reduces curvature of the cornea's anterior surface, and improves spherical equivalence at 12 and 24 months. The comparative retrospective study suggests there is no benefit from delaying PRK compared with undertaking the procedures simultaneously.

4.4 Evidence on epithelium-off CXL with phakic intraocular lens

One case series, graded very low evidence, evaluated the safety and efficacy of an artier foldable antenor iris claw phakic intraocular lens (PIOL) following CXL in 11 eyes with progressive keratoconus. It was set in Peru and included 11 patients. CXL was conducted 6 months prior to the insertion of the PIOL and the mean follow-up was 6 months after PIOL.

Topography

Max K values reduced by 1.2 D at 6 months after CXL and by 2.1 D 6 months after PIOL; the equivalent values for Min K were an increase of 0.2 D at 6 months but a decrease of 1.2 D at 12 months. All values except the increase of 0.2 D were statistically significant.

Visual acuity

Uncorrected visual acuity improved by 0.24 LogMAR 6 months after CXL and by 1.24 LogMAR 6 months after the PIOL procedure; both values were statistically significant. Corrected visual acuity improved by 0.02 LogMAR 6 months after CXL and by 0.1 LogMAR 6 months after PIOL.

Astigmatism and refraction

The sphere values fell by 0.4 D 6 months after CXL and by 5.4 D 6 months after PIOL, both changes were statistically significant. Cylinder values fell by 0.2 D and 0.6 D at the 2 periods, with the latter value being statistically significant.

Intraocular pressure, central corneal thickness and adverse events

No values for intraocular pressure or central corneal thickness were reported. Complications were grouped with other CXL-Plus papers and are reported later.

Conclusion on epithelium-off CXL with phakic intraocular lens

This limited evidence from only 11 eyes showed efficacy in the main parameters but further research with more patients, a comparator arm and longer follow-up is required.

4.5 Evidence on adverse events for CXL-Plus procedures

The various complications reported in the studies of epithelium-off CXL with ICRS, with PRK and with PIOL were grouped.

Corneal haze:

- One paper reported stromal haze in all eyes which resolved;
- Corneal haze intensity: All cases of stromal haze (12/15) resolved without sequelae:
- Corneal haze in all cases in the early postoperative period resolved over time in 1 study. In another study, 13 of 28 eyes (46%) had mild posterior linear stromal haze

at 1 month, which had decreased in density by 12 months but did not completely disappear;
- Mild haze in 2 of 11 (18%) patients resolved in 15 days.

Corneal oedema:

- 8 (19%) eyes had slight sub-epithelial and stromal oedema with cotton like ring-shaped stromal opacities 1 month after CXL, which disappeared within 3 months.

Perforation:

- 2 of 39 (5%) eyes presented with anterior chamber perforation; neither patient received CXL.

Other:

- 9 patients had delayed epithelial healing completed by postoperative day 9;
- Very minimal intracorneal channel deposits in 1 eye (visually insignificant);
- 1 eye developed minimal intracorneal channel deposits which did not affect vision.

In summary, haze was reported as a frequent event for many patients and usually resolved after several weeks. The serious event of perforation was in a control arm not exposed to CXL.

4.6 Evidence on transepithelial (epithelium-on) CXL

There were 4 studies of transepithelial (epithelium-on) CXL, in addition to 1 study of ICRS followed by transepithelial (epithelium-on) CXL after at least 3 months from implantation and another of transepithelial CXL and same-day ICRS. Four were prospective case studies and two were retrospective case studies. Two papers were graded as low evidence and four as very low evidence.

Topography

Results for the 4 studies using transepithelial (epithelium-on) CXL were:

- At 6 months: a statistically significant improvement of 0.7 D and 0.5 D in Max and mean K, respectively;
- At 12 months: an improvement of 0.2 in mean K and 0.2 in Max K;
- At 18 months: a statistically significant improvement of 11.1 in mean K.

The case series of patients with transepithelial (epithelium-on) CXL with same-day corneal implants reported statistically significant improvements in these measures at 36 months. The study of ICRS followed several months later by CXL reported an improved mean K after ICRS of 2.5 K which was maintained 6 months after CXL.

Visual acuity

Results for the 4 studies using transepithelial (epithelium-on) CXL reporting change in visual acuity were:

- At 6 months: an improvement of 0.20 and 0.17 LogMAR in uncorrected and best spectacle-corrected visual acuity;
- At 12 months: an improvement of 0.036 in corrected VA, an improvement in Snellen lines from 20/32 to 20/24, and an improvement in uncorrected visual acuity from 20/133 to 20/67 Snellen lines;

- At 18 months: uncorrected visual acuity improved by 0.23 and corrected visual acuity by 0.11 LogMAR.

The case series of patients with transepithelial (epithelium-on) CXL with same-day corneal implants reported an improvement at 3 years in corrected visual acuity of 0.08 LogMAR. The study of ICRS followed several months later by CXL reported improved uncorrected visual acuity after ICRS of 0.18 which was maintained 6 months after CXL, whilst corrected visual acuity improved by 0.11 after ICRS and by a further 0.02 after CXL (LogMAR).

Astigmatism and refraction

Results for 3 studies using transepithelial (epithelium-on) CXL reported changes in astigmatism and refraction of:

- At 6 months: an improvement of 0.6 D in mean spherical equivalent refractive error which was statistically significant;
- At 12 months: a mean improvement of 0.5 D in mean astigmatism, which was statistically significant, and improvements in cylinder and sphere of 1.2 D and 0.2 D, respectively.

The study of ICRS followed several months later by CXL reported improved sphere and cylinder values after ICRS of 2.8 D and 2.1 D, respectively, which were maintained after CXL.

Central corneal thickness

Two papers reported an increase in central corneal thickness of 9 µm at 6 months and 12 months.

Intraocular pressure

One paper reported a reduction of 0.1 mmHg at 6 months.

Adverse events

Only 2 papers reported complications. The one which provided most information included 20 patients with an 18-month follow-up, whilst the other reported on 51 patients at 12 months follow-up.

Pain:

- Mean pain score 0.43 on day 3 on a scale of 0 to 10;
- No significant ocular pain.

Corneal haze:

- Transient sub-epithelial haze grade 0.5 in 2 of 51 cases, which disappeared at 1 month follow-up and did not affect visual acuity;
- No corneal haze.

Other:

- Conjunctival hyperaemia and mild foreign body sensation in 8 patients (40%), which resolved spontaneously;
- Photophobia in 2 patients (10%), which resolved spontaneously after 4 days.

Conclusions on transepithelial (epithelium-on) CXL

There is weak evidence on the efficacy of the procedure in respect of visual acuity, topography and astigmatism/refraction. There are no additional safety concerns. However, there are only 4 studies and their quality is poor. Hence, the evidence base may be judged insufficient to inform a positive recommendation for normal use.

5. LIMITATIONS

This review of the efficacy and safety of CXL has several limitations. The main limiting factor preventing the inclusion of additional studies in the meta-analyses was the lack of consistent reporting of the key parameters of corneal topography, refraction, and visual acuity across time periods. Where possible the measures used in the studies were grouped. However, it was still not possible to pool many of the results. This weakened the evidence base provided by meta-analyses and, hence, confidence in the results.

Meta-analyses of the epithelium-off CXL papers of the difference between control and intervention arms could only be undertaken for visual acuity and astigmatism and these included a very limited number of papers. As such, the majority of the meta-analysis evidence could only analyse the change from baseline following intervention. Without a matched counterfactual it is impossible to know what the actual effects of the procedure were.

Another limiting factor was the high level of heterogeneity reported for many of the meta-analyses. This may arise because in some instances there were just a few papers, or possibly the patient populations, technique or study design differed. The high heterogeneity and associated wide confidence intervals limits their usefulness in drawing conclusions from the data and generalising the findings to other settings.

There was an absence of long-term studies. Of the few which did provide longer term data, the outcomes were usually reported by small numbers of the original cohort, with no indication of the reasons for drop-out. Thus, it is not possible to ascertain the duration of benefit from the procedure. Well-conducted long–term studies are required to establish the potential benefit of the procedure in avoiding, or at least delaying, corneal transplants.

No evidence was available on the benefit of repeat CXL. Hence, it is not possible to assess if CXL offers potential benefit should progression recur.

No information was available on whether the procedure improved quality of life for patients and enhanced their ability to conduct daily activities. Limiting benefit to the clinical end points may understate the value which patients and families place on the improvement experienced. It would also be useful to have some measure of the patient perspective on the procedure and follow-up.

Most of the evidence consisted of case series which described procedures and outcomes, but these cannot provide evidence of causal effect. The absence of a matched comparator was a weakness in most papers, including those RCTs which used fellow-eyes rather than a matched cohort. Other weaknesses included the poor reporting of drop-out rates and loss to follow-up. The direction of bias from such high rates is unknown.

Case series may also be prone to selection bias and observer bias, notably when selecting patients for the procedure and in reporting outcomes. Single surgeons in single centres may also introduce bias if they have specific skills or experience which will be difficult to replicate. Some papers also reported the early experiences of surgeons with the procedure. Over time the equipment and protocols have changed and this may be reflected in better efficacy and safety outcomes.

Many of the papers had small sample sizes, raising concerns about whether they included sufficient patients to be able to detect meaningful effects of the procedure.

The one randomised controlled trial which gave rise to several papers had a cross-over period at 3 months for the control eyes. Thus, the results after that period did not have the benefit of a control, other than fellow-eyes.

The evidence has mainly been graded low or very low and the conclusions one can draw from it must be seen in that light.

6. CONCLUSIONS

This review describes the current evidence base for the efficacy and safety of CXL, alone, in combination with therapies designed to improve visual acuity (CXL-Plus), and as transepithelial (epithelium-on) CXL. The quality of the evidence and potential biases have already been identified as major limitations to informing robust conclusions.

Judging the strength of evidence also requires a view to be taken on:

- Quantity, quality, and consistency of evidence;
- External validity (generalisability) of studies;
- Directness of application to the target population for the NHS.

For the epithelium-off procedure there are a considerable number of descriptive case series and retrospective case series which consistently reported measures of visual acuity, astigmatism and topography that improved at follow-up compared to baseline. A material number of these values were statistically significant. Benefit has thus been reported repeatedly across papers. This is important given the progressive nature of the disease. However, the majority of these papers were assigned a grade of low or very low based on the trial design, absence of a comparator, often large drop-outs and incomplete reporting.

Analyses of the CXL-Plus interventions, particularly CXL with ICRS and with PRK, included only a few papers but better quality papers. These also demonstrated consistent improvements in the three key parameters over at least a 1-year time horizon following the procedure compared to baseline. However, evidence on the timing and sequencing of procedures is very mall.

Evidence on transepithelial (epithelium-on) CXL was limited to 163 eyes and 4 papers, whilst the 2 papers with this procedure plus ICRS included an additional 35 eyes. Evidence of efficacy in visual acuity and topography was demonstrated.

Overall, evidence from topographic measures and pachymetry is that CXL strengthens and stabilises the cornea, can stop progression, and in some cases reverse progression, of keratoconus and keratectasia. The resultant flattening of the cone may improve the effectiveness of a contact lens and hence increase corrected visual acuity. It also may provide the opportunity to introduce other interventions such as ICRS which are designed to improve visual acuity.

CXL is also not without risk, but the majority of events resolve and the serious reported events may in part arise from poor surgical practice or poor patient compliance.

There remains considerable uncertainty about the duration of benefit, unsurprising given the technique was first piloted in 2003. However, delaying or preventing the need for corneal transplant could be highly valued by people with this disease.

Abbreviations

Av	Average
BCVA	Best corrected distance visual acuity
BSCVA	Best spectacle-corrected visual acuity
CCT	Central corneal thickness
CDVA	Corrected distance visual acuity
CVA	Corrected visual acuity
CH	Corneal hysteresis
CK	Conductive keratoplasty
CL	Contact lens
CRF	Corneal resistance factor
CT	Corneal thickness
CXL	Corneal collagen cross-linkage
D	Dioptres
EAC	External Assessment Centre. Refers to NUTH YHEC EAC unless otherwise specified
ECC	Endothelial cell count
FDA	Food and Drug Administration
FR	Ferrea
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HTA	Health technology assessment
ICRS	Intrastromal corneal ring segments
IOP	Intraocular pressure
IPAC	Interventional Procedures Advisory Committee
IPG	Interventional Procedures Guidance
ITT	Intention to treat
K	Keratometry
LASIK	Laser-assisted in situ keratomileusis
LogMAR	Logarithm of the minimum angle of resolution
MAUDE	Manufacturer and User Facility Device Experience
Max	Maximum
Min	Minimum
NA	Not Available
NEI-RQK	National Eye Institute Refractive Error Quality of Life Questionnaire
NR	Not Reported
NICE	National Institute for Health and Clinical Excellence
NPSA	National Patient Safety Agency
NUTH	Newcastle Upon Tyne Hospitals NHS Foundation Trust
OCT	Optical coherence tomography
PIOL	Phakic intraocular lens
PK	Penetrating keraplasty
PMD	Progressive macular degeneration
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRK	Photorefractive keratectomy

RCT	Randomised controlled trial
SD	Standard deviation
SE	Spherical equivalence
SIGN	Scottish Intercollegiate Guidelines Network
Sim	Simulated
TE	Treatment effect
TG	Topography-guided
TG-PRK	Topography-guided photorefractive keratectomy
US	Ultrasound
UCVA	Uncorrected visual acuity
UDVA	Uncorrected distance visual acuity
UV A	Ultraviolet A
VA	Visual acuity
WL	Wavelength
YHEC	York Health Economics Consortium

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Section 1: Objective of the Review

1.1 BACKGROUND

In November 2009, the National Institute for Health and Clinical Excellence (NICE) issued guidance on the use of collagen cross-linkage for keratoconus (NICE IPG320 2009), stating that, given the inadequate evidence, the procedure should only be used with special arrangements for clinical governance, consent and audit or research.

The guidance was supported by an audit document recommending audit data be collected and advising that details of all adverse events be forwarded to the National Patient Safety Agency's (NPSA) National Reporting and Learning System. The Guidance noted NICE may review the procedure on publication of further evidence.

Subsequently, new evidence was made available, including a Canadian health technology assessment (HTA) (98).

1.2 SCOPING REPORT

Given this development, the Newcastle and York External Assessment Centre (EAC) was commissioned by NICE to provide a systematic review of the literature on photochemical corneal collagen cross-linkage (CXL) using riboflavin and ultraviolet A (UV A) radiation for the management of keratoconus. The first output required was a Scoping Report.

NICE requested the Scoping Report provide clear descriptions and separate evidence and analyses of the epithelium-off CXL technique, different modifications of the CXL technique, and any combinations of the CXL technique with additional treatments.

On being awarded the commission, the EAC and NICE agreed a research question and the parameters for the scoping search. The question was:

> 'What is the current evidence base for the efficacy 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 included population was patients with progressive keratoconus and keratectasia, with each as a separate sub-group. Patients with pellucid marginal degeneration, infectious keratitis and bullous keratopathy were excluded.

The EAC also agreed with NICE a detailed literature search strategy, database sources to be searched, and the inclusion and exclusion criteria to be applied to the papers identified.

The searches were conducted, papers selected, and findings used to inform a Scoping Report. The purpose of the Scoping Report was to inform members of the Interventional Procedure Advisory Committee (IPAC) of the evidence base on CXL techniques, to enable them to finalise the scope for presentation of literature in the full systematic review. IPAC considered the Report on 11 October 2012.

1.3 FRAMEWORK FOR SYSTEMATIC REVIEW

Following discussions, NICE advised the full systematic review should include all randomised controlled trials (RCTs), prospective studies, case series or retrospective analyses, and papers reporting safety events. Full reporting was required for studies of 10 or more patients, longer than 6 months follow-up and all safety studies. NICE also advised that papers reporting patients with keratoconus and keratectasia could be combined and that separate sub-group analyses were not required. NICE confirmed the existing literature search strategy and asked the searches be updated to the end of October 2012.

This report presents the findings of the systematic review conducted in accordance with this framework.

1.4 LAYOUT OF THIS DOCUMENT

The sections of this document are as follows:

- Section 2 provides background to the disease and interventions;
- Section 3 describes the methodology for the systematic review and meta-analysis;
- Section 4 describes epithelium-off CXL papers and meta-analyses;
- Section 5 describes epithelium-off CXL and intrastromal corneal ring segments papers and provides a narrative synthesis;
- Section 6 describes epithelium-off CXL and photorefractive keratectomy papers, including studies of topography-guided photorefractive keratectomy, and provides a narrative synthesis;
- Section 7 describes epithelium-off CXL with phakic intraocular lens and provides a narrative synthesis;
- Section 8 describes transepithelial (epithelium-on) CXL with other interventions and provides a narrative synthesis;
- Section 9 notes the limitations associated with the evidence informing the review and provides conclusions.

Section 2: Background

2.1 DESCRIPTION OF THE UNDERLYING CONDITION

2.1.1 Keratoconus and Keratectasia

Keratoconus is a natural degeneration of the structure of the cornea, the clear tissue covering the front of the eye. The shape of the cornea slowly changes from the normal round shape to a cone shape and is associated with progressive corneal thinning. It may involve a defect in collagen, the tissue that makes up most of the cornea. It has a prevalence of about 0.05% (1 in 2000) of the population (98) and has an earlier onset than most chronic eye diseases with a median age of 25 years.

Keratoconus can also be secondary as a result of an infrequent but serious complication of laser-assisted *in situ* keratomileusis (LASIK) surgery. This is called keratectasia. If the laser removes too much tissue during LASIK, or if the flap is made too deep, the structure of the cornea can be weakened. This weakening can cause the cornea to bulge forward in an irregular fashion, causing increasing astigmatism and distorted vision that cannot be corrected with spectacles, contact lenses, or a LASIK enhancement procedure. Patients with thin corneas prior to LASIK have a higher risk of developing keratectasia.

Diagnosis is often not straightforward and typically requires the use of instruments to assess the corneal topography to inform decisions on the grade of severity of the disease. There are 4 grades on the Amsler-Krumeich scale ranging from mild (grade I) to severe (grade IV).

2.1.2 Current Management and Treatment

Treatment varies with disease severity. In mild to moderate keratoconus, management is by spectacles or contact lenses to correct visual acuity. With disease progression, these cease to be of benefit and rigid gas permeable contact lenses may be fitted or corneal ring segment inserts may be used. However, as the corneal shape deteriorates further some form of corneal surgery may be required, including deep lamellar keratoplasty or penetrating keratoplasty for severe progressive keratoconus.

Prior to CXL, no interventions were available to arrest or slow disease progression, with transplantation required in up to 21% of keratoconic eyes (82). Now there is evidence that CXL with riboflavin drops can be successful in strengthening and stabilising the cornea. The success of CXL in improving the biomechanical structure of the corneal has led to its application in conjunction with other techniques, for example, intracorneal ring segments (ICRS), photorefractive keratectomy (PRK) and topographic PRK, and phakic intraocular lens (PIOL) implantation to improve visual acuity.

2.2 INTERVENTIONAL PROCEDURE UNDER REVIEW

2.2.1 Corneal Collagen Cross-Linkage

Corneal collagen cross-linkage was developed in 1998 to strengthen and stabilise the cornea through the application of riboflavin, a form of vitamin-B2, followed by exposure to UV A light. This induces cross-linkage between the corneal collagen fibres and may prevent the progression of the disease.

The two basic types of corneal cross-linkage are:

- Epithelium-off, which means the thin layer covering the eye's surface, the epithelium, is removed, allowing for faster penetration with liquid riboflavin;
- Transepithelial corneal cross-linkage (epithelium-on) where the corneal epithelial surface is left intact, which requires a longer riboflavin loading time but may reduce the risk of infection[1].

Refinements of both types of corneal cross-linkage include:

- Reduced treatment time;
- Increased intensity of UV A light;
- Laser-assisted technique for administration of riboflavin.

2.2.2 Description of the Procedure

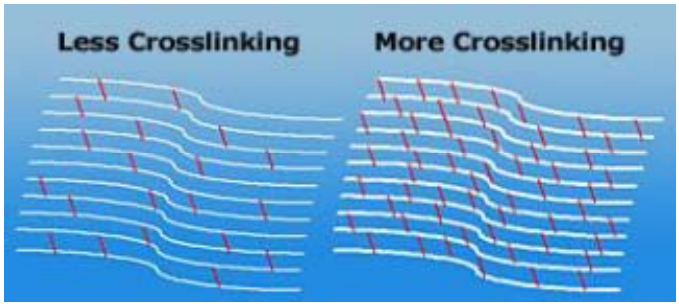
The cross-linkage procedure is undertaken as an outpatient procedure with the use of topical anaesthesia and takes 60 to 90 minutes in most cases. It involves the application of riboflavin, followed by exposure to UV A radiation. Riboflavin promotes the effect of UV light in causing collagen cross-linkage.

With 'epithelium-off cross-linkage', the epithelium is removed with a blunt spatula to allow penetration of riboflavin into the corneal tissue. Riboflavin eye drops are applied to the corneal surface 5 minutes before the procedure and then every 5 minutes during the procedure. The corneal surface is exposed to the UV A radiation, usually for up to 30 minutes. Postoperatively, topical antibiotics and anti-inflammatory drops will normally be prescribed with topical steroids if necessary. In some cases, a bandage contact lens may also be used for a few days. The procedure may need to be repeated at a later date.

The mechanism of action is to increase the number of 'anchors' that bond collagen fibres together and strengthen the cornea. This is expected to stop the progression of the disease but the duration of benefit is uncertain. Figure 2.1 illustrates the cross-linking.

[1] Trattler and Haddrill, 2012. Corneal Cross-linking for Keratoconus and LASIK Complications. http://www.allaboutvision.com/conditions/corneal-crosslinking.htm

Figure 2.1: Cross-Linking



(Source: Trattler and Haddrill, 2012. Corneal Cross-linking for Keratoconus and LASIK Complications. http://www.allaboutvision.com/conditions/corneal-crosslinking.htm.)

2.2.3 CXL in Combination with Other Interventions to Improve Visual Acuity 'CXL-Plus'

The CXL procedure itself is not intended to improve vision; however, the induced changes in corneal topography may result in such improvements. Combined with the CXL procedure, the stronger cornea can, however, be reshaped by various techniques to improve visual acuity. These adjunct procedures have been referred to as 'CXL-Plus'. Evidence exists on the use of the following adjunct procedures with CXL procedures:

- A range of corneal implants, also known as intracorneal ring segments (ICRS);
- Topography-guided and other forms of photorefractive keratectomy (PRK);
- Phakic intraocular lens implantation (PIOL).

2.2.4 Adverse Events

If CXL is performed according to standard protocols and patients comply with postoperative care, it has been found to be a safe procedure (142). Nevertheless, there are some reports of adverse events after CXL. Corneal haze is one of the more frequently reported complications of CXL (10, 47, 65, 107, 114, 115). This is usually minor and not associated with residual scarring or loss of vision.

Serious adverse events reported include infection, most frequently keratitis (130, 133, 137, 138, 143, 144). Other serious complications include corneal melting and perforation (122, 127, 139), corneal ulceration (123, 124), stromal scars (66, 134) and corneal oedema (126, 142).

Other more minor complications which have been reported after epithelium-off CXL include pain, striae and sterile keratitis (26, 114, 115, 117, 120, 125).

2.2.5 Other Relevant NICE Guidance

Interventional Procedures Guidance (IPG) has been provided on two related subjects:

- IPG 227 - Corneal implants for keratoconus;
- IPG 69 - Insertion of hydrogel keratoprosthesis.

Section 3: Methodology

3.1 SEARCH STRATEGY

The literature search strategy was developed in accordance with the guidance provided in Appendix B of the NICE Interventional Procedures Programme Process Guide (92).

It was agreed with the clinical expert, Professor Figueiredo, and NICE that the searches would be limited from year 2000 to 31 October 2012. This was informed by the Canadian literature review (98) and an earlier literature review undertaken by NICE. These identified that the first published study evaluating the effect of CXL methods on the progression of disease in patients with keratoconus was in 2003 (118).

The strategy used to search Ovid MEDLINE is provided in Appendix A. This was adjusted for other databases with examples of the revised searches also provided in Appendix A.

3.2 RESOURCES SEARCHED

The following resources were searched for relevant published, unpublished and grey literature:

- Cochrane Library [comprising Cochrane Database of Systematic Reviews (CDSR), Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) database, Cochrane Central Register of Controlled Trials (CENTRAL) and National Health Service Economic Evaluation Database (NHSEED)];
- MEDLINE and MEDLINE in process;
- EMBASE1;
- Cinahl;
- Science Citation Index;
- Inspec;
- Conference Proceedings Citation Index: Science (Web of Science);
- Science Direct;
- ZETOC;
- OAIster (Open Archives Initiative containing grey literature);
- OpenGrey;
- EuroScan;
- WorldWideScience.org;
- ClinicalTrials.gov;
- International Clinical Trials Registry Platform (ICTRP);
- Nexis;

- National Institute for Health Research (NIHR);
- Australian Safety & Efficacy Register of New Interventional Procedures (ASERNIP).

In addition, further papers were identified by:

- Searching key vision conferences for the past 3 years;
- Checking the reference lists of included papers and recent systematic reviews;
- Citation searching on the included papers.

Separately, a Freedom of Information request was made to the NPSA on reported adverse events with CXL procedures. No events had been reported. The Food and Drug Administration's (FDA) Manufacturer and User Facility Device Experience (MAUDE) database was also searched for information on reported adverse events with CXL procedures. No events were found.

The searches were limited to English language papers. Articles in a foreign language but with an English abstract could be included if safety concerns not otherwise reported were in the abstract or if they provided data on efficacy where the evidence on efficacy was very poor (91).

3.3 FINDINGS FROM SEARCHES

The titles and abstracts found by each search were downloaded to a database and duplicates removed. In total, 3,400 records were found before duplicates were removed, reducing to 1,747 records when duplicates were removed. Of these, 91 were title only records.

3.4 INCLUSION AND EXCLUSION CRITERIA

The EAC adopted the following broad inclusion criteria:

- English-language reports and human studies;
- Patients with keratoconus or keratectasia;
- Reports with interventions using photochemical corneal collagen cross-linkage using riboflavin and ultraviolet radiation alone, or in combination or sequence with other treatments;
- Original reports with defined study methodology;
- Reports including standardised measurements on outcome events such as technical access, safety, efficacy, durability, vision, quality of life or patient satisfaction;
- Systematic reviews, meta-analyses, randomised controlled trials, observational studies, retrospective analyses, case series, case studies, letters, comments and conference abstracts.

The exclusion criteria were:

- Abstracts with no clinical outcomes;
- Non-systematic reviews and editorials;
- Laboratory or animal studies;
- Conference abstracts unless they reported specific adverse events not reported in published literature;
- Papers not reporting the outcomes defined in the protocol, (for example, technical success, measurement of visual acuity, topographic assessment of corneal stability) following a collagen cross-linkage procedure;
- Papers using collagen cross-linkage procedures on other patient groups;
- Papers published before the year 2000;
- Non-English language studies with no English abstract.

Papers on efficacy were included for full extraction if they provided data on 10 or more patients for 6 or more months. Papers with fewer than 10 patients or less than 6 months follow-up were not included in this review and had minimal extraction of the study details and primary outcome. Details of these papers are in Appendix B.

For papers on safety there were no limits placed on study size or length of follow-up.

These eligibility criteria were applied to the abstracts and titles to inform the provisional study selection. The selection was based on a conservative approach to have high sensitivity at the expense of specificity; if a study or title could not be ruled out from the title and/or abstract then it was included. This approach was adopted to minimise the risk of missing any relevant papers, particularly for those for which only a title was available.

A double selection process was adopted. Two researchers reviewed the retrieved abstracts and titles, for those with no abstract, and made their selections independently. Differences were reconciled by mutual agreement. Two hundred and fifteen papers were selected by agreement. On investigation, 17 of these papers were in a foreign language and not retrieved. A further 8 papers could not be obtained. The remaining 190 papers were retrieved online or requested from the University of York library where possible, with British Library loans requested for the remainder.

3.5 EVALUATION FOR INCLUSION OF FULL PAPERS

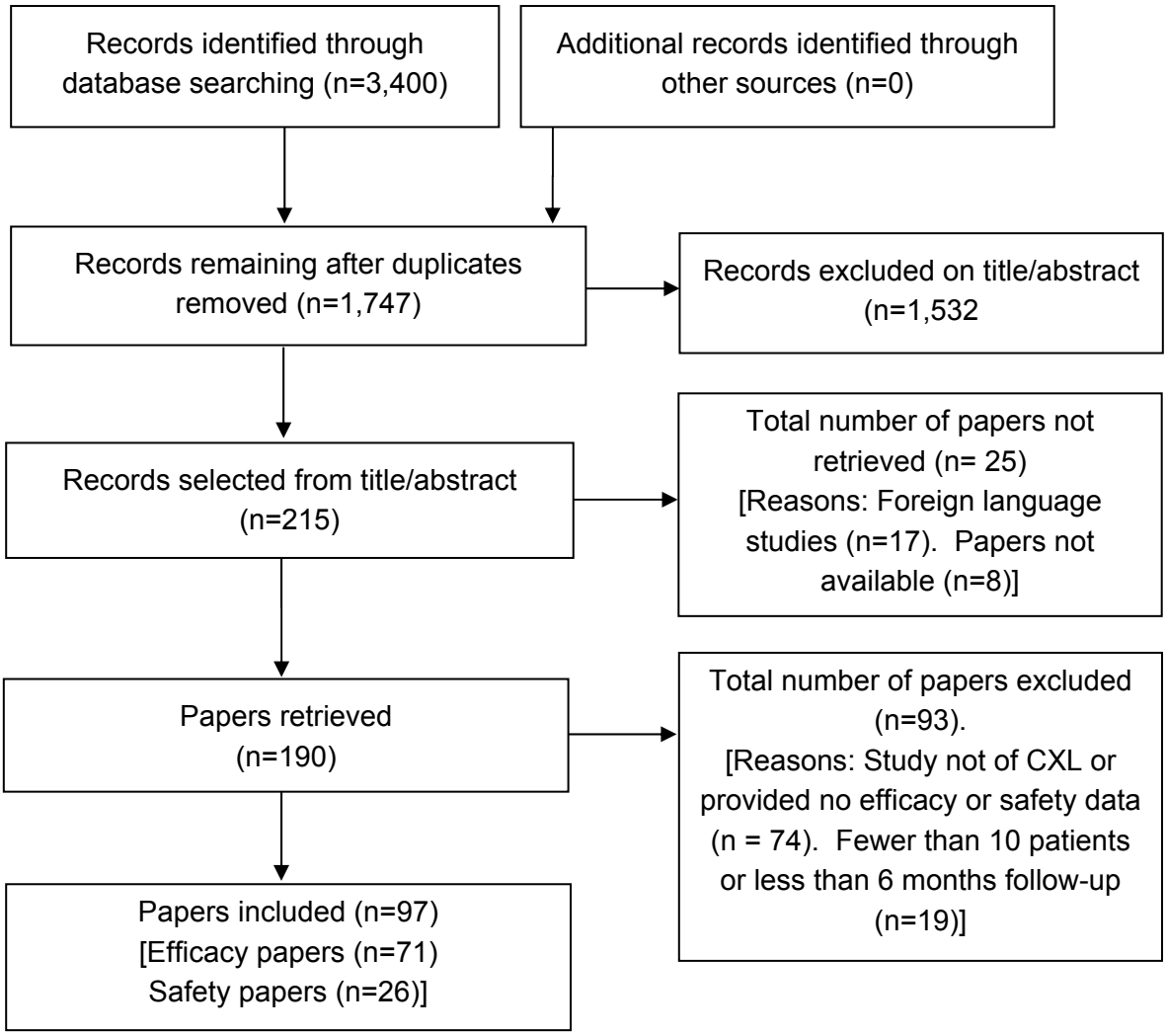
The inclusion and exclusion criteria were applied to the full papers to judge which of the papers retrieved should be included in this study. Seventy-one papers on efficacy and 26 papers on adverse events were selected for full data extraction. In addition a further 19 efficacy studies with fewer than 10 patients or less than 6 months follow-up were partially extracted.

Ninety-three papers were excluded from the analyses. Other than the extraction of the 19 small studies with short follow-up, the excluded papers are not considered further in this paper.

The data from the abstracts where the papers were in a foreign language are listed in Appendix C for completeness.

Figure 3.1 provides a PRISMA flow diagram of the papers identified by the search, those selected after the initial screen using abstracts/titles, and those selected following review of the retrieved full papers.

Figure 3.1: PRISMA flow diagram



3.6 OVERVIEW OF STUDY TYPES

Data extraction forms were developed to capture the key data elements identified during the protocol agreement stage with NICE. Each publication was reviewed and the relevant data extracted by one reviewer. All data extracted were reviewed by a second individual. The data extraction forms are the main source of data for presentation. The papers presented a range of study types and an overview of these for each procedure is provided in Table 3.1.

Table 3.1: Number and type of studies by procedure

Type of study	Number (%)
Epithelium-off CXL	
Randomised controlled trial	8 (16%)
Prospective case series	25 (51%)
Retrospective case series	7 (14%)
Case series	5 (10%)
Prospective comparative case series	4 (8%)
TOTAL	**49**
Epithelium-off with CXL and ICRS	
Randomised controlled trial	3 (50%)
Retrospective case series	2 (33%)
Comparative case series	1 (17%)
TOTAL	**6**
Epithelium-off CXL and PRK	
Prospective case series	5 (56%)
Case series	2 (22%)
Randomised comparative case series	1 (11%)
Retrospective case series	1 (11%)
TOTAL	**9**
Epithelium-off CXL with PIOL	
Case series	1 (100%)
TOTAL	**1**
Transepithelial (epithelium-on) CXL with other interventions	
Retrospective case series	2(41%)
Comparative case series	2 (29%)
Case series	2 (29%)
TOTAL	**6**

Of the 71 efficacy papers, 11 papers (15%) reported RCTs, 30 (42%) reported prospective case series, 12 (17%) reported retrospective case series and 18 (25%) reported other forms of case series.

3.7 GRADING OF EVIDENCE

The Scottish Intercollegiate Guidelines Network (SIGN) has developed a system of grading papers based on US Agency for Health Research and Quality methodology[2]. This has 8 levels of evidence:

1++ High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias.
1+ Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias.
1- Meta-analyses, systematic reviews, or RCTs with a high risk of bias.
2++ High quality systematic reviews of case control or cohort studies. High quality case control or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal.
2+ Well-conducted case control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal.
2- Case control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal.
3 Non-analytic papers, e.g. case reports, case series.
4 Expert opinion.

Each paper was reviewed and graded according to these descriptors.

Each descriptor was mapped to the Grading of Recommendations Assessment, Development and Evaluation (GRADE) categories[3], these being:

High - Further research is very unlikely to change our confidence in the estimate of effect.
Moderate - Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low - Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low - Any estimate of effect is very uncertain.

This was achieved by reviewing whether each paper had any serious limitations, important inconsistencies in the results, or uncertainty about the generalisability of the evidence. For example, the quality of an RCT could be downgraded as a result of limitations in study design, poorly matched patient groups, low patient numbers and high drop-out rates.

Thus, an RCT was graded as 1+ using the SIGN convention if it had a valid control group (randomised, comparable to intervention group) and low drop-out rate (less than 20%); the GRADE score awarded was ‘high’ if it had more than 100 participants or ‘moderate’ if it had fewer than 100 participants. An RCT with a SIGN grade of 1- and a high drop-out rate (more than 20%) was awarded a GRADE of ‘moderate’ if it had more than 100 participants and ‘low’ if it had fewer than 100 participants.

[2] More information is available at the SIGN website: http://www.sign.ac.uk/guidelines/fulltext/50/annexb.html
[3] More information is available at the GRADE website: http://www.gradeworkinggroup.org/

Comparative case series with 12 months follow-up all scored 2- on SIGN gradings (control group, but high risk of confounding/bias and significant risk relationship not causal due to control group not being comparable to intervention group and not a true cohort/case control study). A GRADE of 'low' was adopted for these because further research is likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Comparative case series with less than 12 months follow-up all scored 3 on SIGN gradings and 'very low' on GRADE as any estimate of effect is very uncertain.

Case series without any comparison group also scored 3 on SIGN gradings and 'very low' on GRADE as any estimate of effect is very uncertain.

Of the 71 efficacy papers, 54 (76%) were graded very low, 11 (15%) low and 6 (8%) moderate using the GRADE system.

3.8 SYNTHESIS OF DATA

For publications reporting results using the epithelium-off procedure the extracted data showing effect sizes, study end points and time periods were reviewed and any inconsistencies or unexpected results checked by going back to the original papers. The relevant end points are:

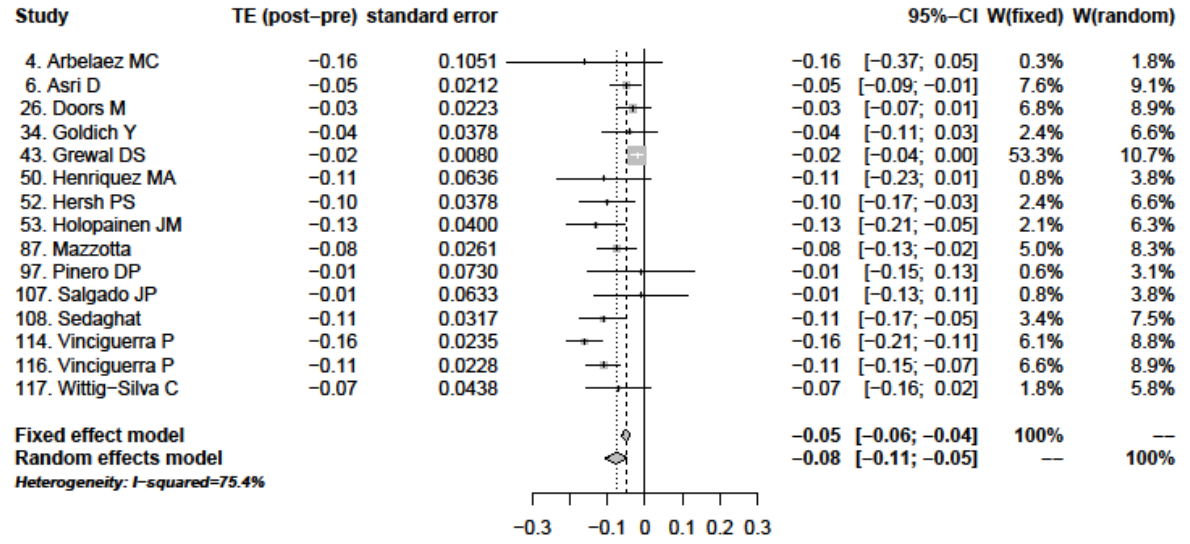
- Change in visual acuity;
- Change in topography;
- Change in refraction and astigmatism;
- Change in intraocular pressure;
- Change in central corneal thickness.

Where sufficient data were available across common time periods the data were synthesised using meta-analysis based on both random effects and fixed effects models. Heterogeneity was identified by using the I^2 statistic.

For the CXL-Plus interventions and the transepithelial corneal cross-linkage (epithelium-on) procedure, a narrative analysis of the same end points is provided.

Meta-analysis results will be reported using forest plots, with an example provided in Figure 3.2. This plot relates to a change in corrected visual acuity (VA) at 6 months.

Figure 3.2: Example forest plot



In terms of interpreting the diagram, the size of the grey box is proportional to the weight of the study under the fixed effects model, 'W (fixed)'. The dashed line is the mean for the fixed effects model whilst the dotted line is the mean of the random effects model. The grey diamonds indicate the confidence intervals for meta-analysis models.

The table on the left side of the figure summarises the data extracted from the studies included in the meta-analysis. This includes a study identifier (under column headed 'Study'); the estimated treatment effect, 'TE (post-pre)', which in this case is the difference between the corrected VA measured after and before the treatment (a negative value corresponds to an improvement); and the standard error of the treatment effect, a measure of the accuracy of the treatment effect estimate.

The heterogeneity of the studies is measured by I^2 and is given at the bottom on the left hand side of the figure. In this case, heterogeneity was high, I^2 = 75.4%. The value ranges from 0%, indicating no heterogeneity, to 100%.

The meta-analysis results can be visualised in the plot in the centre of the figure and are also summarised in the table on the right hand side. The small vertical line for each study corresponds to the treatment effect. These are all below zero in this example. The horizontal line for each study represents the 95% confidence interval (95% CI) for the treatment effect. If zero is inside this interval the treatment effect is not statistically significant, otherwise it is statistically significant. For example, the results reported by study 4 (Arbelaez MC) were not significant, whereas study 6 (Asri D) reported a statistically significant treatment effect.

The weights given to each study are different for the fixed and random effects models. Both these weights are reported on the right hand side table but only those for the fixed effects model are represented in the plot. These are represented by the grey squares which are proportional in area to the weight. In this example, study 43 (Grewal DS) has by far the biggest weight (over 53%). The presence of heterogeneity causes studies to have different weights for the fixed and random effects models. The weights are more equally spread across studies for the random effects model, as the weights take into account the variability between studies, whereas those for the fixed effects model account only for within study variability.

The bottom values on the right hand side table correspond to the results for the fixed and random effects models. These are represented in the plot by a dashed and dotted line respectively. The width of the corresponding grey diamonds represents the 95% confidence intervals. If the confidence intervals include zero the meta-analysis has not found significant evidence of a treatment effect. If, however, the confidence intervals do not include zero (as in this example) then there is evidence of a significant treatment effect. In this example, because there is heterogeneity in the studies, the results for the two models are not the same. However, both models arrive at similar conclusions: there is a significant improvement in corrected VA after 6 months of between -0.05 and -0.08 LogMAR. With very high heterogeneity, the results from the random effects model are more reliable, as this model is more resilient to the presence of heterogeneity.

Section 4: Epithelium-off CXL Results

Data were extracted on the characteristics of included papers and the CXL procedure (Table 4.1) and patient outcomes (Tables 4.2a and b).

4.1 NUMBER, TYPE AND QUALITY OF INCLUDED PAPERS

In total, 49 papers were identified as meeting the inclusion criteria. Of these, 8 papers (16%), (8, 37, 38, 41, 50[4], 52, 96, 117) reported findings from RCTs although these report data from only 4 unique studies (50, 52, 96, 117). For example, 2 papers (8, 38) reported selected sub-groups who underwent CXL but no comparator was reported.

The remaining papers were:

- 7 (14%) retrospective case series (1, 6, 97, 99, 100, 101, 106);
- 25 (51%) prospective case series (4, 7, 10, 11, 14, 20, 26, 33, 34, 35, 43, 53, 64, 68, 71, 75, 84, 90, 104, 107, 108, 114, 115, 116, 118);
- 5 (10%) case series (5, 46, 47, 63, 87);
- 4 (8%) prospective comparative case series (16, 65, 67, 70).

Of the total, 15 (31%) included between 10 and 20 patients, 15 (31%) between 21 and 40 patients, 8 (16%) between 41 and 60 patients, 4 (8%) between 61 and 100 patients, and 6 (12%) over 100 patients. One study (5) did not report the number of patients, but did report the number of eyes. The largest study reported on 413 patients (11). The 4 unique RCTs (50, 52, 96, 117) included 10, 58, 24 and 49 patients (10, 71, 10 and 66 eyes), respectively.

Almost a third of the papers have 20 or fewer patients. Whilst properly designed trials, with small sample sizes, may provide substantial evidence of efficacy and are appropriate in studies of rare diseases, there are concerns about the strength of conclusions derived from such papers. Many of these papers do not have sufficient power to detect clinically meaningful treatment effects, and more particularly safety events.

Only one paper was from the UK and this was of 24 patients (96); 28 (58%) were set in Europe, 7 (15%) in the USA and 13 (27%) in the rest of the world[5]. Thirty of the 49 papers (61%) were definitely from papers conducted in single centres, 9 (18%) were from multi-centres, and the other papers did not report this information.

[4] This paper describes itself as a RCT but text is unclear on randomisation. It may thus be a prospective comparative case study.

[5] Study 63 did not report location.

Only 34 papers reported mean age of the patients. The majority, 20 (59%), reported a mean age in the range 20 to 30 years, whilst 2 (6%) had a mean age of under 20 years and 12 (35%) had a mean age of over 30 years. There were some differences in the upper limit of the age range which varied between 18 and 76 years.

Twenty-eight papers analysed patients by gender, with an estimated 36% of patients being female. Over 60% of the papers, 31 in total, were published in 2010 or later. Some early papers used non-standard equipment; indeed, some of the early sites built their own equipment and hence the accuracy of measurement may be poorer in the earlier papers.

Twenty-nine papers (60%) had a 12-month follow-up, 6 had 6 months follow-up, 4 had 18 months follow-up, 6 were of 24 months duration, 2 reported results at 36 months and 2 reported results at 48 months. Those with longer duration did not always report the number of eyes recorded at each period. For example, of the 8 papers reporting results at 24 months or longer, 1 study (11) noted that the intention to treat numbers of 516 reduced to 182 at 24 months, 93 at 36 months and only 26, 5% of those initially included, at 48 months. Two papers (16, 241) were retrospective cohort studies so may be anticipated to have a low number lost to follow-up.

Across all papers, patients with certain characteristics were generally excluded from the studies. Typically, patients with evidence of corneal scarring, stromal haze, erosion or dystrophy, previous corneal surgery, or with a history of chemical burns were excluded. Patients with corneal or ocular disease other than keratoconus or keratectasia were also usually excluded. People with systemic or autoimmune disease, concurrent corneal infection, or pregnancy or breast feeding were also excluded from many studies.

4.2 QUALITY OF EVIDENCE

Thirty-nine (80%) of the papers were given a SIGN grade of 3; five (10%) (50, 65, 67, 68, 70) a SIGN grade of 2-; four (8%) (37, 41, 52, 96) a SIGN grade of 1+; and the remaining one (2%) (117) a SIGN grade of 1-. A GRADE classification of very low was given to all of the 39 papers with a SIGN grade of 3. Six papers (12%) (50, 65, 67, 68, 70, 117) were GRADE classified as low and the remaining 4 papers (8%) (37, 41, 52, 96) were classed as moderate. Thus, the quality of evidence from the majority of individual papers is low, with only 4 papers providing evidence of moderate quality. This reflects the extent of confidence that any single estimate of effect size is correct within any one paper, and there is clearly the possibility that new research will change the estimated effect size. However, the volume of evidence and the consistency of direction and reported effect sizes across all papers are also relevant to the confidence one can have in the effect size reported by the totality of the evidence. The more consistent the effect size reported is across a large number of papers, the more confidence one can have in the results.

Conflicts of interests which have been declared by authors are reported in Table 4.1.
No authors of papers in subsequent sections declared a conflict of interest.

4.3 DESCRIPTION OF RCTS

As noted, the 8 papers reporting results from RCTs (8, 37, 38, 41, 50, 52, 96, 117) reported 4 unique studies (50, 52, 96, 117). The study which generated several papers is by Hersh, Greenstein and Fry (52). It had 3 groups:

- 71 eyes, of which 49 had a diagnosis of keratoconus and 22 ectasia, received classic CXL;
- 41 eyes, 28 with keratoconus and 22 with ectasia, received riboflavin drops only and at 3 months crossed over to receive classic CXL;
- 30 fellow-eyes, which did not necessarily have evidence of disease, received no interventions and were followed-up.

In paper (52) results were presented at 1, 3, 6 and 12 months for visual acuity, topography, astigmatism and refraction for the entire cohort receiving CXL (112 eyes). Comparisons were provided between those with keratoconus and ectasia and the fellow-eye group at 12 months (no disease).

Two papers (8, 38) reported selected sub-groups from this study (52) who underwent CXL, but no comparator was reported. Paper (8) assessed subjective visual function whilst paper (38) examined the effect of preoperative cone location on 1-year outcomes. Two other papers (37, 41) report outcomes from this study at 1, 3, 6 and 12 months comparing the CXL group with the sham group at 3 months and then the fellow-eye group. The outcomes examined were corneal hysteresis and corneal resistance factor (37) and corneal thickness (41).

The smallest RCT (50) set in Peru, included 10 patients with progressive keratoconus in 1 eye who received CXL with riboflavin and UV A. The control group comprised 10 eyes of volunteers with progressive keratoconus where glasses were the only treatment provided. Outcomes were given for both groups at the beginning of the study and at 12 months.

The RCT reported in paper (96) was set in the UK and enrolled patients with early/moderate bilateral keratoconus with recent progression. One eye from each patient was randomised to undergo CXL with the other eye remaining untreated as a control over the 18-month follow- up period.

The RCT reported in paper (117) was set in Australia and eligible patients had progressive keratoconus. The 66 eyes from 49 patients were randomised to either classic CXL or the control group which was not treated. Follow-up results were reported at 3, 6 and 12 months. However, at the time of publication a large proportion of the eyes had not completed follow-up. For example, of the 33 eyes in the CXL group, 30 had been treated; 24 had 3-month follow-up, 17 had 6-month follow-up and 9 had 12-month follow-up, 1 was lost to follow-up before treatment.

4.4 CXL PROCEDURE

Most papers had similar inclusion and exclusion characteristics, including patients with a confirmed diagnosis of progressive keratoconus, grade I to II, or keratectasia, over 18 years old[6], with no evidence of other eye disorders or diseases of the immune system which could hinder healing, and not pregnant. Where stated, central corneal thickness (CCT) had to be at least 400 µm at the thinnest point. One exception was the RCT reported by Brooks (8), Greenstein (37, 38, 41) and Hersh (52) which excluded patients with a corneal thickness of less than 300 µm. Patients were usually required not to wear rigid lenses for at least 4 weeks before the procedure. Thus, there was a high degree of homogeneity across papers in terms of the patients included.

The procedures carried out were similar and essentially followed the 'Dresden' protocol ('classic CXL') by:

- Applying a preoperative anaesthesia;
- Removing between 6.0 and 9 mm of the central corneal epithelium using a blunt knife or laser. New papers favoured laser and the majority removed 8 to 9 mm;
- Applying riboflavin preoperatively in all cases, either to saturation or with a specified number of drops;
- Irradiating the cornea using UV A light for 25 to 30 minutes; UV A-light diodes (365/370 nm) and a 3 mW/cm^2 irradiance to induce corneal stiffening was used in all papers. Riboflavin was administered every 2 to 3 minutes for 25 to 30 minutes, during irradiation;
- Giving postoperative care in the form of washing the corneal surface, applying a soft bandage contact lens (in all cases reporting after-care), topical antibiotics, non-steroidal anti-inflammatories, and occasionally analgesics and vitamin ointments until the epithelium had healed, with topical steroids prescribed for a further 2 to 3 weeks. Healing was usually after 3 days when the lens bandage was removed.

For papers which admitted patients with thin corneas, hypotonic riboflavin was administered until the stroma had swollen to more than 400 µm.

[6] One admitted patients at aged 10 (87) and the RCT by Hersh *et al.* (52) included patients aged 14 years and older.

4.5 DATA SYNTHESIS

The data synthesis of outcomes is primarily quantitative for these epithelium-off CXL papers, and focuses on the meta-analyses findings. These combined the results of suitable papers; a full report on the meta-analysis undertaken has been submitted as a separate document referred to as Annex A. This document:

- Explains the rationale for including and excluding papers from the meta-analyses;
- Sets out how individual measures were grouped for each end point;
- Explains the methodology adopted;
- Presents the results for each meta-analysis as a table of the statistics for each paper and as a forest plot of the synthesised data. The forest plots are repeated in this report.

A narrative synthesis of all the papers is also provided.

The reporting of change between baseline and postoperative follow-up points for outcomes of interest to this review was variable. There was also variable reporting of p-values for the change between baseline and postoperative follow-up points where only the value at baseline and postoperative follow-up was given. Either the change or the p-value of the change was required for the inclusion of a study in the meta-analysis. As such, not all of the identified papers could be included in the meta-analysis of individual outcomes.

The end points adopted were change in:

- Visual acuity;
- Topography;
- Refraction and astigmatism;
- Central corneal thickness;
- Intraocular pressure.

As will be evident in later sections, some papers focused on one end point only so reporting seems somewhat incomplete; however, that is usually consistent with the study's objectives.

The poorest reported measure was change in intraocular pressure (IOP). However, this is not a significant outcome of CXL but is rather reported to note whether it changed following the increased corneal rigidity. Interpreting the change is quite difficult because there is no expectation of change in any one direction.

Table 4.1: Study and intervention characteristics of included papers of epithelium-off CXL procedures

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Greenstein **Year:** 2012 **Ref:** 37 **Country:** USA **Conflict of interest:** Steven A, Greenstein and Kristen L. Fry have no financial/conflicting interests to disclose. Peter S, Hersh is a consultant for Avedro, Inc.	**Follow-up:** 12 months. **Study type:** RCT. **SIGN grading:** 1+. **GRADE*:** Moderate. **Study aim:** Assess effect of CXL on IOP for patients with keratoconus and LASIK.	**Number of patients:** 56 intervention and 35 control patients. **Number of eyes:** 69 intervention (46 keratoconus and 23 ectasia). 35 control (23 keratoconus and 12 ectasia). **Mean age:** Not Reported. **% female:** Not Reported.	Aged ≥14. Progressive keratoconus or corneal ectasia defined as one or more of the following over 24 months: increase ≥1.0 D in max K, increase ≥1.0 D in manifest cylinder, increase ≥0.5 D in spherical equivalent, corneal thickness > 300 µm.	**Anaesthesia:** Topical anaesthetic. **Preop riboflavin:** 0.1% every 2 minutes for 30 minutes. Absorption confirmed by slit lamp. If cornea was <400µm hypotonic riboflavin added until stroma swollen to > 400µm. **Operative riboflavin:** 0.1% every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 365 nm; 30 minutes. **Postop care:** Antibiotic + corticosteroid and soft contact lens. Contact lens removed after epithelial healing. Antibiotic drops and corticosteroid drops for up to 2 weeks. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Greenstein **Year:** 2011 **Ref:** 41 **Country:** USA **Conflict of interest:** No author has a financial or proprietary interest in any material or method mentioned. Additional disclosure is found in the footnotes. Dr Hersh	**Follow-up:** 12 months. **Study type:** RCT. **SIGN grading:** 1+. **GRADE*:** Moderate. **Study aim:** Assess effect on corneal thickness after CXL for keratoconus and ectasia.	**Number of patients:** 65 intervention; number of patients in control group not reported. **Number of eyes:** 82 intervention (54 keratoconus, 28 ectasia). 41 control (28 keratoconus, 13 ectasia). **Mean age:** Not Reported.	Aged ≥ 14. Progressive keratoconus or corneal ectasia defined as one or more of the following over 24 months: increase ≥1.0 D in max K, increase ≥1.0 D in manifest cylinder, increase ≥0.5 D in spherical equivalent, corneal thickness > 300 µm.	**Anaesthesia:** Topical anaesthetic. **Prop riboflavin:** 0.1% every 2 minutes for 30 minutes. Absorption confirmed by slit lamp. If cornea was <400 µm hypotonic riboflavin added until stroma swollen to > 400 µm. **Operative riboflavin:** 0.1% every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 365 nm; 30 minutes. **Postop care:** Antibiotic + corticosteroid and soft contact lens. Contact lens removed after epithelial healing. Antibiotic drops

Author	Study design	Study population	Inclusion criteria	Intervention
is a consultant and medical monitor for Avedro, Inc.		**% female:** Not Reported.		and corticosteroid drops for up to 2 weeks. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Henriquez **Year:** 2011 **Ref:** 50 **Country:** Peru	**Follow-up:** 1, 3, 6 and 12 months. **Study type:** RCT. **SIGN grading:** 2-. **GRADE*:** Low. **Study aim:** To evaluate the safety and efficacy of CXL by riboflavin/UV light for the treatment of keratoconus.	**Number of patients:** 20. **Number of eyes:** 20. **Mean age:** 29.7. **% female:** 20%.	Diagnosis of keratoconus, no corneal opacities or scarring on slit-lamp examination, central corneal thickness > 450 µm, contact lens intolerance. Progression defined as increase in K max of 1.00 D in 1 year, patient reports of deteriorating visual acuity, or need for new contact lens more than once in 2 years.	**Anaesthesia:** Topical anaesthesia was achieved by instilling 1 drop of proparacaine hydrochloride 0.5% into the eye every 5 minutes for 3 doses. **Preop riboflavin:** 0.1% riboflavin solution, instilled every 5 minutes for 30 minutes it penetrated the cornea as shown by yellow staining in the anterior chamber on slit lamp. **Operative riboflavin:** Riboflavin solution applied to cornea every 5 minutes or sooner if the surface appeared visibly dry. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3.0 +/- 0.3mW/cm^2; wavelength not reported; 30 minutes. **Postop care:** Ofloxacin and bandage of soft contact lens. Acetaminophen 500 mg twice daily for 3 days. Ofloxacin for 7 days. Ketorolac tromethamine 0.5% for 5 days. Fluorometholone twice daily for 5 weeks. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Hersh **Year:** 2011 **Ref:** 52 **Country:** USA	**Follow-up:** 1, 3, 6 and 12 months. **Study type:** RCT. **SIGN grading:** 1+.	**Number of patients:** 71. **Number of eyes:** 142, 71 (49 keratoconus, 22 post-LASIK ectasia).	Aged 14+ Axial topography consistent with keratoconus or corneal ectasia, a corrected distance visual acuity worse than 20/20 and diagnosis of	**Anaesthesia:** Topical anaesthetic administered. **Preop riboflavin:** Riboflavin 0.1% solution every 2 minutes for 30 minutes. US pachymetry if cornea was < 400 µm. Hypotonic riboflavin (0.1% in sterile water) 1 drop every 10 seconds for 2 minutes session. Repeated until adequate thickness confirmed by US pachymetry.

Author	Study design	Study population	Inclusion criteria	Intervention
Conflict of interest: No author has a financial or proprietary interest in any material or method mentioned. Additional disclosure is found in the footnotes. Dr Hersh is a paid medical consultant to Avedro, Inc.	**GRADE*:** Moderate. **Study aim:** To evaluate 1-year outcomes of corneal CXL for treatment for keratoconus and corneal ectasia.	Sham group: 41 eyes (28 keratoconus, 13 ectasia). Fellow-eye: 30 eyes (21 keratoconus, 9 ectasia). **Mean age:** Not Reported. **% female:** Not Reported.	progressive keratoconus or LASIK-induced or photorefractive keratectomy-induced ectasia. Progressive keratoconus or ectasia defined as 1 or more changes over 24 months: An increase in 1.00 D + in steepest K measurement, increase of 1.00 D + in manifest cylinder, an increase of 0.50 D or more in manifest refraction spherical equivalent. Corneal pachymetry < 300 µm.	**Operative riboflavin:** Isotonic riboflavin administration every 2 minutes during UV A exposure. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3.0mW/cm^2; 365 nm; 30 minutes. **Postop care:** Antibiotic and corticosteroid drops continued 4 times daily for 1 week and 2 weeks, respectively. A soft contact lens bandage was placed and the eye re-examined with slit lamp. Contact lens removed after epithelial defect had closed. **Single centre:** No. **Single surgeon:** Not Reported.
Author: O'Brart **Year:** 2011 **Ref:** 96 **Country:** UK	**Follow-up:** 18 months. **Study type:** RCT. **SIGN grading:** 1+. **GRADE*:** Moderate. **Study aim:** To investigate efficacy of CXL in halting progression of keratoconus.	**Number of patients:** ITT 24. Completed follow-up 22. **Number of eyes:** ITT 24. Completed follow-up 22. **Mean age:** 29.6. **% female:** 21%.	Grade I to III keratoconus with progression and reduced visual acuity worsening of astigmatism, keratometry or cone apex power by 0.75 D over 18 months. Central corneal thickness > 400 µm. Non-diabetics.	**Anaesthesia:** Three drops of tetracaine 1% and one of chloramphenicol 0.5% were instilled over 5 minutes. **Preop riboflavin:** Five drops of 0.1%. **Operative riboflavin:** 0.1% administered every 3 to 5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Not Reported. **Single centre:** Yes. **Single surgeon:** Not Reported.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Wittig-Silva **Year:** 2008 **Ref:** 117 **Country:** Australia	**Follow-up:** 3, 6 and 12 months. **Study type:** RCT. **SIGN grading:** 1-. **GRADE*:** Low. **Study aim:** Provide evidence in relation to the efficacy and safety of CXL in the management of progressive keratoconus.	**Number of patients:** 49. **Number of eyes:** 66 (33 treatment, 33 control). **Mean age:** Treatment: 26.9 +/- 6.22; Control: 25.8 +/- 5.9. **% female:** 45% (treatment), 52% (control).	Diagnosis of keratoconus. Progression of ectasia over preceding 6 to 12 months confirmed by 1 or more of the following: increase of at least 1.00 D in K max, increase in astigmatism 1.00 D, increase of 0.50 D in manifest refraction spherical equivalent, 0.1 mm or more decrease in back optic zone radius of the best fitting contact lens. Aged 16 to 50. Minimum corneal thickness > 400 µm.	**Anaesthesia:** Topical anaesthetic (oxybuprocaine hydrochloride 0.4%) instilled 3 times over 10 minutes and 2 drops of topical antibiotic (chloramphenicol 0.5%). **Preop riboflavin:** Riboflavin solution combined with 20% dextran to achieve riboflavin concentration of 0.1%. Drops applied to cornea every 3 minutes for 15 minutes. **Operative riboflavin:** Drops every 2 to 3 minutes during UV A exposure. **Diameter of corneal removed:** 8.5mm. **UV A strength and WL and time:** UV A strength not reported; 370 nm; 30 minutes. **Postop care:** Chloramphenicol 0.5% for 7 days and bandage soft contact lens for 3 days. After contact lens removal fluorometholone acetate 0.1% for 2 weeks. **Single centre:** Not Reported. **Single surgeon:** Not Reported.
Author: Arbelaez **Year:** 2009 **Ref:** 4 **Country:** Oman	**Follow-up:** 6 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To evaluate safety and efficacy of CXL in keratoconic eyes.	**Number of patients:** 19. **Number of eyes:** 20. **Mean age:** 24.4. **% female:** 26%.	Progressive keratoconus where max K increased in several consecutive measurements over 3 to 6 months change in refraction, patient report of deteriorating visual acuity and contact lens intolerance.	**Anaesthesia:** Topical anaesthesia with oxybuprocaine. **Preop riboflavin:** Every 3 to 30 minutes until saturation confirmed by slit lamp. **Operative riboflavin:** Every 5 minutes to saturate. **Diameter of corneal removed:** 6 to 8mm. **UV A strength and WL and time:** 3mW/cm^2; 365nm; 30 minutes. **Postop care:** Contact lens, antibiotics ofloxacin + Pranoprofen for one week until healed when lens removed. Efemoline and

Author	Study design	Study population	Inclusion criteria	Intervention
				artificial tears. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Braun **Year:** 2005 **Ref:** 7 **Country:** USA	**Follow-up:** 6 month intervals (number of intervals not reported). **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluate clinical safety and efficacy of riboflavin / UV A induced CXL for stabilising progressive keratoconus.	**Number of patients:** 22. **Number of eyes:** 27. **Mean age:** Not Reported. **% female:** Not Reported.	Moderate to advanced keratoconus.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Not Reported. **Operative riboflavin:** Riboflavin drops applied to eyes. **Diameter of corneal removed:** Not Reported. **UV A strength and WL and time:** 3mW/cm2; 370nm; 30 minutes. **Postop care:** Not Reported. **Single centre:** Not Reported. **Single surgeon:** Not Reported.
Author: Brooks **Year:** 2012 **Ref:** 8 **Country:** USA **Conflict of interest:** Dr Hersh is medical monitor for Avedro, Inc. No author has a financial or proprietary interest in any material or method mentioned.	**Follow-up:** 1 year. **Study type:** Prospective case series (subgroup of RCT). **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Assess subjective visual function after CXL.	**Number of patients:** 76. **Number of eyes:** 107 (keratoconus - 71, ectasia - 36). **Mean age:** Not Reported. **% female:** Not Reported.	14 years+. Axial topography consistent with keratoconus or corneal ectasia. Corrected distance visual acuity worse than 20/20. A diagnosis of progressive keratoconus or LASIK-induced ectasia. Corneal pachymetry > 300 µm.	**Anaesthesia:** Topical anaesthesia. Absorption confirmed by slit lamp examination. **Preop riboflavin:** Administered every 2 minutes for 30 minutes. If cornea 400µm, hypotonic riboflavin,1 drop every 10 seconds for 2 minutes sessions and repeated until adequate corneal thickness. **Operative riboflavin:** Drops every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3.0mW/cm2; 365 nm; 30 minutes. **Postop care:** Antibiotic (1 week) and corticosteroid (2 weeks)

Author	Study design	Study population	Inclusion criteria	Intervention
				administered and soft contact lens. Contact lens removed after 3 to 5 days, or until epithelial healing. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Caporossi **Year:** 2010 **Ref:** 10 **Country:** Italy	**Follow-up:** 12, 24, 36 and 48 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To report long term results of CXL.	**Number of patients:** 44. **Number of eyes:** 44. **Mean age:** Not Reported. **% female:** Not Reported.	Clinical and instrumentally confirmed progressive keratoconus in previous 6 months. Corneal thickness > 400 µm. Mean K of < 55 D.	**Anaesthesia:** Topical anaesthesia (lidocaine 4%). **Preop riboflavin:** 0.1% soaking for 15 minutes. **Operative riboflavin:** 0.1% every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not reported; 30 minutes. **Postop care:** Soft contact lens bandage with ofloxacin, diclofenac + lacrimal for 4 days. After contact lens removal fluoromethol and lacrimal substitutes for 4 to 6 weeks. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Caporossi **Year:** 2011 **Ref:** 11 **Country:** Italy	**Follow-up:** 48 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To report long term functional analysis of CXL by age group.	**Number of patients:** 413 ITT in 3 groups (≤18 years = 105, 19 to 26 years = 243, ≥27 years = 65). **Number of eyes:** 516 ITT in 3 groups ≤18 years: 152 ITT, 91, 74, 25, 7 at 12, 24, 36 and 48 months respectively. 19 to 26 years: 286 ITT,	Progressive keratoconus in last three months of observation. Defined as uncorrected VA/Best corrected distance VA > 0.5 Snellen lines, increase of sphere/cylinder > 0.5 dioptres, increase of max K > 0.5 D, reduction of thinnest point of cornea by ≥10	**Anaesthesia:** Topical anaesthesia (lidocaine 4%). **Preop riboflavin:** 0.1% 10 minutes soaking. **Operative riboflavin:** 0.1% every 2.5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not reported; 30 minutes. **Postop care:** Soft contact lens for 4 days with ofloxacin, diclofenac and lachrymal substitutes. After contact lens

Author	Study design	Study population	Inclusion criteria	Intervention
		108, 83, 56, 11 at 12, 24, 36, 48 months respectively. ≥27 years: 78 ITT, 35, 25, 12, 8 at 12, 24, 36, 48 months respectively. **Mean age:** Not Reported. **% female:** Not Reported.	µm. Clear cornea at examination.	removal fluorometholone and lacrimal substitutes for 6 to 8 weeks. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Charters **Year:** 2012 **Ref:** 14 **Country:** Argentina	**Follow-up:** 1 week, 6, 12 and 18 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluate refractive improvement and keratometric stability in subclinical keratoconus that underwent simultaneous PRK and CXL.	**Number of patients:** 18. **Number of eyes:** 26. **Mean age:** 34. **% female:** Not Reported.	Keratometry and refraction for 2 years. 22+ years. Sphere not exceeding -4 D. Central corneal thickness of 480 µm to 450 µm. Corneal steepening less than 51 D.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Not Reported. **Operative riboflavin:** 0.1% riboflavin/20% dextran solution every 3 minutes for 60 minutes. **Diameter of corneal removed:** Not Reported. **UV A strength and WL and time:** 3mW/cm^2; 370 +/- 5 nm; 30 minutes. **Postop care:** Moxifloxacin drops and a bandage lens. **Single centre:** Yes. **Single surgeon:** Yes.
Author: Coskunseven **Year:** 2009a **Ref:** 16 **Country:** Argentina	**Follow-up:** Average follow-up 9 +/- 2 (range: 5 to 12) months. **Study type:** Prospective comparative case series.	**Number of patients:** 19. **Number of eyes:** 38. **Mean age:** 22 +/- 5.	Keratoconus grade I to III according to Amsler-Krumeich classification. Aged 18 or over. Contact lens intolerance. Proof of evolution of the	**Anaesthesia:** Topical anaesthetic drops applied. **Preop riboflavin:** 0.1% riboflavin solution in 20% dextran was applied to cornea every 3 minutes for 30 minutes, monitored by slit lamp prior to treatment. **Operative riboflavin:** Riboflavin solution applied every 2 to 3

Author	Study design	Study population	Inclusion criteria	Intervention
Conflict of interest: Dr Jankov is a clinical consultant for Wavelight Lase Technologie AG, Erlangen, Germany. The remaining authors have no proprietary interest in the materials presented herein.	**SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To assess the progression of keratoconus in patients treated with collagen cross-linkage with riboflavin and UV A irradiation.	**% female:** 37%.	disease. Corneal thickness of at least 400 µm at the thinnest point.	minutes to saturate cornea. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Ofloxacin, a bandage contact lens until re-epithelialisation, typically, 3 days postop. Steroid dexamethasone phosphate 0.1% declining over 2 months. **Single centre:** Yes. **Single surgeon:** Yes.
Author: Croxatto **Year:** 2010 **Ref:** 20 **Country:** Argentina	**Follow-up:** 5 hours, 7 days, 2 weeks, and 1, 3, 6, 9, 12, 18, 24 and 36 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluate the short and long term sequential histological changes of the cornea in vivo after corneal CXL.	**Number of patients:** 18. **Number of eyes:** 18 (grade I: 5, grade II: 9, grade III: 4). **Mean age:** Not Reported. **% female:** Not Reported.	Thinnest point pachymetry > 400 µm.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Riboflavin photosensitiser solution (0.1% riboflavin-5 phosphate and 20% dextran T-500) administered every 3 minutes for 30 minutes. **Operative riboflavin:** 0.1% riboflavin-5 phosphate and 20% dextran T-500 every 3 minutes during treatment. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3m/Wcm^2; 370 nm; 30 minutes. **Postop care:** Contact lens for 4 days, ofloxacin, steroids and ketorolac tromethamine until abrasion healed. **Single centre:** Yes. **Single surgeon:** Not Reported.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Doors **Year:** 2009 **Ref:** 26 **Country:** Netherlands	**Follow-up:** 1, 3, 6 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Investigate the stromal demarcation line after CXL in patients with keratoconus.	**Number of patients:** 29. **Number of eyes:** 29 (progressive keratoconus: 28, after laser in situ keratomileusis ectasia: 1). **Mean age:** 35.1 +/- 11.7. **% female:** 31%.	Snellen best corrected distance visual acuity of 0.4 or better. Pachymetry of >400 µm at the thinnest point. Aged 18+. Progression of keratoconus.	**Anaesthesia:** Tetracaine 1% drops applied 3 times before treatment. **Preop riboflavin:** Riboflavin 0.1% solution every 3 minutes over 30 minutes, Slit lamp used to determine if riboflavin present in anterior chamber. **Operative riboflavin:** Riboflavin drops applied every 5 minutes during irradiation. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Soft bandage lens removed after 1 week. Analgesics, artificial tears, non-steroidal anti-inflammatory and antibiotic eye drops. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Gkika **Year:** 2012 **Ref:** 33 **Country:** Greece	**Follow-up:** 3, 6 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To evaluate corneal hysteresis and corneal resistance factor in keratoconic eyes before and after CXL and determine	**Number of patients:** 30 (keratoconus), 50 (non-keratoconus control). **Number of eyes:** 50 (keratoconus), 50 (non-keratoconus control). **Mean age:** 31.1 (keratoconus), 33.3 (control). **% female:** 24%	Progressive keratoconus in consecutive corneal topographies, changes in refractive power and deterioration of the visual acuity within a period of 2 years. Central corneal thickness > 400 µm, K readings < 60 D. Participants must not have autoimmune disease.	**Anaesthesia:** Proparacaine hydrochloride 0.5% drops for topical anaesthesia. **Preop riboflavin:** 0.1% riboflavin in 20% dextran solution instilled to the cornea for 30 minutes (2 drops every 2 minutes), until stroma was completely penetrated and stained yellow. **Operative riboflavin:** One drop of riboflavin was applied every 2 minutes during irradiation. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes.

Author	Study design	Study population	Inclusion criteria	Intervention
	potential correlations with a series of corneal and demographic factors.	(keratoconus) 64% (control).		**Postop care:** Ofloxacin, fluorometholone diclofenac and artificial tears. Soft contact lens was applied until complete re-epithelialisation of cornea. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Goldich **Year:** 2010 **Ref:** 34 **Country:** Israel	**Follow-up:** 1 week, 1, 3, 6, 9 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To assess the possible damage to ocular tissues during treatment of keratoconus with UV A-riboflavin CXL.	**Number of patients:** 14. **Number of eyes:** 14. **Mean age:** 28.2. **% female:** 43%.	Progressive keratoconus documented clinically within 12 months, age 18+, no previous ocular surgery, no corneal opacities, central corneal thickness of > 400 µm.	**Anaesthesia:** Topical anaesthesia with oxybuprocaine hydrochloride 0.4% drops. **Preop riboflavin:** Not Reported. **Operative riboflavin:** Instillation of 0.1% riboflavin in 20% dextran solution every 5 minutes for 40 minutes. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Ofloxacin 0.3% and corticosteroid for 7 days; a soft contact lens for 3 days. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Goldich **Year:** 2012 **Ref:** 35 **Country:** Israel	**Follow-up:** 1 week, 1, 3, 6, 9, 12 and 24 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To assess the	**Number of patients:** 14. **Number of eyes:** 14. **Mean age:** 28.2. **% female:** 43%.	Progressive keratoconus documented clinically, age 18+, no previous ocular surgery, no corneal opacities, central corneal thickness of > 400 µm.	**Anaesthesia:** Topical anaesthesia with oxybuprocaine hydrochloride 0.4% drops. **Preop riboflavin:** Not Reported. **Operative riboflavin:** Instillation of 0.1% riboflavin in 20% dextran solution every 5 minutes for 40 minutes. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not

Author	Study design	Study population	Inclusion criteria	Intervention
	possible damage to ocular tissues during treatment of keratoconus with UV A-riboflavin CXL.			reported; 30 minutes. **Postop care:** Ofloxacin 0.3% and corticosteroid for 7 days; a soft contact lens for 3 days. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Greenstein **Year:** 2012 **Ref:** 38 **Country:** USA **Conflict of interest:** Dr Hersh is a medical monitor for Avedro Inc. The remaining authors have no financial or proprietary interest in the materials presented herein.	**Follow-up:** 12 months. **Study type:** Prospective case series (subgroup of RCT). **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Assess effect of preoperative cone location on 1 year outcomes after CXL.	**Number of patients:** 76. **Number of eyes:** 99 (66 keratoconus and 33 ectasia). **Mean age:** Not Reported. **% female:** Not Reported.	Aged ≥14. Progressive keratoconus or corneal ectasia defined as one or more of the following over 24 months: increase ≥1.0 D in max K, increase ≥1.0 D in manifest cylinder, increase ≥0.5 D in spherical equivalent, corneal thickness > 300 µm.	**Anaesthesia:** Topical anaesthetic. **Preop riboflavin:** 0.1% every 2 minutes for 30 minutes. Absorption confirmed by slit lamp. If cornea was <400µm hypotonic riboflavin added until stroma swollen to > 400µm. **Operative riboflavin:** 0.1% every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 365 nm; 30 minutes. **Postop care:** Antibiotic + corticosteroid and soft contact lens. Contact lens removed after epithelial healing. Antibiotic drops and corticosteroid drops for up to 2 weeks. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Grewal **Year:** 2009 **Ref:** 43 **Country:** India	**Follow-up:** 1 week, 1, 3 and 6 months, 1 year. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 102. **Number of eyes:** 102. **Mean age:** 25.6. **% female:** 46%.	Patients 18+, corneal thickness > 400 µm with progressive keratoconus, (increase in max keratometry of >1.00 D in 1 year or need > than 1 new contact lens in previous 2 years).	**Anaesthesia:** Topical anaesthesia (Lidocaine 4.0%, instilled 3 times over 15 minutes). **Preop riboflavin:** 2 to 4 drops of riboflavin 0.1% in 20.0%. Dextran every 5 minutes for 30 minutes. **Operative riboflavin:** Riboflavin instilled every 5 minutes during UV A exposure.

Author	Study design	Study population	Inclusion criteria	Intervention
	Study aim: To evaluate changes in corneal curvature, elevation and thickness, lens density and foveal thickness after CXL with riboflavin and UV A light in eyes with progressive keratoconus.			**Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3.0mW/cm^2; 370 nm; 30 minutes. **Postop care:** Ofloxacin and dressed with a bandage soft contact lens. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Holopainen **Year:** 2011 **Ref:** 53 **Country:** Finland	**Follow-up:** 3 days (results not available), 1 month (results not available) and 6 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To report the corneal thinning during and after CXL.	**Number of patients:** 30 (24 progressive keratoconus, 2 pellucid marginal degeneration, 3 progressive keratectasia, 1 pseudophakic bullous keratopathy). **Number of eyes:** 30. **Mean age:** 38 +/- 12. **% female:** 30%.	Consecutively scheduled for CXL between January 23 and July 6, 2009.	**Anaesthesia:** Paracetamol 1g 30 minutes before operation. Topical anaesthesia (tetracaine hydrochloride, 1% w/vol). Cornea rinsed with saline. **Preop riboflavin:** Isotonic or hypotonic riboflavin (0.1%) drops applied every 2 minutes for 30 minutes. Slit lamp using blue filter ensured presence of riboflavin in the anterior chamber. **Operative riboflavin:** Riboflavin 0.1% applied to cornea every 3 minutes during UV A exposure. Cornea was hydrated using distilled water or hypotonic riboflavin if corneal thickness was <350µm during CXL treatment. **Diameter of corneal removed:** 8 to 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 +/- 5 nm; 30 minutes. **Postop care:** Soft bandage contact lens applied for 3 days. 5 mg/mL levofloxacin for 5 days. Lubricant drops. Paracetamol-codeine as needed. After re-epithelialisation fluorometholone for 3 days. **Single centre:** Yes.

Author	Study design	Study population	Inclusion criteria	Intervention
				Single surgeon: Not Reported.
Author: Koller **Year:** 2011 **Ref:** 64 **Country:** Switzerland	**Follow-up:** 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To identify preoperative parameters that may predict flattening of the keratoconic cornea after collagen CXL.	**Number of patients:** ITT 192. 12 month follow-up 151 (103 keratoconus and 32 pellucid marginal degeneration, 20 cases differentiation not possible). **Number of eyes:** ITT 192. 12 month follow-up 151. **Mean age:** 29.3 +/- 8.6. **% female:** 36%.	Progressive keratoconus where max K increased by 1.0 D over 6 months. Max K had to be < 76.0 D with contact lens intolerance. Corneal thickness > 350 µm.	**Anaesthesia:** Anaesthesia for 15 minutes with oxybuprocaine and tetracaine. **Preop riboflavin:** 0.1% every 3 minutes for 30 minutes. If corneal thickness <400 µm, extra drops added until thickness exceeded 400 µm. **Operative riboflavin:** 0.1% every 3 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not reported; 30 minutes. **Postop care:** Ofloxacin 0.3% and eye patched. Antibiotic ointment for 3 days. After healing, fluorometholone for 1 week. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Koller **Year:** 2009 **Ref:** 65 **Country:** Switzerland	**Follow-up:** 12 months. **Study type:** Prospective, non-randomised comparative case series with untreated controls. **SIGN grading:** 2-. **GRADE*:** Low. **Study aim:** Compare the geometrical shape of keratoconus corneas after CXL with those of untreated fellow eyes using	**Number of patients:** 21. **Number of eyes:** 42. **Mean age:** 32.3 +/- 9.8. **% female:** 29%.	Progressive keratectasia verified by repeated Scheimpflug imaging over at least 6 months.	**Anaesthesia:** Topical anaesthesia for 15 minutes with oxybuprocaine and tetracaine. **Preop riboflavin:** 0.1% every 3 minutes for 30 minutes. If corneal thickness <400 µm then extra drops added until thickness exceeded 400 µm. **Operative riboflavin:** 0.1% every 3 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not reported; 30 minutes. **Postop care:** Ofloxacin 0.3% and eye patched. Antibiotic ointment for 3 days. After healing, fluorometholone for 1 week.

Author	Study design	Study population	Inclusion criteria	Intervention
	Scheimpflug imaging.			**Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Koppen **Year:** 2011 **Ref:** 67 **Country:** Belgium	**Follow-up:** 6, 12 and 18 months. **Study type:** Prospective non-randomised comparative case series. **SIGN grading:** 2-. **GRADE*:** Low. **Study aim:** To report on the influence of rigid gas permeable contact lens wear on the results of UV A/riboflavin CXL for stabilisation of progressive keratoconus.	**Number of patients:** 20. **Number of eyes:** 27. **Mean age:** 25.85. **% female:** 35%.	Progressive keratoconus that underwent an uneventful riboflavin/uncorrected visual acuity CXL treatment.	**Anaesthesia:** Two tetracaine drops. **Preop riboflavin:** Riboflavin 0.1% in dextran 20% was applied every 2 minutes for 30 minutes. **Operative riboflavin:** Every 3 minutes for 30 minutes. **Diameter of corneal removed:** 8 to 9mm. **UV A strength and WL and time:** 3mW/cm^2; 365 nm; 30 minutes. **Postop care:** A bandage contact lens plus ofloxacin for first week. Contact lens bandage removed when epithelium had healed. Corticosteroids if haze. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Kranitz **Year:** 2012 **Ref:** 68 **Country:** Hungary	**Follow-up:** 12 months. **Study type:** Prospective case series. **SIGN grading:** 2-. **GRADE*:** Low. **Study aim:** To compare corneal changes after CXL.	**Number of patients:** 22. **Number of eyes:** 40 (25 with CXL and 15 control eyes). **Mean age:** 29.92. **% female:** Not Reported.	Progressive keratoconus-increase in K values by >1.00 D in 6 months and subjective vision loss of > 2 lines of corrected visual acuity in 1 year. For control eyes mild to moderate keratoconus.	**Anaesthesia:** Oxybuprocaine-hydrochloride 4mg/ml drops. **Preop riboflavin:** 0.1% riboflavin applied every 5 minutes starting 25 minutes before irradiation. **Operative riboflavin:** Not Reported. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Levofloxacin 5 times a day for 7 days, After re-epithelialisation steroid drops.

Author	Study design	Study population	Inclusion criteria	Intervention
				Single centre: Not Reported. **Single surgeon:** Not Reported.
Author: Kymionis **Year:** 2009 **Ref:** 75 **Country:** Greece	**Follow-up:** 6 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To determine effect of CXL on CCT.	**Number of patients:** 55. **Number of eyes:** 55. **Mean age:** 24.4 +/- 4.1. **% female:** Not Reported.	Progressive keratoconus; corneal thickness > 400 µm. Participants must be without systemic or connective tissue disease.	**Anaesthesia:** Topical anaesthesia with proxymetacaine. **Preop riboflavin:** 0.1% every 3 minutes for 30 minutes. **Operative riboflavin:** 0.1% every 3 minutes for 30 minutes. **Diameter of corneal removed:** 8.5 to 9mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not reported; 30 minutes. **Postop care:** Soft contact lens until re-epithelialization. Diclofenac for 2 days, antibiotic / corticosteroid until contact lens removal. **Single centre:** Not Reported. **Single surgeon:** Not Reported.
Author: Kymionis **Year:** 2012 **Ref:** 71 **Country:** Greece	**Follow-up:** 6 and 12 months. Only data at 12 months provided. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To report outcomes of CXL in patients with thin corneas.	**Number of patients:** 12 (10 keratoconus, 2 post LASIK ectasia). **Number of eyes:** 14. **Mean age:** 26.71 +/- 6.55. **% female:** 33%.	Corneal thickness ≥400 µm. Participants must be without systemic or connective tissue disease.	**Anaesthesia:** Topical anaesthesia with proxymetacaine. **Preop riboflavin:** 0.1% every 3 minutes for 30 minutes. **Operative riboflavin:** 0.1% every 3 minutes for 30 minutes. **Diameter of corneal removed:** 8.5 to 9mm. **UV A strength and WL and time:** 3mW/cm^2; 365 nm; 30 minutes. **Postop care:** Soft contact lens diclofenac, antibiotics, corticosteroid until re-epithelialization. Corticosteroid for 3 weeks and artificial tears for 3 months.

Author	Study design	Study population	Inclusion criteria	Intervention
				Single centre: Not Reported. **Single surgeon:** Not Reported.
Author: Kymionis **Year:** 2012 **Ref:** 70 **Country:** Greece	**Follow-up:** 6 and 12 months. **Study type:** Prospective comparative case series. **SIGN grading:** 2-. **GRADE*:** Low. **Study aim:** Compare the outcomes of CXL for treatment of progressive keratoconus using 2 different techniques for epithelial removal: TG-PRK versus mechanical epithelial debridement.	**Number of patients:** 34. **Number of eyes:** 38. **Mean age:** Group 1: 28 +/- 4.8; Group 2: 28 +/- 3.8. **% female:** Group 1: 23% Group 2: 28%.	Clinical diagnosis of keratoconus based mainly on corneal topography and clinical signs. Participants must be without systemic or connective tissue disease.	**Anaesthesia:** Proxymetacaine hydrochloride 0.5% eye drops. **Preop riboflavin:** Riboflavin 0.1% solution instilled every 3 minutes for 30 minutes. **Operative riboflavin:** Riboflavin solution applied every 3 minutes. **Diameter of corneal removed:** Group 1: 8mm, Group 2: 8mm. **UV A strength and WL and time:** Both groups: 3.0mW/cm²; 370 nm; 30 minutes. **Postop care:** Soft contact lens diclofenac, antibiotics, corticosteroid until re-epithelialization. Corticosteroid for 3 weeks and artificial tears for 3 months. **Single centre:** Not Reported. **Single surgeon:** Not Reported.
Author: Li **Year:** 2010 **Ref:** 84 **Country:** China	**Follow-up:** 1, 3, 6 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluate efficacy and safety of CXL to prevent the progression of post-LASIK corneal ectasia.	**Number of patients:** 11. **Number of eyes:** 20. **Mean age:** 27.4. **% female:** 55%.	Previous LASIK surgery. Ectasia progression indicated by increase in K max over 6 months. Corneal thickness of > 400 µm at thinnest point. Aged 18 to 50 and without autoimmune disease.	**Anaesthesia:** Oxybuprocaine 0.4% eye drops. **Preop riboflavin:** 0.1% riboflavin applied every 3 minutes for approximately 30 minutes. Successful penetration of cornea confirmed by slit lamp bio microscopy. **Operative riboflavin:** Isotonic riboflavin 0.1% solution administered every 3 minutes to saturate cornea. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not reported; 30 minutes.

Author	Study design	Study population	Inclusion criteria	Intervention
				Postop care: Ofloxacin 0.3% and contact lens bandage for 3 days until re-epithelialisation. Fluorometholone for 4 weeks. **Single centre:** Yes. **Single surgeon:** Yes.
Author: Mazzotta **Year:** 2007 **Ref:** 90 **Country:** Italy	**Follow-up:** 1, 3 and 6 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To assess structural changes following CXL.	**Number of patients:** 10. **Number of eyes:** 10. **Mean age:** Not Reported. **% female:** Not Reported.	Aged 18 to 60, without autoimmune disease. Corneal thickness ≥400 µm.	**Anaesthesia:** Topical anaesthesia with lidocaine 4%. **Preop riboflavin:** 0.1% 5 minutes before. **Operative riboflavin:** Not Reported. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; time not reported. **Postop care:** Soft contact lens for 5 days. Cyclopentolate, ofloxacin and diclofenac during first 5 days. **Single centre:** Not Reported. **Single surgeon:** Not Reported.
Author: Romano **Year:** 2012 **Ref:** 104 **Country:** Italy	**Follow-up:** 1, 3 and 6 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To detect any morphological change in the retina of cross-linkage eyes using retinal tomography.	**Number of patients:** Keratoconus: 17; control (healthy): 21. **Number of eyes:** Keratoconus: 21; control (healthy): 21. **Mean age:** Keratoconus: 36 +/- 7; Control: 34 +/- 4. **% female:** Not Reported.	Consecutive patients with progressive keratoconus.	**Anaesthesia:** Not Reported. **Preop Riboflavin:** Not Reported. **Operative riboflavin:** Not Reported. **Diameter of corneal removed:** Not Reported. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Not Reported. **Single centre:** Yes.

Author	Study design	Study population	Inclusion criteria	Intervention
				Single surgeon: Not Reported.
Author: Salgado **Year:** 2010 **Ref:** 107 **Country:** Germany	**Follow-up:** 1, 3, 6 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluate the effect of CXL with riboflavin and UV A as a treatment option for post-LASIK keratectasia.	**Number of patients:** 15. **Number of eyes:** 22. **Mean age:** 38.4 +/- 8.13. **% female:** 40%.	Progressive keratectasia after refractive surgery as well as pachymetry > 400 µm.	**Anaesthesia:** Proxymetacaine hydrochloride 0.5%, 2 drops at 30 second intervals. **Preop riboflavin:** 0.1% riboflavin isotonic solution applied every 5 minutes for 30 minutes. **Operative riboflavin:** Riboflavin applied every 5 minutes during UV A exposure. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Bandage contact lens soaked in levofloxacin 5mg/mL until epithelial closure. Then levofloxacin + carbomer. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Sedaghat **Year:** 2010 **Ref:** 108 **Country:** Iran	**Follow-up:** 6 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To compare CH and CRF before and after CXL for keratoconus.	**Number of patients:** 51. **Number of eyes:** 56. **Mean age:** 23.27 +/- 6.3. **% female:** 39%.	Aged 18 to 40 with no autoimmune disease. Corneal thickness > 400 µm.	**Anaesthesia:** Topical anaesthesia. **Preop riboflavin:** 0.1% every 3 minutes for 30 minutes. **Operative riboflavin:** 0.1% every 5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Bandage contact lens with chloramphenicol. Betamethasone until re-epithelialisation. Then fluorometholone for 6 weeks if haze.

Author	Study design	Study population	Inclusion criteria	Intervention
				Single centre: Yes. **Single surgeon:** Yes.
Author: Vinciguerra **Year:** 2012 **Ref:** 114 **Country:** Italy and Switzerland **Conflict of interest:** Dr Vinciguerra is consultant for Oculus.	**Follow-up:** 6, 12 and 24 months. **Study type:** Prospective case series **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Report refractive, topographic, errometric, and tomographic outcomes 24 months after CXL in patients up to 18 years of age with progressive keratoconus.	**Number of patients:** 40. **Number of eyes:** 40. **Mean age:** 14.2 +/- 1.7. **% female:** Not Reported.	Under 18 years with no autoimmune disease. Documented keratoconus progression over 3 months. Corneal thickness at least 400 µm.	**Anaesthesia:** 30 minutes prior to procedure pain drugs + pilocarpine 2%. 2 applications of lidocaine 4% and oxybuprocaine 0.2%. **Preop riboflavin:** 0.1% every minute for 30 minutes. Presence of riboflavin confirmed with slit lamp with blue filter. **Operative riboflavin:** 0.1% every 5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 +/- 5 nm; 30 minutes. **Postop care:** Cyclopentolate and levofloxacin with soft bandage contact lens for up to 7 days, dexamethasone for 20 days, and sodium hyaluronate for 45 days. Amino acid supplements for 7 days. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Vinciguerra **Year:** 2009 **Ref:** 116 **Country:** Italy	**Follow-up:** 6, 12 and 24 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Report intraoperative and 24 month	**Number of patients:** 28. **Number of eyes:** 28. **Mean age:** Not Reported. **% female:** 29%.	Over 18 years with no autoimmune disease. Documented keratoconus progression over 6 months defined as change in myopia of ≥1.5 D or mean central corneal thickness decrease ≥ 5% in 3 consecutive tomographies. Corneal	**Anaesthesia:** 30 minutes prior to procedure pain drugs + pilocarpine 2%. 2 applications of lidocaine 4% and oxybuprocaine. **Preop riboflavin:** 0.1% every minute for 30 minutes. Presence of riboflavin confirmed with slit lamp with blue filter. **Operative riboflavin:** 0.1% every 5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 +/- 5 nm; 30

Author	Study design	Study population	Inclusion criteria	Intervention
	refractive, topographic, tomographic, and aberrometric outcomes after CXL in progressive advanced keratoconus.		thickness at least 400 µm.	minutes. **Postop care:** Cyclopentolate and levofloxacin with soft bandage contact lens for up to 7 days, dexamethasone for 20 days, and sodium hyaluronate for 45 days. Amino acid supplements for 7 days. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Vinciguerra **Year:** 2009 **Ref:** 115 **Country:** Italy	**Follow-up:** 6 and 12 months. **Study type:** Prospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Report refractive, topographic, tomographic, and aberrometric outcomes 12 months after CXL in eyes with progressive advanced keratoconus.	**Number of patients:** 28. **Number of eyes:** 28. **Mean age:** Not Reported. **% female:** 29%.	Over 18 years with no autoimmune disease. Documented keratoconus progression over 6 months. Corneal thickness at least 400 µm.	**Anaesthesia:** 30 minutes prior to procedure pain drugs + pilocarpine 2%. 2 applications of lidocaine 4% and oxybuprocaine. **Preop riboflavin:** 0.1% every minute for 30 minutes. Presence of riboflavin confirmed with slit lamp with blue filter. **Operative riboflavin:** 0.1% every 5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 +/- 5 nm; 30 minutes. **Postop care:** Cyclopentolate and levofloxacin with soft bandage contact lens for up to 7 days, dexamethasone for 20 days, and sodium hyaluronate for 45 days. Amino acid supplements for 7 days. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Wollensak **Year:** 2003 **Ref:** 118	**Follow-up:** 3 to 47 months (mean: 23.2 +/- 12.9). **Study type:** Prospective case series.	**Number of patients:** 22. **Number of eyes:** 23.	Patients with moderate or advanced progressive keratoconus (maximum K value, 48 to 72 D).	**Anaesthesia:** Proxymetacaine hydrochloride 0.5%. **Preop riboflavin:** Riboflavin 0.1% solution applied 5 minutes before irradiation.

Author	Study design	Study population	Inclusion criteria	Intervention
Country: Germany	**SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluate the clinical usefulness of riboflavin/UV A-induced collagen CXL for bringing the progression of keratoconus to a halt.	**Mean age:** 31.7 +/- 11.9. **% female:** 45%.		**Operative riboflavin:** Riboflavin applied every 5 minutes during irradiation. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Antibiotic ointment was applied until re-epithelialisation. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Agrawal **Year:** 2009 **Ref:** 1 **Country:** India	**Follow-up:** Patients only included with 12 months minimum (range 12 to 16 months). Results recorded at 6 and 12 months. **Study type:** Retrospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To assess the results of CXL with riboflavin using UV A light for keratoconus at one year.	**Number of patients:** 68 intention to treat (ITT); 37 with the required minimum follow-up. **Number of eyes:** 41 ITT. 25 with the required minimum follow-up. **Mean age:** 16.9 +/- 6.35. **% female:** Not Reported.	Progressive keratoconus defined as: increase in keratometry of 1.00 D in a year; patient reported deterioration of best corrected distance visual acuity and need for new contact lens fitting more than once in two years. Corneal thickness ≥ 400 µm.	**Anaesthesia:** Not Reported. **Preop riboflavin:** 0.1% riboflavin every 5 minutes for 25 minutes before irradiation. **Operative riboflavin:** 0.1% riboflavin applied every 5 minutes during irradiation. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** UV A 3mW/cm^2; 370 nm; 25 minutes. **Postop care:** Eye patched for 24 hours. For 7 days: moxifloxacin and prednisolone acetate drops. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Asri **Year:** 2011	**Follow-up:** 1, 3, 6 and 12 months. Potential follow-up bias acknowledged by authors.	**Number of patients:** ITT =142. 6 month = 104. 12 months = 64.	Central corneal thickness > 400 µm. Keratoconus disease progression proven by	**Anaesthesia:** Miotic drop (pilocarpine 1%). **Preop riboflavin:** Intrastromal soaking with riboflavin 0.1% for 20 minutes applied using a retinal lens as a cup at 1 drop per

Author	Study design	Study population	Inclusion criteria	Intervention
Ref: 6 **Country:** France	**Study type:** Retrospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To report outcome and safety data from CXL.	**Number of eyes:** ITT =142. 6 month = 104. 12 months = 64. **Mean age:** 24.12 +/- 7.58. **% female:** 23%.	previous keratometry reports. Subjective loss of vision (loss of at least 2 lines of corrected distance visual acuity in 1 year or keratometry increasing more than 1.0 D in 6 months or 2.0 D in 12 months).	minute. **Operative riboflavin:** 1 drop riboflavin 0.1% every 5 minutes. **Diameter of corneal removed:** 6 to 7mm. **UV A strength and WL and time:** 3mW/cm2; 370nm; 30 minutes (6x5 minutes). **Postop care:** Soft contact lens for 3 days and topical dexamethasone given 4 times daily tapered down over a month. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Pinero **Year:** 2012 **Ref:** 97 **Country:** Spain	**Follow-up:** 3, 6, 12 and 24 months. **Study type:** Retrospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To analyse stigmatic change after CXL and relationship between this change and clinical outcomes.	**Number of patients:** 12. **Number of eyes:** 16. **Mean age:** 32.58. **% female:** 25%.	Keratoconus diagnosed by corneal topography. Prior treatment with intrastromal corneal ring segments with progression at > 3 months after implant. Progression: increase of > 1.0 D in mean K or 0.5 D in manifest refraction. Corneal thickness > 370 µm.	**Anaesthesia:** Antibiotic prophylaxis for 2 days prior to surgery. **Preop riboflavin:** 0.1% applied every 5 minutes for 15 to 20 minutes. **Operative riboflavin:** 0.1% every 3 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Not Reported. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Raiskup **Year:** 2009	**Follow-up:** 1, 6 and 12 months. **Study type:** Retrospective	**Number of patients:** 114 (control), 13 (haze group).	Patients with keratoconus and corneal thickness of less than 400 µm.	**Anaesthesia:** Topical anaesthesia with proxymetacaine hydrochloride 0.5% eye drops. **Preop riboflavin:** 0.1% riboflavin solution applied to cornea 15

Author	Study design	Study population	Inclusion criteria	Intervention
Ref: 100 **Country:** Germany	case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluation of haze development after riboflavin-UV A induced CXL.	**Number of eyes:** 149 (control), 14 (haze group). **Mean age:** 31.53 +/- 8.58. **% female:** Not Reported.		to 20 minutes before irradiation. Slit-lamp used to ascertain if riboflavin penetrated the cornea. **Operative riboflavin:** Drops of riboflavin solution applied to cornea every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Antibiotics, vitamin A applied until re-epithelialisation. Analgesics, artificial tears and steroids prescribed after closure for 3 weeks. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Raiskup **Year:** 2011 **Ref:** 99 **Country:** Germany	**Follow-up:** 12 months. **Study type:** Retrospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To evaluate the 1-year results of keratoconic eyes with thin corneas that was treated by a hypoosmolar riboflavin solution and UV A CXL.	**Number of patients:** 29. **Number of eyes:** 32. **Mean age:** 27.4 +/- 9.4. **% female:** 31%.	Progressive keratoconus and a corneal thickness of at least 400 µm were included. Progression considered an increase in K max and corneal thickness reduction with or without changes in uncorrected visual acuity and best corrected visual acuity within the last year.	**Anaesthesia:** Topical anaesthesia using proxymetacaine hydrochloride 0.5% eye drops. **Preop riboflavin:** 0.1% hypoosmolar riboflavin applied to cornea every 2 minutes for 30 minutes before treatment. **Operative riboflavin:** Hypoosmolar riboflavin applied every 2 minutes to avoid any desiccation of cornea. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm²; 370 nm; 30 minutes. **Postop care:** Antibiotics, artificial tears, analgesics plus contact lens until complete re-epithelialisation. Then steroids for 3 weeks. **Single centre:** Yes.

Author	Study design	Study population	Inclusion criteria	Intervention
				Single surgeon: Not Reported.
Author: Raiskup-Wolf **Year:** 2008 **Ref:** 101 **Country:** Germany	**Follow-up:** 1, 6 months, 1, 2 and 3 years. **Study type:** Retrospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To prove long-term dampening effect of riboflavin and UV A induced CXL on progressive keratoconus.	**Number of patients:** 130. **Number of eyes:** 241. **Mean age:** 30.04 +/- 10.46. **% female:** Not Reported.	Progressive keratoconus based on increase in K max of 1.00 D in 1 year, deteriorating visual acuity or the need for new contact lens fitting more than once in 2 years. Corneal thickness of at least 400 µm. Aged 18+.	**Anaesthesia:** Topical anaesthesia of proxymetacaine hydrochloride 0.5% eye drops. **Preop riboflavin:** 0.1% riboflavin solution applied to cornea 20 minutes before irradiation. **Operative riboflavin:** Drops of riboflavin solution applied to cornea every 4 to 5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; 30 minutes. **Postop care:** Ofloxacin and vitamin A, analgesics until re-epithelialisation. Artificial tears and steroids. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Saffarian **Year:** 2010 **Ref:** 106 **Country:** Iran	**Follow-up:** 1 year. **Study type:** Retrospective case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Evaluate the outcomes of CXL for progressive keratoconus in Iranian patients.	**Number of patients:** 53. **Number of eyes:** 92. **Mean age:** 21.5 +/- 3.4. **% female:** 42%.	Keratoconus progression and corneal thickness of 400 µm at the thinnest point. Keratoconus progression defined by an increase in K max of 1.00 D in 1 year; deteriorating best corrected VA, or the need for new contact lens fitting more than once in 2 years. Corneal thickness > 400 µm.	**Anaesthesia:** Topical anaesthesia (0.5% tetracaine). **Preop riboflavin:** Riboflavin 0.1% solution (10mg riboflavin in 10 mL dextran 20% solution) instilled every 2 minutes for 24 minutes. Riboflavin penetration confirmed by slit lamp examination with blue filter. **Operative riboflavin:** Riboflavin solution applied every 4 minutes. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2; 370 nm; time not reported.

Author	Study design	Study population	Inclusion criteria	Intervention
				Postop care: Ciprofloxacin 0.30% and betamethasone 0.1% with bandage contact lens until re-epithelialisation, then fluorometholone. **Single centre:** Yes. **Single surgeon:** Not Reported.
Author: Asfuroglu **Year:** 2012 **Ref:** 5 **Country:** USA	**Follow-up:** 9 months. **Study type:** Case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Not Reported.	**Number of patients:** Not Reported. **Number of eyes:** 26. **Mean age:** Not Reported. **% female:** Not Reported.	Mild to moderate keratoconus.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Not Reported. **Operative riboflavin:** Not Reported. **Diameter of corneal removed:** Not Reported. **UV A strength and WL and time:** Not Reported. **Postop care:** Not Reported. **Single centre:** Not Reported. **Single surgeon:** Not Reported.
Author: Hafezi **Year:** 2007 **Ref:** 47 **Country:** Switzerland and Greece	**Follow-up:** Between 12 and 25 months. NOTE: Patients 1 to 3 not reported on here, 1 had pellucid marginal degeneration, 1 had high correction with corneal thickness and 1 the cause was not identified. **Study type:** Case series. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 10 (7 - undiagnosed forme fruste keratoconus, 1 - undiagnosed pellucid marginal degeneration, 1 - high correction, 1 - cause not identified). **Number of eyes:** 10. **Mean age:** 36.2. **% female:** 60%.	Patients with progressive keratoconus or iatrogenic keratectasia after refractive laser surgery. Eyes with distinct keratoconus and a minimum stromal thickness of 320 µm to 400 µm after removal of the epithelium.	**Anaesthesia:** Topical anaesthesia of tetracaine 1% and oxybuprocaine 0.4% eye drops. **Preop riboflavin:** Riboflavin (0.1% solution) every 3 minutes for approximately 30 minutes, until stroma was completely penetrated and aqueous was stained yellow. **Operative riboflavin:** Riboflavin treatment applied every 5 minutes during treatment to ensure saturation. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2. 30 minutes. **Postop care:** A contact lens soaked inofloxacin for 72 hours

Author	Study design	Study population	Inclusion criteria	Intervention
	Study aim: To determine whether riboflavin and UV A CXL can be used as an alternative therapy to prevent the progression of keratectasia.			until epithelium healed. Then fluorometholone daily for 6 weeks. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Hafezi **Year:** 2009 **Ref:** 46 **Country:** Switzerland	**Follow-up:** 6 months. **Study type:** Case series. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** To present a modified technique of CXL using hypoosmolar riboflavin solution to induce stromal swelling and increase the stromal thickness before CXL in cases with preoperatively thin corneas.	**Number of patients:** 20. **Number of eyes:** 20. **Mean age:** 29.5. **% female:** 35%.	Progressive keratectasia in corneal topographies using the increase in max K readings over 3 months and changes in refraction reported.	**Anaesthesia:** Topical anaesthetic agent (oxybuprocaine 0.4%) administered every 5 minutes during treatment. **Preop riboflavin:** Riboflavin 0.1% applied at 3 minutes for 30 minutes. Hypoosmolar riboflavin applied every 20 seconds for 5 more minutes and then until corneal thickness reached 400µm. **Operative riboflavin:** Isotonic riboflavin 0.1% solution administered every 5 minutes to saturate the cornea. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm², wavelength not reported; 30 minutes. **Postop care:** Antibiotic ointment and a bandage contact lens soaked in antibiotic agent applied until epithelium healed. Then fluorometholone for 2 weeks. **Single centre:** No. **Single surgeon:** Not Reported.
Author: Kjankov **Year:** 2009 **Ref:** 63 **Country:** Not Reported	**Follow-up:** 3 months, 1 year, 2 years. **Study type:** Case series. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 22. **Number of eyes:** 34. **Mean age:** Not Reported.	Progressive keratoconus in previous 6 months.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Cornea soaked with riboflavin for 15 minutes. **Operative riboflavin:** Not Reported. **Diameter of corneal removed:** Not Reported.

Author	Study design	Study population	Inclusion criteria	Intervention
	Study aim: Not Reported.	**% female:** Not Reported.		**UV A strength and WL and time:** UV A strength and wavelength not reported; 30 minutes. **Postop care:** Not Reported. **Single centre:** Not Reported. **Single surgeon:** Not Reported.
Author: Mazzotta **Year:** 2012 **Ref:** 87 **Country:** Italy	**Follow-up:** 6 and 12 months. **Study type:** Case report. **SIGN grading:** 3. **GRADE*:** Very low. **Study aim:** Investigate links between corneal structure changes and visual acuity and morphological data following CXL.	**Number of patients:** 44. **Number of eyes:** 44. **Mean age:** Not Reported. **% female:** Not Reported.	Age 10 to 40, progressive keratoconus defined as worsening uncorrected visual acuity and best corrected visual acuity over last 3 to 6 months and increased mean (>0.5 D + corneal thickness reduction of ≥10 µm). Mean K≤ 55 D. Corneal thickness ≥400 µm.	**Anaesthesia:** Anaesthesia with lidocaine 4% 15 minutes before and once after epithelial removal and pilocarpine 1% 30 minutes. **Preop riboflavin:** Corneal soaking for 15 minutes in 0.1%. **Operative riboflavin:** 0.1% every 5 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2; wavelength not reported; 30 minutes. **Postop care:** Antibiotics, ofloxacin drops, flurbiprofen and lacrimal substitutes, therapeutic soft contact lens, for 4 days. Steroids after removal. **Single centre:** Not Reported. **Single surgeon:** Not Reported.

***** High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Table 4.2a: Summary of visual acuity and topography outcomes in included papers on epithelium-off CXL

Author	Visual acuity	Topography
Author: Greenstein **Year:** 2012 **Ref:** 37 **Country:** USA	Measured in LogMAR and Snellen Total Group (Keratoconus and ectasia) UCVA LogMAR Baseline: 0.80 +/- 0.34 12 months: 0.71 +/- 0.39 (p=0.001) UCVA Snellen Baseline: 20/126 12 months: 20/103 (p=0.001) CVA LogMAR Baseline: 0.33 +/- 0.24 12 months: 0.23 +/- 0.21 (p<0.001) CVA Snellen Baseline: 20/43 12 months: 20/34 (p<0.001) Keratoconus only UCVA LogMAR Baseline: 0.82 +/- 0.37 12 months: 0.77 +/- 0.40 (p>0.05) CVA LogMAR Baseline: 0.37 +/- 0.26 12 months: 0.25 +/- 0.23 (p<0.05) Ectasia only UCVA LogMAR Baseline: 0.73 +/- 0.29 12 months: 0.59 +/- 0.33 (p<0.05) CVA LogMAR Baseline: 0.26 +/- 0.16 12 months: 0.18 +/- 0.13 (p<0.05).	Measured in dioptres Total Group (Keratoconus and ectasia) Mean K Baseline: 58.00 +/- 9.40 12 months: 56.40 +/- 8.10 (p<0.001) Keratoconus only Max K Baseline: 59.70 +/- 9.70 12 months: 57.80 +/- 8.20 (p<0.05) Ectasia only MaxK Baseline: 54.50 +/- 7.80 12 months: 53.60 +/- 7.20 (p<0.05).
Author: Greenstein **Year:** 2011 **Ref:** 41 **Country:** USA.	Not Reported.	Not Reported.

Author	Visual acuity	Topography
Author: Henriquez **Year:** 2011 **Ref:** 50 **Country:** Peru	Measured in LogMAR UCVA Preop: 1.18 +/- 0.80 1 month: 0.88 +/- 0.72 3 months: 0.61 +/- 0.46 6 months: 0.56 +/- 0.44 12 months: 0.46 +/- 0.36 BCVA: Preop: 0.20 +/- 0.18 1 month: 0.13 +/- 0.12 3 months: 0.09 +/- 0.09 6 months: 0.09 +/- 0.09 12 months: 0.09 +/- 0.09 Fellow eyes Corrected VA 0.16.	Measured in dioptres K max 1 month: Kmax reduced by 0.76 D. 3 months: K max reduced by 1.00 D. 6 months: K max reduced by 1.39 D. 12 months: K max reduced by 2.66 D (p=0.04). K min 1 month: K min reduced by 0.34 D. 3 months: K min reduced by 0.94 D. 6 months: K min reduced by 1.01 D 12 months: Kmin reduced by 1.61 D (p=0.03).
Author: Hersh **Year:** 2011 **Ref:** 52 **Country:** USA	Measured in LogMAR (Snellen equivalent) UCVA All eyes Preop: 0.84 +/- 0.34 (20/137) 1 month: 0.87 +/-0.31 (20/148) (p=0.21) 3 months: 0.82 +/- 0.37 (20/131) (p=0.47) 6 months: 0.81 +/- 0.37 (20/129) (p=0.35) 12 months: 0.77 +/- 0.37 (20/117) (p=0.04) Keratoconus Preop: 0.87 +/- 0.35 (20/150) 1 month: 0.91 +/- 0.31 (20/162) (p>0.05) 3 months: 0.85 +/- 0.37 (20/143) (p>0.05) 6 months: 0.86 +/- 0.40 (20/144) (p>0.05) 12 months: 0.82 +/- 0.39 (20/133) (p>0.05) Ectasia Preop: 0.75 +/- 0.30 (20/112) 1 month: 0.78 +/- 0.30 (20/120) (p>0.05)	Measured in dioptres Change in K max All eyes Preop to 1 month: 1.39 +/- 2.80 (p<0.001) 1 to 3 months: - 1.69 +/- 2.55 (p<0.001) 3 to 6 months: -0.93 +/- 3.02 (p=0.01) 6 to 12 months: -0.48 +/- 3.20 (p=0.21) Preop to 12 months: -1.7 +/- 3.9 (p<0.001) Keratoconus Preop to 1 month: 1.33 +/- 3.03 (p=0.003) 1 to 3 months: -1.70 +/- 2.66 (p<0.001) 3 to 6 months: -0.94 +/- 3.22 (p=0.046) 6 to 12 months: -0.72 +/- 3.58 (p=0.17) Preop to 12 months: 2.00 (p=0.002) Ectasia Preop to 1 month: 1.51 +/- 2.27 (p=0.005) 1 to 3 months: -1.66 +/- 2.35 (p=0.003) 3 to 6 months: -0.91 +/- 2.60 (p=0.12) 6 to 12 months: 0.05 +/- 2.08 (p=0.91)

Author	Visual acuity	Topography
	3 months: 0.74 +/- 0.36 (20/109) (p>0.05) 6 months: 0.70 +/- 0.29 (20/101) (p>0.05) 12 months: 0.65 +/- 031 (20/89) (p>0.05) Mean change in UCVA fellow eye control group 12 months: -0.04 +/- 0.18 CVA All eyes Preop: 0.35 +/- 0.24 (20/45) 1 month: 0.37 +/- 0.29 (20/47) (p>0.05) 3 months: 0.30 +/- 0.22 (20/40) (p<0.05) 6 months: 0.25 +/- 0.21 (20/35) (p<0.05) 12 months: 0.23 +/- 0.21 (20/34) (p<0.001) Keratoconus Preop: 0.39 +/- 0.27 (20/49) 1 month: 0.39 +/- 0.30 (20/50) (p>0.05) 3 months: 0.32 +/- 0.24 (20/42) (p<0.05) 6 months: 0.26 +/- 0.23 (20/36) (p<0.05) 12 months: 0.25 +/- 0.23 (20/36) (p<0.001) Ectasia Preop: 0.26 +/- 0.16 (20/37) 1 month: 0.32 +/- 0.25 (20/42) (p>0.05) 3 months: 0.25 +/- 0.17 (20/35) (p>0.05) 6 months: 0.22 +/- 0.17 (20/33) (p>0.05) 12 months: 0.19 +/- 0.14 (20/31) (p=0.02) CVA mean change All eyes 1 month: 0.02 +/- 0.18 (p=0.33) 1-3 months: -0.07 +/- 0.15 (p<0.001) 3-6 months: -0.05 +/- 0.12 (p<0.001) 6-12 months: -0.02 +/- 0.13 (p=0.27) Keratoconus 1 month: 0.006 +/- 0.18 (p=0.81)	Preop to 12 months: 1.00 (p=0.08) Fellow eye control group change at 12 months: 0.29 +/- 1.19 K flat. Preop: 45.8 12 months: 44.9 (p=0.18).

Author	Visual acuity	Topography
	1-3 months: -0.07 +/- 0.14 (p=0.001) 3-6 months: -0.06 +/- 0.12 (p<0.001) 6-12 months: -0.01 +/- 0.11 (p=0.7) Fellow eye control 12 months: -0.04 +/- 0.14 In ectasia subgroup, changes in CVA were not statistically significant.	
Author: O'Brart **Year:** 2011 **Ref:** 96 **Country:** UK	Measured in mean Snellen decimal equivalent. BCVA Treated eyes: Preop: 0.82 18 months: 0.94 (p=0.01) Untreated eyes: Preop: 0.78 18 months: 0.91 (p=0.02) UCVA Treated eyes: Preop: 0.27 18 months: 0.33 (p=0.2) Untreated eyes: Preop: 0.22 18 months: 0.21 (p=0.5).	Not Reported.
Author: Wittig-Silva **Year:** 2008 **Ref:** 117 **Country:** Australia	Measured in LogMAR BSCVA Treatment group Improvement at: 3 months (n=24): -0.01 6 months (n=17): -0.07 (p=0.06) 12 months (n=9): -0.12 (p=0.07) Control at 12 months: (n=11) 0.12.	Measured in dioptres K max Treatment group Improvement (decrease) at: 3 months (n=24): -0.74 +/- 1.06 (p=0.004) 6 months (n=17): -0.92 +/- 0.98 (p=0.002) 12 months (n=9): -1.45 +/- 1.00 occurred in the steepest meridian (p=0.002) Control group Increased at: 3 months (n=23): +0.60 +/- 1.31 (p=0.041)

Author	Visual acuity	Topography
		6 months (n=17): +0.60 +/- 0.91 (p=0.13) 12 months (n=11): +1.28 (no SD reported) (p<0.001) K average Treatment group Improved (decreased): 12 months: around -1.2 (shown graphically only) Control group: Increased +1.10 over 12 months (p=0.003 vs. baseline).
Author: Arbelaez **Year:** 2009 **Ref:** 4 **Country:** Oman	Measured in LogMAR UCVA Baseline: 1.18 +/- 0.69 6 months: 0.63 +/- 0.32 (p not reported) 12 months: 0.55 +/- 0.32 (p not reported) BCVA Baseline: 0.40 +/- 0.43 6 months: 0.24 +/- 0.19 (p not reported) 12 months: 0.22 +/- 0.17 (p=0.002).	Measured in dioptres Mean K Baseline: 49.93 +/- 5.02 6 months: 48.68 +/- 4.61 (p not reported) 12 months: 48.57 +/- 4.54 (p=0.004) Max K Baseline: 51.89 +/- 7.99 6 months: 50.42 +/- 8.09 (p not reported) 12 months: 50.49 +/- 8.35 (p=0.01).
Author: Braun **Year:** 2005 **Ref:** 7 **Country:** USA	Visual acuity improved slightly in 15 eyes (data not reported).	Measured in dioptres In 12 eyes: Regression with a reduction of maximal keratometry readings by 3.01 D.
Author: Brooks **Year:** 2012 **Ref:** 8 **Country:** USA	Not Reported.	Not Reported.
Author: Caporossi **Year:** 2010	Measured in Snellen lines UCVA (p not reported) 12 months: 2.41 +/- 0.88 24 months: 2.75 +/- 0.79	Measured in dioptres Change in mean K Treated eye (p not reported) 12 months: -1.96 +/- 0.63

Author	Visual acuity	Topography
Ref: 10 **Country:** Italy	36 months: 2.80 +/- 0.76 48 months: 2.85 +/- 0.81 BCVA (p not reported) 12 months: 1.34 +/- 1.13 24 months: 1.93 +/- 1.04 36 months: 1.91 +/- 1.03 48 months: 2.03 +/- 1.04.	24 months: -2.12 +/- 0.65 36 months: -2.24 +/- 0.61 48 months: -2.26 +/- 0.68 Untreated eye (2 years only) (p not reported) 12 months: 1.2 +/- 0.96 24 months: 2.2 +/- 1.24.
Author: Caporossi **Year:** 2011 **Ref:** 11 **Country:** Italy	Measured in Snellen lines UCVA ≤18 years Baseline: 0.42 6 months: 0.53 (p not reported) 12 months: 0.56 (p=0.0037) 24 months: 0.59 (p=0.0043) 36 months: 0.58 (p=0.0051) 48 months: 0.62 (p=0.006) 19 to 26 years Baseline: 0.34 6 months: 0.48 (p not reported) 12 months: 0.47 (p=0.0034) 24 months: 0.50 (p=0.0041) 36 months: 0.46 (p=0.0032) 48 months: 0.48 (p=0.0073) ≥27 years Baseline: 0.48 6 months: 0.53 (p not reported) 12 months: 0.56 (p=0.0036) 24 months: 0.59 (p=0.005) 36 months: 0.58 (p=0.0047) 48 months: 0.62 (p=0.0071) BSCVA ≤18 years Baseline: 0.70 6 months: 0.81 (p not reported) 12 months: 0.85 (p=0.0056)	Measured in dioptres K max ≤18 years Baseline: 50.22 6 months: 49.66 (p not reported) 12 months: 49.53 (p=0.006) 24 months: 49.46 (p=0.0045) 36 months: 49.12 (p=0.051) 48 months: 49.33 (p=0.071) 19 to 26 years Baseline: 51.72 6 months: 51.35 (p not reported) 12 months: 51.12 (p=0.0053) 24 months: 51.20 (p=0.0051) 36 months: 51.41 (p=0.0045) 48 months: 51.15 (p=0.0091) ≥27 years Baseline: 51.88 6 months: 51.68 (p not reported) 12 months: 51.43 (p=0.0065) 24 months: 51.22 (p=0.0074) 36 months: 51.33 (p=0.0095) 48 months: 51.35 (p=0.0091).

Author	Visual acuity	Topography
	24 months: 0.89 (p=0.0031) 36 months: 0.88 (p=0.0059) 48 months: 0.91 (p=0.0079) 19 to 26 years Baseline: 0.66 6 months: 0.73 (p not reported) 12 months: 0.76 (p=0.0052) 24 months: 0.78 (p=0.0045) 36 months: 0.79 (p=0.0056) 48 months: 0.86 (p=0.0075) ≥27 years Baseline: 0.64 6 months: 0.71 (p not reported) 12 months: 0.71 (p=0.0054) 24 months: 0.70 (p=0.0067) 36 months: 0.72 (p=0.0069) 48 months: 0.74 (p=0.0075).	
Author: Charters **Year:** 2012 **Ref:** 14 **Country:** Argentina	BCVA Baseline: between 20/50 and 20/25 18 months: 86% of patients had BCVA > 20/40 and no loss of lines was recorded (p<0.05).	Measured in dioptres K2 Baseline: 45.32 D 18 months: 42.31 D (p<0.05).
Author: Coskunseven **Year:** 2009a **Ref:** 16 **Country:** Argentina	Measured in Snellen lines. UCVA Treatment group Preop: 0.29 +/- 0.15 Postop (mean 9 months): 0.40 +/- 0.18 (p<0.01) Control group Preop: 0.35 +/- 0.25 Postop (mean 9 months): 0.27 +/- 0.22 (p<0.01) BSCVA Treatment group Preop: 0.29 +/- 0.15 Postop (mean 9 months): 0.40 +/- 0.18 (p<0.01)	Measured in dioptres Max K Treatment group Preop: 54.02 +/- 4.15 Postop (mean 9 months): 52.45 +/- 4.01 (p<0.01) Control group Preop: 48.32 +/- 3.00 Postop (mean 9 months): 48.36 +/- 3.27 (p=0.446).

Author	Visual acuity	Topography
	Control group Preop: 0.61 +/- 0.28 Postop (mean 9 months): 0.55 +/- 0.26 (p<0.01).	
Author: Croxatto **Year:** 2010 **Ref:** 20 **Country:** Argentina	Not Reported.	Not Reported.
Author: Doors **Year:** 2009 **Ref:** 26 **Country:** Netherlands	Measured in LogMAR BSCVA Change over 6 months: -0.03 +/- 0.12 (p>0.05) Change over 12 months: -0.02 +/- 0.08 (p>0.05).	Measured in dioptres Central K Mean change over 6 months: 0.64 +/- 1.73 (p>0.05) Mean change over 12 months: 0.19 +/- 2.21 (p>0.05) Max K Mean change over 6 months: -0.29 +/- 2.05 (p>0.05) Mean change over 12 months: 0.08 +/- 1.56 (p>0.05).
Author: Gkika **Year:** 2012 **Ref:** 33 **Country:** Greece	Units of measurement not stated. Assumed to be Snellen lines. UCVA Baseline: 0.2+/- 0.3 3 months: 0.3+/- 0.3 (p=0.007) 6 months: 0.4 +/- 0.3 (p<0.001) 12 months: 0.4 +/- 0.3 (p<0.001) BCVA Baseline: 0.7+/- 0.3 3 months: 0.7 +/- 0.2 (p=0.018) 6 months: 0.7 +/- 0.2 (p=0.014) 12 months: 0.7 +/- 0.2 (p=0.010).	Measured in dioptres Mean K Baseline: 49.2 +/- 4.2 3 months: 47.9 +/- 4.3 (p<0.001) 6 months: 48.6 +/- 3.6 (p=0.049) 12 months: 48.7 +/- 3.7 (p= 0.037).
Author: Goldich **Year:** 2010 **Ref:** 34 **Country:** Israel	Measured in LogMAR BCVA Preop: 0.21 +/- 0.1 6 months: 0.17 +/- 0.1 (p not reported) 12 months: 0.11 +/- 0.1 (p<0.005) UCVA Preop: 0.62 +/- 0.5	Measured in dioptres Kmax Preop: 53.9 +/- 5.9 6 months: 53.1 +/- 5.5 (p not reported) 12 months: 52.1 +/- 5.0 (p=0.006) Kmin Preop: 44.3 +/- 2.6

Author	Visual acuity	Topography
	6 months: 1.02 +/- 0.6 (p not reported) 12 months: 0.78 +/- 0.6 (p=0.67).	6 months: 44.2 +/- 3.3 (p not reported) 12 months: 43.7 +/- 2.8 (p=0.049) Mean simulated K Preop: 46.2 +/- 2.8 6 months: 46.3 +/- 3.3 (p not reported). 12 months: 45.6 +/- 2.9 (p=0.14).
Author: Goldich **Year:** 2012 **Ref:** 35 **Country:** Israel	Measured in LogMAR BCVA Preop: 0.21 +/- 0.1 6 months: 0.17 +/- 0.1 (p=0.631) 12 months: 0.11 +/- 0.1 (p=0.002) 24 months: 0.14 +/- 0.1 (p=0.018) Preop: 0.62 +/- 0.5 6 months: 1.02 +/- 0.6 (p=0.229) 12 months: 0.78 +/- 0.6 (p=0.430) 24 months: 0.81 +/- 0.49 (p=0.475).	Measured in dioptres Kmax Preop: 53.9 +/- 5.9 6 months: 53.1 +/- 5.5 (p=0.045) 12 months: 52.1 +/- 5.0 (p=0.009) 24 months: 52.1 +/- 5.0 (p=0.001) Kmin Preop: 44.3 +/- 2.6 6 months: 44.2 +/- 3.3 (p=0.215) 12 months: 43.7 +/- 2.8 (p=0.150) 24 months: 43.7 +/- 2.8 (p=0.088) Mean simulated K Preop: 46.2 +/- 2.8 6 months: 46.3 +/- 3.3 (p=0.732). 12 months: 45.6 +/- 2.9 (p=0.195) 24 months: 45.6 +/- 2.9 (p=0.112).
Author: Greenstein **Year:** 2012 **Ref:** 38 **Country:** USA	Not Reported.	Not Reported.
Author: Grewal **Year:** 2009 **Ref:** 43	Measured in LogMAR BCVA Preop: 0.22 +/- 0.07 1 week: 0.24 +/- 0.06 1 month: 0.24 +/- 0.04	Not Reported.

Author	Visual acuity	Topography
Country: India	3 month: 0.23 +/- 0.06 6 month: 0.20 +/- 0.04 1 year: 0.20 +/- 0.08 (p=0.89).	
Author: Holopainen **Year:** 2011 **Ref:** 53 **Country:** Finland	Measured in LogMAR UCVA Preop: 0.83 +/- 0.45 6 months: 0.72 +/- 0.46 (p=0.009) BSCVA Preop: 0.31 +/- 0.15 6 months: 0.18 +/- 0.16 (p=0.009) 17% of patients showed no changes 31% gained 1 line 31% gained 2 lines 14% gained 3+ lines 7% lost 1 line No eyes lost 2 or more lines.	Kmax Preop: 48.9 +/- 3.7 6 months: 48.2 +/- 4.2 (p=0.07).
Author: Koller **Year:** 2011 **Ref:** 64 **Country:** Switzerland	Units of measurement not reported. Assumed to be LogMAR Change in corrected distance visual acuity 1 year: 0.55 +/- 0.28.	Measured in dioptres Change in K max 1 year: 0.89 +/- 1.49.
Author: Koller **Year:** 2009 **Ref:** 65 **Country:** Switzerland	Not Reported.	Not Reported.
Author: Koppen **Year:** 2011 **Ref:** 67	Not Reported.	Measured in dioptres K max Contact lens group: Baseline: 60.48 +/- 8.60 Change at 6 months: -1.46 +/- 0.64 (p=0.0448) Change at 12 months: -3.13 +/- 0.73 (p=0.0005)

Author	Visual acuity	Topography
Country: Belgium		Change at 18 months: -2.13 +/- 0.67 (p=0.0075) No contact lens group: Baseline: 54.85 +/- 6.99 Change at 6 months: -0.42 +/- 0.63 (p=0.6294) Change at 12 months: -0.86 +/- 0.66 (p=0.4990) Change at 18 months: -0.90 +/- 0.69 (p=0.4990).
Author: Kranitz **Year:** 2012 **Ref:** 68 **Country:** Hungary	Measured in decimal units UCVA CXL Group Baseline: 0.23 +/- 0.25 12 months: 0.31 +/- 0.25 Control Group Baseline: 0.57 +/- 0.35 (p=0.01 vs. CXL group) 12 months: 0.54 +/- 0.34 (p=0.06 vs. CXL group) CVA CXL Group Baseline: 0.58 +/- 0.28 12 months: 0.72 +/- 0.19 Control Group Baseline: 0.83 +/- 0.26 (p=0.006 vs. CXL group) 12 months: 0.89 +/- 0.15 (p=0.01 vs. CXL group).	Measured in dioptres Flattest K CXL Group Baseline: 45.06 +/- 4.55 12 months: 43.51 +/- 4.67 Control Group Baseline: 44.51 +/- 2.05 (p=0.72 vs. CXL) 12 months: 44.29 +/- 2.20 (p=0.62 vs. CXL) Steepest K CXL Group Baseline: 48.39 +/- 5.41 12 months: 46.71 +/- 5.62 Control Group Baseline: 46.37 +/- 2.60 (p=0.24 vs. CXL) 12 months: 46.41 +/- 2.74 (p=0.86).
Author: Kymionis **Year:** 2009 **Ref:** 75 **Country:** Greece	Measured on decimal scale UCVA Baseline: 0.25 +/- 0.15 12 months: 0.27 +/- 0.17 (p not reported) CVA Baseline: 0.40 +/- 0.20 12 months: 0.49 +/- 0.20 (p not reported).	Measured in dioptres Mean K Baseline: 51.99 +/- 5.57 12 months: 49.33 +/- 4.82 (p not reported).
Author: Kymionis **Year:** 2012	Measure in LogMAR CVA TG-PRK Preop: 0.30 +/- 0.26;	Measured in dioptres. Mean Steep K TG-PRK Preop: 53.07 +/- 7.20;

Author	Visual acuity	Topography
Ref: 71 **Country:** Greece	6 months 0.22 +/- 0.18 (p=0.25); 12 months 0.19 +/- 0.18 (p=0.008) Mechanical debridement Preop: 0.27 +/- 0.20; 6 months 0.21 +/- 0.17 (p=0.66); 12 months 0.20 +/- 0.15 (p=0.65) UCVA TG-PRK Preop: 0.99 +/- 0.71; 6 months 0.66 +/- 0.34 (p=0.048); 12 months 0.63 +/- 0.42 (p=0.02) Mechanical debridement Preop: 0.88 +/- 0.37; 6 months 0.70 +/- 0.51 (p=0.06); 12 months 0.70 +/- 0.35 (p=0.054).	6 months 51.96 +/- 5.90 (p=0.11); 12 months 51.00 +/- 5.10 (p=0.001) Mechanical debridement. Preop: 51.18 +/- 5.00; 6 months 50.62 +/- 5.30 (p=0.56); 12 months 50.84 +/- 4.50 (p=0.64) Mean Flat K TG-PRK Preop: 47.24 +/- 4.50; 6 months 46.11 +/- 3.50 (p=0.41); 12 months 46.68 +/- 4.30 (p=0.65) Mechanical debridement Preop: 47.12 +/- 3.90; 6 months 46.66 +/- 3.60 (p=0.4); 12 months 46.99 +/- 3.40 (p=0.81).
Author: Kymionis **Year:** 2012 **Ref:** 70 **Country:** Greece	Not Reported.	Not Reported.
Author: Li **Year:** 2010 **Ref:** 84 **Country:** China	Measured in LogMAR UCVA Preop: 0.77 +/- 0.32 12 month change: 0.07 +/- 0.07 (p<0.01) BSCVA Preop: 0.36 +/- 0.30 12 month change: 0.13 +/- 0.17 (p<0.01).	Measured in dioptres K max Preop: 45.37 +/- 5.64 12 month change: 2.14 +/- 1.23 (p<0.01) K min Preop: 43.01 +/- 5.52 12 month change: 1.45 +/- 1.72 (p<0.01).
Author: Mazzotta **Year:** 2007	Not Reported.	Not Reported.

Author	Visual acuity	Topography
Ref: 90 **Country:** Italy		
Author: Romano **Year:** 2012 **Ref:** 104 **Country:** Italy	Units of measurement not reported. Assumed to be Snellen lines. BSCVA Baseline: 0.6 +/- 0.20 6 months: 0.7 +/- 0.17 (p=0.12).	Not Reported.
Author: Salgado **Year:** 2010 **Ref:** 107 **Country:** Germany	Measured in LogMAR UCVA Preop: 0.53 +/- 0.38 1 month: 0.67 +/- 0.43 3 months: 0.54 +/- 0.35 6 months: 0.53 +/- 0.35 12 months: 0.40 +/- 0.27 BSCVA Preop: 0.19 +/- 0.21 1 month: 0.25 +/- 0.17 3 months: 0.20 +/- 0.20 6 months: 0.18 +/- 0.21 12 months: 0.15 +/- 0.14 No change statistically significant.	Measured in dioptres K max Preop: 44.12 +/- 3.97 1 month: 46.23 +/- 4.14 (p=0.028) 3 months: 43.88 +/- 4.25 6 months: 45.06 +/- 5.07 12 months: 44.43 +/- 4.06 K min Preop: 41.78 +/- 2.69 1 month: 43.25 +/- 2.66 3 months: 41.20 +/- 2.88 6 months: 42.20 +/- 3.22 12 months: 42.04 +/- 2.67 No other changes statistically significant.
Author: Sedaghat **Year:** 2010 **Ref:** 108 **Country:** Iran	Measured in LogMAR UCVA Baseline: 1.10 +/- 0.79 6 months: 0.76 +/- 0.76 (p<0.001) CVA Baseline: 0.19 +/- 0.21 6 months: 0.08 +/- 0.11 (p<0.001).	Measured in dioptres Max K Baseline: 50.16 +/- 4.11 6 months: 49.61 +/- 3.78 (p<0.001)
Author: Vinciguerra **Year:** 2012	Measured in LogMAR UCVA Baseline: 0.79 +/- 0.21	Measured in dioptres Steepest K Baseline: 51.48 +/- 3.4

Author	Visual acuity	Topography
Ref: 114 **Country:** Italy and Switzerland	6 months: 0.66 +/- 0.17 12 months: 0.62 +/- 0.19 24 months: 0.58 +/- 0.18 BSCVA Baseline: 0.39 +/- 0.10 6 months: 0.23 +/- 0.11 12 months: 0.21 +/- 0.11 24 months: 0.20 +/- 0.09 (p<0.05 for all measures throughout postoperative period.)	6 months: 51.81 +/- 3.4 12 months: 52.16 +/- 3.5 24 months: 50.21 +/- 3.2 (p=0.07) Flattest K Baseline: 46.32 +/- 3.0 6 months: 46.19 +/- 2.9 12 months: 46.26 +/- 2.5 24 months: 45.30 +/- 2.7 (p=0.04) Min K Baseline: 42.95 +/- 1.9 6 months: 42.73 +/- 2.0 12 months: 42.61 +/- 2.2 24 months: 39.47 +/- 1.7 (p=0.01) Average corneal power Baseline: 49.69 +/- 3.2 6 months: 49.57 +/- 2.9 12 months: 49.95 +/- 3.0 24 months: 48.90 +/- 2.8 (p=0.03).
Author: Vinciguerra **Year:** 2009 **Ref:** 116 **Country:** Italy	Measured in LogMAR UCVA Baseline: 0.77 +/- 0.18 6 months: 0.51 +/- 0.22 12 months: 0.57 +/- 0.16 24 months: 0.53 +/- 0.19 (p=0.048) BSCVA Baseline: 0.28 +/- 0.09 6 months: 0.17 +/- 0.08 12 months: 0.14 +/- 0.08 24 months: 0.13 +/- 0.10 (p<0.001).	Measured in dioptres Steepest K Baseline: 50.37 6 months: 49.89 12 months: 49.58 24 months: 49.02 (p=0.03) Flattest K Baseline: 46.10 6 months: 45.45 2 months: 45.44 24 months: 45.43 (p=0.049) Average Baseline: 48.08 6 months: 47.52 12 months: 47.01

Author	Visual acuity	Topography
		24 months: 46.97 (p=0.03).
Author: Vinciguerra **Year:** 2009 **Ref:** 115 **Country:** Italy	Measured in LogMAR UCVA Baseline: 0.77 +/- 0.18 6 months: 0.51 +/- 0.17 12 months: 0.57 +/- 0.16 (p<0.05) BSCVA Baseline: 0.28 +/- 0.09 6 months: 0.17 +/- 0.06 12 months: 0.57 +/- 0.16 (p<0.001).	Measured in dioptres Steepest K Baseline: 50.37 6 months: 49.89 12 months: 44.21 (p=0.0011) Flattest K Baseline: 46.10 6 months: 45.45 12 months: 40.22 (p=0.0003) Average K Baseline: 48.08 6 months: 47.50 12 months: 42.01 (p=0.0004).
Author: Wollensak **Year:** 2003 **Ref:** 118 **Country:** Germany	Measured in Snellen lines BCVA improved statistically significantly in 15 patients (65%) by an average of 1.26 lines (95% CI -0.68 to +2.21; p=0.026).	Postoperative regression in K max value: 2.01 (95% CI 1.23 to 3.07) (p=0.001).
Author: Agrawal **Year:** 2009 **Ref:** 1 **Country:** India	Measured by Snellen's and converted to decimal format Baseline: 0.34 +/- 0.30. Change at 6 month follow-up: -0.04 +/- 0.24 (p not reported) Change at 12 month follow-up: -0.09 +/- 0.24 (p=0.006).	Measured in dioptres Baseline: apex K 64.79 +/- 7.22 D, mean K max 53.26 +/- 5.93 D, mean astigmatism 7.24 +/- 4.67 D Change at 6 months: apex K -2.68 +/- 8.3 D (p not reported), mean K maximum -1.3 +/- 4.33 D (p not reported) Change at 12 months: apex K -2.73 +/- 7.95 D (p=0.004) in 66% of eyes, mean maximum K -2.47 +/- 3.89 D (p=0.004) in 54% of eyes.
Author: Asri **Year:** 2011 **Ref:** 6 **Country:** France	Measured in LogMAR UCVA Baseline: 0.90 +/- 0.52 6 months: 0.78 +/- 0.42 (p=0.01) 12 months: 0.90 +/- 0.45 (p=0.49) CVA Baseline: 0.34 +/- 0.25	Measured in dioptres K max Baseline: 54.09 +/- 6.07 6 months: 52.96 +/- 5.45 (p=0.001) 12 months: 53.60 +/- 5.47 (p=0.045) Kmin

Author	Visual acuity	Topography
	6 months: 0.29 +/- 0.24 (p=0.01) 12 months: 0.33 +/- 0.25 (p=0.045) At 6 months CVA improved in 32.7%, stabilized in 48.1% and worsened in 16.3%. At 12 months CVA improved in 40.0%, stabilized in 47.6% and worsened in 12.0%.	Baseline: 47.43 +/- 4.09 6 months: 46.66 +/- 4.17 (p=0.026) 12 months: 46.86 +/- 4.48 (p=0.047) Mean K Baseline: 50.76 +/- 4.86 6 months: 49.81 +/- 4.63 (p not reported) 12 months: 50.23 +/- 4.65 (p not reported) At 6 months Kmax improved in 35.5%, stabilized in 49.03% and worsened in 15.3%. At 12 months Kmax improved in 21.1%, stabilized in 68.8% and worsened in 9.8%.
Author: Pinero **Year:** 2012 **Ref:** 97 **Country:** Spain	Measured in LogMAR UCVA Baseline: 0.84 +/- 0.38 6 months: 0.56 +/- 0.32 12 months: 0.65 +/- 0.41 24 months: 0.70 +/- 0.27 (p=0.40) CVA Baseline: 0.32 +/- 0.18 6 months: 0.31 +/- 0.23 12 months: 0.27 +/- 0.17 24 months: 0.31 +/- 0.19 (p=0.26).	Measured in dioptres Mean K Baseline: 47.46 +/- 3.30 6 months: 46.68 +/- 2.78 12 months: 47.25 +/- 3.96 24 months: 46.60 +/- 3.37 (p=0.20).
Author: Raiskup **Year:** 2009 **Ref:** 100 **Country:** Germany	Measured in LogMAR UCVA Control: Preop: 0.75 +/- 0.40 1 year: 0.63 +/- 0.38 (p=0.023) Haze group Preop: 0.84 +/- 0.34 1 year: 1.07 +/- 0.32 (p=0.012) BSCVA Control Preop: 0.41 +/- 0.32	Measured in dioptres Mean K Control Preop: 62.1 +/- 13.8 1 year: 60.9 +/- 12.5 Haze group Preop: 71.1 +/- 13.2 (p=0.02 vs. control) 1 year: 71.9 +/- 12.4 (p=0.006 vs. control) K max Control Preop: 53.7 +/- 8.1 1 year: 52.9 +/- 7.6

Author	Visual acuity	Topography
	1 year: 0.30 +/- 0.28 (p=0.001) Haze group Preop: 0.46 +/- 0.36 1 year: 0.66 +/- 0.41 (p=0.004).	Haze group Preop: 58.2 +/- 7.2 (p=0.03 vs. control) 1 year: 58.5 +/- 9.1 (p=0.02 vs. control) Kmin Control Preop: 46.6 +/- 6.2 1 year: 46.1 +/- 6.8 Haze group Preop: 51.3 +/- 6.9 (p=0.005 vs. control) 1 year: 51.3 +/- 6.9 (p=0.012 vs. control).
Author: Raiskup **Year:** 2011 **Ref:** 99 **Country:** Germany	Measured in LogMAR BVCA Baseline: 0.63 +/- 0.37 1 year: 0.59 +/- 0.42 (p=0.662).	Measured in dioptres K value apex Baseline: 65.6 +/- 11.2 1 year: 64.9 +/- 11.0 (p=0.839).
Author: Raiskup-Wolf **Year:** 2008 **Ref:** 101 **Country:** Germany	Measured in LogMAR Mean change +/- SD (%) BCVA 1 year (n=142): -0.08 +/- 0.24 (73.1%) (p<0.01) 2 years (n=66): -0.09 +/- 0.24 (81.0%) 3 years (n=33): -0.15 +/- 0.18 (87.1%) 4 years (n=13): -0.18 +/- 0.11 (91.7%) 5 years (n=5): -0.13 +/- 0.29 6 years (n=5): -0.18 +/- 0.06.	Measured in dioptres Mean change +/- SD (%) K max apex 1 year (n=142): -2.68 +/- 7.61 (78.8%) (p<0.01) 2 years (n=66): -2.21 +/- 5.92 (79.3%) 3 years (n=33): -4.84 +/- 7.47 (80%) 4 years (n=13): -6.87 +/- 8.32 (84.6%) 5 years (n=5): -1.41 +/- 4.56 6 years (n=5): -2.95 +/- 2.35 K max 1 year (n=142): -1.46 +/- 3.76 (85.9%) (p<0.01) 2 years (n=66): -1.91 +/- 4.36 (89.4%) 3 years (n=33): -2.57 +/- 3.71 (67.2%) 4 years (n=13): -2.66 +/- 2.85 (85.6%) 5 years (n=5): -2.47 +/- 2.18 6 years (n=5): -2.44 +/- 2.02.

Author	Visual acuity	Topography
Author: Saffarian **Year:** 2010 **Ref:** 106 **Country:** Iran	Measured in LogMAR UCVA Preop: 0.61 +/- 0.31 1 year: 0.31 +/- 0.25 (p=0.001) BSCVA Preop: 0.06 +/- 0.12 1 year: 0.0 +/- 0.01 (p=0.001).	Measured in dioptres Mean simulated K Preop: 46.94 +/- 2.37 1 year: 46.0 +/- 2.33 Change: 0.94 +/- 0.71 (p=0.001).
Author: Asfuroglu **Year:** 2012 **Ref:** 5 **Country:** USA	Measured in LogMAR UCVA Baseline: 0.28 9 months: 0.21 (p<0.05) BCVA Baseline: 0.15 9 months: 0.10 (p<0.05).	Measured in dioptres Max K 9 months: 1.36 D lower than baseline (p<0.001).
Author: Hafezi **Year:** 2007 **Ref:** 47 **Country:** Switzerland and Greece	Not Reported.	Progression of keratectasia (change in K max ≥ + 1 D) in no patients. Stabilization of the keratectasia (+1.0 D ≥ change in K max + B6 ≤ - 1.0 D) in 12 patients. Regression (change in K max ≥ -1.0 D) in 8 patients (p not reported).
Author: Hafezi **Year:** 2009 **Ref:** 46 **Country:** Switzerland	BSCVA Case 4 Preop: 20/50 12 months: 20/30 Case 5 Preop: 20/30 17 months: 20/30 Case 6 Preop: 20/200 21 months: 20/40 Case 7 Preop: 20/200 20 months: 20/50 Case 8 Preop: 20/50	Measured in dioptres Max K Case 4 Preop: 52.2 12 months: 50.2 Case 5 Preop: 51.6 17 months: 48.8 Case 6 Preop: 55.6 21 months: 53.9 Case 7 Preop: 57.6 20 months: 55.6 Case 8

Author	Visual acuity	Topography
	25 months: 20/25 Case 9 Preop: 20/200 23 months: 20/50 Case 10 Preop: 20/100 17 months: 20/25.	Preop: 59.3 25 months: 59.1 Case 9 Preop: 49.6 23 months: 48.3 Case 10 Preop: 47.6 17 months: 47.1 Calculated means and SD: Preop: 53.36 +/- 4.28 At follow up (various times): 51.86 +/- 4.44.
Author: Kjankov **Year:** 2009 **Ref:** 63 **Country:** Not Reported	Units of measurement not reported. Assumed to be Snellen lines. BVCA Preop: 0.41 +/- 0.18 3 months: 0.6 +/- 0.29 Increased more at 1 to 2 years (data not reported). One third of eyes gained two or more lines of BCVA, no eye lost lines.	Not Reported.
Author: Mazzotta **Year:** 2012 **Ref:** 87 **Country:** Italy	Measured in Snellen lines UCVA Baseline: 0.33 +/- 0.12 6 months: 0.49 +/- 0.13 (p=0.0031) 12 months: 0.51 +/- 0.11 (p=0.000119) BSCVA Baseline: 0.58 +/- 0.09 6 months: 0.69 +/- 0.08 (p=0.00311) 12 months: 0.75 +/- 0.075 (p=0.00023).	Measured in dioptres Mean K Baseline: 51.4 +/- 2.8 6 months: 50.2 +/- 2.6 (p=0.00412) 12 months: 50.1 +/- 2.6 (p=0.00337)

Table 4.2b: Summary of refraction and astigmatism, intraocular pressure and central corneal thickness outcomes in included papers on epithelium-off CXL

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Author: Greenstein **Year:** 2012 **Ref:** 37 **Country:** USA	Not Reported.	Units not specified. Total Group (Keratoconus and ectasia) CH Baseline: 7.66 +/- 1.16 6 months: 7.63 +/- 1.96 (p>0.05) 12 months: 7.71 +/- 1.77 (p=0.78) CRF Baseline: 5.80 +/- 1.31 6 months: 6.00 +/- 1.64 (p>0.05) 12 months: 6.08 +/- 1.77 (p=0.1) Keratoconus only CH Baseline: 7.76 +/- 1.10 6 months: 7.72 +/- 1.84 (p>0.05) 12 months: 7.91 +/- 1.68 (p>0.05) CRF Baseline: 5.89 +/- 1.36 6 months: 6.04 +/- 1.60 (p>0.05) 12 months: 6.20 +/- 1.64 (p>0.05) Ectasia only CH Baseline: 7.48 +/- 1.29 6 months: 7.45 +/- 2.23 (p>0.05) 12 months: 7.31 +/- 1.93 (p>0.05) CRF Baseline: 5.62 +/- 1.21 6 months: 5.94 +/- 1.77 (p>0.05) 12 months: 5.86 +/- 1.95 (p>0.05).	Not Reported.	Not Reported.
Author: Greenstein **Year:** 2011 **Ref:** 41	Not Reported.	Not Reported.	Measured in µm Total Group (Keratoconus and ectasia) Baseline: 472.0 +/- 45.3 6 months: 460.6 +/- 44.9	Not Reported.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Country: USA.			12 months: 468.6 +/- 44.4 (p=0.06) Keratoconus only Baseline: 472.1 +/- 42.6 6 months: 459.1 +/- 42.8 (p<0.05) 12 months: 465.7 +/- 42.9 (p<0.05) Ectasia only Baseline: 471.9 +/- 50.9 6 months: 463.6 +/- 49.4 (p<0.05) 12 months: 474.2 +/- 47.5 (p>0.05).	
Author: Henriquez **Year:** 2011 **Ref:** 50 **Country:** Peru	Measured in dioptres Refractive spheres: Non-significant differences between pre and postop at 1, 3, 6, 12 months. Refractive cylinder: At 12 months Postop mean refractive cylinder decreased by 2.25 D (p=0.02). Spherical equivalent: Preop: -4.57 +/- 3.55 1 month: -3.72 +/- 3.30 3 months: -3.66 +/- 2.62 6 months: -3.11 +/- 2.70 (p=0.36) 12 months: -2.32 +/- 2.08 (p=0.01).	Not Reported.	Measured in µm using US pachymetry Mean CCT. Preop: 471.5 1 month: 466.5 3 months: 462.6 6 months: 462.8 12 months: 462.8.	One eye (of 10) presented 1 day postop with Descemet folds and corneal edema, which resolved after 10 days of topical corticosteroid treatment.
Author: Hersh **Year:** 2011 **Ref:** 52 **Country:** USA	Measured in dioptres Manifest equivalent spherical equivalent (MRSE) Preop: All eyes:-8.63 +/- 5.30 Keratoconus: -9.32 +/- 5.65 Ectasia: -7.08 +/- 4.10 1 month: All eyes: -7.86 +/- 4.61 Keratoconus: -8.34 +/- 4.95 Ectasia: -6.80 +/- 3.62 3 months:	Not Reported.	Not Reported.	Not Reported.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
	All eyes: -7.48 +/- 4.73 Keratoconus: -8.05 +/- 5.08 Ectasia: -6.23 +/- 3.63 6 months: All eyes: -7.74 +/- 4.74 Keratoconus: -8.20 +/- 5.04 Ectasia: -6.73 +/- 3.91 1 year: All eyes: -7.77 +/- 5.40 Keratoconus: -8.47 +/- 5.50 Ectasia: -6.22 +/- 4.93 MRSE change: 1 month: 0.76 +/- 2.13 1-3 months: 0.38 +/- 2.73 3-6 months: -0.26 +/- 1.58 6-12 months: -0.03 +/- 2.58 Manifest astigmatism: Preop: All eyes: 4.76 +/- 2.52 Keratoconus: 5.09 +/- 2.54 Ectasia: 4.05 +/- 2.36 1 month: All eyes: 4.62 +/- 2.30 (p=0.39) Keratoconus: 4.95 +/- 2.21(p>0.05) Ectasia: 3.90 +/- 2.39 (p>0.05) 3 months: All eyes: 4.51 +/- 2.78 (p=0.24) Keratoconus: 5.01 +/- 2.53 (p>0.05) Ectasia: 3.41 +/- 3.05 (p>0.05) 6 month: All eyes: 4.76 +/- 2.50 (p=0.97 Keratoconus: 5.08 +/- 2.53 (p>0.05) Ectasia: 4.05 +/- 2.34 (p>0.05) 1 year: All eyes: 4.81 +/- 2.51(p=0.84)			

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
	Keratoconus: 5.01 +/- 2.43 (p>0.05) Ectasia: 4.39 +/- 2.69 (p>0.05) Manifest astigmatism change in fellow eye control group at 12 months: 0.34 +/- 0.82.			
Author: O'Brart **Year:** 2011 **Ref:** 96 **Country:** UK	Measured in dioptres Spherical equivalent refractive error Treated eyes Preop: -2.34 18 months postop: -1.52 (p=0.06) Untreated eyes Preop: -2.66 18 months postop: -2.55 (p=0.7) Refractive astigmatism (dioptres of cylinder) Treated eyes Preop: -3.8 18 months postop: -4.3 (p=0.1) Untreated eyes Preop: -3.92 18 months postop: -4.56 (p=0.002).	Not Reported.	Measured in µm Treated eyes Preop: 483.4 18 months postop: 486.8 (p=0.5) Untreated eyes Preop: 481.6 18 months postop: 487.7 (p=0.1).	One patient (of 24) with recurrent corneal erosion with discomfort for 9 months postoperatively (settled with lubricants). Two of three patients who were contact lens intolerant preoperatively had ICRS insertion after 18 month follow up.
Author: Wittig-Silva **Year:** 2008 **Ref:** 117 **Country:** Australia	Measured in dioptres No significant changes found for refractive sphere, astigmatism and MSRE at 6 or 12 months in either group.	Not Reported.	Not Reported.	One (highly atopic) patient developed inflammatory reaction in anterior chamber in postop day 2. Reaction resolved when soft contact lens removed and increased antibiotic and corticosteroid treatment. Another patient developed small, sub epithelial, paracentral infiltrate, after prematurely resuming rigid contact lens on day 3, no persistent scarring. Striae most prominent between 1 and 3

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
				months.
Author: Arbelaez **Year:** 2009 **Ref:** 4 **Country:** Oman	Measured in dioptres Sphere Baseline: -3.84 +/- 5.10 6 months: -2.74 +/- 3.57 12 months: -2.58 +/- 3.22 (p=0.033) Cylinder Baseline: -4.04 +/- 1.52 6 months: -3.15 +/- 1.17 12 months: -2.79 +/- 1.13 (p=0.0003).	Not Reported.	Measured in µm at apex and thinnest point Apex Baseline: 463.96 +/- 27.28 12 months: 463.95 +/- 37.36 Thinnest Baseline: 452.25 +/- 29.58 12 months: 455 +/- 37.98.	Not Reported.
Author: Braun **Year:** 2005 **Ref:** 7 **Country:** USA	Measured in dioptres In 12 eyes: Reduction of the refractive error by 2.14 D.	No change in IOP.	Not Reported.	Not Reported.
Author: Brooks **Year:** 2012 **Ref:** 8 **Country:** USA	Not Reported.	Not Reported.	Not Reported.	Not Reported.
Author: Caporossi **Year:** 2010 **Ref:** 10 **Country:** Italy	Measured in dioptres Change given in spherical and cylinder refraction (D) for treated eye only Spherical refraction 12 months: 1.62 +/- 1.03 24 months: 1.87 +/- 1.06 36 months: 1.86 +/- 0.97 48 months: 1.87 +/- 0.98 Cylinder refraction 12 months: -0.52 +/- 0.38	Mean IOP was 14.773 +/- 1.696 mmHg preoperatively. No statistically significant change was found at any point past or including one year follow-up.	Mean preoperatively was 450 +/- 14.54 µm. No statistically significant change was found at any point past or including one year follow-up.	No persistent early or late side effects reported. 70% of patients had stromal oedema which cleared within 30 days. Temporary haze in 9.8% of cases: 14 cases in the first 3 months and 2 cases after 6 months, disappearing progressively after topical preservative-free steroid therapy (fluorometholone preservative-free drops for 1 to 3

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
	24 months: -0.53 +/- 0.37 36 months: -0.53 +/- 0.38 48 months: -0.55 +/- 0.38.			months). No delayed re-epithelialization or endothelial damage was detected during follow-up.
Author: Caporossi **Year:** 2011 **Ref:** 11 **Country:** Italy	Not Reported.	Not Reported.	Not Reported.	Not Reported.
Author: Charters **Year:** 2012 **Ref:** 14 **Country:** Argentina	Measured in dioptres 18 months: Mean manifest refraction decreased from -3.4 to 0.52 D (p<0.05) Mean cylinder decreased from -3.0 to 0.56 D (p<0.05). Mean spherical equivalent decreased from -4.86 to -0.76 D (p<0.05). 90% of preoperative cylinder corrected 70% correction of the sphere.	Not Reported.	Not Reported.	No loss of lines recorded.
Author: Coskunseven **Year:** 2009a **Ref:** 16 **Country:** Argentina	Measured in dioptres Spherical equivalent Treatment group Preop: -5.76 +/- 4.31 Postop: -4.73 +/- 2.90 (p<0.01) Control group Preop: -2.48 +/- 1.67 Postop: -2.45 +/- 1.96 (p=0.441) Cylinder Treatment group Preop: -4.26 +/- 2.04 Postop:-3.22 +/- 1.79 (p<0.01) Control group	Measured in mmHg Treatment group Preop: 9 +/- 2 Postop: 11 +/- 2 (p<0.01) Control group Preop: 11 +/- 2 Postop: 11 +/- 2 (p=0.461).	Measured in µm using pachymetry Treatment group Preop: 457 +/- 21 Postop: 446 +/- 26 (p=0.065) Control group Preop: 469 +/- 19 Postop: 469 +/- 22 (p=0.411).	Some patients showed slight stromal oedema with cotton-like stromal opacities at 1 month follow-up, these disappeared 3 months after treatment.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
	Preop: -2.67 +/- 1.69 Postop: -2.66 +/- 1.88 (p=0.472).			
Author: Croxatto **Year:** 2010 **Ref:** 20 **Country:** Argentina	Not Reported.	Not Reported.	Not Reported.	Not Reported.
Author: Doors **Year:** 2009 **Ref:** 26 **Country:** Netherlands	Measured in dioptres Astigmatism Preop: 4.84 +/- 3.74 Mean change: 1 month: 0.53 +/- 1.53 (p>0.05) 3 months: -0.20 +/- 1.26 (p>0.05) 6 months: -0.59 +/- 1.96 (p>0.05) 12 months: -0.51 +/- 0.78 (p>0.05) Refractive cylinder and topographic astigmatism remained stable during all postop follow-up.	Remained stable at all postop follow-up.	Measured in µm using Pentacam imaging. Preop: 495 +/- 48 Mean change: 1 month: -31 +/- 20 (p<0.001) 3 months: -28 +/- 23 (p<0.001) 6 months: -20 +/- 19 (p<0.001) 12 months: -24 +/- 19 (p=0.017).	All patients reported some pain during first 2 to 3 days after treatment. 1 month after surgery 2/29 eyes had mild Descemet folds that remained present in 1 eye up to 3 months after surgery. In 1 eye, endothelial irregularities were noted at 1 month and disappeared at 3 months without visual limitations. In none of the patients did corneal haze or keratitis develop after treatment.
Author: Gkika **Year:** 2012 **Ref:** 33 **Country:** Greece	Measured in dioptres Corneal astigmatism Baseline: 3.5 +/- 1.7 3 months: 3.1 +/- 1.6 (p=0.041) 6 months: 3.1 +/- 1.4 (p=0.011) 12 months: 3.2 +/- 1.5 (p=0.047) Residual astigmatism Baseline: 0.5 +/- 0.8 3 months: -1.3 +/- 1.8 (p=0.75) 6 months: -1.4 +/- 1.4 (p=0.81) 12 months: -1.5 +/- 1.6 (p=0.83).	Not Reported.	Measured in µm Baseline: 449.5 3 months: 445.3 (p=0.876) 6 months: 448.5 (p=0.987) 12 months: 449.0 (p=0.511).	Not Reported.
Author: Goldich **Year:** 2010 **Ref:** 34	Not Reported.	Not Reported.	Measured in µm Preop: 461 +/- 38 6 months: 441 +/- 47 12 months: 478 +/- 52 (p=0.84).	No macular abnormalities throughout the study period (12 months).

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Country: Israel				
Author: Goldich **Year:** 2012 **Ref:** 35 **Country:** Israel	Measured in dioptres Spherical equivalent Preop: -5.3 +/- 3.8 6 months: -5.2 +/- 3.6 (p=0.583) 12 months: -4.0 +/- 3.2 (p=0.061) 24 months: -4.0 +/- 3.3 (p=0.017).	Not Reported.	Measured in µm Preop: 461 +/- 38 6 months: 441 +/- 47 (p=0.057) 12 months: 478 +/- 52 (p=0.484) 24 months: 466 +/- 46 (p=0.704).	Not Reported.
Author: Greenstein **Year:** 2012 **Ref:** 38 **Country:** USA	Not Reported.	Not Reported.	Not Reported.	Not Reported.
Author: Grewal **Year:** 2009 **Ref:** 43 **Country:** India	Measured in dioptres Spherical equivalent Preop: -6.32 +/- 6.57 1 week: -7.19 +/- 7.28 1 month: -6.55 +/- 4.60 3 month: -5.99 +/- 6.55 6 month:-5.51 +/- 5.71 1 year: 0.20 +/- 0.08 (p=0.22) Mean cylinder vector Preop: 1.58 x 7 +/- 3.8 1 year: 1.41 x 24 +/- 3.5 (p=0.15).	Not Reported.	Measured in µm Preop: 458.9 +/- 40 1 week: 437.8 +/- 44.1 1 month: 436.3 +/- 41.4 3 month: 436.3 +/- 41.4 6 month: 449.7 +/- 46.1 1 year: 450.3 +/- 50.9 (p=0.647).	Not Reported.
Author: Holopainen **Year:** 2011 **Ref:** 53 **Country:** Finland	Measured in dioptres Spherical equivalent Preop: -1.37 +/- 2.38 6 month: -1.22 +/- 2.53 (p=0.50) No patient exhibited an increase in astigmatism of >2.0 D, compared to preop.	Not Reported.	Measured in µm Baseline 483 +/- 54 6 months 471 +/- 50 (p=0.35).	Not Reported.
Author: Koller **Year:** 2011	Not Reported.	Not Reported.	Not Reported.	Not Reported.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Ref: 64 **Country:** Switzerland				
Author: Koller **Year:** 2009 **Ref:** 65 **Country:** Switzerland	Not Reported.	Not Reported.	Minimal thickness in µm CXL group Baseline 452 12 months 440 Change -12.6 +/- 12.7 (p=0.02) Control Baseline 478 12 months 471 Change -7 +/- 12.2 (p=0.22).	At 1 month, anterior stromal haze ranging from trace (+0.5) to +1 and in the deeper stroma the demarcation line was visible in 18/21 eyes at a depth of 50-80% gradually moving forward and fainting at subsequent visits. In 3 eyes at 1 month after treatment, the demarcation line led to the wrong detection of the posterior surface of the cornea and the information of the posterior surface including corneal thickness was neglected. At the 6 months examination, all corneas were clear except 2 where discrete scarring structures were visible in the deep stroma. No irregularity at the endothelial level (e.g. localised oedema or scarring).
Author: Koppen **Year:** 2011 **Ref:** 67 **Country:** Belgium	Change in Sim K astigmatism Control (no contact lens) 6 months: 0.16 12 months: -0.13 18 months: -0.19 (p=0.826) Contact lens 6 months: -1.26 12 months: -1.41 18 months: -1.19 (p=0.054).	Not Reported.	Not Reported.	Not Reported.
Author: Kranitz	Measured in dioptres Sphere	Not Reported.	Measured in µm at thinnest point CXL Group	Not Reported.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Year: 2012 **Ref:** 68 **Country:** Hungary	CXL Group Baseline: -2.55 +/- 3.21 12 months: -1.48 +/- 2.39 Control Group Baseline: -1.35 +/- 2.06 12 months: -1.40 +/- 2.07 (p value for change between groups 0.92) Cylinder CXL Group Baseline: -3.49 +/- 2.45 12 months: -3.00 +/- 2.25 Control Group Baseline: -2.15 +/- 2.12 12 months: -2.26 +/- 2.09 (p value for change between groups 0.34).		Baseline: 472 +/- 33 12 months: 441 +/- 39 Control Group Baseline: 489 +/- 26 12 months: 488 +/- 27 (p value for change between groups <0.001).	
Author: Kymionis **Year:** 2009 **Ref:** 75 **Country:** Greece	Not Reported.	Measured in mmHg Baseline: 9.95 +/- 3.01 6 months: 11.40 +/- 2.89 12 months: 11.35 +/- 3.38.	Not Reported.	Not Reported.
Author: Kymionis **Year:** 2012 **Ref:** 71 **Country:** Greece	Measured in dioptres Spherical equivalent Baseline: -5.60 +/- 4.90 12 months: -4.91 +/- 3.90.	Not Reported.	Not Reported.	No intraoperative or postoperative complications.
Author: Kymionis **Year:** 2012 **Ref:** 70 **Country:** Greece	Measured in dioptres. Mean SE TG-PRK. Preop: -5.52 +/- 5.04; 6 months -4.79 +/- 3.06 (p=0.57); 12 months -4.42 +/- 3.25 (p=0.29) Mechanical debridement.	Not Reported.	Not Reported.	No intraoperative or postoperative complications.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
	Preop: -4.99 +/- 4.10; 6 months -4.80 +/- 3.88 (p=0.90); 12 months -4.77 +/- 3.76 (p=0.74) Mean corneal astigmatism TG-PRK. Preop: -5.84 +/- 3.80; 6 months -5.84 +/- 3.11 (p=0.44); 12 months -4.31 +/- 2.90 (p=0.015) Mechanical debridement. Preop: -4.06 +/- 2.70; 6 months -3.96 +/- 2.40 (p=0.82); 12 months -3.85 +/- 2.80 (p=0.81).			
Author: Li **Year:** 2010 **Ref:** 84 **Country:** China	Measured in dioptres Astigmatism Preop: 2.36 +/- 1.47 12 month: 0.58 +/- 1.04 (p=0.133).	Measured in mmHg Preop: 10.45 +/- 2.37 12 month: gain of 2.85 +/- 2.25 (p<0.01).	Not Reported.	Not Reported.
Author: Mazzotta **Year:** 2007 **Ref:** 90 **Country:** Italy	Not Reported.	Not Reported.	Measured in µm Baseline: 441 +/- 29 1 month 463 +/- 43 6 months: 453 +/- 39.	Transient corneal edema and sensation of foreign body for 24 to 48 hours postoperatively; oedema disappeared by 6 months.
Author: Romano **Year:** 2012 **Ref:** 104 **Country:** Italy	Measured in dioptres Mean spherical equivalent Baseline: -4.0 +/- SD 4.9 1 month:-6.2 +/- SD 5.1 3 months: -5.1 +/- SD 5 6 months: -4.8 +/- SD 4.9	Not Reported.	Not Reported.	No statistically significant changes in retinal morphology (i.e. retinal damage).
Author: Salgado	Measured in dioptres	Not Reported.	Not Reported.	Trace haze present in 10/22 eyes

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Year: 2010 **Ref:** 107 **Country:** Germany	Sphere Preop: -1.15 1 month: -2.30 3 months:-1.73 6 months: -1.48 12 months: -1.06 Cylinder Preop:-2.59 +/- 1.86 1 month:-2.17 +/- 1.38 3 months: -1.88 +/- 1.57 6 months:-2.15 +/- 1.59 12 months:-2.10 +/- 1.58 (All p>0.05) Spherical equivalent Preop: -2.39 +/- 2.30 1 month: -3.31 +/- 3.33 3 months: -2.67 +/- 2.38 6 months: -2.56 +/- 2.65 (p=0.04 at 6 months p>0.05 at all other periods) 12 months: -2.07 +/- 2.18 Topographic astigmatism Preop: -2.34 +/- 2.09 1 month: -2.98 +/- 1.97 3 months: -2.69 +/- 1.79 6 months: -2.86 +/- 2.22 12 months: -2.39 +/- 1.80 (p>0.05).			postop but disappeared during first 3 months.
Author: Sedaghat **Year:** 2010 **Ref:** 108 **Country:** Iran	Not Reported.	Measure in mmHg IOP (Goldman correlated) Baseline: 10.47 +/- 3.0 6 months: 10.07 +/- 3.0 (p=0.281) IOP (corneal compensated) Baseline: 13.98 +/- 2.9 6 months: 13.14 +/- 2.8 (p=0.027) CH Baseline: 7.99 +/- 1.5 6 months: 8.20 +/- 1.5 (p=0.253)	Measured in µm Baseline: 477.00 +/- 49.9 6 months: 454.92 +/- 77.6 (p=0.054).	Not Reported.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
		CRF Baseline: 7.36 +/- 1.4 6 months: 7.59 +/- 1.5 (p=0.240).		
Author: Vinciguerra **Year:** 2012 **Ref:** 114 **Country:** Italy and Switzerland	Measured in dioptres Mean spherical equivalent Baseline: -3.63 +/- 3.45 24 months: -2.06 +/- 2.21 (p=0.02) Sphere Baseline: -2.32 +/- 2.87 24 months: -1.38 +/- 1.64 (p=0.01) Cylinder Baseline: -2.87 +/- 1.12 24 months: -1.56 +/- 1.38 (p=0.02).	Not Reported.	Measured in µm Pupil centre thickness Baseline: 489 6 months: 471 (p=0.04) 12 months: 480 24 months: 522 Thinnest point Baseline: 467 6 months: 452 12 months: 462 24 months: 481 (p>0.05).	Abrasion related discomfort in most patients in the immediate postop period. No ocular or systemic adverse events were noted, apart from a 5% incidence of blepharitis and 3% mild photophobia at 4 months. CXL-specific golden striae in 62%. 6.9% with 1+ haze that resolved with steroids after 1 month.
Author: Vinciguerra **Year:** 2009 **Ref:** 116 **Country:** Italy	Measured in dioptres Cylinder Baseline: -4.27 6 months: -4.44 12 months: -3.99 24 months: -3.80 (p=0.03).	Not Reported.	Measured in µm Pupil centre thickness Baseline: 490.63 +/- 30.69 12 months: 470.09 +/- 29.01 (p=0.045) 24 months: 479.91 +/- 32.21.	No ocular or systemic adverse events seen. 43.5% developed golden striae and 12.7% 1+ haze. Haze resolved within 1 month with topical steroids. Complaints of night glare and haloes in first 3 months (number of patients not stated).
Author: Vinciguerra **Year:** 2009 **Ref:** 115 **Country:** Italy	Measured in dioptres Mean spherical equivalent Treated eye Baseline: -6.73 +/- 1.03 12 months: -6.3 +/- 0.78 Untreated eye Baseline: -3.52 +/- 0.82 12 months: -4.21 +/- 0.56 Cylinder Baseline: -3.02 +/- 1.74 12 months: -2.76 +/- 1.11 (p<0.05).	No significant changes in IOP seen.	Measured in µm Pupil centre thickness Baseline: 490.68 +/- 30.69 12 months: 470.09 +/- 29.01 (p<0.05).	Not Reported.
Author: Wollensak	Measured in dioptres Postop regression in refractive	Measured in mmHg Preop: 13.6 +/- 2.0	Not Reported.	Slight transient stromal edema until re-epithelialisation after 3

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Year: 2003 **Ref:** 118 **Country:** Germany	error (spherical equivalent) 1.14 +/- 2.18 (p=0.03).	Postop: 13.8 +/- 2.5 (p=0.612).		days. No side effects.
Author: Agrawal **Year:** 2009 **Ref:** 1 **Country:** India	Measured in dioptres Baseline: mean astigmatism 7.24 +/- 4.67 D Change at 6 months: mean astigmatism -0.7 +/- 3.98 D Mean astigmatism -1.2 +/- 4.02 D (p=0.005) in 47% of eyes. Remaining eyes were stable.	Not Reported.	Baseline: (using ultrasonic pachymetry) 478 +/- 45 µm. Change at 6 month follow-up: 10 +/- 7.5 µm (p not reported). 12 month follow-up not recorded.	Not Reported.
Author: Asri **Year:** 2011 **Ref:** 6 **Country:** France	Measured in dioptres Baseline: Astigmatism (D) = 6.60 +/- 3.58 6 months: Astigmatism (D) = 6.19 +/- 2.96 12 months: Astigmatism (D) = 6.67 +/- 3.60.	Corneal resistance factor (CRF) and corneal hysteresis (CH) reported in 77 patients at baseline, 45 at 6 months and 25 at 12 months. CRF in mmHg Baseline: 7.02 +/- 1.67 6 months: 6.91 +/- 1.72 (p=0.48) 12 months: 6.81 +/- 1.64 (p=0.95) CH in mmHg Baseline: 8.25 +/- 1.42 6 months: 8.24 +/- 1.59 (p=0.26) 12 months: 8.13 +/- 1.49 (p=0.87).	Three methods used which varied by site with numbers receiving each method not reported. Methods were scanning-slit tomography (SST), rotating Scheimpflug tomography (RST) and optical coherence tomography (OCT). SST Baseline: 442 +/- 49 6 months: 384 +/- 61 12 months: 409 +/- 67 RST Baseline: 482 +/- 59 6 months: 444 +/- 42 12 months: 471 +/- 47 OCT Baseline: 468 +/- 36 6 months: 467 +/- 36 12 months: 451 +/- 47.	Total complication rate of 7.0% with 5/142 eyes (3.5%) having a reduction in vision of at least 2 Snellen lines (2 had haze at 3 months, 1 had haze at 6 months, 1 had corneal burn diagnosed at 1 month, 1 had corneal oedema at 1 month); another 5 eyes (3.5%) had corneal haze without loss of vision (3 at 3 months, 1 at 6 months, 1 at 1 year). 4 patients (2.8%) were referred for deep anterior lamellar keratoplasty (corneal transplant) for evolution of keratoconus at 1 year, low CVA at 1 year despite stabilisation of keratoconus, central corneal opacity 1 month after CXL or progression of keratoconus and loss of CVA at 6 months.
Author: Pinero **Year:** 2012	Measured in dioptres Astigmatism Baseline: 3.91 +/- 3.17 6 months: 2.50 +/- 2.06	Provided on a graph that cannot be easily read. Text states that a small significant increase in CRF was found at 6 months and	No statistically significant change in thickness found from baseline.	Not Reported.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
Ref: 97 **Country:** Spain	12 months: 3.88 +/- 2.96 24 months: 3.75 +/- 2.97 (p=0.99) Cylinder Baseline: -3.90 +/- 2.79 6 months: -1.83 +/- 1.01 12 months: -2.91 +/- 1.67 24 months: -3.46 +/- 2.77 (p=0.36) Sphere Baseline: -2.30 +/- 4.39 6 months: -2.67 +/- 3.92 12 months: -1.80 +/- 3.73 24 months: -1.86 +/- 4.19 (p=0.42).	decrease in CH at 12 to 24 months.		
Author: Raiskup **Year:** 2009 **Ref:** 100 **Country:** Germany	Not Reported.	Not Reported.	Not Reported.	No sterile or infectious infiltrate in corneal stroma, no side effects, all corneas transparent at 1 year without scarring.
Author: Raiskup **Year:** 2011 **Ref:** 99 **Country:** Germany	Not Reported.	Not Reported.	Not Reported.	No side effects observed.
Author: Raiskup-Wolf **Year:** 2008 **Ref:** 101 **Country:** Germany	Measured in dioptres Mean change +/- SD (%). Astigmatism 1 year (n=142): -0.93 +/- 3.67 (85.6%) (p<0.01) 2 years (n=66): -1.20 +/- 3.87 (84.8%) 3 years (n=33): -1.45 +/- 3.05 (68.2%) 4 years (n=13): -1.49 +/- 1.79	Measured in mmHg 1 year: 0.2 +/- 1.4 (p>0.05) 2 years: -0.3 +/- 1.4	Measured in µm 1 year: -2 +/- 12 (p<0.05) 2 years: 21 +/- 31.	Two patients had neurodermatitis and progression of keratoconus at follow-up (at 18 and 21 months).

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
	(85.6%) 5 years (n=5): -1.47 +/- 3.39 6 years (n=5): -0.90 +/- 1.60.			
Author: Saffarian **Year:** 2010 **Ref:** 106 **Country:** Iran	Measured in dioptres Change in spherical power: -0.18 +/- 0.79 (p>0.05) Change in cylindrical power: 0.78 +/- 1.49 (p<0.001) Change in Spherical equivalent: 0.57 +/- 1.04 (p<0.001).	Not Reported.	Not Reported.	No significant complications such as persistent epithelial defect, infectious keratitis, or corneal haze and cataract formation occurred during this study.
Author: Asfuroglu **Year:** 2012 **Ref:** 5 **Country:** USA	Not Reported.	Not Reported.	Not Reported.	Not Reported.
Author: Hafezi **Year:** 2007 **Ref:** 47 **Country:** Switzerland and Greece	Sphere and Cylinder (CyL) (only cases 4-10 keratoconus) Case 4 Preop: Sphere: -1 Cyl: -3 12 months: Sphere: -1, Cyl: -2.5 Case 5 Preop: Sphere: +1 Cyl: -3 17 months: Sphere: 0.5 Cyl: -1.5 Case 6 Preop: Sphere: -5 Cyl: -5.5 21 months: Sphere: -4, Cyl: -3.5 Case 7 Preop: Sphere: -7 Cyl: -4 20 months: Sphere: -5.5 Cyl: -3.4 Case 8 Preop: Sphere: -2 Cyl: -3.5 25 months: Sphere: -1.75 Cyl: -2.3 Case 9 Preop: Sphere: -3 Cyl: -5.25 23 months: Sphere:-3.75 Cyl: -3.3	Not Reported.	Measured in µm using optical pachymetry and US pachymetry Case 4 Preop: Optical: 410, US: 410 12 months: Optical: 400, US: 420 Case 5 Preop: Optical: 425, US: 420 17 months: Optical: 400, US: 440 Case 6 Preop: Optical: 400, US: 405 21 months: Optical: 410, US: 400 Case 7 Preop: Optical: 420, US: 420 20 months: Optical: 410, US: 430 Case 8 Preop: Optical: 480, US: 475 25 months: Optical: 460, US: 500 Case 9 Preop: Optical: 465, US: 470	Not Reported.

Author	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events
	Case 10 Preop: Sphere: -3.5 Cyl: -3.75 17 months: Sphere: -3.75 Cyl: -2.3 Calculated means and SD: Preop: Sphere: -2.93 +/- 2.62, Cyl: -4 +/- 1.01 Post: Sphere: -2.75 +/- 2.07, Cyl: -2.69 +/- 0.74.		23 months: Optical: 450, US: 480 Case 10 Preop: Optical: 420, US: 425 17 months: Optical: 420, US: 440 Calculated means and SD: Preop: Opt: 431.43 +/- 29.54, US: 432.14 +/- 28.41 Post: Opt: 421.43 +/- 24.10, US: 444.29 +/- 34.57.	
Author: Hafezi **Year:** 2009 **Ref:** 46 **Country:** Switzerland	Not Reported.	Not Reported.	Not Reported.	1/10 case of endothelial irregularity and some opacity, this cleared 12 months after cross-linkage. In the early postoperative phase, all corneas had haze in the anterior stroma (not sub-epithelial); all clear by 12 months.
Author: Kjankov **Year:** 2009 **Ref:** 63 **Country:** Not Reported	Not Reported.	Not Reported.	Not Reported.	No eye lost any lines of BCVA.
Author: Mazzotta **Year:** 2012 **Ref:** 87 **Country:** Italy	Not Reported.	Not Reported.	No statistically significant change at 6 months and 12 months.	Epithelial thinning associated with stromal oedema and keratocytes apoptosis explained initial tendency towards slightly reduced visual acuity and more glare one month postoperatively in 70% of eyes.

4.6 SUMMARY OF EFFICACY FINDINGS FOR EPITHELIUM-OFF CXL PAPERS

In summarising efficacy findings the main focus is on RCTs (both individually and in meta-analysis where feasible) and on the meta-analysis results of the intervention arms of all papers. The majority of these compare changes in values for the outcomes as measured before and after the procedure.

The measure of heterogeneity used is the quantity I^2, which informs on the consistency of the results of papers in meta-analyses. When a meta-analysis has a high I^2 value there may be a variety of underlying causes, including that the underlying papers are not homogeneous, the papers have somewhat inconsistent results, or it may be there are just very few of them. This limits the robustness of drawing conclusions from the data and generalising findings to other settings, in this case to the NHS setting. Where a meta-analysis displays high heterogeneity, the results of the random effects model are more reliable than those from the fixed effects model.

4.6.1 Topography for Epithelium-off CXL Papers

Although there were several different measures of topography used in the identified papers, following clinical advice these measures were grouped together as mean keratometry (K), maximum (Max) K and minimum (Min) K as shown in Table 4.3.

Table 4.3: Topography groupings for analysis

Measurement	Measurement group
Max K, maximum K, Kmax	Max K
Steepest K	
Min K, minimum K, Kmin	Min K
Flattest K	
Mean K	Mean K
Central K	
Mean sim K, sim K	

4.6.1.1 RCT evidence

Three unique RCTs were identified that provided measures of topography (50, 52, 117). All 3 papers reported reductions in Max K 12 months postoperatively that were statistically significant compared with the no treatment arm ($p=0.03$, $p<0.001$ $p=0.002$, respectively). The reductions in Max K were 2.66 D, 1.7 D and 1.45 D, respectively.

Outcomes for patients in a sub-group of one of the RCTs (52) were reported by Greenstein (38) showing the change over 12 months for mean K in those undergoing the CXL procedure. A reduction of 1.6 D, which was statistically significant, was reported. The same RCT (52) reported Min K 12 months postoperatively, showing a non-statistically significant reduction of 0.9 D in those undergoing the CXL procedure.

A meta-analysis of the change between intervention and control arms could not be undertaken as there were insufficient data across the papers on the same measures of topography.

4.6.1.2 Meta-analysis of preoperative/postoperative changes

Table 4.4 shows the number of papers (RCTs and non-RCTs) that provided sufficient data on postoperative changes at different time periods to allow meta-analysis of the different topography measures.

Table 4.4: Number of papers providing evidence of preoperative/postoperative change by follow-up and topography measure

	6 months	12 months	24 months
Max K	10	18	6
Min K	4	8	-
Mean K	7	12	-

Max K

Forest plots for 6, 12 and 24 months comparing change in the Max K value before the operation and postoperatively are provided in Figures 4.1, 4.2 and 4.3, respectively.

Figure 4.1: Change in Max K (dioptres) at 6 months pre and postoperation

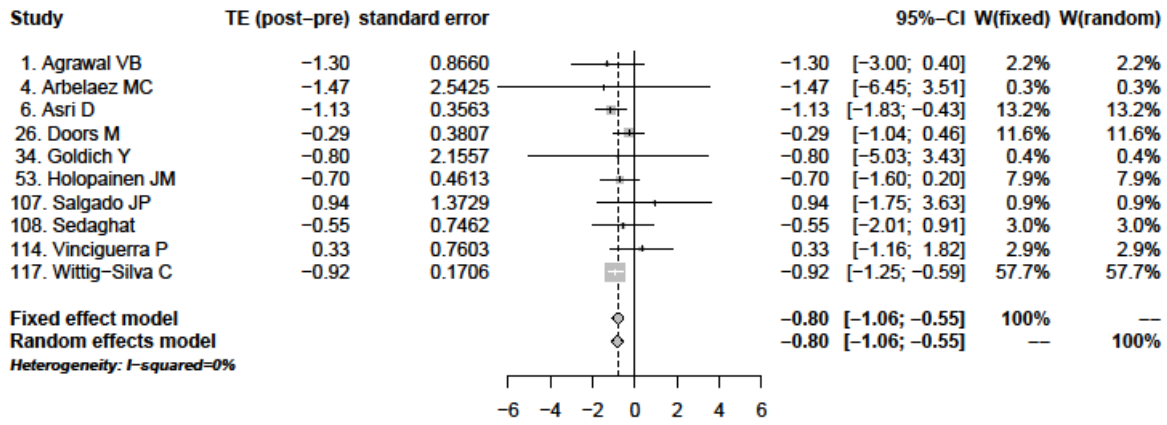


Figure 4.2: Change in Max K (dioptres) at 12 months pre and postoperation

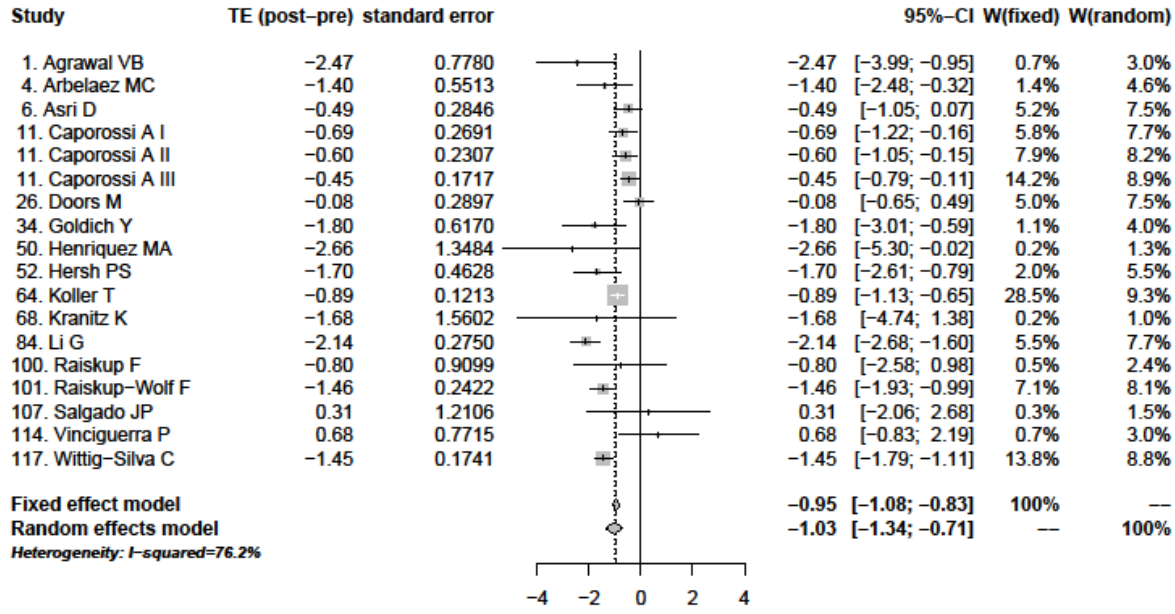
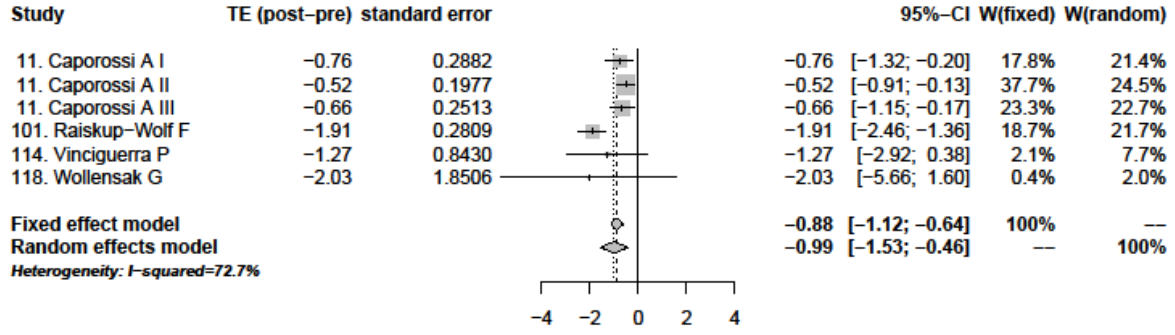


Figure 4.3: Change in Max K (dioptres) at 24 months pre and postoperation



Whilst several of the individual papers failed to show a statistically significant change in Max K, notably at 6 months, both the fixed and random effects models suggest there is a reduction in Max K over 6, 12 and 24 months following CXL that is statistically significant. In the random effects model this change was -0.8 D at 6 months, -1.03 D at 12 months and -0.99 D at 24 months.

Min K

Forest plots for changes in the Min K value at 6 and 12 months postoperation compared to the value before the procedure are provided in Figures 4.4 and 4.5, respectively.

Figure 4.4: Change in Min K (dioptres) at 6 months pre and postoperation

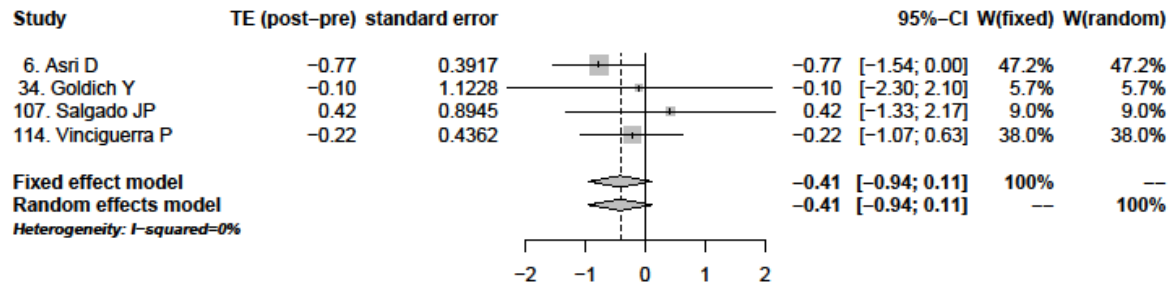
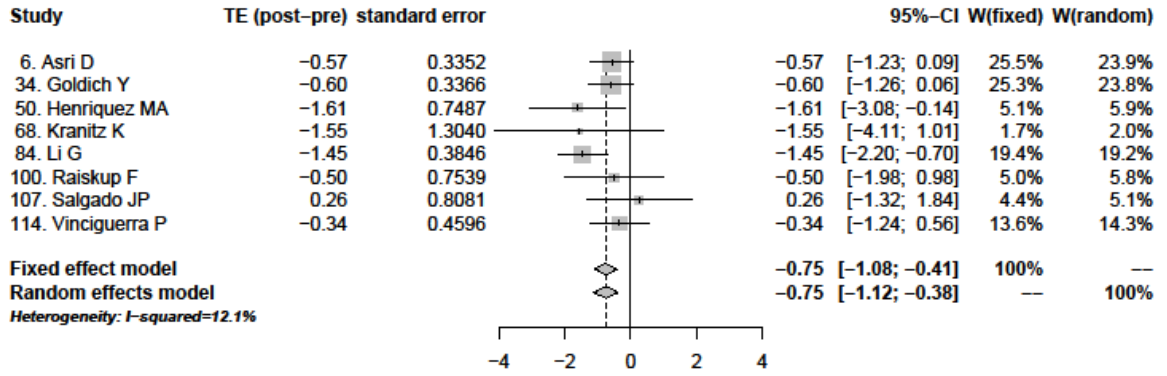


Figure 4.5: Change in Min K (dioptres) at 12 months pre and postoperation



At 6 months postoperatively, in both the fixed and random effects models there was no statistically significant evidence that Min K had changed, although 3 of the 4 papers reported a reduction. At 12 months postoperatively, however, both the random and fixed effect models suggested a reduction in Min K in the order of -0.75 D that was statistically significant.

Mean K

Forest plots for changes in the mean K value at 6 and 12 months postoperation compared to the value before the procedure are provided in Figures 4.6 and 4.7, respectively.

Figure 4.6: Change in mean K (dioptres) at 6 months pre and postoperation

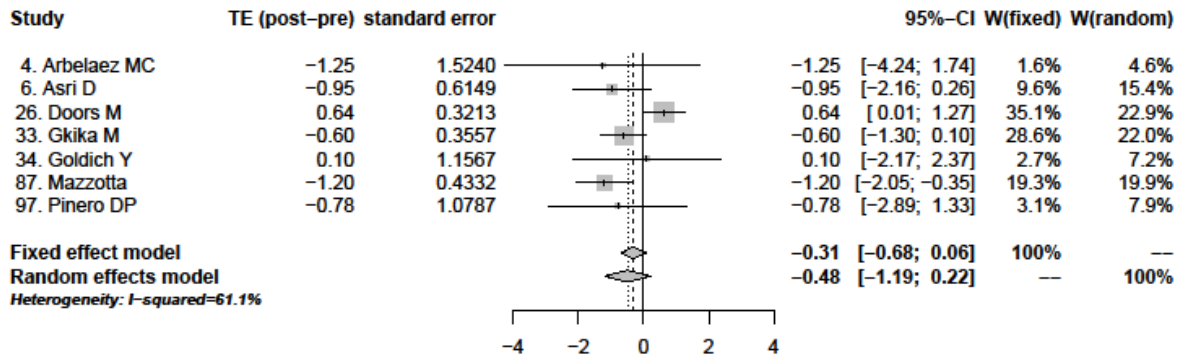
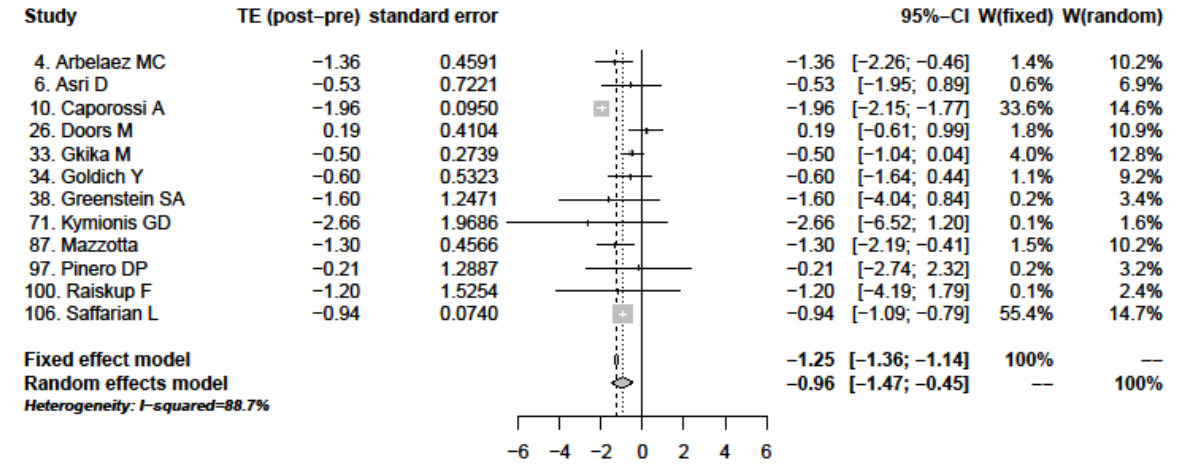


Figure 4.7: Change in mean K (dioptres) at 12 months pre and postoperation



At 6 months postoperatively, in both the fixed and random effects models there was no statistically significant evidence that mean K had changed. At 12 months postoperatively, however, both the random and fixed effect models suggested a reduction in mean K that was statistically significant. The random effects model suggested that this change was in the order of -0.96 D. Note, these models had high I^2 values (61% and 89%) and, thus, are a heterogeneous group of papers.

4.6.1.3 Evidence from all papers

In total, 38 papers reported measures of topography using a number of different parameters. These were grouped using the convention set out in Table 4.4:

- Maximum keratometry;
- Minimum keratometry;
- Mean keratometry.

Three time periods were used to group the results: 6, 12 and 24 months. A further simplification was made to provide some aggregation of papers whilst using as much of the data as possible. Papers reporting at 9 months were included under the 12-month period and those reporting at 18 months under the 24-month period.

Papers reporting end points where the units measured were unclear, or used measures which could not be aggregated with others, were not included. The remaining results were used to calculate the mean value of the change reported for each measure/time period combination.

These assumptions and methodology were adopted for all parameters (topography, VA, astigmatism, IOP and CCT). These estimates are not offered as a precise estimate of the change in measures as a result of CXL, rather they give an indication of the size effect and its direction. They are intended to display the trend in evidence for each group of similar parameters but do no more than that.

All but 2 papers (107, 114) reported an improvement in keratometry post procedure. Study 107 reported an increased mean value of 0.5 D for the 4 measures: Max K and Min K at 6 and 12 months. The study was of 22 eyes with iatrogenic keratectasia. The changes were not statistically significant. Study 114 reported an increase in Max K at 6 months (0.3 D) and increases in Max K and mean K values at 12 months (0.7 D and 0.3 D, respectively). At 24 months, all measures showed a reduction in K values, with the reductions in mean and minimum values being statistically significant. This paper reported 40 eyes of patients aged 9 up to 18 years.

In total, 104 results were provided which could be used for the three time periods, with 41 (38%) reporting statistically significant improvements in K values. Four papers (4, 11, 34, 50) reported statistically significant differences at 12 months but not at 6 months, and where values were reported for both periods, the improvement at 12 months usually exceeded the improvement at 6 months. Of the 8 papers reporting data and grouped at 12 and 24 months, the 24-month values showed an improvement or no change on the 12-month values in all cases (10, 11, 35, 97, 101, 114, 116) but one (67).

The mean improvements in K values at each time period are shown in Table 4.5 for the 3 categories.

Table 4.5: Reported change in K values by category and time period

K category	Change by time periods and number of papers per period		
	At 6 months	At 12 months	At 24 months
Maximum	0.77 D from 17 papers	1.55 D from 11 papers	1.83 D from 9 papers
Mean	0.72 D from 24 papers	1.40 D from 16 papers	1.01 D from 12 papers
Flat	0.51 D from 8 papers	1.12 D from 7 papers	1.58 D from 3 papers

Five papers (10, 16, 67, 68, 117) reported a comparative arm of no treatment. One of these (117), an RCT, has already been discussed. The other 4 papers all reported improvements in the CXL arm which materially exceeded the values reported for the controls; in 3 papers (10, 16, 68), the comparators reported an increase in K values.

One study (38) compared keratoconus and keratectasia eyes and improvements were recorded for both groups.

One study (101) reported changes in K values beyond 24 months but noted there was a steady reduction in the number of included patients. At 2 years the change in K max was -1.91 D, which had risen slightly to -2.6 D by the end of year 3, reaching a plateau in years 4 to 6 at -2.66 D,-2.47 D and -2.44 D, respectively. By this period only 5 eyes were reported.

4.6.1.4 Conclusion

Three RCTs reported statistically significant reductions in Max K values in treated arms compared with untreated arms. The values were reductions of 2.66 D, 1.7 D and 1.45 D.

Before and after studies also reported statistically significant reductions. Max K values were synthesised at 6, 12 and 24 months and these were statistically significant, reporting reductions of -0.8 D, -1.0 D and -1.0 D, respectively, from 10, 18 and 6 papers, respectively.

The meta-analyses of the before and after studies also reported a statistically significant reduction in mean K (-1.0 D) at 12 months. This was informed by 12 papers. The reduction of 0.5 D estimated at 6 months from 7 papers was not statistically significant.

Similarly, the change in Min K value was statistically significant at 12 months (-0.8 D) and reported from 8 papers, whereas the change of -0.4 D at 6 months and reported from 4 papers was not statistically significant.

These findings were supported by analyses of the 38 papers reporting topography, with 38% of the reported results showing a significant reduction in K values. The size of the reductions in Max K and Min K increased over time up to 24 months. Evidence beyond this period comes from one study (101) with a high drop-out rate but suggested the reduction in K value is maintained.

4.6.2 Visual Acuity for Epithelium-off CXL Papers

For the purposes of this analysis only papers that provided measures of visual acuity on the LogMAR or decimal scales were included. The decimal scale was converted into the LogMAR scale using the following formula:

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

Papers that did not report the measure used for visual acuity were not included in the quantitative synthesis. Also, 1 study (10) reported changes from baseline for several follow-up periods in Snellen lines. The results from this study were not included, as it not possible to transform the changes in Snellen lines into either the decimal equivalent or the LogMAR scale.

Results for both corrected and uncorrected visual acuity (corrected and uncorrected VA) were analysed. Distance visual acuity measures were used; where this aspect was not reported the values were assumed to be a distance measure.

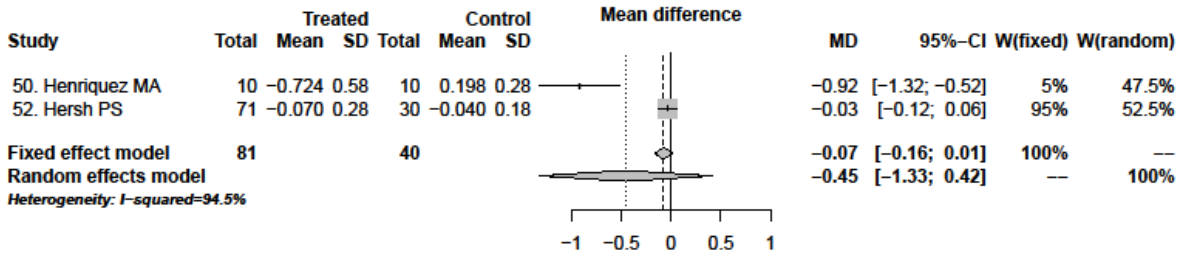
4.6.2.1 RCT evidence

Four RCTs (50, 52, 96, 117) provided measures of the difference in change in visual acuity in LogMAR or decimal scales between intervention and control arms.

Only 1 small, prospective RCT of 20 eyes (50) reported any statistically significant difference in the change in uncorrected VA between intervention and control eyes at any follow-up point (12 months).

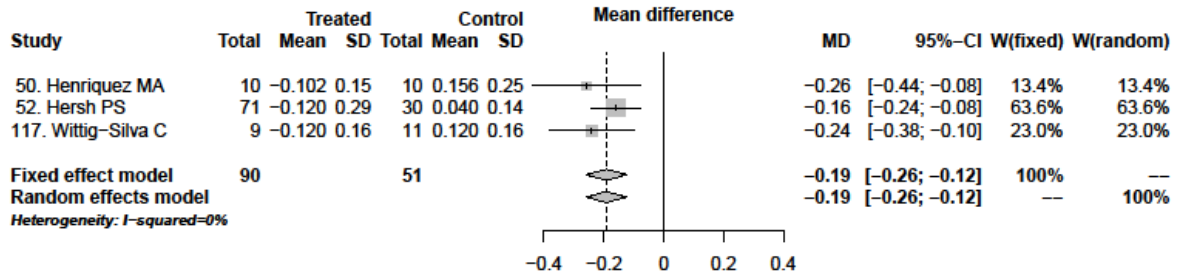
Inconsistency in the time of follow-up between papers resulted in meta-analysis only being feasible at 12 months for 2 papers (50, 52) of uncorrected VA. The forest plot of the analysis is shown in Figure 4.8. This analysis suggested that there were no statistically significant differences in uncorrected VA between intervention and control eyes. There was also considerable heterogeneity between the papers (I^2 = 95%).

Figure 4.8: Difference between intervention and control patients for change from baseline in uncorrected VA (LogMAR) at 12 months



Three of the 4 RCTs reported on the change in corrected VA between intervention and control arms at 12 months (50, 52, 117). The magnitude of the mean differences in the treated eyes was between -0.102 and -0.12 LogMAR, compared with increases of between +0.04 and +0.16 in the untreated group. A forest plot of the meta-analysis of these papers is shown in Figure 4.9. There was low heterogeneity between papers (I^2 = 0%), producing equivalent results from the fixed and random effects models. These estimated the improvement in corrected VA for CXL compared with the control was equivalent to -0.19 LogMAR. This was statistically significant.

Figure 4.9: Difference between intervention and control patients for change from baseline in corrected VA (LogMAR) at 12 months



In contrast to the findings at 12 months, 1 RCT based in the UK (96) of 22 patients reported no statistically significant improvement in uncorrected VA or corrected VA after 18 months. The meta-analysis findings of uncorrected and corrected VA at 12 months compared with this study, as well as findings from another RCT (117) at 3 months (uncorrected VA) and 6 and 12 months (corrected VA), are shown in Figures 4.10 and 4.11.

Figure 4.10: Comparison of meta-analysis findings on corrected VA (LogMAR) at 3, 6, 12 and 18 months for intervention versus control

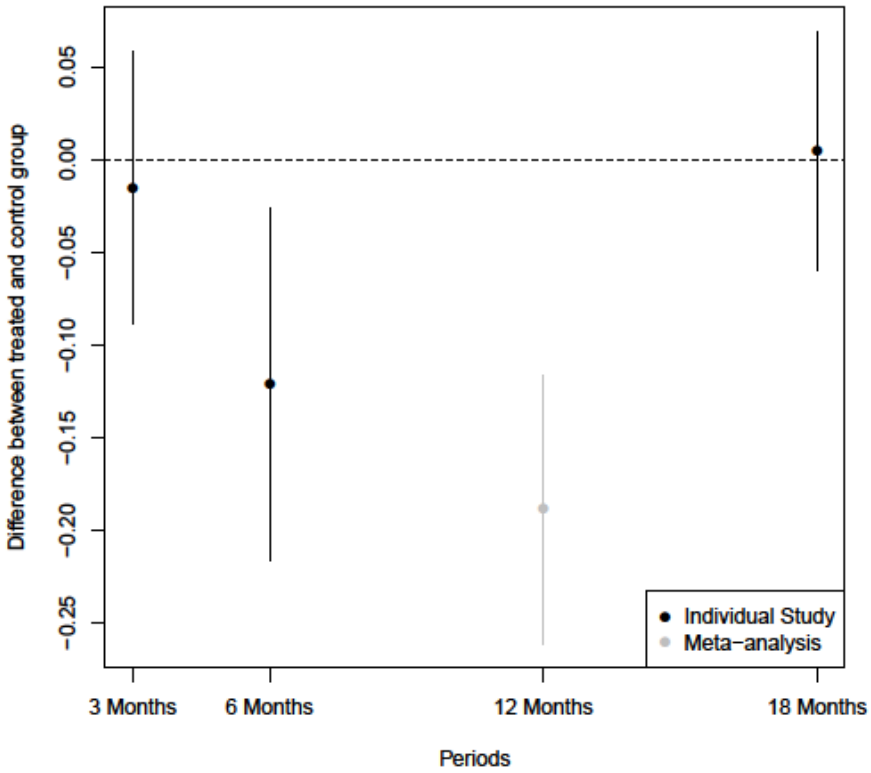
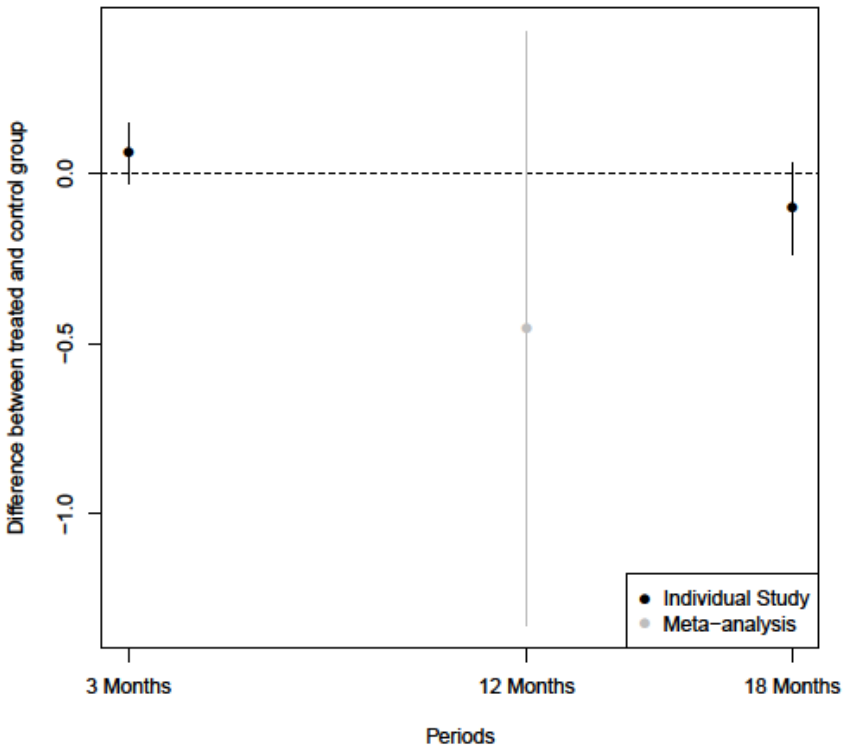


Figure 4.11: Comparison of meta-analysis findings on uncorrected VA (LogMAR) at 3, 6, 12 and 18 months for intervention versus control



4.6.2.2 Meta-analysis of preoperative/postoperative changes

Table 4.6 shows the number of papers (RCTs and non-RCTs) that provided sufficient data on postoperative changes at different time periods to allow meta-analysis of uncorrected and corrected VA.

Table 4.6: Number of papers providing evidence of preoperative/postoperative change by follow-up and VA measure

	6 months	12 months	24 months
Uncorrected VA	12	18	6
Corrected VA	15	22	7

Uncorrected VA

Forest plots for changes in uncorrected VA at 6 and 12 months postoperation compared to the value before the procedure are provided at Figures 4.12, 4.13 and 4.14, respectively.

Figure 4.12: Change in uncorrected VA (LogMAR) at 6 months pre and postoperation

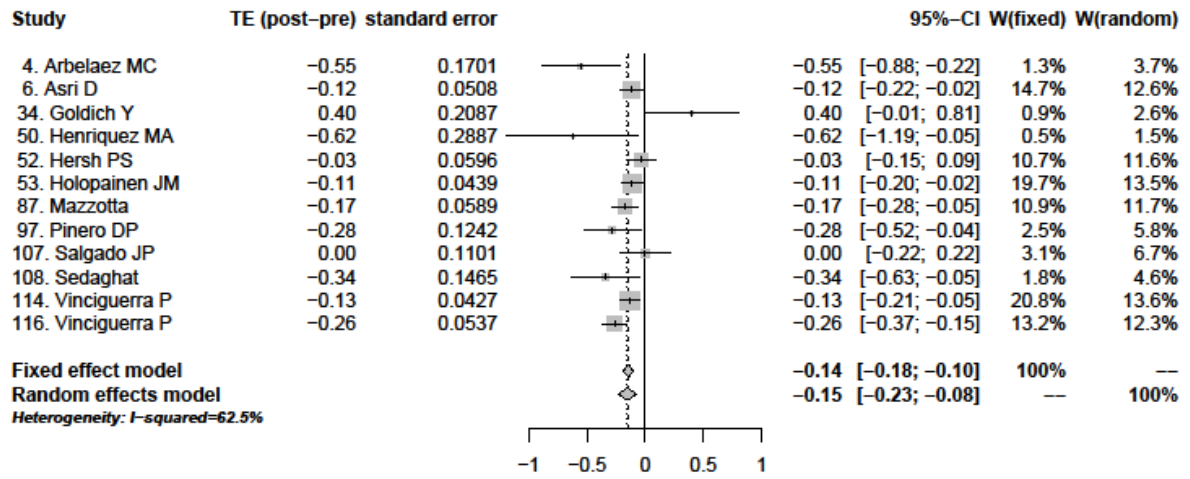


Figure 4.13: Change in uncorrected VA (LogMAR) at 12 months pre and postoperation

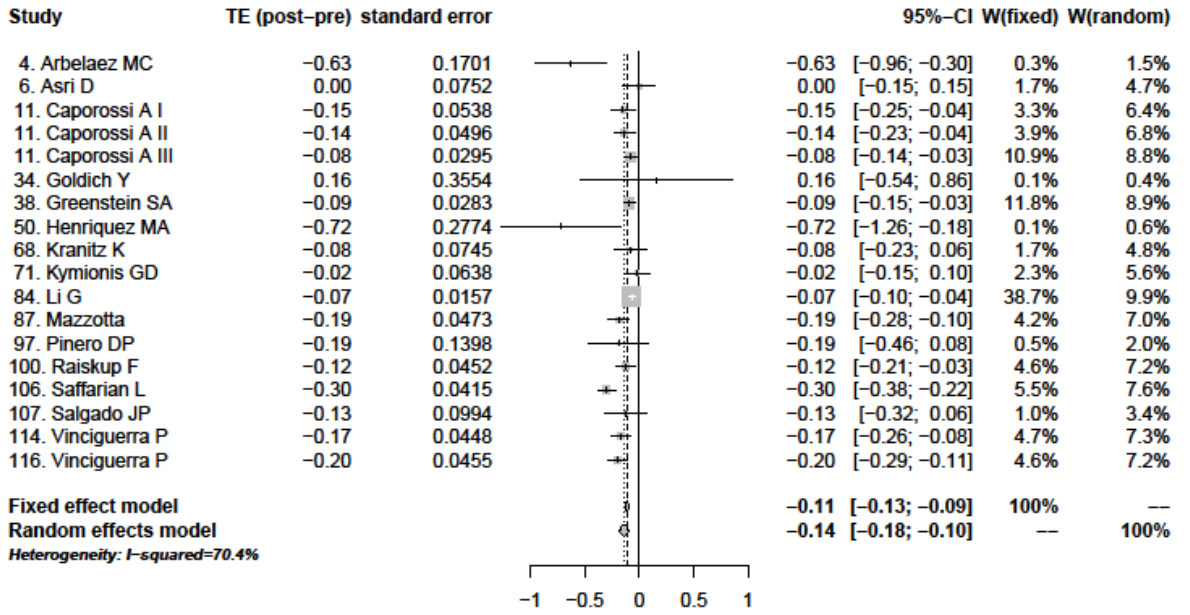
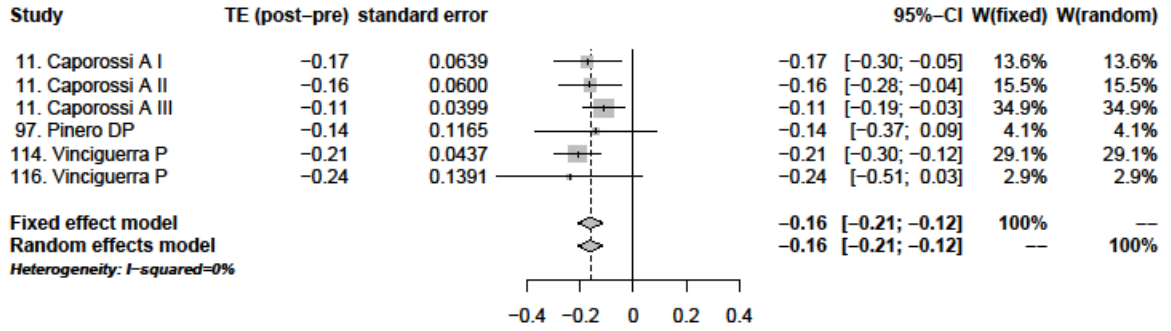


Figure 4.14: Change in uncorrected VA (LogMAR) at 24 months pre and postoperation



Meta-analysis of pre and postoperative change data at 6, 12 and 24 months showed statistically significant improvements in uncorrected VA postoperatively in both the fixed and random effects models. There was little difference in the random or fixed effects models in the magnitude of the change. This remained relatively constant after 6 months with the random effects model suggesting changes in LogMAR of -0.15, -0.14 and -0.16 at 6, 12 and 24 months postoperatively, respectively.

The Goldich study (34, 35) was the only one reporting a decrease in uncorrected VA at 6 and 12 months.

Corrected VA

Forest plots for 6, 12 and 24 months postoperative change from baseline before the procedure in corrected VA are provided in Figures 4.15, 4.16 and 4.17, respectively.

Figure 4.15: Change in corrected VA (LogMAR) at 6 months pre and postoperation

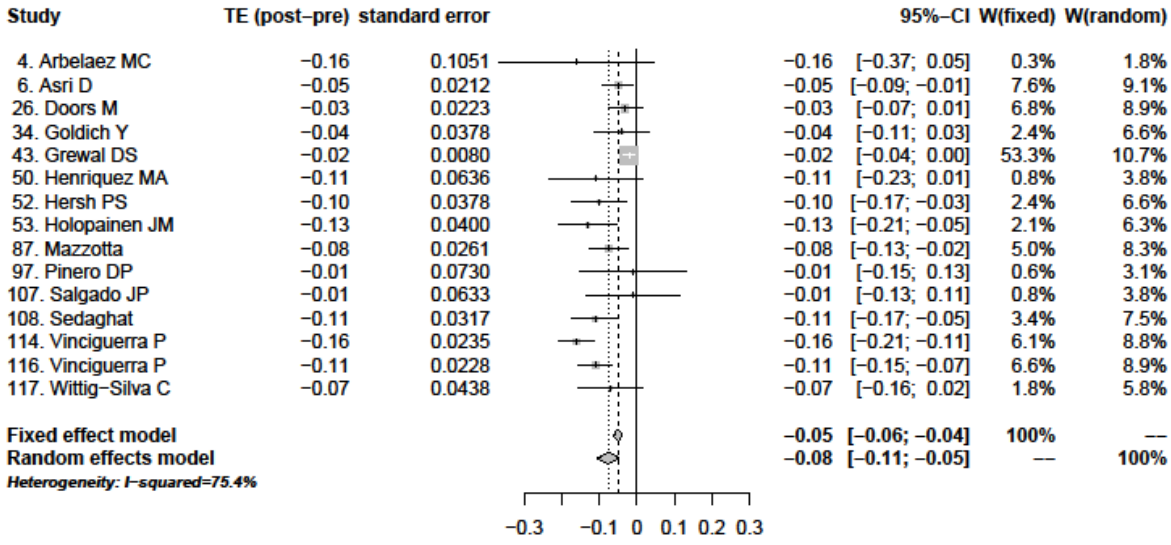


Figure 4.16: Change in corrected VA (LogMAR) at 12 months pre and postoperation

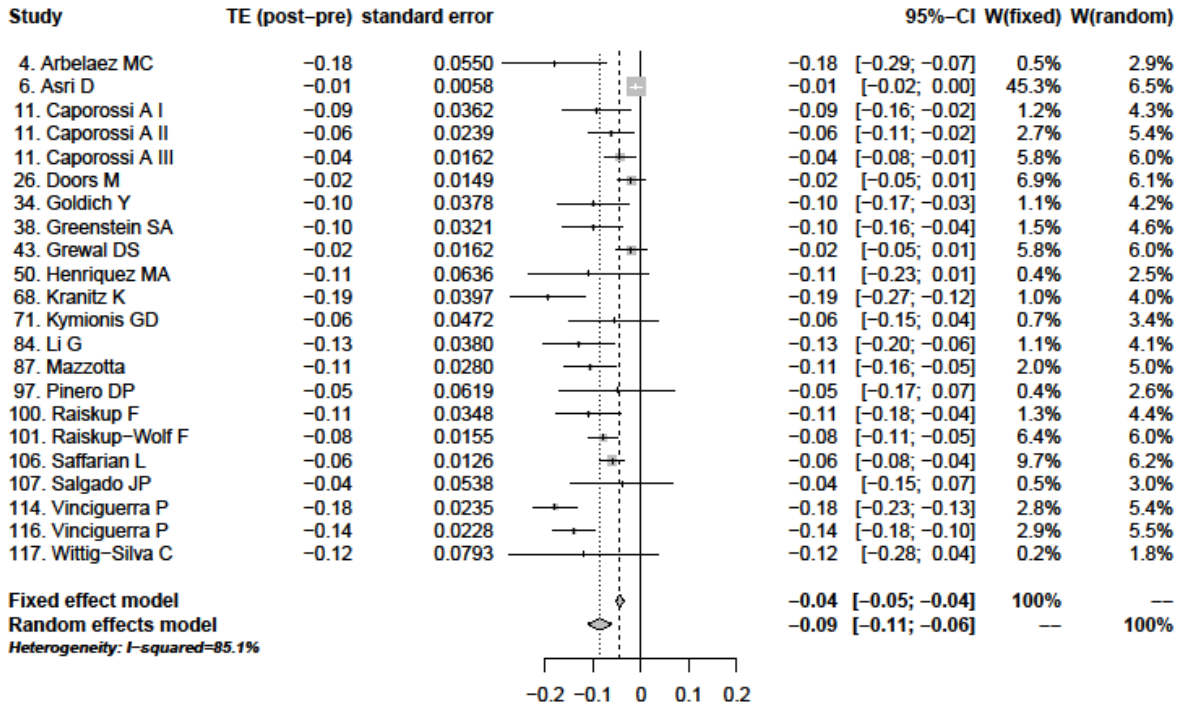
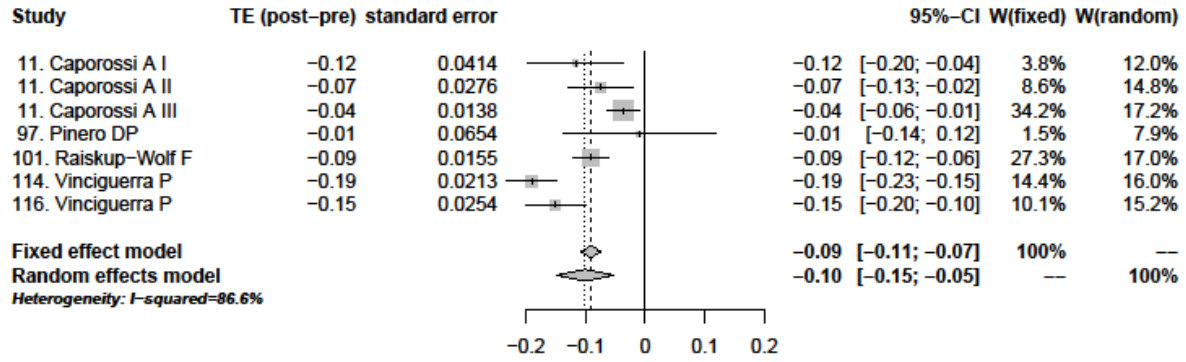


Figure 4.17: Change in corrected VA (LogMAR) at 24 months pre and postoperation



As was the case with uncorrected VA, the meta-analysis of pre and postoperative change data showed statistically significant improvements in corrected VA at 6, 12 and 24 months postoperatively in both the fixed and random effects models. However, given the high I^2 values the random effects model is the more appropriate.

Again, there was little absolute difference in the size effect reported by the random or fixed effects models, which also appeared to stay largely constant after 6 months. The random effects model reported changes in LogMAR of -0.08, -0.09 and -0.10 at 6, 12 and 24 months postoperatively, respectively. No papers reported a decrease in corrected VA after the procedure.

4.6.2.3 Evidence from all papers

In total, 38 papers reported 104 usable results on visual acuity of which 52 (50%) reported significant improvements in visual acuity. The majority of the papers (25) reported results using LogMAR measurements (4, 5, 6, 26, 34, 35, 38, 43, 50, 52, 53, 64, 70, 84, 97, 100, 101, 106, 107, 108, 114, 115, 116, 117). Four reported using decimal expression (1, 68, 71, 96) and six using Snellen lines (10, 11, 16, 33, 87, 118). Papers which did not report the measurement were excluded, as were those where it could not be ascertained with certainty.

Table 4.7 presents an estimate of the improvement recorded for uncorrected and corrected VA for each time period. Table 4.8 provides the number of papers included in the calculation of each combination of time period and measure. Please note these are indications of the effect size only and should not be interpreted as precise values.

Table 4.7: Change in VA by time period and VA measure

	Uncorrected VA at: (months)			Best corrected VA at: (months)			Corrected distance VA at: (months)		
	6	12	24	6	12	24	6	12	24
LogMAR	0.20	0.19	0.10	0.08	0.10	0.35	0.07	0.14	0.01
Snellen	0.15	0.60	1.45	0.06	0.35	1.03	NA		
Decimal Equivalent	NA	0.05	0.06	NA	NA	0.12	NA	0.12	NA

Table 4.8: Number of papers providing change in VA by time period and VA measure

	Uncorrected VA at: (months)			Best corrected VA at: (months)			Corrected distance VA at: (months)		
	6	12	24	6	12	24	6	12	24
LogMAR	13	17	4	11	14	5	6	7	1
Snellen	3	5	2	3	5	2	NA		
Decimal Equivalent	NA	2	1	NA	NA	1	NA	2	NA

The results suggest a trend towards improvement in all measures at 12 months. The change in benefit between 12 and 24 months cannot be discerned from these data because of the relatively few papers reporting data at 24 months.

One paper (101) reported best corrected VA for later years. At 24 months the change in LogMAR value was 0.09, which increased to 0.15 and 0.18 at months 36 and 48, respectively. However, these were reported by only 33 and 13 patients, respectively, compared with 66 patients at year 2.

One study (34, 35) reported a decline in uncorrected VA in treated eyes from a baseline of 0.62 LogMAR, to 1.02 at 6 months, 0.78 at 12 months and 0.81 at 24 months. None of the values were statistically significant. Corrected VA improved by 0.04, 0.10 and 0.07, respectively, over the same periods (LogMAR), with the values at 12 and 24 months not statistically significant.

RCTs were addressed earlier; only 2 non-RCTs provided comparative data (16, 68). In both papers, visual acuity in the untreated eyes declined or showed a small improvement, in contrast to the greater improvements in the treated eyes.

One RCT (52) compared the benefits gained in patients treated for keratoconus compared with those in patients treated for keratectasia. The gain was consistently higher in the keratoconus group, (for example, 0.8 D versus 0.65 D at 12 months for uncorrected VA).

4.6.2.4 Conclusion

The meta-analyses of papers reporting preoperative and postoperative results found significant improvements in uncorrected and corrected VA at 6, 12 and 24 months. The analysis of all the papers confirms these results and, indeed, reports slightly greater improvements than the papers included in the meta-analyses.

4.6.3 Refraction and Astigmatism for Epithelium-off CXL Papers

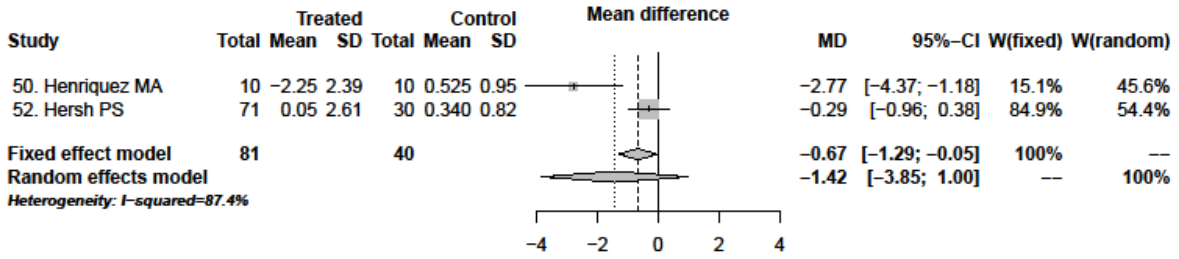
The various papers reported 12 measures of astigmatism. Expert advice was requested on the potential to group these. Acting on that advice, the following measures of astigmatism were grouped in the statistical analyses: manifest astigmatism, mean astigmatism, topographic astigmatism, cylinder, cylinder refraction, refractive astigmatism cylinder and refractive cylinder.

Similarly for refraction, 7 measures were used in papers and the advice given was that five could be grouped. These were: mean spherical equivalent, spherical equivalent, manifest refraction spherical equivalent, sphere and spherical equivalent refractive error.

4.6.3.1 RCT evidence

There was sufficient data to synthesise 2 RCTs (50, 52) to provide a comparison of change in astigmatism at 12 months between the CXL arm and comparator (see Figure 4.18).

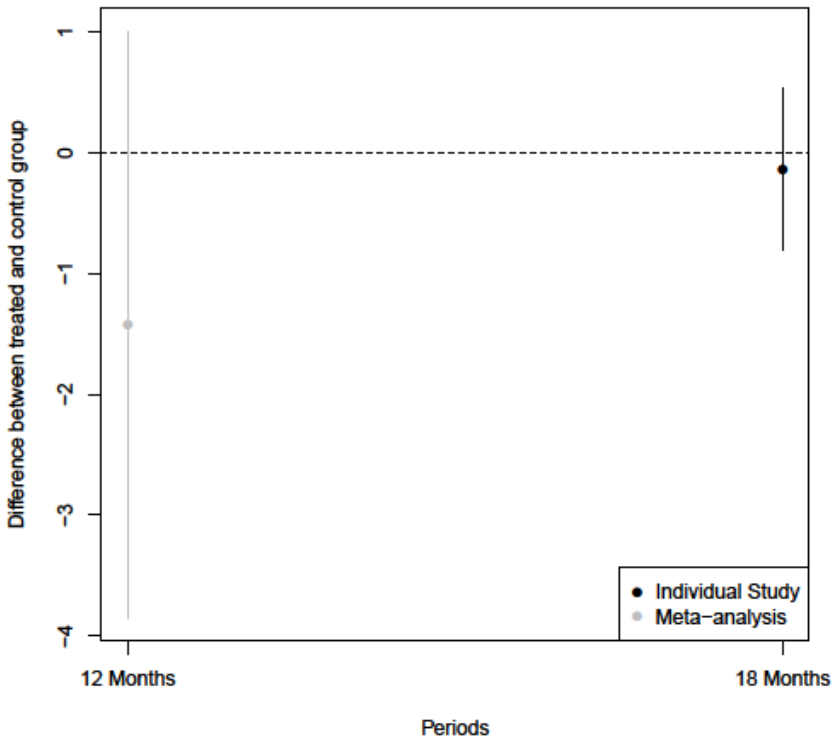
Figure 4.18: Difference between intervention and control patients for change from baseline in astigmatism (dioptres) at 12 months



Both papers reported a higher mean reduction in astigmatism with the CXL arm. Under the fixed effects model, the weighted mean difference shows a statistically significant reduction of 0.67 D in the CXL arm compared with the control, whereas with the random effects model the difference fails to reach statistical significance. However, the absolute benefit is greater at -1.42 D. Given the high level of heterogeneity (I^2 = 87%) the results from the random effects model are the more appropriate.

A third RCT based in the UK (96) provided data on this parameter at 18 months. Figure 4.19 provides a comparison of the RCT data across the two time periods.

Figure 4.19: Comparison of meta-analysis findings on astigmatism (dioptres) at 12 and 18 months for the intervention versus control



The relative benefit found at 12 months was reduced at 18 months to virtually no difference between the arms.

No RCTs reported consistent measures of refraction that could be synthesised.

4.6.3.2 Astigmatism measures comparing preoperative and postoperative changes

Seven, 13 and 5 papers provided sufficient information to enable the data to be combined on astigmatism at 6, 12 and 24 months, respectively. RCTs described in 2 papers (50, 52) were included at 12 months and one of these (52) also at 6 months.

The forest plots are provided in Figures 4.20 to 4.22. These all report a statistically significant reduction in astigmatism from -0.45 D at 6 months, to -0.68 D at 12 months and -0.54 D at 24 months from the pre procedure baseline value. The values are those reported by the random effects model, which was used given the high level of heterogeneity across the papers in the first 2 time periods (I^2 = about 52%).

Figure 4.20: Change from baseline in astigmatism (dioptres) at 6 months pre and postoperation

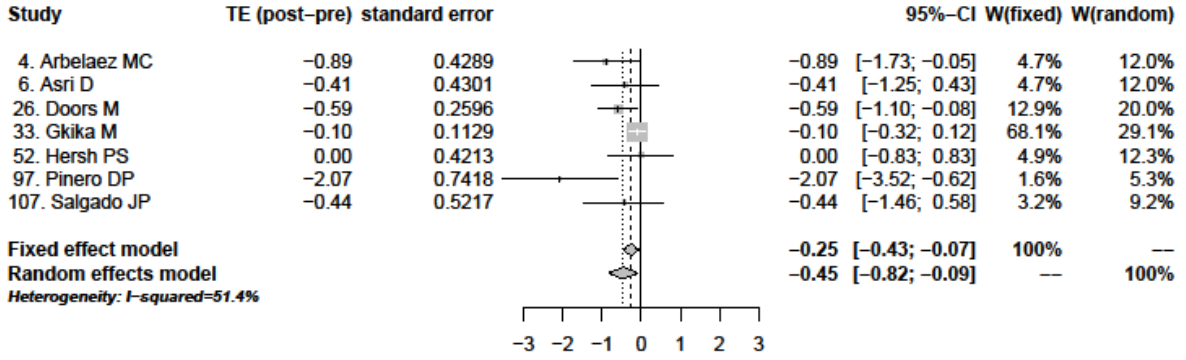


Figure 4.21: Change from baseline in astigmatism (dioptres) at 12 months pre and postoperation

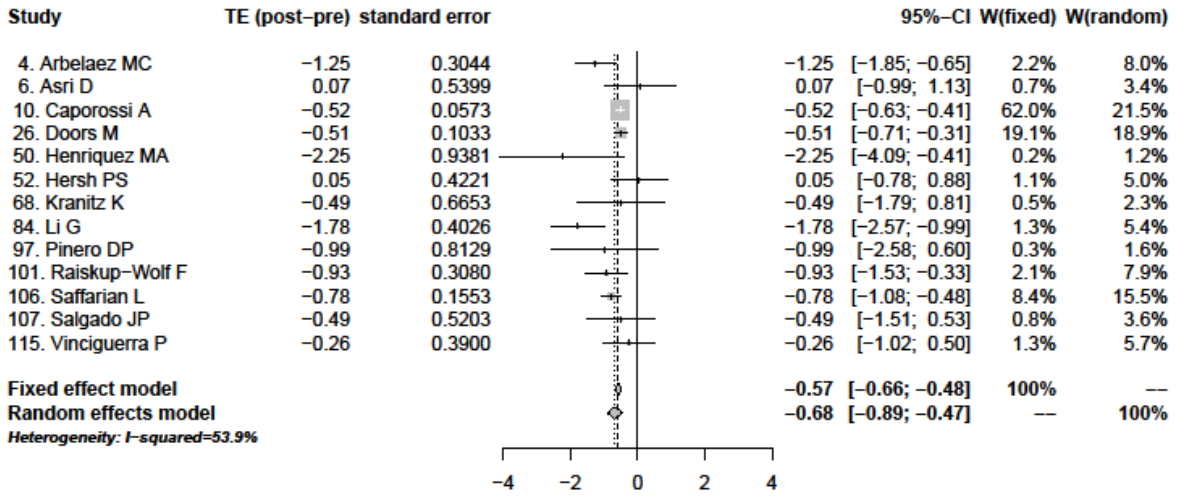
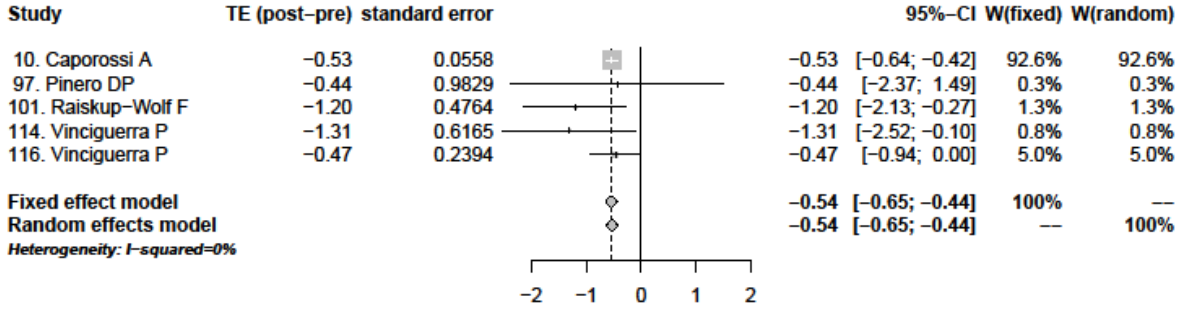


Figure 4.22: Change from baseline in astigmatism (dioptres) at 24 months pre and postoperation



4.6.3.3 Refraction measures comparing preoperative and postoperative changes

Eight and 10 papers provided sufficient information to enable the data on spherical equivalent measures to be combined at 6 and 12 months, respectively. Figures 4.23 and 4.24 report the synthesised data for these refraction measures grouped at 6 and 12 months, respectively. The Hersh and Henrique RCTs (50, 52) were included in both analyses.

At 12 months there was a statistically significant reduction in spherical equivalence of 0.51 D, an increase from the improvement noted at 6 months (0.30 D). This was not statistically significant.

Figure 4.23: Change from baseline in spherical equivalence measures (dioptres) at 6 months pre and postoperation

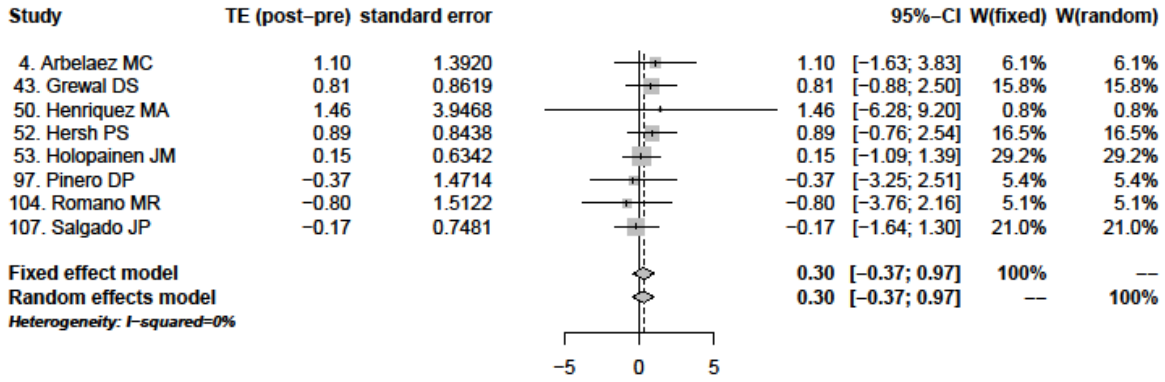
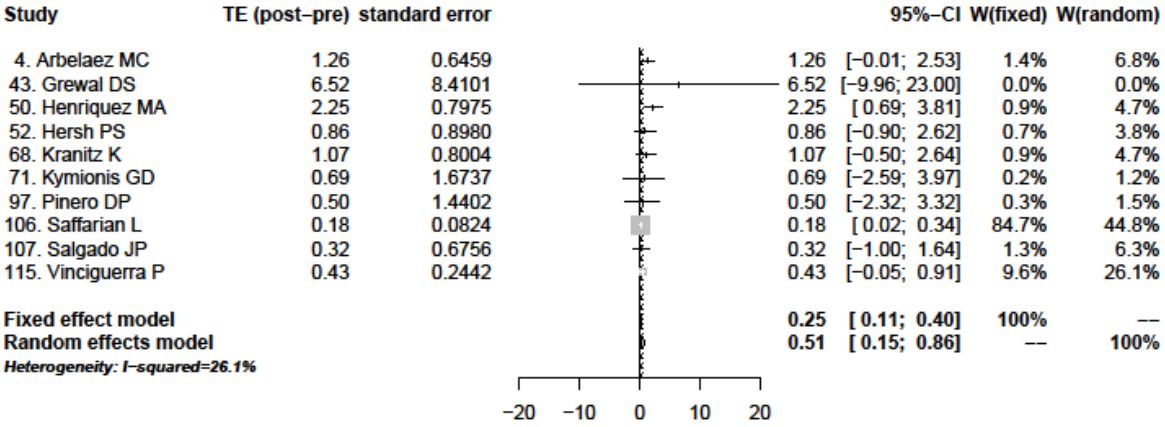


Figure 4.24: Change from baseline in spherical equivalence measures (dioptres) at 12 months pre and postoperation



4.6.3.4 Evidence from all papers

Thirty-one papers provided results of astigmatism and refraction measures. These were grouped into measures of mean astigmatism, sphere and cylinder measures and reported over 6, 12 and 24 months.

Of the 88 usable measures reported, 21 (23%) were statistically significant.

Table 4.9 provides an estimated effect size for the reduction in astigmatism and refraction and provides the number of papers contributing to the mean estimates. Again, please note these are offered as indications only and are not precise estimates. The measure of spherical change at 12 months excluded the results from paper 43 which was an outlier;including this result increased the reduction to 1.31 D.

Table 4.9: Measures of astigmatism and refraction by time period

Measure	At 6 months:		At 12 months:		At 24 months:	
	Mean reduction	Number of papers	Mean reduction	Number of papers	Mean reduction	Number of papers
Mean astigmatism	0.54 D	10	0.90 D	13	0.29 D	3
Sphere	0.42 D	11	1.31 D	17	0.39 D	6
Cylinder	0.68 D	4	0.88 D	12	-0.02 D	4

Three non-RCTs (16, 67, 68) reported the change in treated eyes compared with untreated eyes. All untreated eyes reported an increase in astigmatism, sphere and cylinder measures whereas all treated eyes reported a reduction in these measures. The data are summarised in Table 4.10.

Table 4:10: Comparison of treated and untreated eyes from preoperative baseline

Paper reference	Paper 16	Paper 67	Paper 68
Mean: Astigmatism at 6 months		-1.26D vs 0.16 D	
Mean: Astigmatism at 12 months		-1.41 vs -0.13 D	
Mean: Astigmatism at 18 months		-1.19 vs-0.19 D	
Sphere at 12 months	1.03 vs 0.03 D		1.07 vs -0.05 D
Cylinder at 12 months	1.04 vs 0.01 D		0.49 vs -0.11 D

One study (101) provided data beyond 2 years. This reported mean change in astigmatism and the values reported at 2, 3 and 4 years were -1.2,-1.4 and -1.5 D, respectively. The values reported at year 4 were from only 13 patients compared with 66 patients at year 2.

4.6.3.5 Conclusion

Evidence from a meta-analysis of 2 RCTs provided evidence of a reduction in mean astigmatism at 12 months of-1.4 D, but this was not statistically significant. A third RCT (96) reported a value of almost zero at 18 months.

Pre and post procedure comparisons provided statistically significant evidence of a reduction in astigmatism of -0.4 D at 6 months, -0.7 D at 12 months and -0.5 D at 24 months, from 7, 13 and 5 papers, respectively. Estimates of the reduction for other measures of refraction were 0.3 D at 6 months and 0.5 D at 12 months. The latter value was statistically significant and estimated from 10 papers.

These reductions were consistently reported across all papers, together with improvements in treated eyes compared with untreated eyes which deteriorated.

4.6.4 Intraocular Pressure for Epithelium-off CXL papers

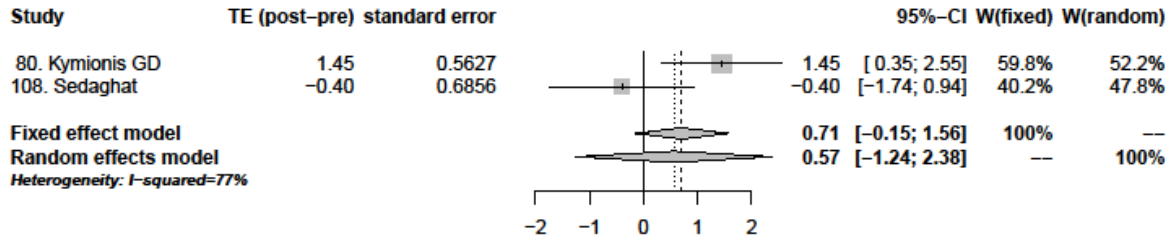
Intraocular pressure (IOP) is not a significant outcome of CXL. The main reason for including this parameter is because it can change due to increased corneal rigidity. There is no preferred direction of change.

No RCT evidence could be synthesised for IOP. Twelve papers (7, 10, 16, 26, 37, 75, 84, 97, 101, 108, 115, 118) provided evidence on changes in IOP postoperatively following epithelium-off CXL but this was often qualitative (7, 10, 26, 97, 115). The results from paper (6) were excluded because of the very high drop-out rate from 45 patients at 6 months to 25 patients at 12 months. On clinical advice, the analysis focused on IOP measured in mmHg using Goldmann correlated or corneal compensated techniques. Of the remaining papers, only 2 (75, 108) provided data on change pre and postoperatively that could be used in a meta-analysis. Neither of these was an RCT and they provided data for 6 months follow-up only.

4.6.4.1 Meta-analysis of preoperative/postoperative changes

The findings of the meta-analysis of the 2 papers that provided usable data on change in IOP postoperatively is shown in the forest plot in Figure 4.25.

Figure 4.25: Change in IOP (mm/Hg) at 6 months pre and postoperation



The papers had different treatment effect directions: one found the procedure increased IOP (75) and the second found the procedure reduced it (108). Neither the fixed nor random effects model found a statistically significant change in IOP 6 months postoperatively.

4.6.4.2 Evidence from all papers

Of the 12 papers reporting usable results for the change in IOP-related variables, 2 measured both corneal hysteresis (CH) and corneal resistance factor (CRF) (37, 108), and 6 measured mean IOP (16, 75, 84, 101, 108, 118).

Of the 5 papers reporting qualitatively, 4 papers stated IOP (7, 10, 26, 115) was unchanged over all time periods, whilst one (97) noted a small increase in CRF at 6 months and a decrease in CH at 12 to 24 months.

One paper (84) reported a statistically significant increase in IOP at 12 months of 2.9 mmHg. This was the only statistically significant value reported.

Three parameters were reported at 6, 12 and 24 months:

- Two papers (37, 108) reported a mean increase in CH of 0.1 mmHg, falling to 0.05 (37) at 12 months;
- Two papers reported a mean increase in CRF of 0.2 mmHg (37, 108), rising slightly to 0.3 mmHg at 12 months (37);
- Two papers reported a mean increase in IOP of 0.5 mmHg at 6 months (75, 108), 4 papers reported a mean increase of 1.6 mmHg at 12 months (16, 75, 84, 101), and 2 papers (102, 118) reported that the increase had reduced to 0.05 mmHg at 24 months.

Overall, 3 negative values, with a mean value of -0.3 mmHg were reported, compared with 11 positive values with a mean value of 0.8 mmHg.

4.6.4.3 Conclusion

Only 7 papers contributed to the quantitative analyses, with five others reporting no statistically significant change in the values pre and post procedure. The limited data suggest that IOP has an increased probability of being higher at 6 and 12 months compared with pre procedure levels in patients undergoing CXL. However, no comparative data are available so the cause of the increase cannot necessarily be attributed to the procedures. Moreover, the absolute changes are small and may have little clinical significance.

4.6.5 Central Corneal Thickness for Epithelium-off CXL papers

Several methods were adopted to measure the central corneal thickness (CCT), such as ultrasound (US), anterior segment optical coherence tomography (OCT), Obscan and Pentacam imaging. These use different optical principles to construct the image of the anterior segment. On clinical advice, papers reporting outcomes using scanning–slit tomography were excluded from the meta-analyses.

4.6.5.1 RCT evidence

One paper (41) reported a sub-group of an RCT and provided evidence on change in CCT (measured in µm) in intervention eyes compared with a control. It did not provide a statistical test of the difference in CCT between the intervention and control. However, both the control and intervention groups saw statistically insignificant changes in CCT at 12 months.

4.6.5.2 Meta-analysis of preoperative/postoperative changes

Six papers provided data on change in CCT that were suitable to be used in a meta-analysis at both 6 and 12 months from the date of procedure. The findings from the meta-analysis are shown in forest plots in Figures 4.26 and 4.27.

Figure 4.26: Change in CCT (µm) at 6 months pre and postoperation

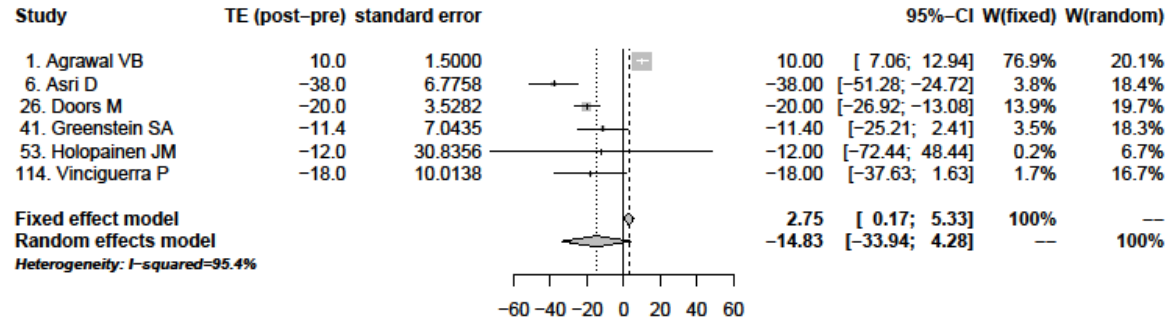
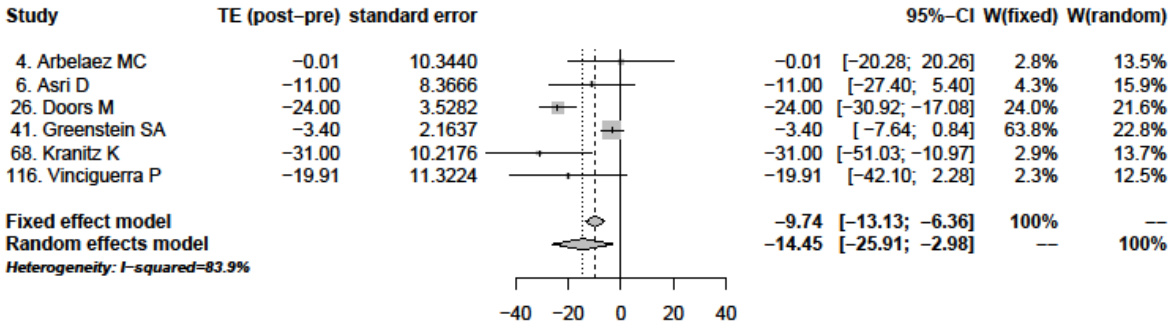


Figure 4.27: Change in CCT (µm) at 12 months pre and postoperation



At 6 months there is evidence of a high level of heterogeneity between the papers which suggests a random effects model is more appropriate. The random effects models suggest that there is no statistical evidence of any change in CCT 6 months following epithelium-off CXL, but provide statistically significant evidence that the procedure reduced CCT in the order of -14.45 µm at 12 months. Again, there was a high level of heterogeneity across the papers as measured by the I^2 value.

The results at 6 months are influenced by the gain of 10 µm reported in Agrawal (1). There is no discussion of the value in the paper. It is possible that the author has reported the change as an absolute value and the change should be a reduction.

4.6.5.3 Evidence from all papers

In total, 25 papers reported on CCT measurements, with three simply stating there were no statistically significant differences at any time period (10, 87, 97). Two reported statistically significant reductions at 6 months (26) and 12 months (26, 65). Two papers reported an increase in CCT at 6 months (1, 90). The magnitude of reported gains was similar at 10 to 12 µm. [Note comment on the poor reporting of the change in direction in one paper (1) earlier].

The calculated mean changes at 6 and 12 months were -11.6 µm and -8.2 µm, reported by 12 papers in both cases.

Two of the three papers with comparator arms (65, 68) reported that patients undergoing the CXL procedure had greater reductions in CCT at 12 months compared with untreated eyes. The mean reduction was -4.0 µm at 12 months. The third paper was an RCT (96) which reported an increase in CCT at 18 months in both arms: a rise of 3.4 µm in the CXL procedure arm and 6.1 µm in the control.

Greenstein (41) reported changes in CCT for patients with keratoconus and keratectasia. The main difference was that the patients with keratectasia regained the pre procedure level of CCT at 12 months, whilst patients with keratoconus had a reduced CCT of 6.4 µm.

4.6.5.4 Conclusion

The majority of papers reported that at 6 and 12 months post procedure CCT was lower than baseline values in patients undergoing CXL procedures.

4.7 SAFETY FOR EPITHELIUM-OFF CXL PAPERS

In addition to the adverse events extracted from the 49 efficacy papers, 26 papers were identified that reported on safety events specifically for epithelium-off CXL. These comprised 23 case studies, 1 RCT (128) and 2 retrospective chart reviews (66, 141). A recent review of complications of CXL (121) was also retrieved in order to establish the completeness of this selection. The safety data are presented in Table 4.11.

Mr Tim Jackson, eye surgeon Kings College Hospital London, advised which of the events had serious consequences for the patient and this informed the narrative synthesis.

Table 4.11: Characteristics of safety papers for epithelium-off CXL

Author	Study population	Adverse events
Author: Arora **Year:** 2012 **Ref:** 120 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 8.	**Intervention:** CXL for keratoconus. **Adverse events:** Sterile infiltrates in the immediate postoperative period and coexisting vernal keratoconjunctivitis. **Treatment:** Topical steroid therapy and topical 2% cyclosporine A eye drops. **Outcome:** Problem was resolved.
Author: Eberwein **Year:** 2008 **Ref:** 122 **Country:** Germany	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 45.	**Intervention:** Patient with severe atopic disease and keratoconus who had CXL and deep anterior lamellar keratoplasty. **Adverse events:** Corneal melting due to subclinical infection with herpes simplex virus. **Treatment:** Penetrating keratoplasty and intensive antiviral and immunosuppressive medical treatment. **Outcome:** Infection controlled.
Author: Faschinger **Year:** 2000 **Ref:** 123 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 25.	**Intervention:** PRK. **Adverse events:** Corneal ulceration several days after treatment; central scar developed resulting in discomfort and reduction in visual activity. **Treatment:** Scar treated by phototherapeutic keratectomy (25-µm depth, 5mm ablation zone). **Outcome:** Scar tissue cleared slowly over a few years. The induced hyperopia decreased from 5.00 to 1.37 D, and BCVA increased from 20/60 preoperatively to 20/20 at 28 months.

Author	Study population	Adverse events
Author: Garcia-Delpech **Year:** 2010 **Ref:** 124 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 23.	**Intervention:** CXL. **Adverse events:** Patient presented with corneal ulcer 4 weeks following CXL procedure. Microbiological studies revealed Fusarium species as the etiological pathogen. **Treatment:** Not Reported. **Outcome:** Not Reported.
Author: Ghanem **Year:** 2012 **Ref:** 125 **Country:** Not Available	**Number of patients:** 7. **Number of eyes:** 7. **Mean age (years):** Not Available.	**Intervention:** Patients had progressive keratoconus and underwent CXL. **Adverse events:** Patients presented with peripheral stromal infiltrates. The ring-like infiltrates were superficial and were present at the 9.0-mm zone. Sterile infiltration was diagnosed. **Treatment:** Topical corticosteroids. **Outcome:** Complete resolution was achieved after a few weeks of treatment.
Author: Gokhale **Year:** 2011 **Ref:** 126 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 37.	**Intervention:** After central epithelial debridement, cornea was cross-linkage for 25 minutes using riboflavin solution and UV A, 370 nm with an irradiance of 30mW/cm^2. **Adverse events:** One month after CXL treatment, the patient presented with massive corneal oedema. **Treatment:** 1% prednisolone and carboxymethylcellulose 1% eye drops, 4 x daily for 3 months. Specular microscopy with endothelial cell counting was performed after resolution of the corneal oedema 6 months after cross-linkage. **Outcome:** A ring-shaped corneal scar remained, and UCVA was finger counting. Cell density after resolution was 1776 cells/mm^2 in affected eye compared with 2978 cells/mm^2 in untreated fellow eye.

Author	Study population	Adverse events
Author: Gokhale **Year:** 2010 **Ref:** 127 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** Not Available.	**Intervention:** CXL and diclofenac and proparacaine eye drops for keratoconus. **Adverse events:** The patient presented 1 week later with corneal melt and perforation. **Treatment:** Treated initially with tissue glue and bandage contact lens application followed by a penetrating keratoplasty on day 12. **Outcome:** The graft was clear at 1 month.
Author: Greenstein **Year:** 2010 **Ref:** 128 **Country:** USA	**Number of patients:** 85. **Number of eyes:** 91. **Mean age (years):** Treatment group = 36.8 +/- 11.1; Control group = 34.8 +/- 10.3.	**Intervention:** Treatment group had UV A/riboflavin CXL therapy (n=41 eyes). Control riboflavin alone, no epithelial debridement (n = 50 eyes). **Adverse events:** Corneal haze peaked at 1 month and changed little at 3 months. Between 3 and 6 months haze decreased, and again between 6 and 12 months. By 12 months corneal haze had returned to baseline in ectasia group, but not keratoconus group. **Treatment:** Not Reported. **Outcome:** Change in haze did not correlate with postoperative clinical outcomes.
Author: Hafezi **Year:** 2011 **Ref:** 129 **Country:** Switzerland	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 21.	**Intervention:** CXL in left eye using hypoosmolar riboflavin. **Adverse events:** Haze at 4 weeks and 6 months postoperatively. At 12 months haze had consolidated to deep stromal opacity (equivalent to deep stromal haze). **Treatment:** Not Reported. **Outcome:** BCVA improved by 12 months.
Author: Hafezi **Year:** 2012 **Ref:** 130	**Number of patients:** 1 with adverse events. **Number of eyes:** 1. **Mean age (years):** 27.	**Intervention:** CXL which was uneventful. Did not attend follow-up, or comply with postoperative prophylactic ofloxacin drops. **Adverse events:** Six days after CXL presented with left paracentral infectious corneal infiltrate of 3mm diameter with *Staphylococcus aureus*.

Author	Study population	Adverse events
Country: Switzerland		**Treatment:** Intensive therapy with topical antibiotic (alternating ofloxacin and garamycin) for 10 days. **Outcome:** After 3 weeks, infiltrate turned into a scar; Stromal hyper-reflectivity down to 280µm and close to CXL-induced stromal demarcation line at 300 µm. Visual acuity improved by 3 weeks.
Author: Herrmann **Year:** 2008 **Ref:** 131 **Country:** Germany	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 41.	**Intervention:** CXL. **Adverse events:** Postoperatively there were a diffuse sub-epithelial opacification and a paracentral corneal thinning. **Treatment:** Intensive therapy. **Outcome:** Superficial scarring in the sense of a 'haze' disappeared only gradually.
Author: Koller **Year:** 2009 **Ref:** 66 **Country:** Switzerland	**Number of patients:** 99. **Number of eyes:** 117. **Mean age (years):** Group 1: 37.7; Group 2: 29.2.	**Intervention:** Pachymetry with ultrasound plus hypoosmolar riboflavin. **Adverse events:** Of 105 eyes, 3 lost 2 Snellen lines of CVA at 12 months a complication rate of 2.9% (95% CI: 0.6, 8.5). At 1 month virtually all had stromal haze grade 0.78, falling to 0.18 at 6 months and 0.06 +/- 0.18 at 12 months. Eight eyes (7.6%, 95% CI: 3.3, 14.7) had an increase in Max K of >1.00 D at 12 months, indicating failure of the CXL treatment. Sterile infiltrates occurred in 7.6% of eyes. A stromal scar developed in 3 eyes (2.9%). No other adverse events. **Treatment:** The sterile infiltrates resolved within 4 weeks with treatment of dexamethasone 4 x daily. None of the complications resulted in a significant loss of CVA. **Outcome:** In all 3 cases with stromal scars, the UCVA increased significantly. The scars faded appreciably within the first postoperative year.
Author: Koppen **Year:** 2009 **Ref:** 132	**Number of patients:** 4. **Number of eyes:** 4. **Mean age (years):** Not Available.	**Intervention:** UV A CXL, using riboflavin as a photosensitizer. **Adverse events:** Patients experienced delayed (after > 24 hours) symptoms and signs of inflammation. The eyes showed pronounced ciliary redness with cells in the anterior chamber and central keratic precipitates; multiple white infiltrates had developed at the edge and within the area of CXL.

Author	Study population	Adverse events
Country: Belgium		**Treatment:** High-dose topical or sub-conjunctival corticosteroids. **Outcome:** Rapid initial improvement of symptoms and signs. The location of the scarring determined the amount of loss of visual acuity: in 2 eyes, there was a persistent decrease in BSCVA.
Author: Kymionis **Year:** 2007 **Ref:** 133 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 21.	**Intervention:** CXL. **Adverse events:** Five days postoperatively, patient presented with geographic epithelial keratitis and iritis. Diagnosis was herpetic disease. **Treatment:** Oral steroids and acyclovir. **Outcome:** Two months postoperatively, the visual acuity was improved and there was no evidence of herpetic disease recurrence.
Author: Labiris **Year:** 2011 **Ref:** 81 **Country:** Greece	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 23.	**Intervention:** Uneventful CXL treatment according to the Dresden protocol for keratoconus cornea stage 1 to 2. **Adverse events:** First postoperative day, intense photophobia, watering and non-specific ocular discomfort. Redness in limbal region, severe corneal haze with non-specific endothelial precipates and few inflammatory cells in anterior chamber. **Treatment:** Postoperative medicine modified to ofloxacin drops 4 x daily, dexamethasone drops every 2 hours, frequent use of carboxymethylcellulose 0.5% drops and oral acyclovir 400 mg 4 x daily. Also underwent test for autoimmune and infectious disease - all clear. Patient found to be hypersensitive to riboflavin. **Outcome:** Subjective improvement of ocular discomfort and disappearance of the inflammatory cells in the anterior chamber. Cornea presented slow re-epithelialisation and progressive thinning so patient underwent uncomplicated penetrating keratoplasty with uneventful postoperative period.

Author	Study population	Adverse events
Author: Lim **Year:** 2011 **Ref:** 134 **Country:** Singapore	**Number of patients:** 2. **Number of eyes:** 2. **Mean age (years):** Both cases: 23 years.	**Intervention:** Riboflavin UV A CXL. **Adverse events:** Case 1: at 3 months dense, deep paracentral scar noted adjacent to apex of the cone at 300µm depth on anterior segment OCT. Case 2: deep stromal haze developed similar, but smaller to case 1. **Treatment:** Case 1 and 2: Increase in astigmatism corrected by rigid gas permeable lens. **Outcome:** Cases 1 and 2: at 6 months, visual acuity corrected with lens.
Author: Mangioris **Year:** 2010 **Ref:** 135 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** Not Applicable.	**Intervention:** Advancing keratoconus treated with CXL with UV A light and riboflavin. **Adverse events:** Early in the postoperative period, the patient presented with 11 deep stromal infiltrates of 1 to 2mm with clear demarked edges in a circle near the limbus with some clear cornea. Corneal cultures were negative. **Treatment:** Treatment consisted of antibiotic ofloxacin and tobramycin 4 x daily, and dexamethasone drops 6 x daily. **Outcome:** After 2 months, scars remained evident.
Author: Mazzotta **Year:** 2007 **Ref:** 136 **Country:** Italy	**Number of patients:** 2. **Number of eyes:** 2. **Mean age (years):** Not Applicable.	**Intervention:** Keratoconus treated with CXL with UV A light and riboflavin. **Adverse events:** Two cases stromal haze (from 40 eyes) which developed at 2 to 3 months post-procedure, scarring observed. **Treatment:** Did not respond to topical steroids. **Outcome:** Haze unchanged at 6 months. Did not affect visual acuity.
Author: Perez-Santonja **Year:** 2009 **Ref:** 137 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 29.	**Intervention:** Keratoconus treated with CXL with UV A light and riboflavin. **Adverse events:** Several infiltrates appeared in the upper midperipheral; *Staphylococcus epidermidis* keratitis was confirmed by microbiological studies. **Treatment:** Topical fortified antibiotic agents. **Outcome:** Mild residual haze in the upper midperipheral cornea at 5 months.

Author	Study population	Adverse events
		BSCVA 20/22 (20/25 before CXL).
Author: Pollhammer **Year:** 2009 **Ref:** 138 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** Not Applicable.	**Intervention:** CXL for keratoconus. **Adverse events:** Patient complained of increasing pain, redness and blurred vision in the treated eye starting on the first postoperative day. Clinical examination showed multiple stromal infiltrations and moderate anterior chamber inflammation. Corneal scraping revealed an *Escherichia coli* infection. **Treatment:** Treated with fortified tobramycin and cefazolin eye drops for several weeks. **Outcome:** Infection cleared, but resulted in an avascularised corneal scar and permanent reduction of visual acuity.
Author: Rama **Year:** 2009 **Ref:** 139 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 32.	**Intervention:** Riboflavin/UV A (CXL) for keratoconus. **Adverse events:** Corneal melting 5 days after treatment and corneal scraping positive for Acanthamoeba. **Treatment:** Because of corneal perforation, a large therapeutic keratoplasty à chaud was performed. **Outcome:** Not Reported.
Author: Rodriguez-Ausin **Year:** 2011 **Ref:** 140 **Country:** Not Available	**Number of patients:** 2. **Number of eyes:** 2. **Mean age (years):** 16.	**Intervention:** CXL procedures for grade 3 keratoconus. **Adverse events:** Multiple peripheral stromal precipitates, which extended centripetally, were observed 48 hours after the procedure. Sample cultures were negative for bacteria, fungi and parasites. **Treatment:** Combined topical antibiotic / antifungal / povidone / steroids treatment. **Outcome:** Cornea infiltrates slowly resolved. Final BCVA was 20/25 for patient 1, after uneventful bilateral toric intraocular contact lens implantation, but faint and paracentral scarring persisted. Final BCVA was 20/25 for patient 2 with gas-permeable contact lens wear, despite stromal scarring.

Author	Study population	Adverse events
Author: Sharma **Year:** 2012 **Ref:** 141 **Country:** India	**Number of patients:** 10 with adverse events of 350 patients. **Number of eyes:** 10. **Mean age (years):** 22 +/- 5.	**Intervention:** CXL treatment used with Dresden protocol with corneal thickness of more than 400 µm after epithelium was removed. **Adverse events:** Postoperative corneal oedema occurred within 24 hours and corneal oedema and anterior chamber inflammation increased for 2 to 3 weeks. Also, marker deep corneal vascularisation (2/10 eyes), iris atrophy (6/10), pigment dispersion (5/10), corneal epithelial defect present for more than 6 days (3/10) and infectious keratitis (1/10). **Treatment:** Prednisolone acetate 1.0% drops 3 x daily, carboxymethylcellulose 1% 4 x daily, and homatrophine 1% twice daily. Topical steroids were stopped after 6 weeks of treatment. Five patients improved leaving 5 not improved. Surgical options offered to patients when improvement plateaued for 3 months; 2 patients underwent penetrating keratoplasty. **Outcome:** In those patients treated, corneal edema improved in 4 patients and resolved in 1.
Author: Sharma **Year:** 2010 **Ref:** 142 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 19.	**Intervention:** CXL with UV A and riboflavin to treat keratoconus. **Adverse events:** Three days of pain, redness, and diminution of vision from one day after CXL. Severe keratitis with a 7.0mm x 6.0mm central infiltrate was present. Culture results from patient's contact lens and corneal scrapings were positive for *Pseudomonas aeruginosa.* **Treatment:** Not Reported. **Outcome:** Not Reported.
Author: Yuksel **Year:** 2011 **Ref:** 143 **Country:** Not Available	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 31.	**Intervention:** CXL with UV A and riboflavin to treat progressive keratoconus. **Adverse events:** Four days postoperatively, a dendritic ulcer developed in treated eye. The diagnosis was herpes simplex. **Treatment:** Not Reported. **Outcome:** The keratitis resolved in 10 days with treatment. At 1 month, visual acuity was stable, but a mild superficial opacity was noted.

Author	Study population	Adverse events
Author: Zamora **Year:** 2009 **Ref:** 144 **Country:** Australia	**Number of patients:** 1. **Number of eyes:** 1. **Mean age (years):** 32.	**Intervention:** CXL with UV A and riboflavin to treat keratoconus. **Adverse events:** Severe keratitis with central 8mm corneal epithelial defect, 360-degree ring infiltrate and dense fibron reaction throughout anterior chamber. Two smaller infiltrates at 9 and 10 'o' clock position; 2mm clear zone between limbus and the area debrided and subjected to UV light treatments. **Treatment:** Microbiological specimens positive for *S.savlivarius and S.ovalis*. Subsequently admitted and given fortified cephalothin 5% and gentamicin 0.9% hourly and homatrophine 2% 3 x daily. After discharge ofloxacin eye drops and steroids slowly added. **Outcome:** After 2 months, visual acuity of eye 20/50. On slit lamp exam, residual central corneal stromal haze and a sub-epithelial scar in a ring-like configuration were present.

4.8 ANALYSIS OF ADVERSE EVENTS

The various adverse events reported in the safety papers, together with those reported in the 49 papers addressing the CXL epithelium-off procedure, were grouped.

Infection (all serious):

- Infection rates were reported as none in 2 studies (99, 106);
- Infectious corneal infiltrate with *Staphylococcus aureus*: single case report; after 3 weeks, infiltrate turned into a scar; visual acuity improved by 3 weeks (130);
- Herpetic epithelial keratitis and iritis: single case report; 2 months postoperatively, visual acuity was improved and there was no evidence of herpetic disease recurrence (133);
- *Staphylococcus epidermidis* keratitis; single case report; mild residual haze in the upper midperipheral cornea at 5 months and best spectacle-corrected VA of 20/22 (20/25 before CXL) (137);
- *Escherichia coli* infection; single case report; infection cleared, but resulted in an avascularised corneal scar and permanent reduction of visual acuity (138);
- Single case report; 3 days of pain, redness, and diminution of vision from 1 day after CXL; severe keratitis with a 7.0 mm x 6.0 mm central infiltrate was present; culture results from patient's contact lens and corneal scrapings were positive for *Pseudomonas aeruginosa* (142);
- Single case report; 4 days postoperatively, a dendritic ulcer developed in treated eye; the diagnosis was herpes simplex; the keratitis resolved in 10 days with treatment; at 1 month, visual acuity was stable, but a mild superficial opacity was noted (143);
- Single case report of infectious keratitis in a patient with postoperative corneal oedema (141);
- Severe keratitis; microbiological specimens positive for *S. savlivarius* and *S. ovalis*; after 2 months, visual acuity of eye 20/50; on slit lamp exam, residual central corneal stromal haze and a sub-epithelial scar in a ring-like configuration were present (144).

Corneal melting and perforation (all serious):

- Single case report of corneal melting due to subclinical infection with herpes simplex virus: penetrating keratoplasty and intensive antiviral and immunosuppressive medical treatment; infection controlled (122);
- Single case report of corneal melt and perforation at 1 week after intervention; treated initially with tissue glue and bandage contact lens application followed by a penetrating keratoplasty on day 12; the graft was clear at 1 month (127);
- Single case report of corneal melting 5 days after treatment and corneal scraping positive for *Acanthamoeba*; because of corneal perforation, a large therapeutic keratoplasty à chaud was performed (139).

Corneal ulceration or burn (all serious):

- Single case report of corneal ulceration; scar treated by phototherapeutic keratectomy, scar tissue cleared slowly over a few years; BCVA increased from 20/60 preoperatively to 20/20 at 28 months (123);
- Single case report of corneal ulceration; treatment and outcome not reported (124);
- One (0.7%) of 142 patients in 1 study had corneal burn diagnosed at 1 month (6).

Stromal scar (all serious):

- Stromal scar developed in 3 eyes (2.9%); in all 3 cases the UCVA increased significantly, but the scars faded appreciably within the first postoperative year (66);
- Single case report of deep paracentral scar; at 6 months, visual acuity was corrected with lens (134).

Repeat surgery (all serious):

- Repeat surgery was required in 2.8% (4 patients underwent deep anterior lamellar keratoplasty) (6) to 8% (2 of 22 patients had ICRS insertion) (96) after the 18 months follow-up; these are not judged to be consequential to the CXL procedure;
- Hypersensitivity to riboflavin: single case report; subjective improvement of ocular discomfort and disappearance of the inflammatory cells in the anterior chamber; cornea presented slow re-epithelialisation and progressive thinning so patient underwent uncomplicated penetrating keratoplasty with uneventful postoperative period (81).

Sterile keratitis (serious – where associated with residual scarring or loss of vision, or requiring keratoplasty):

- Four (3.4%) of 117 patients; treated with high-dose topical or subconjunctival corticosteroids; rapid initial improvement of symptoms and signs; the location of the scarring determined the loss in visual acuity there was a persistent decrease in best spectacle-corrected VA in 2 eyes (132);
- Single case report of deep stromal infiltrates; treatment consisted of antibiotic ofloxacin and tobramycin and dexamethasone drops; scars remained evident after 2 months (135).

Sterile keratitis (minor – not associated with residual scarring or loss of vision, or requiring keratoplasty):

- Non-infectious keratitis rates of zero were reported in 2 papers (26, 99) and 1.5% (one highly atopic patient of 66 patients) in 1 study (117);
- Single case report; problem was resolved with topical steroid therapy and topical 2% cyclosporine eye drops (120);
- Seven patients reported with sterile keratitis; complete resolution was achieved after a few weeks of treatment with topical corticosteroids (125);
- Sterile infiltrates in 7.6% of eyes; resolved within 4 weeks with treatment of dexamethasone 4 x daily; none resulted in a significant loss of corrected distance VA (66);
- Multiple peripheral stromal precipitates, which extended centripetally, were observed 48 hours after the procedure; sample cultures were negative for bacteria, fungi and parasites in 2 patients; cornea infiltrates slowly resolved; final best corrected VA was 20/25 for patient 1, after uneventful bilateral toric intraocular contact lens implantation, but faint and paracentral scarring persisted; best corrected VA was 20/25 for patient 2 with gas-permeable contact lens wear, despite stromal scarring (140).

Corneal haze (serious – where associated with residual scarring or loss of vision, or requiring keratoplasty):

- Single case report of diffuse sub-epithelial opacification and a paracentral corneal thinning; superficial scarring in the sense of a ‘haze’ disappeared only gradually (131).

Corneal haze (minor – not associated with residual scarring or loss of vision, or requiring keratoplasty):

- Three papers reported no corneal haze (26, 99, 106);
- Six papers reported early haze (6.9%, 10%, 12.7%, 45%, 86%, 100%) (114, 10, 116, 107, 65, 46) that reduced progressively over 1 to 12 months;
- One RCT reported 91 cases of haze; these reduced over 12 months; change in haze did not correlate with postoperative clinical outcomes (128);
- Single case report of haze (grade 1.0) at 4 weeks and 6 months (grade 2.0) postoperatively; at 12 months the haze had consolidated to deep stromal opacity; best corrected VA had improved by 12 months (129);
- Deep stromal haze in 2 cases; at 6 months, visual acuity corrected with lens (134);
- Two (5%) of 40 eyes developed corneal haze at 2 to 3 months post procedure and scarring was observed; haze was unchanged at 6 months but did not affect visual acuity (136).

Corneal oedema (serious – where associated with residual scarring or loss of vision, or requiring keratoplasty):

- Postoperative corneal oedema occurred within 24 hours and corneal oedema and anterior chamber inflammation increased for 2 to 3 weeks in 10 patients; there was also marked deep corneal vascularisation (2/10 eyes), iris atrophy (6/10), pigment dispersion (5/10), corneal epithelial defect present for more than 6 days (3/10), and infectious keratitis (1/10); in those patients treated, corneal oedema improved in 4 patients and resolved in 1 (141);
- Single case report of corneal oedema treated with 1% prednisolone and carboxymethylcellulose 1% eye drops, 4 times daily for 3 months; the corneal oedema was resolved 6 months after cross-linkage but a ring-shaped corneal scar remained; uncorrected VA was finger counting (126).

Corneal oedema (minor – not associated with residual scarring or loss of vision, or requiring keratoplasty):

- Corneal oedema was reported as a common, early, after procedure effect, e.g. slight transient stromal oedema until re-epithelialisation after 3 days (118);
- Transient corneal oedema and sensation of foreign body occurred for 24 to 48 hours postoperatively (90);
- Two papers (10, 87) reported that 70% of patients had stromal oedema;
- Corneal or stromal oedema cleared within 1 to 6 months (6, 10, 16, 90).

Corneal erosion (all minor):

- One paper reported that 1/24 (4%) patients had recurrent corneal erosion with discomfort for 9 months postoperatively, which was settled with lubricants (96).

Pain (all minor):

- Most (114) or all (26) patients reported some pain during the first 2 to 3 days after treatment.

Other (minor – not associated with residual scarring or loss of vision, or requiring keratoplasty):

- A 5% incidence of blepharitis and 3% incidence of mild photophobia at 4 months, and CXL-specific golden striae in 62% in 1 study (114);
- An incidence of 44% golden striae and complaints of night glare and haloes in first 3 months (number of patients not stated) in 1 study (116);
- Striae most prominent between 1 and 3 months (number of patients not stated) in 1 study (117);
- Descemet folds were reported in 2 studies (26, 50) in 7% and 10% of patients, respectively; these were resolved in 2 of the 3 eyes before 3 months but remained present in the third eye at 3 months;

- Endothelial irregularities ranged from none (65) through 3% (noted at 1 month and disappeared at 3 months without visual limitations) (26) to 10% (1 case of 10, which cleared within 12 months) (46);
- Macular/retinal abnormalities were reported as none in 2 studies (34, 104).

Overall complications:

- Some authors reported 'no complications' without further specification (74, 75, 99).

Conclusion

Forty serious disorders were reported: 8 serious infections, corneal melting/perforation in 3 patients, ulceration or burns in 3 patients, serious scarring in 4 patients, sterile keratitis in 5 patients, 1 case of serious corneal haze, and serious oedema in 11 patients. Five patients required repeat surgery including 4 transplants.

None of the procedure-related papers reported an infection rate. The individual case reports suggest some of these infections can be managed without long-term impact on visual acuity.

4.9 QUALITY OF LIFE FOR EPITHELIUM-OFF CXL PAPERS

Only one paper (5) reported as a poster contained quality of life measures. The paper used a National Eye Institute Refractive Error Quality of Life Questionnaire (NEI-RQK) to analyze the effect of cross-linkage on patients with progressive keratoconus. The paper included 26 eyes with mild to moderate keratoconus that were evaluated before treatment and up to 9 months after treatment. The results showed statistically significant improvements in nine subscales of the NEI-RQK ($P < .001$) but no further details were available on this outcome. No details on the intervention were available.

4.10 DISCUSSION OF EPITHELIUM-OFF CXL PAPERS

4.10.1 Overview of the Papers and Generalisability of Findings to NHS

The identified evidence comprised 49 papers of the efficacy of epithelium-off CXL and 26 of the safety of epithelium-off CXL. Of the 49 efficacy papers, 8 were RCTs, reporting 4 unique studies with the main comparator being fellow-eyes (50[7], 52, 96); the exception was the Australian RCT (117) which did randomise eyes matched for disease status. This paper had a good trial design but only reported preliminary results; for example, not all patients randomised to the CXL arm had undergone the procedure. Thus, there is no high or moderate quality evidence from completed studies comparing eyes with progressive keratoconus undergoing CXL and those not receiving the procedure.

[7] Study 50 did have a sham control but at 3 months patients crossed-over to undergo a CXL procedure.

The remaining papers reported changes before and after the procedure, which limits the ability to draw conclusions on the causal nature of the effect presented. However, given the disease is progressive, evidence of halting progression or indeed reversing it is supportive of a beneficial effect.

Of the non-RCT papers, the majority (25) were prospective case series, usually with well-defined inclusion criteria, and a robust description of the procedure and methodology adopted for measurement. Very few papers reported the drop-out rates and reasons for drop-out, thereby limiting the strength of the evidence.

Seven of the remaining papers were retrospective reviews, often using patient records as the data source. Using such data has strengths including that they reflect actual outcomes in settings which may be similar to those of the NHS and, thus, are representative of clinical practice. Hence, the results should be replicated in other studies in similar settings. However, there is concern about the potential for bias in patient selection, given these were not consecutive patients and there is the risk of misclassification of information. For example, the use of chart reviews may give rise to under-reporting of adverse events because the information was not clearly recorded.

Almost 60% of the papers were set in European tertiary centres, with a further 15% set in the USA; all undertook very similar CXL procedures. These settings are anticipated to be comparable to NHS settings and, thus, there are no major concerns about the external validity of the results.

Overall, 39 of the papers were graded as very low evidence, six as low and four as moderate. Those graded moderate reported on 4 RCTs but, as noted, these do not provide comparative evidence in similar eyes.

Papers with fewer than 10 patients were excluded but still almost a third of papers reported on fewer than 20 patients. The small study size has been partially addressed through meta-analyses which can add power to the calculation of the end point. However, this cannot address the problem that the numbers in the studies are too small to measure rarer complications and safety-related events. Thus, these are likely to be under-reported.

Many of the meta-analyses displayed moderate to high heterogeneity across the papers, giving wide confidence intervals and suggesting the studies were not consistent in their conduct.

Finally, there may be some uncertainty as to whether patients in the NHS would be similar to those treated within the studies reported. Only 2 papers explicitly excluded patients with Amsler-Krumeich scale grade IV studies (16, 96), with the main inclusion criterion being progressive keratoconus. This does not, therefore, seem an issue.

4.10.2 Summary of Findings of Epithelium-off CXL Papers

4.10.2.1 Topography

Due to a lack of data, no meta-analyses of change between treated and control groups could be undertaken for measures of topography. The meta-analysis results for differences between post-treatment and baseline values for treated patients reported significant improvements for Max K at 6, 12 and 24 months; these improvements were -0.8 D at 6 months and around -1.0 D at 12 and 24 months. For Min K and mean K, meta-analysis was only undertaken at 6 and 12 months (as less data were available for these measures). The meta-analysis results were only significant at 12 months; average changes of around -1.0 D and -0.7 D were found for mean K and Min K, respectively.

The number of papers synthesized was for:

- Max K: 10, 18 and 6 papers at 6, 12 and 24 months, respectively;
- Min K: 4 and 8 papers at 6 and 12 months, respectively;
- Mean K: 7 and 12 papers at 6 and 12 months, respectively.

In total, 38 papers reported 104 comparable measures of topography over the three time periods, with 41 (38%) reporting statistically significant improvements in K values. The improvement increased over time with 4 papers (4, 11, 34, 50) reporting statistically significant differences at 12 months but not at 6 months. Of the 8 papers reporting data at 12 and 24 months, the 24-month values showed an improvement or no change on the 12-month values in all cases but one (67). Papers reporting a longer follow-up showed the improvement continued into year 3 and was then maintained to year 6. However, the number of patients lost to follow-up was large, thereby limiting the weight one can place on these results.

No precise estimate of the benefit across all papers is possible. However, a simple arithmetic mean calculated from the 104 measures gave an improvement of 1.5 D for Max K, 1.4 D for mean K and 1.1 D for Min K at 12 months, which were slightly higher than the results from the meta-analyses.

4.10.2.2 Visual acuity

Due to a lack of data, a meta-analysis of change between treated and control groups was only undertaken for visual acuity (corrected and uncorrected) at 12 months. Only 3 studies contributed to the meta-analysis of corrected VA (50, 52, 117), and only two to the meta-analysis of uncorrected VA (50, 52). No significant difference was found between the treatment and control groups for uncorrected VA, whereas a significant difference of around -0.20 (LogMAR) was found for corrected VA.

The differences between treatment and control groups over time, which included the results from another paper (96) at 18 months, found no significant differences for uncorrected VA. For corrected VA, there seemed to be an improvement over time, as the difference between the treatment and control groups was not significant at 3 months but was significant at both 6 and 12 months (-0.12 and -0.19 LogMAR, respectively). However, non-significant differences were reported at 18 months between the treatment and control groups (96).

Based on results for differences between post-treatment and baseline values for treated patients, significant improvements were reported for corrected and uncorrected VA at 6, 12 and 24 months. These were calculated using data from 12, 18 and 6 papers for uncorrected VA and 15, 22 and 7 papers for corrected VA, at 6, 12, and 24 months, respectively. The improvements on the LogMAR scale were in the order of -0.15 for uncorrected VA and -0.10 for corrected VA across the various time points.

In total, 38 papers reported 104 usable results on visual acuity of which 52 (50%) reported significant improvements in visual acuity measures. The arithmetic mean of the differences calculated from this larger data set was similar to those from the meta-analyses. For uncorrected and corrected VA the estimated benefit at 12 months was 0.19 and 0.10, respectively, on the LogMAR scale.

4.10.2.3 Astigmatism and cylinder measures

Due to a lack of data, meta-analysis was only undertaken for grouped astigmatism measured at 12 months. Only 2 studies contributed to the meta-analysis (50, 52) and no significant differences (random effects model) were found between the treatment and control groups.

The meta-analysis results for differences between post-treatment and baseline values for treated patients showed statistically significant improvements in astigmatism at 6, 12 and 24 months, in the order of -0.4 D at 6 months, -0.7 D at 12 months and -0.5 D at 24 months. For spherical equivalent, meta-analysis was only undertaken at 6 and 12 months. The meta-analysis results, which were only significant at 12 months, showed a reduction of between 0.25 and 0.5 D.

These analyses included 7, 13 and 5 papers on astigmatism at 6, 12 and 24 months, respectively, and 8 and 10 papers on spherical equivalence at 6 and 12 months, respectively.

In total, 31 papers provided 88 usable results of astigmatism and refraction measures, of which 21 (23%) were statistically significant. Eleven values reported in 8 papers were negative (increase in a negative value), showing deterioration in the measure, but none were statistically significant. Analysing the usable results from all papers provided estimates of the reduction at 12 months of:

- 0.9 D for astigmatism, somewhat higher than the value from the meta-analysis;
- 1.0 D in spherical equivalence.

4.10.2.4 Central corneal thickness

Due to a lack of data, no meta-analyses of change between treated and control groups could be undertaken for central corneal thickness (CCT). Two meta-analyses of data from 6 papers estimated differences in CCT values between post-treatment and baseline values for treated patients at 6 and 12 months. A significant decrease of 14 µm in CCT was found at 12 months. No significant difference was found in the meta-analysis of 6-month results.

In total, 25 papers reported on CCT measurements, of which three noted no statistical differences at any time period and two reported statistically significant reductions at 12 months. The arithmetic mean of the changes across the 23 papers providing usability data at 6 and 12 months were -12 µm and -8 µm, respectively, which support the results of the meta-analyses.

One paper (41) reported changes in CCT for patients with keratoconus and keratectasia. Patients with keratectasia regained the pre procedure level of CCT at 12 months, whilst patients with keratoconus had a reduced CCT of about 6 µm.

4.10.2.5 Intraocular pressure

No meta-analyses of change between treated and control groups could be undertaken for intraocular pressure (IOP). Following clinical advice, only 2 studies were included in an analysis of differences between post-treatment and baseline values for treated patients, and this was undertaken at 6 months only. No significant differences were found.

Four papers stated IOP was unchanged over all time periods, and one reported a statistically significant increase in IOP at 12 months of 2.9 mmHg. This was the only statistically significant value reported. Overall, 3 negative values with a mean value of -0.3 mmHg were reported, compared with 11 positive values with a mean value of 0.8 mmHg.

4.10.2.6 Adverse events and complications

Table 4.12 summarises the adverse events reported in the 49 efficacy studies and 26 safety papers. In total, 40 serious complications were reported in 39 patients. To address events which did not resolve, 4 patients had corneal transplants and 1 an unspecified procedure. Four patients suffered reduced VA and 6 had unresolved corneal oedema.

Several studies reported pain, corneal oedema and corneal haze as common side effects. Sterile keratitis was reported in 20 patients. Other minor complications included striae, Descemet, blepharitis, endothelial irregularities and mild photophobia. These resolved over time.

Table 4.12: Adverse events and complications in epithelium-off CXL papers

Complication	Status	Occurrence	Consequences
Infections	Serious	8 single case reports.	4 with no major long-term adverse impact; 1 with reduced VA; 3 not reported.
Corneal melting and perforation	Serious	3 single case reports.	2 with no major long-term adverse impact; 1 further procedure.
Corneal ulcer or burn	Serious	3 single case reports.	1 with improved corrected VA; 2 not reported.
Stromal scar	Serious	4 cases (3 in one study).	3 with improved uncorrected VA despite scars; 1 with vision corrected with lens.
Repeat surgery	Serious	4 patients (2.8%) required deep anterior lamellar keratoplasty; 1 patient required surgery due to riboflavin intolerance.	Post-treatment vision reported as good for 4 patients. For the case study, the outcome was described as uneventful.
Sterile keratitis	Serious	5 cases (4 in one study).	2 had persistent decrease in VA; 1 had scars at 2 months.
Sterile keratitis	Minor	20 cases.	Resolved with treatment; 2 had residual scarring.
Corneal haze	Serious	1 case.	Haze disappeared gradually.
Corneal haze	Minor	Rate 7% to 100% in 6 studies; 5 case studies plus 91 cases from RCT.	Haze disappeared over 12 months and no loss of VA.
Corneal oedema	Serious	11 cases.	1 resolved, 4 improved, 6 unresolved, with 1 case left with very poor VA.
Corneal oedema	Minor	Ranged from common to 70% of patients.	All resolved in 6 months.
Corneal erosion	Minor	1 case.	Settled.
Pain	Minor	Ranged from most to all patients.	Settled.
Other minor	Minor	Striae, Descemet; blepharitis, endothelial irregularities and photophobia.	Settled.

4.11 CONCLUSION FROM CONSIDERATION OF EPITHELIUM-OFF CXL PAPERS

The evidence from 49 papers of the efficacy of epithelium-off CXL and 26 of the safety of epithelium-off CXL for each parameter examined is:

- Improvements in measures of topography were found for Max K, mean K and Min K, respectively at 6, 12 and 24 months. Benefit increased to 12 months and then stabilised. This evidence came from a comparison of baselines before the procedure and post procedure; no randomised control data were available.

- For measures of visual acuity, meta-analysis of change between treated and control groups at 12 months found no significant differences for uncorrected VA but a significant difference of around -0.20 (LogMAR) for corrected VA. One RCT reporting at 18 months only, however, found non-significant differences between the treatment and control groups in corrected VA.

- The results for differences between post-treatment and baseline values for treated patients showed significant improvements in corrected and uncorrected VA at 6, 12 and 24 months. Improvement was also indicated by the results from all papers reporting this outcome.

- No significant differences were found between the treatment and control groups for measures of astigmatism. Differences between post-treatment and baseline values for treated patients showed statistically significant reductions in astigmatism at 6, 12 and 24 months and for spherical equivalent significant differences at 12 months.

- A meta-analysis of 6 papers found a statistically significant reduction in CCT values between post-treatment and baseline values for treated patients at 12 months. Evidence from 25 papers was supportive of a reduction.

- The evidence on intraocular pressure is poor but suggestive of a tendency to higher IOP after the procedure.

- The procedure is generally reported as safe but serious complications were reported, including the need for 4 patients to have corneal transplant, and a similar number suffering long-term loss in visual acuity. The cause of the events was seldom disclosed. For example, some infections may be due to the patient failing to comply with advice on after care and other events may be due to operator error. Most events did resolve over time with no major consequences for the patient.

Section 5: Epithelium-off with CXL and Intrastromal Corneal Ring Segments Results

Data were extracted on the characteristics of the included studies and procedures (Table 5.1), and patient outcomes (Table 5.2).

5.1 NUMBER, TYPE AND QUALITY OF INCLUDED PAPERS

Six studies (3, 17, 21, 28, 29, 62) were identified that provided information on 10 or more patients with more than 6 months follow-up for epithelium-off CXL with intrastromal corneal ring segments (ICRS) implantation. Three papers (50%), (17, 21, 29) reported findings from RCTs. Of the remaining papers, two (33%) (3, 62) were retrospective case series and one (17%) was a comparative case series.

Two studies (33%) included between 10 and 20 patients, two (33%) contained between 21 and 40 patients, one (17%) between 41 and 60 patients and one (17%) (62) reported 105 patients. The 3 unique RCTs (17, 21, 29) included 43, 31 and 10 patients, respectively.

None of the studies were set in the UK or USA; one (17%) was set in Europe (Spain) and 5 (83%) in the rest of the world (Turkey, Egypt and Brazil).

All but 1 study reported the mean age of patients, with 4 reporting a mean age in the range 21 to 30 years; the remaining study, had a mean age of just over 30 years.

Five of the 6 papers analysed patients by gender with 52% overall being female.

Five of the 6 papers were published in 2010 or later.

Two studies had a 12-month follow-up, 3 had a 6-month follow-up and the sixth reported a follow-up of 24 months. All studies reported the number of eyes recorded at each period.

5.2 QUALITY OF EVIDENCE

Three of the papers (3, 28, 62) were given a SIGN grade of 3, two (17, 21) a SIGN grade of 1+ and one (29) a grade of 1-. Three of the papers (3, 28, 62) were given a GRADE classification of very low, one (29) was classified as low and the remaining two (17, 21) were classified as moderate.

5.3 DESCRIPTION OF RCTS

The RCT reported in paper (17) enrolled 48 eyes with keratoconus from 43 people who were randomised to 2 groups. In group1, patients received CXL followed by ICRS implantation, whilst in group 2 patients received ICRS implantation followed by CXL. The 2 treatments took place with a mean interval of 7 months. Postoperative follow-up outcomes are provided at a mean of 6 months.

The RCT reported in paper (21) enrolled 31 patients and 39 eyes that were randomised to 2 groups. In the CXL group patients underwent classic CXL. Patients in group 2 received riboflavin eye drops for 1 month. After 3 months, all patients underwent insertion of ICRS. The 8 patients with both eyes included in the trial received riboflavin drops in their right eye and CXL in their left eye. Follow-up examinations were performed for up to 24 months in both groups.

The RCT reported in paper (29) enrolled 10 patients and 16 eyes with progressive mild to moderate keratoconus. The eyes were randomly divided into 2 groups. Patients in group 1 underwent ICRS insertion followed by CXL 6 months later. Patients in group 2 underwent both procedures on the same day. Postoperative results were available for both groups at 12 months.

5.4 CXL WITH ICRS PROCEDURE

ICRS are typically made from polymethyl methacrylates and are inserted in the cornea of the eye by making a small incision. Two crescent or semi-circular shaped ring segments are normally inserted between the layers of the corneal stroma, one on each side of the pupil. Embedding the rings in the cornea should flatten the cornea and change the refraction of light passing through the cornea. By regularising the front surface of the cornea the vision impairment may be reduced.

ICRS achieved FDA approval for this indication in June 2004. In April 2010 the FDA approved the expanded range of corneal implants, which are placed in a channel in the cornea.

The CXL procedure adopted in the studies followed the classic epithelium-off protocol. Paper (28) did not describe the CXL process. This had been conducted successfully 6 months prior to the implant of the ICRS.

5.5 SUMMARY OF PATIENT AND PROCEDURAL DIFFERENCES ACROSS PAPERS

Four of the papers required patients to have progressive keratoconus (3, 17, 28, 29) for inclusion. This was not a requirement in the other 2 studies. One paper (3) included patients with a minimum corneal thickness of >370 µm; others required at least 400 µm or 450 µm (29). Exclusion criteria were poorly reported with only 3 papers reporting these; two (3, 17) excluded advanced/grade 4 keratoconus. As such it is difficult to ascertain precisely the comparability of patients across the studies but the details available do not give rise to concern.

Beyond small differences in the diameter of epithelium removed and preoperative administration of riboflavin there was no difference in the actual CXL procedure. There were differences across studies when the ICRS was implanted following CXL, ranging from at the same time as CXL to 6 months post CXL.

Details of patients and procedures in the included studies are provided in Table 5.1.

Table 5.1: Study and intervention characteristics of included papers of epithelium-off CXL with ICRS

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Coskunseven **Year:** 2009 **Ref:** 17 **Country:** Turkey	**Follow-up:** Mean interval between treatment steps 7 months, mean follow-up after second step 6 months. **Study type:** RCT. **Primary aim of study:** Compare 2 sequences of combined ICRS implantation and UV A / riboflavin mediated CXL in progressive keratoconus (sequence CXL ICRS versus ICRS CXL). **SIGN grading:** 1+. **GRADE*:** Moderate.	**Number of patients:** 43. **Number of eyes:** 48. **Mean age:** 21 +/- 5. **% female:** 42%.	Keratoconus grade 1 to 3; older than 14 years with no systemic disease; contract lens intolerance; proof of keratoconus evolution; endothelial cell count < 1000 cells/mm^2; corneal thickness at the thinnest point of at least 400 µm.	**Anaesthesia:** Topical anaesthesia eye drops applied preop. During operation topical aesthetic agent applied every 2 to 3minutes. **Preop riboflavin:** Riboflavin 0.1% solution in 20% dextran applied to the cornea every 3 minutes for 30 minutes. Saturation monitored by slit lamp. **Operative riboflavin:** Riboflavin solution applied every 2 to 3 minutes to saturate cornea. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2. 30 minutes. **ICRS:** Group 1 CXL followed by ICRS versus group 2 ICRS versus CXL. Mean period between procedures was 7 months. **Postop care:** Ofloxacin 0.3% applied and bandage contact lens fitted to corneal surface and left in place until re-epithelialisation. Topical dexamethasone phosphate 0.1% 4 x daily with gradual tapering over next 2 months.
Author: Da Candelaria **Year:** 2012 **Ref:** 21 **Country:** Brazil	**Follow-up:** 24 months (p values only given for between groups statistically significant). **Study type:** RCT. **Primary aim of study:** Report refractive,	**Number of patients:** 31. **Number of eyes:** 39. **Mean age:** Riboflavin group (G1): 30.4 +/- 9.1 CXL group (G2): 28.3 +/- 9.3. **% female:** 74%.	Keratoconus with BCVA <= 0.48; increasing or proven intolerance to contact lenses; penetrating keratoplasty, corneal thickness >= 400µm at thinnest point; good health with no autoimmune disease; between 15 and 60 years.	**Anaesthesia:** Proxymetacaine hydrochloride 0.5% eye drops applied for anaesthesia before surgery. During surgery topical anaesthesia applied as needed. **Preop riboflavin:** Riboflavin 0.1% solution applied every 5 minutes for 30 minutes. **Operative riboflavin:** Eye rinsed with riboflavin.

Author	Study design	Study population	Inclusion criteria	Intervention
	outcomes at 24 months after CXL, and insertion of ICRS in keratoconic eyes. (CXL ICRS with 3 month delay (group 2) versus riboflavin only and ICRS at 3 months (group 1). **SIGN grading:** 1+. **GRADE*:** Moderate.			**Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2. 370 +/- 5nm. 30 minutes. **ICRS:** After 3 months, all patients underwent insertion of ICRS. **Postop care:** Soft bandage contact lens applied until re-epithelialisation was complete. Moxifloxacin 0.5% and dexamethasone phosphate 0.1% prescribed 4 x daily for 2 weeks.
Author: El Raggal **Year:** 2011 **Ref:** 29 **Country:** Egypt	**Follow-up:** 3 days, 1 week, 1, 3, 6, 9 and 12 months after final intervention. Mean 6 months. **Study type:** RCT. **Primary aim of study:** Evaluate the safety of same day ICRS CXL (group 2) versus 6 month delay (group 1). **SIGN grading:** 1-. **GRADE*:** Low.	**Number of patients:** 10. **Number of eyes:** 16. **Mean age:** 27.9 +/- 4.8. **% female:** 60%.	Progressive keratoconus; contact lens intolerant; clear cornea; max K <60D; minimal corneal thickness > 450µm; scotopic pupil diameter < 5mm. No autoimmune or systemic disease.	**Anaesthesia:** Topical anaesthesia. **Preop riboflavin:** Riboflavin 0.1% solution applied every 3 minutes for 30 minutes, until stroma completely saturated and stroma stained yellow. **Operative riboflavin:** Riboflavin solution applied every 3 minutes to ensure saturation. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2. 30 minutes. **ICRS:** Group 1: 9 eyes that underwent ICRS and CXL 6 months later: Group 2 7 eyes ICRS and CXL on same day. **Postop care:** Bandage contact lens for 3 days. Ofloxacin eye drops, diclofenac for 2 weeks. Artificial tears for 1 month. Fluorometholone eye drops 3 x daily for 2 weeks.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Alio **Year:** 2011 **Ref:** 3 **Country:** Spain	**Follow-up:** 12 months. **Study type:** Retrospective case series. **Primary aim of study:** Evaluate and compare clinical and confocal microscopic outcomes achieved with 2 different procedures (or techniques) for CXL. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 21. **Number of eyes:** 27. **Mean age:** Classic group: 31.93 Intrastromal group: 29.25. **% female:** 29%.	Keratoconic patients treated by ICRS implantation with evident signs of progression at least 3 months after implantation. Minimum corneal thickness < 370 µm.	**Anaesthesia:** Both techniques: topical anaesthesia. **Preop riboflavin:** Riboflavin 0.1% solution every 5 minutes for 15 to 20 minutes. Intrastromal technique: Riboflavin 0.1% injected directly into the corneal pocket. **Operative riboflavin:** Classic: 1 drop riboflavin 0.1% solution every 3 minutes. **Diameter of corneal removed:** Classic: 9mm, Intrastromal: 7mm. **UV A strength and WL and time:** Both: 3mW/cm^2. 370nm. **ICRS:** CXL after ICRS versus creation of intrastromal pocket for riboflavin. Classic: 30 minutes, Intrastromal: 20 minutes. **Postop care:** Not Reported.
Author: Kilic **Year:** 2012 **Ref:** 62 **Country:** Turkey	**Follow-up:** Mean = 7.07 +/- 4.66 months (range 1 to 25) months. **Study type:** Retrospective case series. **Primary aim of study:** Evaluate the efficacy of CXL and ICRS implantation on same day. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 105. **Number of eyes:** 131. **Mean age:** Not Available. **% female:** Not Available.	Keratoconus eyes with contact lens intolerance; pachymetry greater than 400µm; no corneal scarring.	**Anaesthesia:** 0.5% proparacaine and 2% pilocarpine every 2 minutes and 5 minutes respectively for 30 minutes. **Preop riboflavin:** Riboflavin drops every 3 minutes for 30 minutes. **Operative riboflavin:** Continued topical riboflavin application every 3 minutes through procedure. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2. 370nm.

Author	Study design	Study population	Inclusion criteria	Intervention
				ICRS: Combined CXL and ICRS on same day. **Postop care:** Artificial tears, dexamethasone 1mg/ml and tobramycin 3mg/ml were used for 1 week.
Author: El Raggal **Year:** 2011 **Ref:** 28 **Country:** Egypt	**Follow-up:** 6 months (no p-values). All measurements are preop. **Study type:** Comparative case series. **Primary aim of study:** Evaluate the effect of CXL on femtosecond laser channel creation for ICRS in keratoconic eyes. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 11. **Number of eyes:** 20. **Mean age:** 27 years. **% female:** 55%.	Progressive keratoconus; CXL 6 months previously; contact lens intolerance; a clear cornea; max K reading after CXL < 60 D; minimum cornea.	Study comparing 3 groups of 5 patients with different laser settings for ICRS channels all of whom had CXL with 5 patient having ICRS but not CXL. CXL not described.

***** High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Table 5.2: Summary of outcomes in included papers on epithelium-off CXL with ICRS

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
Author: Coskunseven **Year:** 2009 **Ref:** 17 **Country:** Turkey	Group 1. After CXL and before ICRS: increase >0.5 lines in UCVA ($p<0.05$), increase 0.5 line in CVA ($p>0.05$). After CXL and ICRS: increase 1 line in UCVA ($p<0.01$) and CVA ($p<0.01$). Group 2. After ICRS and before CXL: increase in UCVA 2 lines ($p<0.01$) and CVA 3 lines ($p<0.01$). After ICRS and CXL: increase in UCVA ($p<0.05$) 1 line and CVA 0.5 lines ($p>0.05$).	Group 1. After CXL and before ICRS: decrease 0.88 D in mean K value ($p<0.01$). After CXL and ICRS: decrease in mean K 3.28 D ($p<0.01$). Group 2. After ICRS and before CXL: decrease in mean K 2.94 D ($p<0.01$). After ICRS and CXL: decrease in mean K value 1.08 D ($p<0.01$).	Group 1. After CXL and before ICRS: decrease 1.39 D in SE ($p<0.05$); decrease in manifest cylinder (0.44 D) ($p>0.05$). After both: decrease in SE 2.76 D ($p<0.01$); decrease in manifest cylinder (1.32 D) ($p<0.01$). Group 2. After ICRS and before CXL: decrease in SE 3.31 D ($p<0.01$); decrease in manifest cylinder (2.05 D) ($p<0.01$). After both: decrease in SE 0.93 D ($p<0.01$) and manifest cylinder (0.43 D) ($p>0.05$).	Group 1. After CXL and before ICRS: increase 2 mmHg in mean IOP ($p<0.01$). After CXL and ICRS: marginal change in IOP ($p>0.05$). Group 2. After ICRS and before CXL: decrease 1 mmHg in IOP ($p>0.05$). After ICRS and CXL: increase 1 mmHg in IOP ($p>0.05$).	Group 1. After CXL and before ICRS: decrease mean pachymetry (6 µm) ($p>0.05$). After CXL and ICRS: decrease in mean pachymetry (28 µm) ($p<0.05$). Group 2. After ICRS and before CXL: decrease in pachymetry (6 µm) ($p>0.05$). After ICRS and CXL: increase in pachymetry (5 µm) ($p<0.05$).	8 eyes had slight sub-epithelial and stromal oedema with cotton lie stromal opacities 1 month after CXL; disappeared within 3 months.	Group 1. After CXL and before ICRS: decrease in ECC (39 cells/mm^2) ($p>0.05$). After both: increase in ECC (15 cells/mm^2) ($p>0.05$). Group 2. After ICRS and before CXL: increase in ECC (1 cell/mm^2). After ICRS and CXL: decrease in ECC (15 cell/mm2) ($p>0.05$).
Author: Da Candelaria **Year:** 2012 **Ref:** 21 **Country:** Brazil	UCVA mean (LogMAR): G1: pre intervention = 0.84; post ICRS 24 month = 0.62 (p=NA) G2: pre intervention = 1.12; post ICRS 24 month = 0.79	G1: Baseline average keratometry = 51.75 D, 24 months = 50.52 D (p=NA) G2: Baseline average	G1: mean preop SE = -5.45 D; 24 months = -4.19 D (p=NA); mean sphere preop = -3.42; 24 months = -2.65 (p=NA); mean net cylinder preop =	IOP measured with Goldmann application tonometer. GI preop = 8.7 mmHg; 24 months = 9.8 mmHg (p=NA).	Visante (µm) (other devices reported too). G1: central position: preop = 453.9; 24 months = 457.5 (p=NA).	2 eyes presented with anterior chamber perforation and were excluded from the study.	Endothelial results: non-significant difference (p=0.71) between baseline and 24 months. Contrast sensitivity: no significant differences

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
	(p=NA) BSCVA (LogMAR): G1: pre intervention = 0.45; post ICRS 24 month = 0.32 (p=NA) G2: pre intervention = 0.68; post ICRS 24 month = 0.52 (p=NA).	keratometry = 53.65 D, 24 months = 51.63 D (p=NA).	-4.0; 24 months = -3.21 (p=NA). G2: mean preop () SE = -7.38 D; 24 months = -5.49 D (p=NA); mean sphere preop = -5.17; 24 months = -4.03 (p=NA); mean net cylinder preop = -4.0 D; 24 months = -3.21 D (p=NA).	G2 preop = 8.3 mmHg; 24 months = 9.3 mmHg (p=NA) Measured with dynamic controutonometer. G1 preop = 13.2 mmHg; 24 months = 9.6 mmHg (p=NA). G2 preop = 11.6 mmHg; 24 months = 9.5 mmHg (p=NA).	Thinnest position: preop = 429.3; 24 months = 433.1 (p=NA). G2: central position: preop = 444.9; 24 months = 447.2 (p=NA). Thinnest position: preop = 417.9; 24 months = 420.6 (p=NA).		between groups.
Author: El Raggal **Year:** 2011 **Ref:** 29 **Country:** Egypt	UCVA mean: Group 1: preoperative = 0.13, postoperative = 0.4 (p<0.001) Group 2: preoperative = 0.11, postoperative = 0.4(p=0.0056). CVA mean: Group 1: preoperative = 0.36, postoperative = 0.72 (p<0.001). Group 2: preoperative = 0.33, postoperative = 0.69 (p<0.001).	Mean K values: Group 1: preoperative = 50.42, postoperative = 47.32 (p<0.001). Group 2: preoperative = 50.16, postoperative = 44.94 (p<0.001).	SE (D): Group 1: preoperative = -4.1, postoperative = -1.58 (p<0.001) Group 2: preoperative = -4, postoperative = -1.46 (p<0.001) Cylindrical error (D): Group 1: preoperative = 5.53, postoperative = 4.67 (p=0.018) Group 2: preoperative = 5.14, postoperative = 4.29 (p=0.045).	Not available.	Not available.	Very minimal intracorneal channel deposits in 1 eye in group 1. Stromal haze in all eyes, which was more marked and persistent in group 2, but finally resolved in both groups. No other complications were recorded.	Not available.

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
Author: Alio **Year:** 2011 **Ref:** 3 **Country:** Spain	Mean UCVA: Classic group: baseline 0.85 +/- 0.37; 12 months 0.71 +/- 0.38 (p<0.01). Intrastromal group:- baseline 0.89 +/- 0.46; 12 months 0.66 +/- 0.45 (p=0.27) Mean CVA: Classic group: baseline 0.37 +/- 0.12; 12 months 0.31 +/- 0.16 (p=0.08). Intrastromal group: baseline 0.31 +/- 0.23; 12 months 0.28 +/- 0.34 (p=0.27).	Only preoperative results reported.	Sphere: Classic group: baseline -2.23 +/- 4.39; 12 months -0.5 +/- 2.01 (p=0.46). Intrastromal group: baseline -1.05 +/- 2.24; 12 months 0.25 +/- 1.45 (p=0.07).	Only preoperative results reported.	Central corneal thickness (µm): Classic group: - baseline 441.73; 12 months 452.10 (p=0.92). Intrastromal group: baseline487.89; 12 months 513.2 (p=0.99).	Corneal haze in all cases in early postoperative period; resolved over time though in some cases corticosteroid therapy had to be changed. No postoperative pain reported with new technique.	Not available.
Author: Kilic **Year:** 2012 **Ref:** 62 **Country:** Turkey	UCVA mean (LogMAR): preop 0.2 +/- 0.18; postop 0.47 +/- 0.19 (p<0.05). CVA (LogMAR): preop 0.38 +/-0.2; postop 0.62 +/- 0.17 (p<0.05).	Mean K (D): preop 50.50 +/- 5.26; postop 46.03 +/- 4.51.	Cylinder (D): preop - 3.89 +/- 1.97; postop -2.27 +/- 2.18. Sphere (D): preop - 3.87 +/- 4.85; postop -1.25 +/- 2.31.	Not available.	Not available.	Not available.	Not available.

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
Author: El Raggal **Year:** 2011 **Ref:** 28 **Country:** Egypt	UCVA: CXL group 0.13 +/- 0.09; Control group 0.11 +/- 0.05. CVA: CXL group 0.45 +/- 0.2; Control group 0.46 +/- 0.11. Only baselines presented.	Steep K (D): CXL group 54.61 +/- 0.77; Control group 54.1 +/- 1.6. Flat K (D): CXL group 48.63 +/- 1.66; Control group 48.8 +/- 1.15. Only baselines presented.	Spherical error (D): CXL group -4.06 +/- 1.5; Control group -4.40 +/- 1.39. Cylindrical error (D): CXL group 5.36 +/- 0.86; Control group 5.4 +/- 0.65. Only baselines presented.	Not available.	Pachymetric reading (µm): CXL group 435.33 +/- 23.1; Control group 438 +/- 14.8. Only baselines presented.	9 eyes developed stromal haze; 4 were grade 1; 4 were grade 2 and 1 was grade 3. All cases resolved without sequelae.	Not available.

5.6 QUALITATIVE SUMMARY OF PATIENT OUTCOMES

Table 5.2 details the patient outcomes of interest for this review for epithelium-off CXL with ICRS. Each of the outcomes in now examined, reporting the results of the RCTs and then other papers. One paper (28) only presented adverse events post procedure: data on other parameters were baseline data only.

5.6.1 Visual Acuity

One RCT (17) compared outcomes from two groups: one receiving CXL followed at 7 months by ICRS (group 1) and the second receiving ICRS followed by CXL after 7 months. At 6 months post both procedures each group gained one Snellen line in uncorrected VA, with group 1 gaining one line in corrected VA but group 2 only half a line. All results were statistically significant.

The second RCT (21) compared the results of ICRS administered after drops of riboflavin (group 1) or with classic CXL (group 2). The results, shown in Table 5.3, indicate that the CXL arm received the greater improvement in uncorrected VA at 6 months, but the benefit from CXL tapered until at 24 months the two interventions were virtually equivalent. The benefit at 6 months was less marked for best corrected VA measures. No statistically significant differences were reported.

Table 5.3: Comparison of VA results after riboflavin or CXL

Group	UCVA change at: (months) post procedure			CVA change at: (months) post procedure		
	6	12	24	6	12	24
1	0.27	0.29	0.22	0.19	0.22	0.13
2	0.48	0.39	0.25	0.22	0.33	0.16

The third RCT (29) compared ICRS followed in 6 months by CXL and same-day procedures. The results reported statistically significant increases in uncorrected and corrected VA for each arm at 6 months. The absolute change was the same for corrected VA 0.36 LogMAR and similar for uncorrected VA (0.29 versus 0.27) in favour of same-day procedure.

The large retrospective case study of CXL and ICRS performed on the same day (62) reported statistically significant improvements in uncorrected VA (0.27 LogMAR) and corrected VA (0.24 LogMAR) at 6 months.

The final paper (3) reporting changes in VA compared classic CXL and CXL using an intrastromal pocket for the riboflavin solution. The uncorrected measures improved by 0.14 and 0.23 LogMAR, respectively, and best corrected vision by 0.06 and 0.24 LogMAR, respectively. None of the results were statistically significant.

Conclusions

The evidence from the RCTs and other papers on VA suggests preferences in favour of:

- Sequencing of CXL before ICRS rather than after it;
- Using CXL rather than riboflavin only before ICRS;
- Same-day procedures, with the benefit of the same-day procedure supported by one paper (62).

There was no statistically significant evidence on the relative clinical efficacy of an intrastromal pocket.

5.6.2 Topography

Both groups in one RCT (17) reported statistically significant improvement in mean K values, with group 1 (CXL then ICRS) reporting the greater change (3.28 D versus 1.08 D).

The results for the second RCT (21), which compared ICRS administered after drops of riboflavin (group 1) with insertion after classic CXL (group 2), are shown in Table 5.4. None of the changes were statistically significant. All measures were an improvement on baseline, with the CXL group gaining the greater benefit.

Table 5.4: Comparison of topography results after riboflavin or CXL

Group	Max K change at: (months) post procedure			Mean K change at: (months) post procedure			Min K change at: (months) post procedure		
	6	12	24	6	12	24	6	12	24
1	3.10	3.00	3.2	1.09	1.38	1.23	1.31	1.16	1.17
2	3.73	3.57	3.64	2.23	1.72	2.02	2.02	1.53	1.33

The third RCT (29) reported statistically significant improvements in mean K in each arm, with the same-day procedure arm having a greater benefit than delaying CXL for 6 months (5.2 versus 3.1).

One paper (62) reported an improvement in mean K at 6 months of 4.5 D. One paper (3) did not report this outcome.

Conclusion

The evidence from the RCTs and other papers on topography suggests preferences in favour of:

- Sequencing of CXL before ICRS rather than after it;
- Using CXL rather than riboflavin only before ICRS;
- Same-day procedures, with the benefit of the same-day procedure supported by one paper (62).

5.6.3 Astigmatism and Refraction

Both groups in one RCT (17) reported statistically significant improvements in sphere values at 6 months; group 1 also reported a statistically significant improvement in cylinder measures. For each measure the gain was greater in group 1 (sequencing CXL before ICRS).

The results for the second RCT (21), which compared ICRS administered after drops of riboflavin (group 1) or classic CXL (group 2), were mixed and not significant.

The third RCT (29) reported statistically significant improvements in spherical equivalence (SE) and cylinder error in the two groups. The changes between groups 1 and 2 at 6 months were similar (2.52 versus 2.54 for SE and 0.86 versus 0.89 for cylinder error).

One paper (62) reported an improvement in sphere and cylinder values at 6 months of 2.6 D and 1.6 D, respectively, compared to baseline. One paper (3) did not report this outcome.

Conclusion

The evidence from the RCTs and other papers on astigmatism and refraction suggests preferences in favour of:

- Sequencing of CXL before ICRS rather than after it;
- Same-day procedures (CXL and ICRS), which improve these measures compared with delays.

5.6.4 Central Corneal Thickness

Only 3 papers reported on this parameter.

Group 1 in the first RCT (17) reported a reduction in central corneal thickness (CCT) at 6 months of 28 µm compared with an increase of 5 µm for group 2 (ICRS before CXL). These values were statistically significant.

The results for the second RCT (21) comparing ICRS administered after drops of riboflavin (group 1) with classic CXL (group 2) showed both groups experienced slightly increased thickening of the CCT at 24 months, with the riboflavin group gaining 3.6 µm compared with 2.3 µm in the CXL group. These differences were not statistically significant.

One paper (3) comparing classic CXL with a procedure creating an intrastromal pocket reported a gain in each arm at 12 months; none of the values were statistically significant.

Conclusion

The evidence on this parameter was inconclusive.

5.6.5 IOP and Adverse Events

The authors of one RCT (17) reported that in group 1 (CXL then ICRS) there was a marginal change in IOP compared with a 1-mmHg increase at 6 months.

The results for the second RCT (21) comparing ICRS administered after drops of riboflavin (group 1) or classic CXL (group 2) showed that the CXL arm experienced a lower increase in IOP at 6 and 12 months (0.2 and 0.1 increase in mmHg, respectively) compared with the riboflavin arms (increases of 1.1 and 0.4 mmHg, respectively).

These were the only papers reporting change in IOP. None of the values were statistically significant.

Complications reported in these papers were grouped with other CXL-Plus papers and are reported in Section 7.3.

5.7 CONCLUSIONS ON CXL WITH ICRS

The evidence on VA, topography and astigmatism/refraction comes from 3 RCTs and 3 case series, providing a mix of moderate and low quality evidence. It supports:

- Same-day procedures (CXL and ICRS) in preference to a delay of several months;
- The conduct of CXL before ICRS if, however, a delay is necessary.

There is insufficient evidence to draw conclusions on the other interventions.

Section 6: Epithelium-off CXL with Photorefractive Keratectomy Results

This grouping includes studies of epithelium-off CXL and photorefractive keratectomy (PRK), including studies of topography-guided photorefractive keratectomy (TG-PRK).

Data were extracted on the characteristics of the included studies, details of the CXL procedure with PRK (Table 6.1) and patient outcomes (Table 6.2).

6.1 NUMBER, TYPE AND QUALITY OF INCLUDED PAPERS

Nine studies provided information on 10 or more patients with more than 6 months follow-up for epithelium-off CXL with PRK.

Five studies included between 21 and 40 patients (49, 56, 57, 73, 77), 3 studies included between 10 and 20 patients (58, 79, 112) and 1 study had 117 patients (59). Five of the 9 papers reported studies which were set in Europe (Greece). The remaining papers reported studies set in the USA and Greece (1), Saudi Arabia (1), and the USA (1); one did not report geographical setting.

Seven papers reported the mean age of patients, with six reporting a mean age in the range 21 to 30 years and one a mean age of over 30 years.

Only 3 of the 9 papers analysed patients by gender, of these 41% were female.

Six of the studies were published in 2010 or later.

Two studies (77, 112) had a 12-month follow-up. Of the other 7 studies, one had a mean follow-up of 11 months (79), and the others had between 19.5 and 36 months follow-up. All studies reported the number of eyes recorded at each period.

6.2 QUALITY OF EVIDENCE AND TYPE OF STUDIES

All of the included studies were case series. There were 5 prospective case series (57, 73, 77, 79, 112), 1 retrospective comparative case series (59), 1 randomised comparative case series (56) and two case series (49, 58). Seven papers (49, 57, 58, 73, 77, 79, 112) were given a SIGN grade 3 and a GRADE classification of very low. The remaining 2 papers (56, 59) were given a SIGN grade of 2- and a GRADE classification of low. Three papers (73, 77, 79) were authored by Kymionis and four by Kanellopoulos (56, 57, 58, 59).

6.3 CXL WITH PRK INCLUDING TG-PRK

This is a two-stage process. The outer layer of the cornea is first removed prior to ablation using a laser with the aim of normalising the cornea. With TG-PRK the laser uses topographically supported customised software to guide the ablation process. The depth of epithelium removed is usually less than that required for CXL (56). After the ablation, classic CXL is conducted. There is uncertainty on the optimal timing of these procedures, and whether they should be conducted sequentially or simultaneously.

6.4 SUMMARY OF PATIENT AND PROCEDURAL DIFFERENCES ACROSS PAPERS

Five papers (56, 59, 73, 77, 70) included patients with progressive keratoconus, one (57) included patients with ectasia, one (112) included those with keratoconus stage 1 and 2, and one (58) described the included eyes as 'early keratonic corneas'. One paper (49) did not report this information. Another difference was in the thickness of the minimum corneal thickness for inclusion:

- Two papers included patients if the anticipated CCT after PRK exceeded 400 µm (73, 79);
- Actual thickness of at least 440 µm (112), 450 µm (56) and 500 µm (58) were also used.

These were the only notable differences in inclusion and exclusion criteria.

There were differences in the diameter of epithelium removed (5.5 to 9.0 mm), where reported in 7 papers (56, 57, 58, 59, 73, 79, 112), and the wavelength of light used with PRK was lower (213 versus 370 nm) in 3 papers (73, 77, 79). The study reported in one paper (58) used a laser to create an intrastromal pocket before proceeding to CXL. The CXL technique used exposed the cornea to UV light fluence of 7 mW/cm^2 for 15 minutes. Another paper (56) by the same author compared two groups: group A received 7 mw/cm^2 for 15 minutes and group B received the standard 3 mW/cm^2 for 30 minutes. A third paper by the same author (59) also included two groups. The first group underwent CXL with subsequent TG-PRK performed 6 months later (sequential group) and the second group underwent CXL and PRK in a combined procedure on the same day (simultaneous group). Details of patients and procedures in the included studies are provided in Table 6.1.

Table 6.1: Study and intervention characteristics of included papers of epithelium-off CXL with PRK

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Kanellopoulos, Binder **Year:** 2011 **Ref:** 57 **Country:** Greece and USA	**Follow-up:** Mean 27 months. **Study type:** Prospective case series. **Primary aim of study:** Evaluate a series of patients with corneal ectasia after LASIK that underwent PRK to reduce or eliminate induced myopia and astigmatism with CXL on same day. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 22. **Number of eyes:** 32. **Mean age:** 32. **% female:** 50%.	Patients with corneal ectasia after LASIK who have undergone combined, same-day TG-PRK and subsequent UV A collagen CXL to achieve stabilisation of corneal ectasia and enhance visual rehabilitation.	**Anaesthesia:** Topical 1% proparacaine. **Preop riboflavin:** 0.1% riboflavin solution applied topically every 2 minutes for 10 minutes. **Operative riboflavin:** Riboflavin solution applied every 2 minutes during 30 minutes treatment. **Diameter of corneal removed:** 6.5mm. **UV A strength and WL and time:** 3mW/cm². Mean 370 nm (365 to 375 nm). 30 minutes. **Postop care:** Bandage contact lens placed on cornea (for 5 days). Topical ofloxacin used 4 x daily for first 10 days and prednisolone acetate 1% used 4 x daily for 60 days. Sunglasses worn and 1000 mg vit C daily for 60 days.
Author: Kymionis **Year:** 2010 **Ref:** 77 **Country:** Greece	**Follow-up:** 6 and 12 months. **Study type:** Prospective case series. **Primary aim of study:** To report the development of posterior linear stromal haze after simultaneous PRK followed by CXL. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 23. **Number of eyes:** 28. **Mean age:** 30 +/- 9.35. **% female:** Not Available.	Progressive keratoconus in corneal topographies increase of maximal K-readings and central thinning of the cornea over a period of 6 months with reported change in refraction.	**Anaesthesia:** Proparacaine hydrochloride 0.5% used to anesthetise eye. **Preop riboflavin:** After PRK riboflavin 0.1% solution instilled repeatedly for 30 minutes. **Operative riboflavin:** Riboflavin solution applied every 5 minutes to saturate cornea. **Diameter of corneal removed:** Not Applicable. **UV A strength and WL and time:** 213 nm during PRK; 365nm during CXL. 30 minutes. **Postop care:** Bandage contact lens until re-epithelialisation (5 days). Antibiotic-corticosteroid used for 15 days.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Kymionis **Year:** 2009 **Ref:** 79 **Country:** Greece	**Follow-up:** Mean = 10.59 +/- 5.95 range 3 to 16 months. **Study type:** Prospective case series. **Primary aim of study:** Present the results after simultaneous PRK followed by corneal CXL for progressive keratoconus. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 12. **Number of eyes:** 14. **Mean age:** 28. **% female:** Not Applicable.	Progressive keratoconus; hard contact lens with full spectacle correction intolerance; expected CCT after PRK >400 µm.	**Anaesthesia:** Tetracaine 1% and oxybuprocaine 0.4% eye drops. **Preop riboflavin:** Riboflavin 0.1% solution applied every 3 minutes for 20 minutes until the stroma was completely penetrated and aqueous was stained yellow. **Operative riboflavin:** During treatment riboflavin applied every 5 minutes to ensure saturation. **Diameter of corneal removed:** 8.5mm. **UV A strength and WL and time:** 3mW/cm². 213 nm during PRK procedure. 30 minutes. **Postop care:** Bandage contact lens applied until epithelium healed, then fluorometholone 0.1% eye drops for 2 weeks.
Author: Kymionis **Year:** 2011 **Ref:** 73 **Country:** Greece	**Follow-up:** Mean 19.53 months. **Study type:** Prospective case series. **Primary aim of study:** Present the long-term results after simultaneous PRK followed by corneal CXL for keratoconus. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 26. **Number of eyes:** 31. **Mean age:** 29.3 +/- 8.5 **% female:** 31%.	Progressive keratoconus; expected corneal thickness at the apex of the cone after PRK >400 µm and no other corneal pathologic signs.	**Anaesthesia:** Tetracaine 1% and oxybuprocaine 0.4% eye drops. **Preop riboflavin:** Riboflavin 0.1% solution applied every 3 to 5 minutes for 30 minutes until the stroma completely penetrated and aqueous stained yellow. **Operative riboflavin:** Riboflavin solution applied every 3 to 5 minutes to ensure saturation. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm². 213 nm for PRK. 30 minutes. **Postop care:** Bandage contact lens until re-epithelialisation. Antibiotic-corticosteroid drops used for 14 days.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Tuwairqi **Year:** 2012 **Ref:** 112 **Country:** Saudi Arabia	**Follow-up:** 12 months. **Study type:** Prospective case series. **Primary aim of study:** Evaluate 1 year visual, topographic, safety and efficacy of CXL with TG-PRK to achieve near emmetropia in eyes with low grade keratoconus. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 15. **Number of eyes:** 22. **Mean age:** 26.6 +/- 6.07. **% female:** Not Available.	Patients over 18 years with topography consistent with keratoconus; an inferior-superior ratio >1.5 on topography mapping; stage 1 and 2 keratoconus; corneal thickness >440 µm at thinnest location; preoperative CVA 0.8 or better; max keratometry readings <51 D; stable refraction.	**Anaesthesia:** Topical anaesthetic agent. **Preop riboflavin:** Riboflavin 0.1% every 2 minutes for 30 minutes. Additional hypoosmolar riboflavin solution was given for 10 minutes to swell the cornea to reach at least 400 µm. **Operative riboflavin:** Isotonic riboflavin administration continued every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm². 365 nm. 30 minutes. **Postop care:** Antibiotic, corticosteroid drops and bandage soft contact lens. Contact lens removed after epithelium closed and drops continued for 7 days.
Author: Kanellopoulos **Year:** 2008 **Ref:** 59 **Country:** Greece	**Follow-up:** Mean 36 +/- 18 months. **Study type:** Retrospective comparative case study. **Primary aim of study:** Safety and efficacy of CXL and PRK using a different sequences and timing (CXL and PRK same day and CXL followed by PRK in 6 months). **SIGN grading:** 2-. **GRADE*:** Low.	**Number of patients:** Not Reported. **Number of eyes:** 325. **Mean age:** Mean age in sequential: 21.5 and simultaneous group 20.5. **% female:** 43%.	Progressive keratoconus with progressive corneal steepening of > 1.00 D in keratometry, plus documented progression of increasing myopia and/or astigmatism over a period of 3 or more months.	**Anaesthesia:** PRK epithelial removal with topical 1% proparacaine. **Preop riboflavin:** 0.1% riboflavin sodium phosphate ophthalmic solution applied every 2 minutes. **Operative riboflavin:** Not Applicable. **Diameter of corneal removed:** 5.5mm. **UV A strength and WL and time:** 370nm at 3mW/cm^2. 30 minutes. **Postop care:** Ofloxacin for 10 days; steroids, sunglasses and Vit C for 60 days. Bandage contact lens removed at day 5 on re-epithelialisation.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Kanellopoulos **Year:** 2012 **Ref:** 56 **Country:** Greece	**Follow-up:** Minimum 28 months. **Study type:** Randomised comparative case series. **Primary aim of study:** Hypothesising if increasing UV light fluence equals a faster procedure (as the fluence time is shortened) and a shorter keratocyte exposure time and potentially less fibrocyte cornea damage caused. **SIGN grading:** 2-. **GRADE*:** Low.	**Number of patients:** 21. **Number of eyes:** 42. Group A: 1 eye per person. Group B: other 21 eyes. **Mean age:** Not Available. **% female:** Not Available.	Topographic and tomographic evidence of bilateral keratoconus (K>45 and/or inferior steepening greater than 1 D to the superior half of the cornea, and 1 diameter of tomographic cylinder progression over 1 year). Minimum cornea thickness > = 450 µm. Age >= 18.	**Anaesthesia:** Topical 1% proparacaine. **Preop riboflavin:** 0.1ml of 0.1% of riboflavin solution administered every 30 seconds for 5 minutes until de-epithelialised cornea bright yellow. **Operative riboflavin:** Not Applicable. **Diameter of corneal removed:** 6.5mm. **UV A strength and WL and time:** Group A: 7mW/cm². 15 minutes. Group B 3mW/cm². 30 minutes. Average WL 370 nm (range: 365 to 375). **Postop care:** Topical ofloxacin 4 x daily for 1 week; 1% prednisolone acetate 4 x daily for 1 month and 2 x daily for another month; 1000 mg vit C daily for 2 months. TG-PRK on same day or with 6 months delay.
Author: Kanellopoulos **Year:** 2009 **Ref:** 58 **Country:** USA	**Follow-up:** Mean 26 months (range: 18 to 36). **Study type:** Case series. **Primary aim of study:** Evaluate the safety and efficacy of a femtosecond laser-assisted technique for intrastromal administration of riboflavin and higher fluence UV A light in collagen CXL for keratoconus. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 10. **Number of eyes:** 10. **Mean age:** Not Available. **% female:** Not Available.	Topographic evidence of keratoconus (K>48D and/or inferior steeping >1D in the superior half of the cornea). Minimum corneal thickness >= 500µm and aged >=18 years old.	**Anaesthesia: T**opical 1% proparacaine. **Preop Riboflavin:** Riboflavin 0.1% administered twice with 25-gauge air cannula. **Operative riboflavin:** Not Available. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 7mW/cm^2. 365-375 nm. 15 minutes. **Postop care:** Ofloxacin and steroids for 1 week.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Hasson **Year:** 2011 **Ref:** 49 **Country:** Not Available	**Follow-up:** 19.5 months. **Study type:** Case series. **Primary aim of study:** Single arm study. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 26. **Number of eyes:** 31. **Mean age:** 29.3. **% female:** Not Available.	Not Available.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Not Available. **Operative riboflavin:** Not Available. **Diameter of corneal removed:** Not Available. **UV A strength and WL and time:** Not Available. **Postop care:** Not Available.

***** High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Table 6.2: Summary of outcomes in included papers on epithelium-off CXL with PRK

Author	Visual acuity	Topography	Refraction and astigmatism	Central corneal thickness	Adverse events
Author: Kanellopoulos **Year:** 2011 **Ref:** 57 **Country:** Greece and USA	UCVA improved in 27 eyes, was unchanged in 4 eyes and worsened in 1 eye.	Not Available.	Mean refractive error decreased by more than 2.5D in 27 eyes, increased by 0.75D in 3 eyes and remained stable in 2 eyes.	Not Available.	Not Available.
Author: Kymionis **Year:** 2010 **Ref:** 77 **Country:** Greece	CVA (LogMAR): preop 0.27 +/- 0.21; 12 months 0.18 +/- 1 0.17. No eye lost lines of visual acuity.	Not Available.	Not Available.	Value not reported but authors noted CCT not restored to preop thickness at 12 months.	At 1 month, mild posterior linear stromal haze in 13 of 28 eyes (46%). At 12 months, posterior haze had decreased density but had not completely disappeared.
Author: Kymionis **Year:** 2009 **Ref:** 79 **Country:** Greece	Measured in LogMAR. UCVA: preop 0.99 +/-0.81; final follow-up 0.16 +/- 0.15 (p=NA). BSCVA: preop 0.21 +/-0.19; final follow-up 0.11 +/- 0.15 (p=NA).	Measured in dioptres. Mean steep K: preop 48.20 +/-3.4; final follow-up 45.13 +/- 1.8 (p=NA).	Measured in dioptres. Mean SE: baseline -3.03 +/- 3.23; final follow-up -1.29 +/- 2.05 (p<0.01).	Not Available.	Not Available.
Author: Kymionis **Year:** 2011 **Ref:** 73 **Country:** Greece	Measured in LogMAR. UCVA: preop 0.21 +/- 0.18; postop 0.12 +/- 0.15. BCVA: preop 0.81 +/- 0.65; postop 0.35 +/- 0.36 (p<0.001).	Measured in dioptres. Steep K reduced by 2.35 (p<0.001). Flat k: preop 49.8 +/- 5.3; postop 47.46 +/- 4.3 (p<0.001). Flat K reduced by 1.18 (p=0.013).	Measured in dioptres. Manifest refraction SE: preop -2.3 +/- 2.8; postop - 1.08 +/- 2.41 (p<0.001).	Not Available.	Not Available.
Author: Tuwairqi **Year:** 2012	Measured in Log MAR. UCVA: preop 1.72 +/- 2.32; 12 months -0.01 +/- 0.072 (p<0.0001). CVA:	Measured in dioptres. Steep K: preop 46.15 +/- 1.74; 12 months 43.15 +/-	Measured in dioptres. SE: preop -2.23 +/- 1.58; 12 months -0.15 +/- 0.94	Not Available.	Not Available.

Author	Visual acuity	Topography	Refraction and astigmatism	Central corneal thickness	Adverse events
Ref: 112 **Country:** Saudi Arabia	preop -0.025 +/- 0.077; 12 months -0.04 +/- 0.063 (p<0.0001).	1.55 (p<0.0001). Flat K: preop 43.94 +/- 1.65; 12 months 41.89 +/- 1.64 (p=0.0027).	(p<0.0001). Manifest astigmatism: preop -2.23 +/- 1.32; 12 months -0.35 +/- 0.42 (p<0.0001).		
Author: Kanellopoulos **Year:** 2009 **Ref:** 59 **Country:** Greece	Measured in LogMAR. Sequential group. UCVA: preop 0.9 +/- 0.3; postop 0.49 +/- 0.25 (p=NA). BSCVA: preop 0.41+/- 0.25; postop 0.16 +/- 0.22 (p=NA). Simultaneous group. UCVA: preop 0.96 +/- 0.2; postop 0.3 +/- 0.2 (p=NA). BSCVA: preop 0.39+/- 0.3; postop 0.11 +/- 0.16. Simultaneous group superior for BSCVA (p< 0.001).	Measured in dioptres. Sequential group: mean reduction in K 2.75 +/- 1.3 (p=NA). Simultaneous group. Mean reduction in K 3.50 +/- 1.3 Simultaneous group superior (p<0.005).	Measured in dioptres. Sequential group. Mean reduction in SE refraction 2.50 +/- 1.2. Simultaneous group. Mean reduction in SE refraction 3.20 +/- 1.4 Simultaneous group superior (p<0.005).	Measured in µm. Sequential group. Mean CCT: preop 465 +/- 45; postop 395 +/- 25 (p=NA). Simultaneous group. Mean CCT: preop 475 +/- 55; postop 405 +/- 35 (p=NA).	Sequential group. Mean haze score 1.2 +/- 0.5. Simultaneous group. Mean haze score 0.5 +/- 0.3 (p=NA).
Author: Kanellopoulos **Year:** 2012 **Ref:** 56 **Country:** Greece	Measured in Snellen lines. 7mW/cm^2 Group. UCVA: preop 20/60; postop 20/38. CVA: preop 20/30; postop 20/25. 3mW/cm^2 Group. UCVA: preop 20/62; postop 20/40. CVA: preop 20/30; postop 20/25 (p=NA).	Measured in dioptres. 7mW/cm^2 Group. Change in steepest K: -3.4 (range: -1.6 to -4.1). 3mW/cm^2 Group. Change in steepest K: -2.9 (range: -1.7 to –3.8) (p=NA).	Measured in dioptres. 7mW/cm^2 Group. Change in refractive cylinder: -2.9 (range -1.5 to –3.4). Change in SE: -2.5 (-1.4 to -3.1). 3mW/cm^2 Group. Change in refractive cylinder: -2.8 (range -1.6 to – 3.3). Change in SE: -2.3 (-1.3 to -2.9) (p=NA).	Not Available.	9 patients had delayed epithelial healing but there were no complications.
Author: Kanellopoulos **Year:** 2009 **Ref:** 58 **Country:** USA	UCVA: preop 20/40.5; postop 20/32.5.	Measured in dioptres. Mean K: preop 48.7; postop 47.9.	Not Applicable.	Preop = 519 µm, postop = 521 µm.	None.

Author	Visual acuity	Topography	Refraction and astigmatism	Central corneal thickness	Adverse events
Author: Hasson **Year:** 2011 **Ref:** 49 **Country:** Not Available	Measured in LogMAR. UCVA decreased by 0.46 (p<0.001). BCVA decreased by 0.084 (p<0.001).	Measured in dioptres. Steep keratometry fell by 2.35D (p<0.001) and flat keratometry fell by 1.18 (p=0.013).	Not Reported.	Not Reported.	Not Reported.

6.5 QUALITATIVE SUMMARY OF PATIENT OUTCOMES

Table 6.2 details the patient outcomes of interest for this review of epithelium-off CXL with PRK. No intraocular pressure outcomes were reported. Each of the outcomes is now examined, reporting first the results of the randomised comparative case series (56) and then the other studies.

6.5.1 Visual Acuity

The randomised study (56) compared CXL with an increased light fluence of 7 mW/cm^2 for 15 minutes (group A) with the standard UV A light fluence of 3 mW/cm^2 for 30 minutes (group B). In all eyes, 50 µm of epithelium was removed by PRK. The paper reported that at 24 months:

- Uncorrected VA improved from 20/60 to 20/38 and corrected VA from 20/30 to 20/25 Snellen lines in group A;
- Uncorrected VA improved from 20/62 to 20/40 and corrected VA from 20/30 to 20/25 Snellen lines in group B.

No p-values were provided.

The comparative study of CXL and PRK on the same day and with a 6-month gap (59) found that the simultaneous group had the bigger improvement in both uncorrected VA (0.66 versus 0.41 LogMAR) and in corrected VA (0.28 versus 0.25 LogMAR). Statistical comparison reported that the simultaneous group had performed superiorly with a better BSCVA ($p<0.001$).

At 12 months, 3 papers (77, 79,112) reported:

- A mean improvement of 1.3 in corrected VA;
- A 0.1 improvement in best corrected vision (77) and best spectacle-corrected vision (79);
- A mean improvement of 0.04 in corrected VA from 2 papers (79 and 112) (all measured using LogMAR).

The values reported in one paper (112) were statistically significant.

Three remaining studies reported longer term results at 26 months (58), and 19.5 months (49, 73). From 2 studies (49, 73) there was a mean improvement in uncorrected VA of 0.28 LogMAR, and a 0.27 LogMAR improvement in corrected VA. All results were statistically significant. The other study (58) reported an improvement in Snellen lines from 20/40.5 to 20/32.5.

Conclusion

This evidence, albeit of low to very low quality, suggests epithelium-off CXL with PRK improves VA at 12 and 24 months.

6.5.2 Topography

Results from the randomised study (56) at 24 months reported a reduction of 3.4 D in the Max K value in group A and a reduction of 2.9 D in group B. No p-values were provided.

The comparative study of CXL and PRK on the same day and with a 6-month gap (59) found that the simultaneous group had the bigger improvement in mean K (3.5 D versus 2.8 D); this was not significant.

At 12 months, 2 papers (79,112) reported a mean improvement of 3.0 D in Max K; one also reported a 2.1 D improvement in Min K (112). Both values in the paper reporting Max K and Min K values (112) were statistically significant.

Longer term follow-up in 1 study (73) showed a reduction in 'steep and flat keratometry' of 2.35 D at 19.5 months ($p<0.05$). Another paper (49) reported similar reductions in Max K and Min K at 24 months: 2.35 D for max K and 1.2 D for Min K. One paper (58) reported a reduction in mean K of 0.8 D.

Conclusion

This evidence, albeit of low quality, suggests epithelium-off CXL with PRK reduces the curvature of the anterior surface of the cornea at 12 and 24 months.

6.5.3 Astigmatism and Refraction

Results from the randomised study (56) at 24 months showed reductions in spherical equivalence of 2.5 D and 2.3 D in groups A and B, respectively. The reductions in refractive cylinder change were 2.9 D and 2.8 D, respectively. No p-values were provided.

The simultaneous group also showed the greater improvement in spherical equivalent refraction compared with the sequential group (3.2 D versus 2.5 D) (59).

At 12 months, there was a mean reduction in spherical equivalence of 1.9 D from 2 papers (79, 112) ($p<0.05$ in both papers). The reduction of 1.15 D at 24 months reported in another paper (73) was also statistically significant. No other papers reported this parameter.

Conclusion

This evidence, albeit from low quality evidence, suggests epithelium-off CXL with PRK improves spherical equivalence values at 12 and 24 months.

6.5.4 IOP, Central Corneal Thickness and Adverse Events

No results were reported for IOP. One paper (59) reported that the change in central corneal thickness was identical in both groups (70 µm). Complications reported in these papers were grouped with other CXL-Plus papers and are reported in Section 7.3.

6.6 CONCLUSIONS ON CXL WITH PRK

The evidence from 9 studies, seven graded as very low quality, suggests that CXL with PRK improves VA, reduces the curvature of the anterior surface of the cornea, and improves spherical equivalence at 12 and 24 months. The comparative retrospective study suggests there is no benefit from delaying PRK compared with undertaking the procedures simultaneously.

Section 7: Epithelium-off CXL with PIOL

7.1 NUMBER, TYPE AND QUALITY OF INCLUDED PAPERS

This section contains one case study (54) which evaluated the safety, efficacy and stability of the artier foldable antenor iris claw phakic intraocular lens (PIOL) following CXL in 11 eyes with progressive keratoconus. It was set in Peru and included 11 patients with a mean age of 29 years, of whom 46% were female.

CXL was conducted 6 months prior to the insertion of the PIOL and the mean follow-up was 6 months after PIOL.

The paper was a case series with a SIGN grading of 3 and a GRADE classification of very low.

Details of the study, patients, procedures and patient outcomes are provided in Tables 7.1 and 7.2.

Table 7.1: Study and intervention characteristics of included papers of epithelium-off CXL with PIOL

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Izquierdo **Year:** 2011 **Ref:** 54 **Country:** Peru	**Follow-up:** 6 months after CXL and 6 months after PIOL. **Study type:** Case series. **Primary aim of study:** Evaluate the safety, efficacy and stability of the artifex foldable antenor iris claw PIOL following CXL in select cases of progressive keratoconus.	**Number of patients:** 11. **Number of eyes:** 11. **Mean age:** 29.09 +/- 4.54. **% female:** 46%.	Progressive keratoconus; no corneal opacities or scarring; CCT >450 µm; endothelial cell count >2500 cells/mm²; anterior chamber depth >3.2 mm from epithelium to anterior capsule; spherical equivalent refraction >4.50 D; low quality of vision and contact lens intolerance.	**Anaesthesia:** Proparacaine hydrochloride 0.5% drops on eye every 5 minutes for 3 doses prior to procedure. **Preop riboflavin:** Riboflavin 0.1% solution instilled every 5 minutes for 30 minutes. **Operative riboflavin:** 9mm. **Diameter of corneal removed:** Riboflavin drops applied every 5 minutes or sooner if cornea surface appeared visibly dry. **UV A strength and WL and time:** UV A strength 3.0 +/- 0.3mW/cm². 30 minutes. **Postop care:** Bandage soft contact lens for 4 days. Acetaminophen for 3 days; ofloxacin for 7 days; ketorolac tromethamine for 5 days fluorometholone for 5 weeks after contact lens removed. **Subsequent procedures:** PIOL.

Table 7.2: Summary of outcomes in included papers on epithelium-off CXL with PIOL

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
Different interventions							
Author: Izquierdo **Year:** 2011 **Ref:** 54 **Country:** Peru	Preop UVA 1.40 LogMAR; 1.16 6 months (p=0.04) after CXL; 0.16 6 months after PIOL (p<0.001) p=0.04: CDVA preop 0.14 LogMAR; 0.12 (p=0.16) 6 months after CXL; 0.04 6 months after PIOL (p<0.001). UDVA gain of 5 lines or more 6 months after PIOL and all patients had 20/40 vision or better.	Max K: 6 months after CXL fell by 1.27D (p=0.02) and 6 months after PIOL fell by 2.14 (p<0.001). Min K: 6 months after CXL increased by 0.24D (p=0.63); 6 months after PIOL fell by 1.17D (p=0.02).	Mean spherical value fell 0.45 D (p=0.03) and 5.43 D (p<0.001) 6 months after CXL and PIOL respectively. Cylinder value fell 0.16 D (p=0.13) and 0.55 D after CXL and PIOL respectively (p=0.04).	Not Applicable.	Not Applicable.	None; mild haze in 2 patient resolved in 15 days no drugs.	Not Applicable.

7.2 QUALITATIVE SUMMARY OF PATIENT OUTCOMES

7.2.1 Visual Acuity

Uncorrected VA improved by 0.24 LogMAR 6 months after CXL and by 1.24 LogMAR 6 months after the PIOL procedure; both values were statistically significant. Corrected VA improved by 0.02 LogMAR 6 months after CXL and by 0.1 LogMAR 6 months after PIOL.

7.2.2 Topography

Max K values reduced by 1.2 D at 6 months after CXL and by 2.14 D 6 months after PIOL; the equivalent values for Min K were an increase of 0.24 D at 6 months but a decrease of 1.17 D at 12 months. All values except the increase of 0.24 D were statistically significant.

7.2.3 Astigmatism and Refraction

The sphere values fell by 0.45 D 6 months after CXL and by 5.43 D 6 months after PIOL, both changes were statistically significant. Cylinder values fell by 0.16 D and 0.55 D at the 2 periods, with the latter value being statistically significant.

7.2.4 IOP, Central Corneal Thickness and Adverse Events

No values for IOP or central corneal thickness were reported. Complications were grouped with other CXL-Plus papers and are reported in Section 7.3.

7.2.5 Conclusion on Epithelium-off CXL with PIOL

This limited evidence from only 11 eyes showed efficacy in the main parameters but further research with more patients, a comparator arm and longer follow-up is required.

7.3 ADVERSE EVENTS FOR CXL-PLUS PROCEDURES

The various complications reported in the studies of epithelium-off with CXL and intrastromal corneal ring segments (ICRS), epithelium-off CXL and photorefractive keratectomy (PRK) and epithelium-off CXL with PIOL were grouped.

Corneal haze

- Stromal haze in all eyes, more marked and persistent in group with same day CXL and ICRS but finally resolved in both groups (29);
- Corneal haze intensity: 12 out of 15 patients; all cases of stromal haze resolved without sequelae (28); the different groups had different laser power settings;
- Corneal haze in all cases in the early postoperative period, resolved over time though in some cases corticosteroid therapy had to be changed (3);
- Mild posterior linear stromal haze at 1 month in 13 of 28 eyes (46%); at 12 months, posterior haze had decreased in density but did not completely disappear (77);

- Mild haze in 2 of 11 patients resolved in 15 days without any change in medication (54).

Corneal oedema

- Slight sub-epithelial and stromal edema with cotton like ring-shaped stromal opacities in 8 (18.6%) eyes 1 month after CXL; this disappeared within 3 months (17).

Perforation

- Anterior chamber perforation in 2 of 39 eyes: 1 eye (non-CXL group) presented on the first postoperative day with local corneal oedema evident at the temporal segment; the segment was explanted; the other eye (non-CXL group) presented on the seventh postoperative day with anterior chamber perforation in the temporal segment, which was explanted (21).

Other

- Delayed epithelial healing completed by postoperative day 9 in 9 patients (56);
- Very minimal intracorneal channel deposits in 1 eye in group 1 (visually insignificant) (29);
- Minimal intracorneal channel deposits developed in 1 eye in group 1; they did not affect the patient's vision (29).

In conclusion, haze was reported as a frequent event for many patients but usually resolved after several weeks. The serious event of perforation was in a control group not exposed to CXL.

Section 8: Transepithelial (Epithelium-on) CXL with Other Interventions

8.1 NUMBER OF INCLUDED PAPERS

Six studies met the inclusion criteria and provided information on 10 or more patients with more than 6 months follow-up for transepithelial (epithelium-on) CXL either by itself (24, 32, 83, 110) or coupled with other interventions (27, 113). Four were prospective case studies (24, 27, 32, 83) and two were retrospective case studies (110, 113).

Three studies included between 10 and 20 patients (27, 32, 113), one included between 21 and 40 patients (24), and two contained between 51 and 60 patients (83, 110). One paper was set in Europe (110), one in Iran (24), one in Egypt (27) and one in the USA (113), and two did not report geographical setting.

Four papers reported that the mean age of patients ranged from 20 to 30 years (24, 27, 32, 83), whilst 2 papers reported a mean age of over 30 years (110, 113). Five papers reported the proportion of participants that were female (15% to 50%); one paper did not report the proportion of females (113).

All studies were published in 2010 or later.

Follow-up varied from 6 months (24, 27), to 12 months (83, 110), 18 months (32) and 3 years (113).

Details are provided in Table 8.1.

8.2 QUALITY OF PAPERS AND STUDY TYPE

All 6 included studies were case series, of which two were comparative case series (32, 83) and two were retrospective case series (110, 113). Two (32, 83) of the papers were given a SIGN grading of 2- and a GRADE category of low, and the remaining four (24, 27, 110, 113) a SIGN grading of 3 and a GRADE category of very low.

8.3 SUMMARY OF PATIENT AND PROCEDURAL DIFFERENCES ACROSS PAPERS

For the 4 studies of transepithelial (epithelium-on) CXL only with no additional intervention, the patients were comparable in terms of age but clinical presentation varied between early presentation of keratoconus in 1 study (24) and progressive keratoconus in 3 studies (32, 83, 110).

For the 2 studies of additional interventions, a comparison of patient groups is of limited value as the procedures were different. The intervention reported in 1 paper (27) was ICRS followed by transepithelial (epithelium-on) CXL after at least 3 months of implantation. The intervention reported in the other paper (113) was transepithelial CXL and same-day ICRS.

Details of patients and procedures in the included studies are provided in Table 8.1.

Table 8.1: Study and intervention characteristics of included papers of transepithelial (epithelium-on) CXL with other interventions

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Derakhshan **Year:** 2011 **Ref:** 24 **Country:** Iran	**Follow-up:** 6 months. **Study type:** Case series. **Primary aim of study:** To assess the efficacy of CXL and UV A radiation for treatment of early keratoconus. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 22. **Number of eyes:** 31. **Mean age:** 22.3 +/- 6.8. **% female:** 50%.	Early keratoconus, no autoimmune disease, central corneal thickness >400 µm.	**Additional intervention:** None. **Anaesthesia:** Topical anaesthesia. **Preop riboflavin:** Riboflavin (0.1% in 20% dextran) was instilled every 3 minutes for 30 minutes. **Operative riboflavin:** Every 4 to 5 minutes. **Diameter of corneal removed:** Not Available. **UV A strength and WL and time:** 3mW/cm^2. 370 nm. 30 minutes. **Postop care:** After cross-linkage, a topical antibiotic was prescribed for 5 days.
Author: El Awady **Year:** 2011 **Ref:** 27 **Country:** Egypt	**Follow-up:** Mean 5.67 +/- 1.89 months. **Study type:** Case series. **Primary aim of study:** To assess the outcome of CXL in keratoconus eyes after implantation of Kera intracorneal ring segments. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 13. **Number of eyes:** 21. **Mean age:** 21.36. **% female:** 39%.	Absence of corneal scarring; corneal thickness >400 µm; endothelial cell count >3000 per mm^2.	**Additional intervention:** ICRS. **Anaesthesia:** Benoxinate hydrochloride 0.04% every 5 minutes for 30 minutes. **Preop riboflavin:** Riboflavin 0.1% and 20% dextran every 2 minutes for 30 minutes. **Operative riboflavin:** Every 2 minutes. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2. 370 nm. 30 minutes. **Postop care:** Bandage contact lens. Topical ofloxacin 4 times a day for 10 days and prednisolone 4 times a day for 60 days.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Filippello **Year:** 2011 **Ref:** 32 **Country:** Not Available.	**Follow-up:** 18 months. **Study type:** Comparative case series. **Primary aim of study:** To evaluate the clinical effects of transepithelial CXL in patients with bilateral keratoconus. **SIGN grading:** 2-. **GRADE*:** Low.	**Number of patients:** 20. **Number of eyes:** 20. **Mean age:** 27. **% female:** 30%.	Corneal thickness >380 µm; keratoconus grades II or III; evidence of progression [increase in max cone apex curvature of >1 D, reduction in CCT >2% and/or increase in central cornea astigmatism of >1 D over 6 months].	**Additional intervention:** None. **Anaesthesia:** Oxybuprocaine hydrochloride (0.2%) 1 drop every 5 minutes, 20 minutes prior to intervention. **Preop riboflavin:** Enhanced riboflavin (0.1%) instilled 30 minutes before exposure. **Operative riboflavin:** Every 3 to 5 minutes. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** UV A strength 3mW/cm^2. 30 minutes. **Postop care:** Single dose norfloxacin, 1 drop 3 times a day. Sodium hyaluronate 0.15% with amino acids, 1 drop 3 times a day for 20 days, and a liposome spray over closed lids 3 times a day for 20 days.
Author: Leccisotti **Year:** 2010 **Ref:** 83 **Country:** Not Available.	**Follow-up:** 12 months. **Study type:** Comparative case series. **Primary aim of study:** To evaluate the clinical effects of transepithelial CXL on keratoconus eyes. **SIGN grading:** 2-. **GRADE*:** Low.	**Number of patients:** 51. **Number of eyes:** 51. **Mean age:** 26.9 +/- 6.3. **% female:** 35%.	Age 18 to 40 with no autoimmune disease or diabetes, non-smokers, keratoconus progressive over 12 months, endothelial cell count >2000/mm^2 and CCT >400µm at the thinnest point.	**Additional intervention:** Eyes pre-treated with substances enhancing epithelial permeability. **Anaesthesia:** Ribomicin eye drops every 15 minutes for 3 hours. **Preop riboflavin:** Riboflavin 0.1% solution in 20% dextran and oxybuprocaine every 5 minutes for 30 minutes. **Operative riboflavin:** Every 5 minutes for 30 minutes. **Diameter of corneal removed:** 7.5mm. **UV A strength and WL and time:** UV A strength 3mW/cm^2. 30 minutes. **Postop care:** Eye rinsed with salt solution and a 3-day treatment with gentamicin and unpreserved 0.1% hyaluronate artificial tears.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Stojanovic **Year:** 2012 **Ref:** 110 **Country:** Norway	**Follow-up:** 12 months. **Study type:** Retrospective case series. **Primary aim of study:** To evaluate the efficacy and safety of transepithelial CXL using a multifactorial approach to achieve proper stromal riboflavin saturation. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 53. **Number of eyes:** 61. **Mean age:** 32 +/- 10. **% female:** 15%.	Progression of keratoconus in previous 12 months; CCT >= 400 µm at thinnest point; age between 18 and 45; keratoconus classified between 2 and 4.	**Additional intervention:** None. **Anaesthesia:** Proparacaine 0.5%, 2 drops then 1 drop every minute for 5 minutes. **Preop riboflavin:** Riboflavin 0.5% solution 2 drops every minute until saturation after at least 25 minutes. **Operative riboflavin:** Not Available. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm². 365 nm. 30 minutes. **Postop care:** Atropine and gentamicin applied. Soft bandage contact lens for 12 to 18 hours. Dexamethasone and chloromycetin for 7 days. Artificial tears used as needed.
Author: Vicente **Year:** 2010 **Ref:** 113 **Country:** USA	**Follow-up:** 3 years. **Study type:** Retrospective case series. **Primary aim of study:** To analyse factors that correlate with best corrected visual acuity improvement after corneal implants and trans-epithelial CXL with riboflavin-carboxymethylcellulose. **SIGN grading:** 3. **GRADE*:** Very low.	**Number of patients:** 10. **Number of eyes:** 14. **Mean age:** 35. **% female:** Not Available.	Keratoconus or keratectasia who received both CXL with riboflavin-carboxymethylcellulose and corneal implants on same day.	**Additional intervention:** ICRS. **Anaesthesia:** Tetracaine every 5 minutes for 15 minutes. **Preop riboflavin:** Every 5 minutes for 15 minutes. **Operative riboflavin:** Every 3 minutes for 30 minutes. **Diameter of corneal removed:** Not Applicable. **UV A strength and WL and time:** 3mW/cm^2. 370 nm. 30 minutes. **Postop care:** Not Available.

***** High: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low: Any estimate of effect is very uncertain.

Table 8.2: Summary of outcomes in included papers on transepithelial (epithelium-on) CXL with other interventions

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
Author: Derakhshan **Year:** 2011 **Ref:** 24 **Country:** Iran	Mean Snellen UCVA was 0.31 +/-0.21 preop and 0.51 +/- 0.27 postop. Mean Snellen BSCVA was 0.72 +/- 0.18 preop and 0.89 +/- 0.20 postop. Comparison of preop and 6-month follow-up data showed an increase of 2.0 +/- 1.8 lines in UCVA (p<0.001) and 1.7 +/- 1.1 lines in BSCVA (p< 0.001).	Preop max and mean K values (D) were 51.21 +/- 4.97 and 48.38 +/- 4.24 respectively. Postop max and mean K values (D) were 50.56 +/- 3.87 (p=0.007) and 47.87 +/- 3.85 (p=0.005) respectively.	Mean SE refractive error (D) was -5.13 +/-3.67 preop and -4.58 +/- 3.27 postop (p=0.004).	Mean IOP (mmHg) was 13.5 +/- 2.1 preop and 13.6 +/- 2.2 postop (p =0.565).	Mean CCT (µm) was 485 +/- 29.6 before treatment and 494 +/- 30.8 after; CCT increased by an average of 9.1 +/- 11.2 µm (p<0.001).	None.	Not Available.
Author: El Awady **Year:** 2012 **Ref:** 27 **Country:** Egypt	UCVA: preop 0.05 +/- 0.02; postop both 0.23 +/- 0.17 (p=NA). BCVA: preop 0.18 +/- 0.1; postop both 0.41 +/- 0.18	Mean K: preop 48.5 +/- 2.8 D; postop both 45.9 +/- 2.9 D (p=NA).	Cylindrical refraction (D): preop -4.9 +/- 0.97; postop both -2.7 +/- 1.3. SE: preop -6.3 +/- 2.6; postop both -3.4 +/- 2.8 (p=NA).	Not Available.	Not Available.	None Reported.	Not Available.
Author: Filippello **Year:** 2012 **Ref:** 32 **Country:** Not Available	UCVA: CXL: before 0.71 +/- 0.12; 18 months 0.48 +/- 0.34 (p>0.05). Control: before 0.84 +/- 0.23; 18 months 0.98 +/- 0.41 (p=NA). CVA: CXL: before 0.35 +/- 0.23; 18 months 0.24 +/- 0.77 (p>0.05). Control: before 0.46 +/- 0.21; 18	Apical K CXL: before 59.12 +/- 1.10; 18 months 48.05 +/- 0.21 (p<0.05). Control: before 58.89 +/- 2.02; 18 months 52.12 +/- 0.47 (p=NA).	Not Available.	Not Available.	Not Available.	Hypermia of conjunct-iva and mild foreign body sensation (resolved within 24	Central K: CXL: before 51.02 +/- 1.10; 18 months 48.08 +/- 0.21(p=NA). Control: before 51.12 +/-1.02; 18 months 52.12 +/- 0.47 (p=NA). Sim K flat: CXL: before 45.13 +/- 0.97; 18 months 44.43 +/- 0.35 (p=NA). Control: before 46.05

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
	months 0.64 +/- 0.39 (p=NA).					hours in 8 patients (40%).	+/- 0.99; 18 months 60.93 +/- 1.21 (p=NA). Sim Ks: CXL: before 5.89; 18 months 3.62 (p=NA). Control: before 5.07; 18 months 5.24 (p=NA).
Author: Leccisotti **Year:** 2010 **Ref:** 83 **Country:** Not Available	CVA (LogMAR): mean difference -0.036 +/- 0.049 for CXL (p<0.05) and 0.039 +/- 0.032 (p<0.05) for control.	K apex (D): mean difference 0.51 +/- 7.79 for CXL (p>0.05) and 1.61 +/-6.28 for control (p>0.05).	SE (D): mean difference -0.35 +/- 0.66 for CXL (p<0.05) and 0.83 +/- 0.88 for control (p<0.05).	Not Available.	Not Available.	None.	Av Sim K (D): mean difference -0.1 +/- 1.44 for CXL (p>0.05) and 0.88 +/-2.35 for control (p>0.05). Index of surface variance mean difference 0.9 +/- 4.69 (p>0.05) compared to 5.3 +/- 7.3 for control (p>0.05)
Author: Stojanovic **Year:** 2012 **Ref:** 110 **Country:** Norway	UCVA (Snellen): preop 20/133 +/- 20/57; 12 months 20/67 +/- 20/42 (p=0.00). CDVA (Snellen): preop 20/32 +/- 20/33; 12 months 20/24 +/- 20/28 (p=0.00).	Mean K (D): preop 46.97 +/- 5.21; 12 months 46.77 +/- 5.31 (p=0.06). Max K: preop 55.55 +/- 6.01; 12 months 54.98 +/- 5.78 (p=0.02).	Sphere (D): preop 0.05 +/- 3.03; 12 months 0.21 +/- 2.43 (p=0.61). SE: preop -1.97 +/- 3.19; 12 months -1.23 +/-2.46 (p=0.05). Cylinder: preop -4.03 +/- 2.53; postop -2.88 +/- 2 (p=0.00).	Not Available.	CCT (µm): preop 451 +/-45; 12 months 460 +/- 47 (p=0.15); n=50 out of initial n=61.	No serious complications in the follow-up period.	Not Available.
Author: Vicente **Year:** 2010 **Ref:** 113 **Country:** USA	The mean BCVA (Snellen chart) after 3 years improved from 0.24 to 0.16 +/- 0.2 LogMAR (range: 0 to 0.54) (p=0.34).	K-steep: 48.37 +/- 2.94 D preop changed to 45.86 +/- 14.06 D (p=0.0054). K-flat: 43.29 +/- 3.13 D preop changed to 42.21 +/- .31 (p=0.0114). K-average:	Not Applicable.	Not Available.	Not Available.	None Reported.	Not Available.

Author	Visual acuity	Topography	Refraction and astigmatism	Intraocular pressure	Central corneal thickness	Adverse events	Other outcomes
		45.83 +/- 12.45D changed to 44.03 +/- 3.58 D p=0.0023). K-power: improved from 47.33 +/- 12.81 D preop to 45.04 +/- 3.32 D (p=0.0038).					

8.4 QUALITATIVE SUMMARY OF PATIENT OUTCOMES

Table 8.2 details the patient outcomes of interest for this review for transepithelial (epithelium-on) CXL. Each of the outcomes in now examined, reporting the results of the 4 papers using transepithelial (epithelium-on) CXL only techniques and then the 2 papers of CXL with same-day corneal implants (113) and ICRS followed at 4.5 months by transepithelial (epithelium-on) CXL (27).

8.4.1 Visual Acuity

The results for the 4 studies using transepithelial (epithelium-on) CXL reporting change in VA were:

- At 6 months: an improvement of 0.20 and 0.17 LogMAR (24) in uncorrected and best spectacle-corrected VA;
- At 12 months: an improvement of 0.036 in corrected VA, an improvement in Snellen lines from 20/32 to 20/24 (110) and an improvement in uncorrected VA from 20/133 to 20/67 Snellen lines (110); corrected VA also improved by 0.036 LogMAR in a second study (83);
- At 18 months: uncorrected VA improved by 0.23 and corrected VA by 0.11 LogMAR (32).

The case series of patients with transepithelial (epithelium-on) CXL with same-day corneal implants reported an improvement at 3 years in corrected VA of 0.08 LogMAR (113). The study of ICRS followed several months later by CXL (27) reported improved uncorrected VA after ICRS of 0.18 which was maintained 6 months after CXL, whilst corrected VA improved by 0.11 after ICRS and by a further 0.02 after CXL (LogMAR).

Conclusion

This low grade evidence suggests some improvement in VA from using transepithelial (epithelium-on) CXL.

8.4.2 Topography

The results for the 4 studies using transepithelial (epithelium-on) CXL reporting change in keratometry (K) values were:

- At 6 months: an improvement of 0.7 D and 0.5 D in Max and mean K, respectively (24), which was statistically significant;
- At 12 months: an improvement of 0.2 in mean K (83,110) and 0.2 in Max K (110);
- At 18 months: an improvement of 11.1 in mean K (32) which was statistically significant.

The case series (113) of patients with transepithelial (epithelium-on) CXL with same day corneal implants reported improvements in maximum, mean and minimum K values at 36 months; all were statistically significant. The study of ICRS followed several months later by CXL (27) reported an improved mean K after ICRS of 2.5 which was maintained 6 months after CXL.

Conclusion

This low grade evidence suggests some improvement in K values from using transepithelial (epithelium-on) CXL.

8.4.3 Astigmatism and Refraction

The results for the 3 studies using transepithelial (epithelium-on) CXL reporting change in astigmatism and refraction were:

- At 6 months: an improvement of 0.6 D (24) in mean spherical equivalent refractive error which was statistically significant;
- At 12 months: a mean improvement of 0.5 D in mean astigmatism (83,110), which was statistically significant, and improvements in cylinder and sphere of 1.2 D and 0.2 D, respectively (110).

The study of ICRS followed several months later by CXL (27) reported improved sphere and cylinder values after ICRS of 2.8 D and 2.1 D, respectively, which were maintained after CXL.

Conclusion

This low grade evidence suggests some improvement in astigmatism and refraction from using transepithelial (epithelium-on) CXL.

8.4.4 Central Corneal Thickness

Only 2 papers reported on this parameter. Both reported an increase in CCT of 9 µm at 6 months (24) and 12 months (110).

8.4.5 IOP

One paper reported a reduction in IOP of 0.1 mmHg at 6 months (24).

8.5 ADVERSE EVENTS TRANSEPITHELIAL (EPITHELIUM-ON) CXL

Only 2 papers reported complications. One paper (32), which provided the most information, included 20 patients with an 18-month follow-up, whilst the other paper (83) reported on 51 patients at 12 months follow-up.

Pain:

- Pain was assessed by an interview 3 days after surgery in 16 patients. Patients graded pain on a 10-point scale with 0 being no pain and 10 maximum pain. The mean pain score was 0.43 (SD 0.51) (range: 0 to 1) (83). The Discussion implies such a pain score supports the hypothesis that pain levels are lower with this technique than standard epithelium-off CXL.
- No significant ocular pain (32).

Corneal haze:

- Transient subepithelial haze grade 0.5 in 2 of 51 cases; this disappeared at 1 month follow-up and did not affect visual acuity (83);
- No corneal haze (32).

Other:

- Conjunctival hyperaemia and mild foreign body sensation (resolved spontaneously) within the first 24 hours in 8 patients (40%) (32);
- Photophobia in 2 patients (10%); this resolved spontaneously after 4 days (32).

8.6 CONCLUSIONS ON CXL USING TRANSEPITHELIAL (EPITHELIUM-ON) CXL

The evidence on VA, topography and astigmatism/refraction suggests some efficacy from this procedure but, in the absence of comparative data and preferably randomised studies, no conclusions can be drawn.

Section 9: Limitations and Conclusions

9.1 LIMITATIONS

This review of the efficacy and safety of CXL has several limitations. The main limiting factor preventing the inclusion of additional studies in the meta-analyses was the lack of consistent reporting of the key parameters of corneal topography, refraction, and visual acuity across time periods. Where possible the measures used in the studies were grouped. However, it was still not possible to pool many of the results. This weakened the evidence base provided by meta-analyses and, hence, confidence in the results.

Meta-analyses of the epithelium-off CXL papers of the difference between control and intervention arms could only be undertaken for visual acuity and astigmatism and these included a very limited number of papers. As such, the majority of the meta-analysis evidence could only analyse the change from baseline following intervention. Without a matched counterfactual it is impossible to know what the actual effects of the procedure were.

Another limiting factor was the high level of heterogeneity reported for many of the meta-analyses. This may arise because in some instances there were just a few papers, or possibly the patient populations, technique or study design differed. The high heterogeneity and associated wide confidence intervals limits their usefulness in drawing conclusions from the data and generalising the findings to other settings.

There was an absence of long-term studies. Of the few which did provide longer term data the outcomes were usually reported by small numbers of the original cohort, with no indication of the reasons for drop-out. Thus, it is not possible to ascertain the duration of benefit from the procedure. Well-conducted long–term studies are required to establish the potential benefit of the procedure in avoiding, or at least delaying, corneal transplants.

No evidence was available on the benefit of repeat CXL. Hence, it is not possible to assess if CXL offers potential benefit should progression recur.

No information was available on whether the procedure improved quality of life for patients and enhanced their ability to conduct daily activities. Limiting benefit to the clinical end points may understate the value which patients and families place on the improvement experienced. It would also be useful to have some measure of the patient perspective on the procedure and follow-up.

Most of the evidence consisted of case series which described procedures and outcomes, but these cannot provide evidence of causal effect. The absence of a matched comparator was a weakness in most papers, including those RCTs which used fellow-eyes rather than a matched cohort. Other weaknesses included the poor reporting of drop-out rates and loss to follow-up. The direction of bias from such high rates is unknown.

Case series may also be prone to selection bias and observer bias, notably when selecting patients for the procedure and in reporting outcomes. Single surgeons in single centres may also introduce bias if they have specific skills or experience which will be difficult to replicate. Some papers also reported the early experiences of surgeons with the procedure. Over time the equipment and protocols have changed, which may be reflected in better efficacy and safety outcomes.

Many of the papers had small sample sizes raising concerns about whether they included sufficient patients to be able to detect meaningful effects of the procedure.

The one RCT by Hersh which gave rise to several papers had a cross-over period at 3 months for the control eyes. Thus, the results after that period did not have the benefit of a control, other than fellow-eyes.

The evidence has, in the main, been graded low or very low and the conclusions one can draw from it must be seen in that light.

9.2 CONCLUSIONS

This review describes the current evidence base for the efficacy and safety of CXL, alone, in combination with therapies designed to improve visual acuity (CXL-Plus), and as transepithelial (epithelium-on) CXL. The quality of the evidence and potential biases have been identified already as major limitations to informing robust conclusions.

Judging the strength of evidence also requires a view to be taken on:

- Quantity, quality, and consistency of evidence;
- External validity (generalisability) of studies;
- Directness of application to the target population for the NHS.

For the epithelium-off procedure there are a considerable number of descriptive case series and retrospective case series which consistently reported measures of visual acuity, astigmatism and topography that improved at follow-up compared to baseline. A material number of these values were statistically significant. Benefit has thus been reported repeatedly across papers. This is important given the progressive nature of the disease. However, the majority of these papers were assigned a grade of low or very low based on the trial design, absence of a comparator, often large drop-outs and incomplete reporting.

Analyses of the CXL-Plus interventions, particularly CXL with ICRS and with PRK, included fewer but possibly better quality papers. These also demonstrate consistent improvement in the three key parameters over at least a 1-year time horizon following the procedure compared to baseline. However, evidence on the timing and sequencing of procedures is small.

Evidence on transepithelial (epithelium-on) CXL was limited to 163 eyes and 4 papers, whilst the 2 papers with this procedure plus ICRS included an additional 35 eyes. Evidence of efficacy in visual acuity and topography was demonstrated.

Overall, evidence from topographic measures and pachymetry is that CXL strengthens and stabilises the cornea, can stop progression, and in some cases reverse progression, of keratoconus and keratectasia. The resultant flattening of the cone may improve the effectiveness of a contact lens and hence increase corrected visual acuity. It also may provide the opportunity to introduce other interventions such as ICRS which are designed to improve visual acuity.

CXL is also not without risk, but the majority of events resolve and the serious reported events may in part arise from poor surgical practice or poor patient compliance.

There remains considerable uncertainty about the duration of benefit, unsurprising given the technique was first piloted in 2003. However, delaying or preventing the need for corneal transplant could be highly valued by people with this disease.

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Appendix A

SEARCH STRATEGY

Search Strategy

Literature searches were conducted to identify relevant published, unpublished and grey literature evaluating photochemical CXL using riboflavin and UV A for keratoconus and keratectasia. The literature search strategy was developed in accordance with the guidance provided in Appendix B of the NICE Interventional Procedures Programme Process guide (92). It was agreed that the searches would be limited from year 2000 onwards. This was informed by the Canadian literature review (98) and an earlier literature review undertaken by NICE. These identified that the first published paper evaluating the effect of the cross-linkage methods on the progression of disease in patients with keratoconus was in 2003 (118).

The following databases / information sources were searched:

- MEDLINE and MEDLINE in process;
- EMBASE1;
- Cochrane Database of Systematic Reviews (CDSR);
- Database of Abstracts of Reviews of Effects (DARE);
- Health Technology Assessment (HTA) database;
- Cochrane Central Register of Controlled Trials (CENTRAL);
- NHS Economic Evaluation Database (NHS EED);
- Cinahl;
- Science Citation Index;
- Conference Proceedings Citation Index: Science (Web of Science);
- Inspec;
- ClinicalTrials.gov;
- Science Direct;
- ZETOC;
- WorldWideScience.org;
- International Clinical Trials Registry Platform (ICTRP);
- OAIster (Open Archives Initiative containing grey literature);
- OpenGrey;
- EuroScan;
- Nexis;
- National Institute for Health Research (NIHR);
- Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP).

The results of the searches are presented in Table A.1. Searching a number of databases produces a degree of duplication in the results. To manage this issue, the titles and abstracts of bibliographic records were downloaded and imported into EndNote bibliographic management software and duplicate records were removed using several algorithms.

Table A.1: Results of the searches

Database / information source	Records identified
MEDLINE and MEDLINE in process	674
EMBASE	824
Cochrane Database of Systematic Reviews (CDSR)	0
Database of Abstracts of Reviews of Effects (DARE)	1
Health Technology Assessment (HTA) database	4
Cochrane Central Register of Controlled Trials (CENTRAL)	24
NHS Economic Evaluation Database (NHS EED)	0
CINAHL	32
Science Citation Index (SCI-Expanded) / Conference Proceedings Citation Index: Science (CPCI-S)	936
Inspec	61
ClinicalTrials.gov	93
Science Direct	126
ZETOC	455
WorldWideScience.org	21
International Clinical Trials Registry Platform (ICTRP)	51
OAIster	16
OpenGrey	3
Euroscan	3
Nexis	73
National Institute for Health Research (NIHR)	3
Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP)	0
TOTAL	**3,400**
TOTAL after deduplication	**1,747**

Database Searches

Database / information source: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) 1946 to Present
Interface / URL: OvidSP
Search date: 30/10/12
Retrieved records: 674
Search strategy:

1	keratoconus.ti,ab.	3282
2	(keratectasia or keratoectasia).ti,ab.	170
3	ectasia$.ti,ab.	3388
4	keratoconus/	3070
5	((cone or conical) adj4 cornea$).ti,ab.	83
6	corneal stroma/	3617
7	dilatation, pathologic/ and exp cornea/	285
8	dilatation, pathologic/ and corneal diseases/	219
9	corneal ulcer/	4078
10	or/1-9	14282
11	collagen$.ti,ab.	147894
12	(crosslink$ or cross link$).ti,ab.	66270
13	cxl.ti,ab.	219
14	riboflavin.ti,ab.	6858
15	ultraviolet.ti,ab.	47231
16	(uncorrected VA or puva).ti,ab.	7226
17	cross-linking reagents/	19630
18	exp collagen/	93600

19	exp riboflavin/	10780
20	exp ultraviolet therapy/	6883
21	ultraviolet rays/	61108
22	photosensitizing agents/	8659
23	exp photochemotherapy/	11952
24	photosensiti$.ti,ab.	16464
25	photochemotherap$.ti,ab.	1746
26	oxidants, photochemical/	1841
27	photochemical processes/	2577
28	photochemistry/	20213
29	photochem$.ti,ab.	17852
30	phototherapy/	5177
31	phototherap$.ti,ab.	5366
32	or/11-31	389897
33	10 and 32	1440
34	animals/ not humans/	3705463
35	33 not 34	1002
36	limit 35 to yr="2000 -Current"	674

Database / information source: Embase 1974 to 2012 Week 43
Interface / URL: OvidSP
Search date: 30/10/12
Retrieved records: 824
Search strategy:

1	keratoconus.ti,ab.	3810
2	(keratectasia or keratoectasia).ti,ab.	187
3	ectasia$.ti,ab.	4281
4	keratoconus/	4460
5	((cone or conical) adj4 cornea$).ti,ab.	84
6	cornea stroma/	3377
7	endothelium damage/ and exp cornea/	57
8	endothelium damage/ and exp cornea disease/	30
9	cornea ulcer/ or cornea edema/	9835
10	or/1-9	21305
11	collagen$.ti,ab.	176800
12	(crosslink$ or cross link$).ti,ab.	74339
13	cxl.ti,ab.	223
14	riboflavin.ti,ab.	7890
15	ultraviolet.ti,ab.	49860
16	(uncorrected VA or puva).ti,ab.	9689
17	cross-linking reagent/	4956
18	exp *collagen/ or collagen fibril/ or collagen fiber/	56317
19	exp riboflavin/	12833
20	exp ultraviolet radiation/	84443
21	ultraviolet rays/	70316
22	*photosensitizing agent/	4138
23	*photosensitization/	2600
24	photosensiti$.ti,ab.	19572
25	photochemotherap$.ti,ab.	2395
26	corneal collagen cross linking/	33
27	post corneal collagen cross linking haze/	1
28	*phototherapy/	6476
29	photochem$.ti,ab.	22201
30	phototherap$.ti,ab.	7146
31	collagen cross linkage/	73

32	protein cross linking/	7825
33	or/11-32	414523
34	10 and 33	1675
35	limit 34 to yr="2000 -Current"	1059
36	limit 35 to animal studies	235
37	35 not 36	824

Database / information source: CDSR / DARE / HTA / CENTRAL / NHS EED
Interface / URL: Cochrane Library/Wiley - **Issue 10 of 12, Oct 2012 online**
Search date: 30/10/12
Retrieved records: 29
Search strategy:

#1	keratoconus:ti,ab,kw	141
#2	(keratectasia or keratoectasia):ti,ab,kw	2
#3	ectasia*:ti,ab,kw	27
#4	MeSH descriptor: [Keratoconus] explode all trees	68
#5	((cone or conical) near/4 cornea*):ti,ab,kw	0
#6	MeSH descriptor: [Corneal Stroma] explode all trees	119
#7	MeSH descriptor: [Dilatation, Pathologic] explode all trees	107
#8	MeSH descriptor: [Cornea] explode all trees	1327
#9	(#7 and #8)	8
#10	MeSH descriptor: [Corneal Diseases] explode all trees	856
#11	(#8 and #10)	309
#12	MeSH descriptor: [Corneal Ulcer] explode all trees	81
#13	(#1 or #2 or #3 or #4 or #5 or #7 or #9 or #11 or #12)	575
#14	collagen*:ti,ab,kw	3393
#15	(crosslink* or cross link*):ti,ab,kw	1486
#16	cxl:ti,ab,kw	12
#17	riboflavin:ti,ab,kw	345
#18	ultraviolet:ti,ab,kw	1686
#19	(uncorrected VA or puva):ti,ab,kw	602
#20	MeSH descriptor: [Cross-Linking Reagents] this term only	55
#21	MeSH descriptor: [Collagen] explode all trees	1638
#22	MeSH descriptor: [Riboflavin] explode all trees	186
#23	MeSH descriptor: [Ultraviolet Therapy] explode all trees	504
#24	MeSH descriptor: [Ultraviolet Rays] explode all trees	470
#25	MeSH descriptor: [Photosensitizing Agents] explode all trees	352
#26	MeSH descriptor: [Photochemotherapy] explode all trees	511
#27	photosensiti*:ti,ab,kw	670
#28	photochemotherap*:ti,ab,kw	637
#29	MeSH descriptor: [Oxidants, Photochemical] this term only	46
#30	MeSH descriptor: [Photochemical Processes] this term only	4
#31	MeSH descriptor: [Photochemistry] this term only	12
#32	photochem*:ti,ab,kw	739
#33	MeSH descriptor: [Phototherapy] this term only	560
#34	phototherap*:ti,ab,kw	1177
#35	(#14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34)	8476
#36	(#13 and #35)	29

Result subsets:
CDSR: 0
DARE: 1
HTA: 4
CENTRAL: 24
NHS EED: 0

Database / information source: CINAHL
Interface / URL: EBSCO
Search date: 30/10/12
Retrieved records: 32
Search strategy:

S27	S8 and S26	(32)
S26	S9 or S10 or S11 or S12 or S13 or S14 or S15 or S16 or S17 or S18 or S19 or S20 or S21 or S22 or S23 or S24 or S25	(8765)
S25	(MH "Phototherapy")	(1047)
S24	TI phototherap* OR AB phototherap*	(381)
S23	(MH "Oxidants, Photochemical")	(24)
S22	TI photochem* OR AB photochem*	(122)
S21	TI photosensiti* OR AB photosensiti*	(215)
S20	(MH "Photochemotherapy")	(196)
S19	(MH "Photosensitizing Agents")	(174)
S18	(MH "PUVA Therapy")	(65)
S17	(MH "Ultraviolet Therapy")	(105)
S16	(MH "Riboflavin")	(270)
S15	(MH "Collagen")	(2755)
S14	TI (uncorrected VA or puva) OR AB (uncorrected VA or puva)	(99)
S13	TI ultraviolet OR AB ultraviolet	(780)
S12	TI riboflavin OR AB riboflavin	(259)
S11	TI cxl OR AB cxl	(8)
S10	TI (crosslink* or cross link*) OR AB (crosslink* or cross link*)	(778)
S9	TI collagen* OR AB collagen*	(4150)
S8	S1 or S2 or S3 or S4 or S5 or S6 or S7	(358)
S7	(MH "Corneal Ulcer")	(28)
S6	TI pathologic dilatation N4 cornea* OR AB pathologic dilatation N4 cornea*	(0)
S5	TI corneal stroma OR AB corneal stroma	(15)
S4	TI ((cone N4 cornea*) or (conical N4 cornea*)) OR AB ((cone N4 cornea*) or (conical N4 cornea*))	(3)
S3	TI ectasia* OR AB ectasia*	(208)
S2	TI (keratectasia or keratoectasia) OR AB (keratectasia or keratoectasia)	(11)
S1	TI keratoconus OR AB keratoconus	(125)

Database / information source: Science Citation Index (SCI-Expanded) / Conference Proceedings Citation Index: Science (CPCI-S)
Interface / URL: Web of Knowledge
Search date: 30/10/12
Retrieved records: 936
Search strategy:

Databases=SCI-EXPANDED, CPCI-S Timespan=2000-01-01 - 2012-10-30
Lemmatization=On

11 936 (#10 AND #7) AND Language=(English)
10 302,858 (#9 OR #8) AND Language=(English)
9 60,424 (TS=(photosensiti* or photochem* or phototherap*)) AND Language=(English)
8 249,449 (TS=(collagen* or crosslink* or "cross link" or "cross linking" or "cross linked" or cxl or riboflavin or ultraviolet or uncorrected VA or puva)) AND Language=(English)
7 5,977 (#6 OR #5 OR #4 OR #3 OR #2 OR #1) AND Language=(English)
6 21 ((TS=(dilatation) AND TS=(cornea*))) AND Language=(English)
5 823 ((TS="corneal ulcer") or (TS="corneal ulcers")) AND Language=(English)
4 21 (TS=(dilatation) AND TS=(cornea*)) AND Language=(English)
3 1,051 ((TS="corneal stroma")) AND Language=(English)
2 301 ((TS=(cone or conical) AND TS= (cornea*))) AND Language=(English)
1 4,013 (TS=(keratoconus or keratectasia or keratoectasia or ectasia*)) AND Language=(English)

Database / information source: Inspec 1987 to 2012 Week 43
Interface / URL: OvidSP
Search date: 30/10/12
Retrieved records: 61
Search strategy:

1	keratoconus.ti,ab.	85
2	(keratectasia or keratoectasia).ti,ab.	2
3	ectasia$.ti,ab.	14
4	((cone or conical) adj4 cornea$).ti,ab.	8
5	corneal stroma.ti,ab.	95
6	(dilatation adj5 cornea$).ti,ab.	0
7	corneal ulcer$.ti,ab.	9
8	or/1-7	208
9	collagen$.ti,ab.	7348
10	(crosslink$ or cross link$).ti,ab.	23526
11	cxl.ti,ab.	12
12	riboflavin.ti,ab.	229
13	ultraviolet.ti,ab.	55239
14	(uncorrected VA or puva).ti,ab.	550
15	exp proteins/	100394
16	exp ultraviolet spectra/	47988
17	exp photodynamic therapy/	2491
18	photosensiti$.ti,ab.	10654
19	photochemotherap$.ti,ab.	124
20	exp photochemistry/	40560
21	photochem$.ti,ab.	12927
22	phototherap$.ti,ab.	280
23	or/9-22	260532
24	8 and 23	61

Database / information source: clinicaltrials.gov
Interface / URL: http://www.clinicaltrials.gov/
Search date: 31/10/12
Retrieved records: 93
Search strategy:

1) Found 40 studies with search of: (keratoconus OR keratectasia OR keratoectasia OR ectasia OR corneal ulcer) AND (collagen or crosslink OR cxl OR riboflavin OR ultraviolet OR uncorrected VA OR puva) Interventional Studies;
2) Found 53 studies with search of: (keratoconus OR keratectasia OR keratoectasia OR ectasia OR corneal ulcer) AND (photosensitizing OR photosensitising OR photochemistry OR photochemotherapy OR phototherapy) Interventional Studies.

Database / information source: Science Direct
Interface / URL: http://www.sciencedirect.com/
Search date: 31/10/12
Retrieved records: 126
Search strategy:

126 articles found for: pub-date > 1999 and TITLE-ABSTR-KEY(keratoconus or keratectasia or keratoectasia or ectasia* or "corneal ulcer" or "corneal ulcers") and TITLE-ABSTR-KEY(collagen* or crosslink* or "cross link" or "cross linking" or "cross linked" or cxl or riboflavin or ultraviolet or uncorrected VA or puva or photosensiti* or photochem* or phototherap*).

Database / information source: ZETOC
Interface / URL: http://zetoc.mimas.ac.uk/
Search date: 31/10/12
Retrieved records: 455
Search strategy:

140 for: general: keratoconus collagen, 2000-2012
63 for: general: keratoconus crosslink*, 2000-2012
38 for: general: keratoconus cxl, 2000-2012
81 for: general: keratoconus riboflavin, 2000-2012
46 for: general: keratoconus ultraviolet*, 2000-2012
39 for: general: keratoconus uncorrected VA, 2000-2012
0 for general: keratoconus puva, 2000-2012
13 for: general: keratectasia collagen, 2000-2012
10 for: general: keratectasia crosslink*, 2000-2012
5 for: general: keratectasia cxl, 2000-2012
8 for: general: keratectasia riboflavin, 2000-2012
6 for: general: keratectasia ultraviolet*, 2000-2012
6 for: general: keratectasia uncorrected VA, 2000-2012
0 for: general: keratectasia puva, 2000-2012.

Database / information source: WorldWideScience.org
Interface / URL: http://worldwidescience.org/
Search date: 31/10/12
Retrieved records: 21
Search strategy:

Title: keratoconus OR keratectasia OR keratoectasia OR ectasia OR corneal ulcer OR corneal ulcers / Beginning Date Range: 2000-01-01 / Ending Date Range: 2012-12-31-01

Results were scanned and 21 records selected for retrieval.

Database / information source: International Clinical Trials Registry Platform (ICTRP)
Interface / URL: http://apps.who.int/trialsearch/
Search date: 31/10/12
Retrieved records: 51
Search strategy:

1) Found 48 records of 48 trials for: keratoconus AND collagen* OR keratoconus AND cross* OR keratoconus AND cxl OR keratoconus AND riboflavin OR keratoconus AND ultraviolet* OR keratoconus AND uncorrected VA OR keratoconus AND puva;
2) Found 3 records of 3 trials for: keratectasia AND collagen* OR keratectasia AND cross* OR keratectasia AND cxl OR keratectasia AND riboflavin OR keratectasia AND ultraviolet* OR keratectasia AND uncorrected VA OR keratectasia AND puva.

Database / information source: OAIster
Interface / URL: http://oaister.worldcat.org/
Search date: 31/10/12
Retrieved records: 16
Search strategy:

Search results for 'kw:(keratoconus OR keratectasia OR keratoectasia OR ectasia OR "corneal ulcer" OR "corneal ulcers") AND (collagen or crosslink* OR "cross link" OR "cross linking" OR "cross linked" OR cxl OR riboflavin OR ultraviolet* OR uncorrected VA OR puva OR photosensiti* OR photochem* OR phototherap*)' > '2000..2012' > 'English' limited to Libraries Worldwide: 16 records found.

Database / information source: OpenGrey
Interface / URL: http://www.opengrey.eu/
Search date: 31/10/12
Retrieved records: 3
Search strategy:

keratoconus OR keratectasia OR keratoectasia OR ectasia OR "corneal ulcer" OR "corneal ulcers"

Database / information source: Euroscan
Interface / URL: http://euroscan.org.uk/
Search date: 31/10/12
Retrieved records: 3
Search strategy:

The following search terms were searched individually in the Technology search option:
Keratoconus
Riboflavin
Crosslinkage
“Cross linkage”
Ultraviolet
The results of records retrieved from a search of the ‘Ophthalmology’ section were also assessed. 3 potentially relevant records were downloaded.

Database / information source: Nexis
Interface / URL: http://www.lexisnexis.com/uk/nexis/
Search date: 02/11/12
Retrieved records: 73
Search strategy:

(((keratoconus OR keratectasia OR keratoectasia OR ectasia! OR "corneal ulcer!") AND (collagen! OR crosslink! OR "cross link!" OR "cross-link!" OR cxl OR riboflavin OR ultraviolet OR uncorrected VA OR puva OR photosensiti! OR photochem! OR phototherap!))) and DATE(>=2000-01-01 and <=2012-11-02)

Results were scanned and those which indicated possible reference to published research were selected for retrieval.

Database / information source: National Institute for Health Research (NIHR)
Interface / URL: http://www.nihr.ac.uk/Pages/default.aspx
Search date: 31/10/12
Retrieved records: 3
Search strategy:

Advanced search page:
1. Any of these words - keratoconus keratectasia keratoectasia ectasia
2. This exact phrase – corneal ulcer
3. This exact phrase – corneal ulcers

3 records of possible interest were selected for retrieval.

Database / information source: Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP)
Interface / URL:
Search date: 31/10/12
Retrieved records: 0
Search strategy:

The following search terms were searched individually using the site search option:

Keratoconus
Keratectasia
Keratoectasia
Ectasia
Corneal Ulcer
Corneal Ulcers

Appendix B

Papers with Fewer Than 10 Patients or Less Than 6 Months Follow-Up

Table B1a: Description of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL

Author	Study design	Study population	Inclusion criteria	Intervention
Author: El Raggal **Year:** 2009 **Ref:** 30 **Country:** Not Stated	**Follow-up:** Follow-up at 3 days for contact lens removal, then after 1 week, 1, 3 and 6 months. **Primary outcome:** UCVA, BSCVA, spherical, cylindrical errors, keratometric readings and pachymetry. **Comparator:** No comparator.	**Number of patients:** 9. **Number of eyes:** 15. **Disease severity:** Grade I - III keratoconus (according to Amsler-Krumeich classification). **Corneal thickness:** >420 µm.	Clear cornea; average K reading <54 D; minimal CT >420 µm.	**Additional intervention:** Riboflavin UV A irradiation CXL. **Anaesthesia:** Anaesthetic eye drops administered initially and every 10 minutes throughout procedure. **Preop riboflavin:** Riboflavin 0.1% solution every 3 minutes for 30 minutes until stroma completely saturated. **Operative riboflavin:** Riboflavin 0.1% solution applied every 5 minutes throughout procedure. **Diameter of corneal removed:** 8.5mm. **UV A strength and WL and time:** UV A strength: 3mW/cm^2. 30 minutes. **Postop care:** Lomefloxacin and bandage contact lens. Okacin for 1 week, diclofenac for 1 month, and fluorometholone used.
Author: Mazzotta **Year:** 2011 **Ref:** 88 **Country:** Italy	**Follow-up:** 12 months. **Primary outcome:** UCVA and BSCVA. **Comparator:** No comparator.	**Number of patients:** 1. **Number of eyes:** 1. **Disease severity:** Progressive corneal ectasia and hyperopic shift. **Corneal thickness:** 423 µm.	Case report of one patient.	**Additional intervention:** Riboflavin UV A irradiation CXL. **Anaesthesia:** Lidocaine 4% drops applied 15 minutes before procedure. **Preop riboflavin:** Pre-irradiation stromal soaking with riboflavin 0.1% every 2 minutes for 10 minutes. **Operative riboflavin:** Riboflavin 0.1% applied every 2 minutes during procedure. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** UV A strength: 3mW/cm^2. 30 minutes. **Postop care:** Soft contact lens bandage applied for 4 days.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Richoz **Year:** 2012 **Ref:** 103 **Country:** Not Stated	**Follow-up:** 12 to 19 months. **Primary outcome:** Progression of recurrent ectasia. **Comparator:** No comparator.	**Number of patients:** 3. **Number of eyes:** 3. **Disease severity:** Recurrent keratoconus after PRK. **Corneal thickness:** Not reported.	Not Available.	**Additional intervention:** Standard protocol CXL. **Anaesthesia:** Not Available. **Preop riboflavin:** Not Available. **Operative riboflavin:** Not Available. **Diameter of corneal removed:** Not Available. **UV A strength and WL and time:** Not Available. **Postop care:** Ofloxacin and bandage contact lens until epithelium healed. Fluorometholone for 2 weeks.
Author: Spadea **Year:** 2012 **Ref:** 109 **Country:** Italy	**Follow-up:** 2 years. **Primary outcome:** BSCVA. **Comparator:** No comparator.	**Number of patients:** 1. **Number of eyes:** 1. **Disease severity:** Moderate stage keratoconus. **Corneal thickness:** 413 µm.	Case report of one patient.	**Additional intervention:** Topographically guided, transepithelial excimer laser PRK. **Anaesthesia:** Lidocaine 15 minutes before epithelial tissue removal. **Preop riboflavin:** Corneal soaking for 15 minutes in riboflavin solution. **Operative riboflavin:** 9mm. **Diameter of corneal removed:** Riboflavin applied every 2.5 minutes for 30 minutes. **UV A strength and WL and time:** UV A strength: 3mW/cm^2. 30 minutes. **Postop care:** Soft bandage contact lens. Ofloxacin and flurbiprofen drops for 2 weeks. Corticosteroid for 1 month

Table B1b: Outcomes for papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
Author: El Raggal **Year:** 2009 **Ref:** 30	UCVA: preop = 0.11 +/- 0.07; postop = 0.15 +/- 0.06 (p=0.005). BSCVA: preop = 0.51 +/-0.11; postop = 0.53 +/- 0.09 (p=0.189).	Mean K (D): preop = 49.97 +/- 2.81; postop = 48.34 +/- 2.64 (p<0.05).	Mean SE (D): preop = -3.2 +/- 1.46; postop = -2.73 +/- 1.56 (p<0.05). Mean cylindrical error (D): preop = 49.97 +/- 2.81; postop = 48.37 +/- 2.64 (p<0.05).	Not Available.	Pachymetry (um): preop = 444 +/- 18.42; postop = 446.67 +/- 18.39.	All eyes developed faint stromal haze. Cleared in all but 1 eye within a month; 1 eye left with faint corneal scar.	Not Available.
Author: Mazzotta **Year:** 2011 **Ref:** 88	UCVA: preop = 0.25; 12 months = 0.6 (p=NA). BSCVA: preop = 0.3; 12 months = 0.8 (p=NA).	Mean K (D): preop = 52.48; 12 months = 50.51 (p=NA).	Not Available.	Not Available.	Pachymetry (um): 12 months = 427 (p>0.05).	Not Available.	Surface asymmetry index (D): preop = 7.77; 12 months = 7.62.
Author: Richoz **Year:** 2012 **Ref:** 103	BCVA: Case 1: preop = 20/100; 12 months = 20/100. Case 2: preop = 20/40; postop = 20/40. Case 3: preop = 20/40; postop = 20/40.	Max K: Case 1: preop = 53.7; postop = 53.3. Case 2: preop = 47.2; postop = 47.8. Case 3: preop = 53.6; postop = 51.3.	Not Available.	Not Available.	Not Available.	Not Available.	Not Available.
Author: Spadea **Year:** 2012 **Ref:** 109	UCVA: 24 months = 20/80. BSCVA: preop 20/33; 24 months = 20/20.	Baseline: Max K 45.5 D; Flattest 43.7 D; Apex 59.4 D. 24 months: Max K 43.7 D; Flattest 41.3 D; Apex 59.4 D.	Not Available.	Not Available.	Corneal thickness: 401 um preop and at 24 months.	None.	Not Available.

Table B2a: Description of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with ICRS

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Henriquez **Year:** 2012 **Ref:** 51 **Country:** Peru	**Follow-up:** 6 months after CXL and 6 months after ferrera (FR) implantation. **Study type:** Case study. **Primary aim of study:** Report the postoperative results of each eye of a patient with postoperative LASIK ectasia for whom ICRS and CXL were performed.	**Number of patients:** 1. **Number of eyes:** 2. **Mean age:** 27. **Age range:** Not Available. **% female:** 0%.	Keratoconus; no corneal opacities or scarring; CCT 450 µm; low quality of vision and contact lens intolerance; preoperative cylinder value >= 5 D.	**Anaesthesia:** Proparacaine hydrochloride 0.5% instilled every 5 minutes for 3 doses before procedure. **Preop riboflavin:** Riboflavin solution instilled every 5 minutes (or sooner) for 30 minutes. **Operative riboflavin:** Riboflavin solution applied every 5 minutes or sooner if cornea surface visibly dry. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** UV A strength: 3 +/- 0.3mW/cm². 30 minutes. **Postop care:** Ofloxacin and bandaged soft CL till day 4. Acetaminophen for 3 days; ofloxacin for 7 days; ketorolac tromethamine then fluorometholone for 5 weeks from day 5.
Author: Kamburoglu **Year:** 2008 **Ref:** 55 **Country:** Turkey	**Follow-up:** 8 months for right eye and 7 months for left eye. **Study type:** Prospective study. **Primary aim of study:** Evaluate the safety, efficacy and stability of sequential CXL and ferrara ICRS implantation in selected patients with progressive keratoconus.	**Number of patients:** 9. **Number of eyes:** 9. **Mean age:** 21 +/- 2.12 **Age range:** 18 to 24 years. **% female:** 11%.	Case study so not available.	**Anaesthesia:** Not reported. **Preop riboflavin:** Riboflavin 0.1% solution applied topically every 2 minutes for 30 minutes. **Operative riboflavin:** Instilled every 2 minutes during treatment. **Diameter of corneal removed:** Not reported. **UV A strength and WL and time:** 3mW/cm^2. 370 nm. 30 minutes. **Postop care:** Topical polyacrylic gel used for 10 days.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Saelens **Year:** 2011 **Ref:** 105 **Country:** The Netherlands	**Follow-up:** 11.72 +/- 3.6 months. **Study type:** Case series. **Primary aim of study:** Report 12 month outcomes after same day treatment with CXL and ICRS in eyes with keratoconus.	**Number of patients:** 7. **Number of eyes:** 7. **Mean age:** 33.31 +/- 9.50. **Age range:** 20 to 42 years. **% female:** Not Reported.	Progressive keratoconus; contact lens intolerance; average keratometry of <53 D; BCVA >0.4.	**Anaesthesia:** Oxybuprocaine eye drops applied as topical anaesthesia. **Preop riboflavin:** Riboflavin 0.1% solution every 3 minutes for 25 minutes to cornea and injected into intrastromal canals. Penetration confirmed by slit lamp. **Operative riboflavin:** Riboflavin further applied every 3 minutes. **Diameter of corneal removed:** 8.5mm. **UV A strength and WL and time:** 3mW/cm^2. 370 nm. 30 minutes. **Postop care:** Soft contact lens, diclofenac, ofloxacin and dexamethasone. After re-epithelialisation. Contact lens removed and ofloxacin discontinued and dexamethasone tapered.

Table B2b: Outcomes for papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with ICRS

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
Author: Henriquez **Year:** 2012 **Ref:** 51 **Country:** Peru	Measured in LogMAR. UCVA: preop = 1.11 +/- 0.31; 6 months after CXL = 0.75 (p=0.03); 6 months after FR = 0.23 (p<0.001). BCVA: preop = 0.26 +/- 0.21; 6 months after CXL = 0.24 (p=0.87); 6 months after FR = 0.12 +/- 0.14 (p=0.05).	Mean max K (D): 6 months after CXL reduced by 0.57 (p=0.57); 6 months after FR reduced by 5.58 (p<0.001). Mean min K (D): 6 months after CXL reduced by 0.36 (p=0.36); 6 months after FR reduced by 4.17 (p<0.001).	Mean spherical value (D): preop to 6 months after CXL decreased by 0.53 (p=0.75); 6 months after FR decreased by 2.39 (p=0.02). Cylinder value (D): preop to 6 months after CXL reduced by 1.75 (p<0.001); 6 months after FR decreased by 3.97 (p<0.001).	Not Available.	Not Available.	Not Available.	Not Available.
Author: Kamburoglu **Year:** 2008 **Ref:** 55 **Country:** Turkey	Right eye: UCVA 20/100; at 8 months 20/30 BSCVA 20/60; at 8 months 20/25. Left eye: UCVA 20/160; at7 months 20/30. BSCVA 20/80; at 7 months 20/25.	Right eye: K 53.1/59.6 D (mean 56.2); at 8 months 45/49.5 D (mean 47.2). Left eye: K 49.5/52 D (mean 50.7); at 7 months 41.7/46.9 D (mean 44.2).	Not Reported.	Not Reported.	Only reported before treatment.	Not Reported.	Not Reported.
Author: Saelens **Year:** 2011	Mean UCVA: baseline = 0.1 +/- 0.07; 1 year = 0.6 +/- 0.24	Mean K: baseline = 46.81 +/- 2.13;1 year =	Mean SE (D): baseline = -4.16 +/- 2.41; 1 year = -0.68 +/- 1.49 (p=NA).	Not Reported.	Not Reported.	One patient 4 months after treatment reported	Three patients wore contact lens, 1 patient still contact

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
Ref: 105 **Country:** The Netherlands	(p=NA). Mean BSCVA: baseline = 0.56 +/- 0.08; 1 year = 0.82 +/- 0.25 (p=NA).	43.97 +/- 2.22 (p>0.05).				irritation; little migration so the inferior ring towards the incision was seen; small epithelial defect at the site of incision. Although the ring segment was not wholly extruded, ring was explanted. Three months later mean K value increased by 1.7 D.	lens-intolerant and 2 had no correction because of excellent UCVA.

Table B3a: Description of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with PRK

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Kapasi **Year:** 2012 **Ref:** 60 **Country:** Canada	**Follow-up:** 1 month. **Study type:** Retrospective analysis. **Primary aim of study:** Compare visual outcomes of patients treated with either phototherapeutic keratectomy or mechanical epithelial removal prior to CXL.	**Number of patients:** 34. **Number of eyes:** 34: 17 with PRK epithelial removal and 17 with mechanical CXL epithelial removal. **Mean age:** 31.6 +/- 1.8 years. **Age range:** 16 to 60 years. **% female:** 21%.	14 to 60 years old with keratoconus (keratometry, astigmatism or myopic shift) and consistent topographic data.	**Anaesthesia:** One drop before treatment: Isopticarpine (pilocarpine hydrochloride 2%). **Preop riboflavin:** If pachymetry >400 µm: 0.1% riboflavin in 0.5% isotope tears used. If pachymetry <400 µm, hypotonic 0.1% riboflavin in balanced salt solution used until pachymetry >400 µm. Riboflavin applied every 3 minutes for 30 minutes if pachymetry >400 µm. **Operative riboflavin:** Riboflavin drops continued through treatment at 1 drop every 3 minutes. **Diameter of corneal removed:** 6.5mm. **UV A strength and WL and time:** UVA strength: 3mW/cm². 30 minutes. **Postop care:** Bandage contact lens for 1 week with Vigamox. Fluorometholone for 1 month.
Author: Kymionis **Year:** 2009 **Ref:** 73 **Country:** Greece	**Follow-up:** 1 month. **Study type:** Case series. **Primary aim of study:** Present the results after simultaneous PRK followed by CXL for progressive keratoconus.	**Number of patients:** 12. **Number of eyes:** 14. **Mean age:** 28. **Age range:** 20 to 29 years. **% female:** Not Reported.	Progressive keratoconus; CCT >400 µm; no other corneal or anterior segment pathological signs.	**Anaesthesia:** Proxymetacaine hydrochloride 0.5% eye drops. **Preop riboflavin:** Riboflavin 0.1% solution instilled every 3 minutes for 30 minutes. **Operative riboflavin:** Riboflavin solution applied every 3 minutes. **Diameter of corneal removed:** Both groups 8mm. **UV A strength and WL and time:** Both groups: 3.0mW/cm². 370 nm. 30 minutes. **Postop care:** Bandage contact lens until re-

Author	Study design	Study population	Inclusion criteria	Intervention
				epithelialisation. Diclofenac for 2 days and tobramycin / corticosteroid until removal of contact lens, then corticosteroid drops tapering for 3 weeks.
Author: Kymionis **Year:** 2010 **Ref:** 74 **Country:** Greece	**Follow-up:** Mean 19.53 months (range 12 to 25 months). **Study type:** Case study. **Primary aim of study:** A case of a keratoconic patient who underwent epithelial removal with TG-PRK using a solid-state laser system followed by CXL.	**Number of patients:** 1. **Number of eyes:** 2. **Mean age:** 24. **Age range:** Not Available. **% female:** 0%.	Progressive keratoconus; hard contact lens with full spectacle correction; expected CCT after PRK >400 µm.	**Anaesthesia:** Tetracaine 1% and oxybuprocaine 0.4% eye drops. **Preop riboflavin:** Riboflavin 0.1% solution applied every 3 minutes for 20 minutes until the stroma was completely penetrated. **Operative riboflavin:** During treatment riboflavin applied every 5 minutes to ensure saturation. **Diameter of corneal removed:** 8.5mm. **UV A strength and WL and time:** 213 nm during PRK procedure at 3mW/cm². 30 minutes. **Postop care:** Bandage contact lens until the epithelium healed followed by fluorometholone for 2 weeks.

Table B3b: Outcomes of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with PRK

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
Author: Kapasi **Year:** 2012 **Ref:** 60 **Country:** Canada	Not Reported.	Not Reported.	Change in mean refractive spherical equivalent of 1.68 +/- 0.80.	Not Reported.	Not Reported.	Not Reported.	Not Reported.
Author: Kymionis **Year:** 2009 **Ref:** 73 **Country:** Greece	Measured in LogMAR. UCVA: preop 0.21 +/- 0.18; postop follow-up 0.12 +/- 0.15. BCVA: preop 0.81 +/- 0.65; postop follow-up: 0.35 +/- 0.36.	Measured in dioptres. Steep and flat K. Preop: 49.8 +/- 5.3, postop follow-up: 47.46 +/- 4.3.	Measured in dioptres. Manifest refraction SE: preop -2.3 +/- 2.8; postop follow-up -1.08 +/- 2.41.	Not Reported.	Not Reported.	50% of patients had stromal haze.	Not Reported.
Author: Kymionis **Year:** 2010 **Ref:** 74 **Country:** Greece	UCVA improved from 20/63 to 20/32.	Not Reported.	Not Reported.	Not Reported.	Not Reported.	Not Reported.	Not Reported.

Table B4a: Description of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with TG-PRK

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Krueger **Year:** 2010 **Ref:** 69 **Country:** Greece	**Follow-up:** 30 months. **Study type:** Case report. **Primary aim of study:** To follow the stability of simultaneously delivered therapy that corrects aberrations and stiffens the corneal collagen of eyes.	**Number of patients:** 2. **Number of eyes:** 2. **Mean age:** Case 1: 24; Case 2: 21. **Age range:** 21 to 24 years. **% female:** 0%.	Not Reported.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Riboflavin sodium phosphate 0.1% drops placed on eye 2 minutes before treatment. **Operative riboflavin:** Riboflavin sodium phosphate 0.1% every 2 minutes for 30 minutes. **Diameter of corneal removed:** 6.5mm. **UV A strength and WL and time:** 3mW/cm². 370 nm. 30 minutes. **Postop care:** Soft contact lens with antibiotic and steroid drops until re-epithelialisation. Topical steroid tapered over several weeks.
Author: Kymionis **Year:** 2011 **Ref:** 72 **Country:** Greece	**Follow-up:** Only 1 patient and follow-up data only provided for 12 months. **Study type:** Case report. **Primary aim of study:** Present a patient with post-LASIK ectasia who had simultaneous TG-PRK and CXL in the left eye.	**Number of patients:** 1. **Number of eyes:** 1. **Mean age:** 39. **Age range:** Not Available. **% female:** 0%.	Not Reported.	**Anaesthesia:** Proparacaine 0.5%. **Preop riboflavin:** Riboflavin 0.1% solution instilled repeatedly for approximately 30 minutes. **Operative riboflavin:** Riboflavin every 5 minutes during treatment to saturate cornea. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** Not reported. 30 minutes. **Postop care:** Bandage contact lens until re-epithelialisation. Diclofenac for 2 days and antibiotic / corticosteroid drops until the removal of contact lens.

Table B4b: Outcomes of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with TG-PRK

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
Author: Krueger **Year:** 2010 **Ref:** 69 **Country:** Greece	Measured in Snellen lines. Case 1: CVA improved from 20/50 to 20/30. Case 2: CVA improved from 20/30 to 20/15.	Not reported.	Not reported.	Not reported.	Not reported.	Not reported.	Not reported.
Author: Kymionis **Year:** 2011 **Ref:** 72 **Country:** Greece	VA improved from 20/100 to 20/40 at 3 months and CVA from 20/40 to 20/25. Snellen lines and maintained at 12 months.	Not reported.	Not reported.	Not reported.	Not reported.	Not reported.	Not reported.

Table B5a: Description of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with other interventions

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Daxer **Year:** 2010 **Ref:** 23 **Country:** Austria	**Follow-up:** 3 months. **Study type:** Case study. **Primary aim of study:** Report use of CXL with corneal pocket into which riboflavin was instilled, removing need for drops.	**Number of patients:** 1. **Number of eyes:** 1. **Mean age:** Not Available. **Age range:** Not Available. **% female:** 100%.	Not Available.	**Anaesthesia:** Topical anaesthesia. **Preop riboflavin:** Riboflavin 0.1% over 3 minutes. **Operative riboflavin:** Not reported. **Diameter of corneal removed:** 9mm. **UV A strength and WL and time:** 3mW/cm^2. 365 nm. 30 minutes. **Postop care:** Not Reported.
Author: Guell **Year:** 2012 **Ref:** 44 **Country:** Spain	**Follow-up:** Median 36.9 months. **Study type:** Case series, retrospective study. **Primary aim of study:** To report the long-term results of CXL and toric PIOL implantation to correct myopic astigmatism in patients with progressive mild to moderate keratoconus.	**Number of patients:** 9. **Number of eyes:** 17. **Mean age:** 27 +/- 4. **Age range:** 21 to 35 years. **% female:** 33%.	Progressive keratoconus SE > -3.00 D with any degree of regular myopic astigmatism; CVA of 20/50 or better; clear cornea; thinnest corneal point >3.2 mm; central ECC greater than 2300 cells/mm².	**Anaesthesia:** Proparacaine 0.5% 1 drop every 5 minutes, 3 times immediately before surgery. **Preop riboflavin:** Riboflavin 0.1% solution every 5 minutes for 20 minutes until corneal stroma completely soaked. **Operative riboflavin:** Riboflavin applied every 5 minutes throughout procedure. **Diameter of corneal removed:** 7 to 8mm. **UV A strength and WL and time:** 2.7 to 3.3mW/cm². 370nm. 30 minutes. **Postop care:** Tobradex instilled and bandage soft contact lens. Metamizole if required; ofloxacin. Contact lens removed once complete re-epithelialisation followed by fluorometholone tapered over 6 weeks. Artificial tears prescribed

Author	Study design	Study population	Inclusion criteria	Intervention
				4 to 6 times daily for 3 months.
Author: Kaya **Year:** 2011 **Ref:** 61 **Country:** Turkey	**Follow-up:** 6 weeks. **Study type:** Case study. **Primary aim of study:** To examine the CXL effect with a customised epithelial debridement technique in thin corneas using anterior segment optical coherence tomography and confocal microscopy.	**Number of patients:** 2. **Number of eyes:** 2. **Mean age:** Patient 1: 46; patient 2: 18. **Age range:** 18 to 46 years. **% female:** 50%.	Patients with progressive keratoconus and re-epithelialised corneal thickness <400 µm at the area of steepening.	**Anaesthesia:** Proparacaine 0.5%. **Preop riboflavin:** Riboflavin 0.1% solution every 3 minutes for 30 minutes. **Operative riboflavin:** Riboflavin every 5 minutes to ensure saturation. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2. 365 nm. 30 minutes. **Postop care:** Combination steroid and antibiotic drop (Tobradex, 4 times daily) was prescribed for use 4 times daily. Bandage soft contact lens kept in place until full corneal re-epithelialisation occurred.
Author: Kymionis **Year:** 2010 **Ref:** 76 **Country:** Greece	**Follow-up:** 3 months. **Study type:** Case study. **Primary aim of study:** To evaluate the combined effect of conductive keratoplasty followed by CXL in 2 patients with keratoconus.	**Number of patients:** 2. **Number of eyes:** 2. **Mean age:** Case 1: 22 years. Case 2: 23 years. **Age range:** 22 to 23 years. **% female:** 0%.	Bilateral keratoconus with more advanced keratoconus in 1 eye; treated with corneal keratoplasty followed by CXL.	**Anaesthesia:** Tetracaine 1% and oxybuprocaine 0.4% eye drops. **Preop riboflavin:** Riboflavin 0.1% solution applied every 3 minutes for 30 minutes. **Operative riboflavin:** Riboflavin solution every 2 to 3 minutes to ensure saturation. **Diameter of corneal removed:** Not Reported. **UV A strength and WL and time:** UV A strength: 3mW/cm^2. 30 minutes. **Postop care:** Bandage contact lens applied and remaining in place until epithelium healed completely. Topical fluorometholone 0.1% eye drops applied twice daily for 2 weeks.

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Kymionis **Year:** 2009 **Ref:** 78 **Country:** Greece	**Follow-up:** Mean 36 months. **Study type:** Case study. **Primary aim of study:** To describe a modified method for de-epithelialisation prior to CXL.	**Number of patients:** 2. **Number of eyes:** 2. **Mean age:** Not Reported. **Age range:** Not Reported. **% female:** Not Reported	Two patients with progressive keratectasia and corneal pachymetry < 400 microns at the area of topographic steepening.	**Anaesthesia:** Proparacaine 0.5% (alkaline). **Preop riboflavin:** 0.1% solution riboflavin-5-phosphate every 3 minutes for 15 minutes. **Operative riboflavin:** Every 4 minutes for 30 minutes. **Diameter of corneal removed:** 8mm. **UV A strength and WL and time:** 3mW/cm^2. 365 nm. 30 minutes. **Postop care:** Combination steroid and antibiotic drop (Tobradex, 4 times daily) was administered in all patients and a bandage soft contact lens was kept in place until full corneal re-epithelialisation occurred.

Table B5b: Outcomes of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL with other interventions

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
Author: Daxer **Year:** 2010 **Ref:** 23 **Country:** Austria	BSCVA: preop 0.4; postop 0.67 (p=NA). UCVA: preop 0.05; postop 0.25 (p=NA).	Sphere (D): preop -6.0; postop -.05 (p=NA). Cylinder (D): preop -4.0; postop -2.5 (p=NA). SE (D): preop -8.0; postop -1.75. K: preop 59.23; postop 47.97 (p=NA).	Not Available.	Not Available.	Not Available.	Not Available.	Not Available.
Author: Guell **Year:** 2012 **Ref:** 44 **Country:** Spain	Measured in LogMAR. UCVA: preop <1.00; postop 0.17. CVA: preop 0.1; postop 0.1 (p=NA).	Mean difference between preop and last follow-up in simulated K value = 0.17 +/- 0.45 D (p>0.05).	SE (D): preop -6.99; postop -0.22 (p>0.05). Cylinder (D): preop -3.54; postop -.62 (p>0.05).	Not Available.	US pachymetry: preop 476; postop 481 (p=NA).	One person needed steroids for up to 4 weeks after PIOL.	Not Available.
Author: Kaya **Year:** 2011 **Ref:** 61 **Country:** Turkey	Not Reported.	Not Reported.	Not Reported.	Not Reported.	Not Reported.	Not Reported.	Not Reported.
Author: Kymionis **Year:** 2010 **Ref:** 76 **Country:** Greece	BSCVA and UCVA unchanged (p=NA).	Case 1: topography pattern similar to preop; disease regressed all other parameters unchanged. Case 2 preop 20/63 +2 -	No change (p=NA).	Not Available.	Not Available.	Not Available.	Not Available.

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
		6*75; 2 months postop 20/63 +2.5 -5.75 *80; (p=NA).					
Author: Kymionis **Year:** 2009 **Ref:** 78 **Country:** Greece	UCVA: sequential group: preop 0.9; postop 0.49; simultaneous group: preop 0.96; postop 0.3. BSCVA: sequential group preop 0.41; postop 0.16; simultaneous group: preop 0.39; postop 0.11.	Mean reduction in SE (D): 2.5 in sequential group; 3.2 in simultaneous group. Mean reduction in K (D): 2.75 in sequential group; 3.5 in simultaneous group. No p-values.	Not Available.	Not Available.	Mean decrease in CCT: 465 to 395 in sequential group; 475 to 405 in simultaneous group (p=NA).	Haze stroma: 1.2 in sequential group and 0.5 in simultaneous group.	40% of patients experienced pain after procedures.

Table B6a: Description of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL Transepithelial (epithelium-on)

Author	Study design	Study population	Inclusion criteria	Intervention
Author: Ertan **Year:** 2009 **Ref:** 31 **Country:** Turkey	**Follow-up:** 3 months. **Study type:** Retrospective analysis. **Primary aim of study:** To evaluate the efficacy of transepithelial CXL in keratoconus eyes after corneal implantation.	**Number of patients:** 17. **Number of eyes:** 25. **Mean age:** 25.14. **Age range:** 16 to 39. **% female:** Not Reported.	Bilateral keratoconus without corneal scarring; contact lens intolerance; corneal thickness >400 µm; endothelial cell count >3000 per mm^2.	**Anaesthesia:** Proparacaine 0.5% and 2% pilocarpine every 2 and 5 minutes, respectively for 30 minutes. **Preop riboflavin:** Riboflavin 0.1% and 20% dextran every 2 minutes for 30 minutes. **Operative riboflavin:** Riboflavin 0.1% and dextran every 3 minutes. **Diameter of corneal removed:** 7mm. **UV A strength and WL and time:** 3mW/cm^2. 370 nm. 30 minutes. **Postop care:** Artificial tears for a few days.
Author: Hase, Bhakta **Year:** 2011 **Ref:** 48 **Country:** USA	**Follow-up:** 2 years. **Study type:** Case study. **Primary aim of study:** Not Reported.	**Number of patients:** 1. **Number of eyes:** 1. **Mean age:** Not Available. **Age range:** Not Available. **% female:** 0%.	Not Available.	**Anaesthesia:** Not Reported. **Preop riboflavin:** Riboflavin 0.1% solution every 2 minutes for 30 minutes. **Operative riboflavin:** Not Reported. **Diameter of corneal removed:** Every 2 minutes. **UV A strength and WL and time:** WL: 365 nm. 30 minutes. **Postop care:** Antibiotic, steroid, nonsteroidal anti-inflammatory drugs, artificial tears and therapeutic bandage contact lens.

Table B6b: Outcomes of papers with fewer than 10 patients or less than 6 months follow-up: Epithelium-off CXL Transepithelial (epithelium-on)

Author	Change in visual acuity	Change in topography	Change in refraction and astigmatism	Change in intraocular pressure	Change in central corneal thickness	Adverse events	Other outcomes
Author: Ertan **Year:** 2009 **Ref:** 31 **Country:** Turkey	Measured in Snellen lines. UCVA: preop 1.61 +/- 1.23; after corneal implants 3.58 +/- 2.29; after CXL 4.8 +/- 2 ($p<0.05$). BCVA: preop 4.18 +/- 2.09; after implant 6.54 +/- 2.02; after CXL 7.27 +/- 2.02 ($p<0.05$).	Mean K: preop 49.9 +/- 4.59; after implants 47.6 +/- 3.68; after CXL 47.46 +/-3.54 ($p>0.05$).	Measured in dioptres. Spherical value: preop -3.89 +/- 4.89; postop -1.68 +/- 2.18 ($p<0.05$). Cylindrical value: preop -3.74 +/- 1.9; postop -3.11 +/- 2.32 ($p>0.05$).	Not Available.	Not Available.	None Reported.	Not Available.
Author: Hase, Bhakta **Year:** 2011 **Ref:** 48 **Country:** USA	Baseline: 20/32 right eye and 20/50 left eye. 2 years: 20/30 right eye and 20/40 left eye (p=NA).	Not Reported.	Not Reported.	Not Reported.	Not Reported.	Not Reported.	Not Reported.

Appendix C

FOREIGN LANGUAGE PAPERS

Seventeen papers were selected from the abstracts where the full paper was only available in a foreign language. The information within the abstracts is now presented. All studies were of patients with keratoconus except that by Kohlhaas *et al.*, (2005) which was of a patient with keratectasia. No patient, eye or follow-up information was available for Constantin *et al.*, (2009) and Mazzotta *et al.*, (2009) and these were excluded from the evidence table.

Should the available efficacy data in English language papers be insufficient, then the IPAC should consider whether some or all of these papers should be translated and included.

Table C.1: Papers for epithelium-off CXL with riboflavin

Study reference and year	Patients N	Eyes N	Follow-up months	Study type and comment†
Da Candelaria Renesto 2011	Not stated	39	24	RCT of ICRS and CXL after 3 months versus riboflavin.
Fournie 2009	20	20	18	Prospective non-randomised CXL. Standard protocol used.
Raiskup 2010	127	163	12	Retrospective analysis; CXL. Standard protocol. 9% developed scar linked to thinner cornea.
Hoyer 2010	111	153	Up to 72	Study type not stated. CXL standard protocol. Three patients had disease progression and repeat CXL.
Hoyer 2009	111	153	Up to 90	Study type not stated. CXL standard protocol. High drop off in follow-up.
Bikbov 2011	77	87	12	Study type not stated. CXL standard protocol.
Kampik 2011	45	46	24	Case study. CXL standard protocol.
Strmenova 2010	35	40	12	Study type not stated. CXL standard protocol. Results presented by 3 age groups and severity; AE was stromal haze.
Mate-Istvan 2010	27	32	12	Case study. CXL standard protocol.
Jankov 2nd 2008	20	25	6	Study type not stated. CXL standard protocol.
Baumeister 2009	20	20	6	Case study. CXL standard protocol.
Constantin 2009	4	4	12	Case study. CXL standard protocol.
Mate-Istvan 2010	1	2	Not stated	Case study. ICRS CXL.
Kohlhaas 2005	1	2	18	Case study. CXL standard protocol.
Tahzib and Van Der Lelij	'Corneal cross-linkage' as treatment for progressive keratoconus.			Review.

† Randomised control trial (RCT), intrastromal corneal ring segments (ICRS), corneal collagen cross-linkage (CXL), adverse events (AE).