

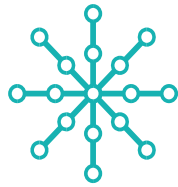


Clinical and cost effectiveness of epithelium-off corneal crosslinking (CXL) to treat adults with keratoconus

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Evidence Appraisal Report¹

Review of systematic reviews and additional primary studies

Clinical and cost effectiveness of epithelium-off corneal crosslinking (CXL) to treat adults with keratoconus

1. Health problem

Keratoconus is a non-inflammatory, bilateral eye condition, characterised by a progressive thinning and distortion of the cornea, causing a cone-shaped bulge to develop. This results in vision problems such as short-sightedness, blurred vision, astigmatism or light sensitivity (Wollensak et al. 2003). The condition typically develops in children and young adults and can deteriorate over time. Approximately 27% of patients with keratoconus progression require corneal transplantation for visual recovery (Rabinowitz et al. 1998).

In 2013 it was estimated that there were 50,000 individuals with keratoconus in the UK (Gore et al. 2013), with approximately 2000-3000 in Wales (Expert reviewers). It is not clear what proportion of these individuals would be eligible for an interventional procedure. The number of reported cases is thought to be increasing, but it is not known whether this is attributable to an increasing incidence of the condition or better recognition/reporting.

The cause of keratoconus is not known. However, incidence is proportionally higher in Indian and Pakistani populations, and family history is also associated with the condition, suggesting that genetic factors may be involved (Rabinowitz et al. 1998). Environmental factors such as allergies, asthma, eczema and chronic eye rubbing, are also associated with the keratoconus. Several reports also describe an association with Down's syndrome, Leber's congenital amaurosis (a degenerative retinal disease) and mitral valve prolapse (Rabinowitz et al. 1998).

2. Health technology

2.1. Corneal cross linking

One of the surgical interventions available for people in whom keratoconus is progressing rapidly (and sight loss cannot be corrected) is corneal crosslinking (CXL). Riboflavin (vitamin B2) drops are administered in conjunction with ultraviolet light (UVA, 365nm). The photochemical reaction between riboflavin and UV light leads to the formation of additional covalent bonds between collagen molecules, with consequent

¹ Rapid systematic literature search of published evidence and websites to identify the best clinical and economic evidence. This is critically evaluated by researchers and the draft Evidence Appraisal Report is issued to experts for review and discussed by Health Technology Wales multidisciplinary advisory groups.

biochemical stiffening and strengthening of the cornea (Wollensak et al. 2003). The exact mechanism of action of the CXL procedures is not fully understood: they may increase the number of 'anchors' that bond collagen fibres together and strengthen the cornea. This is expected to slow or stop the progression of the disease but the duration of benefit is uncertain (NICE 2013, Wollensak et al. 2003), and the degree of effect is often clinically unpredictable (Nordstrom et al. 2017). The procedure is also known as CCL, Corneal Collagen Cross Linking with Riboflavin (C3-R), and KCL (in the US).

Definitions of keratoconus progression vary, and include:

- up to 1 diopter (D) of change in the steep keratometry, and manifest cylinder (Expert reviewer)
- an increase in maximum keratometry or K2 (vertical keratometry measure) of 1.5 D or more over at least 3 months (Expert reviewer)
- an increase of at least 0.75 D in the steepest keratometry, a degradation of visual acuity, and an increase of 0.75 D or more in the manifest cylinder over the preceding 12 months (Kobashi and Rong 2017).

Criteria for treatment generally include:

- proven progression of keratoconus
- age < 30 years
- corneal thickness > 400-450 microns (Expert reviewers).

Box 1. The Dresden Protocol

The original cross-linking procedure (commonly referred to as the 'Dresden protocol') involves anaesthetising the eye (for example with proxymetacaine hydrochloride 0.5% drops), removing the central 8-10mm of the epithelium and applying a riboflavin solution (0.1% riboflavin-5-phosphate and 20% dextran T-500) to the corneal surface 30 minutes before irradiation and at 5 minutes intervals during the course of a 30 minute exposure to 370 nm UVA with an irradiance of 3 mWcm⁻².

After treatment, antibiotic eye drops are applied and a therapeutic soft contact lens with good oxygen transmissibility placed upon the eye to decrease pain without decreasing the quality of the regrowing epithelium. Application of topical antibiotics is required for 1 week after the operation and mild steroids may also be prescribed. Patients are usually pain-free within 5-7 days when the contact lens is removed.

As described by UK Cross-linking consortium website <http://sites.cardiff.ac.uk/ukcxl/standard-procedure/> with reference to Wollensak et al. (2003), Abad and Panesso (2008) and Spoerl et al. (2007).

Young people are targeted for treatment because the incidence of corneal scarring increases with age (Sykakis et al. 2015). The ideal candidate for CXL is a person who has early keratoconus with evidence of progression and a corneal epithelium of 450 microns thickness or more, although any patient with proven progression may benefit if the cornea is thick enough. Corneas below the limit of 450 microns may have hypotonic riboflavin before the procedure; if thickness then increases above 450 microns CXL can be carried out (Expert reviewer).

The standard CXL procedure follows the Dresden protocol. This is an "epithelium-off" procedure: the epithelium of the cornea is removed to allow penetration of riboflavin into the corneal tissue. Box 1 describes the Dresden protocol in more detail.

2.2. Alternative treatment options

In accelerated CXL procedures, higher illumination intensities are applied for a shorter period of time to deliver the same level of UVA exposure. Expert reviewers noted that very short exposure times may be less effective and carry a risk of collateral damage due to deeper penetration of UVA.

Intrastromal Corneal Ring Segments (ICRS) flatten the cornea and may slow disease progression (NICE 2007). This procedure may be suitable for some patients with keratoconus. The ideal candidate is a patient who has early to moderate keratoconus who is unable to fit rigid contact lenses. The ring segments may reshape the cornea in a way that the patient may be able to better tolerate contact lenses or glasses. There is little evidence of impact on slowing down or stopping keratoconic progression (Expert reviewers).

Some alternative procedures are not routinely available via the NHS. For example, NICE recommends that the following procedures are only carried out under special arrangements for clinical governance, consent and audit or research (NICE 2013):

- In "epithelium-on" CXL (also called transepithelial CXL), the corneal epithelium is left intact, requiring a longer riboflavin loading time.
- CXL procedures are sometimes used in combination with other interventions to improve visual acuity or halt the progression of keratoconus, including ICRS implantation, photorefractive keratectomy or phakic intraocular lens implantation. These combination procedures are referred to as 'CXL plus'.

Photorefractive intrastromal crosslinking (PiXL) is a refractive procedure; it is not indicated for halting keratoconus progression and is therefore beyond the scope of this review.

2.3. Clinical pathway and use of the procedure in Wales

A new corneal pathway was agreed earlier this year among eye health stakeholders and Welsh Government (Expert reviewer).

The usual patient pathway is:

- Patient referred to outpatient clinic by optometrist.
- Ninety-minute appointment (seen in turn by nurse, technician, optometrist and consultant).
- The current NICE interventional procedure guidance (2013) indicates that treatment may be performed when progressive ectasia has been demonstrated. However, some surgeons will treat children (< 17 years) and adults on presentation.
- This initial appointment can lead to several outcomes
 - (i) a few patients will be discharged because they do not have keratoconus, are not suitable for treatment, or they don't want treatment
 - (ii) some will be listed for surgery at the initial appointment (severe disease in the other eye, relative youth)
 - (iii) others will need to be seen again for assessment for progression of their disease.
- Follow-up assessment appointments may be done by nurses/optometrists and further tests for suitability will be carried out at this stage (Expert reviewer).

A single surgeon offers CXL treatment as indicated to all eligible patients within Abertawe Bro Morgannwg University Health Board (ABMUHB) (Expert reviewers). A variation of the Dresden protocol is used, with VibeX Rapid drops (Avedro Inc.) for 10 minutes, followed by 30 minutes of CXL treatment. Referrals for CXL for adult patients living elsewhere in Wales are currently considered independently by each health board on a case by case basis, depending on the clinical circumstances of the patient (Expert reviewers).

Twenty-four funding applications have been made for adults to NHS Wales for corneal crosslinking since 2015 (Expert reviewer).

The University Hospitals Bristol NHS Foundation Trust, Queen Victoria Hospital NHS Foundation Trust (East Grinstead), the Royal Liverpool and Broadgreen University Hospitals NHS Trust and Moorfields Eye Hospital NHS Foundation Trust (London) undertake CXL procedures; health boards in Wales may commission treatment from these hospitals.

3. Evidence search methods

The Population-Intervention-Comparator-Outcomes framework for the evidence appraisal (Appendix 1) was developed following comments from the Health Technology Wales (HTW) Assessment Group and UK experts.

A systematic literature search to study clinical effectiveness was undertaken on 23-25 August 2017 (search strategy available on request). This aimed to identify the following types of evidence:

- (i) systematic reviews of randomised controlled trials (RCTs) and cost effectiveness studies published after 2000, chosen as a cut-off date as CXL is a relatively new procedure, first used in the early 2000s (Wollensak et al. 2003),
- (ii) RCTs published after 2013 (this date cut-off was chosen because the scoping stage identified systematic reviews that summarise the evidence on CXL published up to this time), and
- (iii) ongoing clinical trials.

Background studies and other papers identified at the scoping stage were also assessed for relevance.

Databases searched included Medline, Embase and the Cochrane database of systematic reviews. In addition, guideline and technology appraisal databases and relevant websites were searched. The latter included those specifically relevant to healthcare and government in Wales. Terms used in all searches included: keratoconus, collagen, crosslink*, epitheli*and adult.

The searches returned 101 articles. Appendix 2 summarises the selection of articles for inclusion in the review. Three systematic reviews included evidence solely from RCTs; the others all included non-randomised studies and so did not meet inclusion criteria. An additional 21 RCTs and three papers with some economic relevance were shortlisted as potentially relevant. The most recent systematic review of RCTs (Kobashi and Rong 2017) was chosen as being most relevant to the decision problem. Of the two older systematic reviews, one (Li 2015) was judged to be of insufficient methodological quality and is not discussed further; the other (Sykakis et al. 2015) was similar in scope to the review by Kobashi and Rong (2017) and is summarised in Appendix 3.

As the most recent systematic review was based on a literature search carried out in January 2016. RCTs published before 2016 were excluded. The same systematic review studied the effectiveness of CXL after one year of follow up; studies were excluded at this stage if they did not report a follow-up period of at least one year.

For ongoing clinical trials, a search of Current Controlled Trials (which includes the ISRCTN register and the metaRegister of Controlled Trials), OpenTrials.net and WHO Clinical Trial portal found 72 unique records. Of these, 62 were excluded because they had been abandoned, findings had not been reported within a reasonable time frame, or they were not relevant to the decision problem. Of the 10 remaining trials, five were excluded because they had a maximum length of follow up of six months for the primary outcome measure. The remaining five trials were investigated to assess the likelihood of relevant new evidence in the near future.

For patient safety, the systematic review and RCTs included in the clinical effectiveness section were reviewed. Organisational and patients' issues were identified in the papers reviewed for clinical effectiveness and expert advice; no specific searches were undertaken.

Forest plots to illustrate the results of the meta-analyses for the four primary outcomes of the systematic review were reproduced for clarity using RevMan version 5.3 (Cochrane Collaboration 2014).

4. Clinical effectiveness

4.1. Systematic review

The objective of the systematic review conducted by Kobashi and Rong (2017) was to evaluate the efficacy of epithelium-off CXL one year after treatment of keratoconus compared to no treatment.

Studies were included in the 2017 review if they met the following criteria:

- Patients with a diagnosis of progressive keratoconus (Amsler-Krumeich grades I and III)
- Randomised controlled trials
- Compared treatment with Dresden protocol CXL to no treatment, using either different patients or the contralateral eye of the same patients as controls
- Minimum of one year follow-up post treatment
- Followed the Dresden protocol for CXL
- Reported original clinical data pre- and post-operatively.

Progression of keratoconus was defined as an increase of at least 0.75 diopter (D) in the steepest keratometry, a degradation of visual acuity, and an increase of 0.75 D or more in the manifest cylinder over the preceding 12 months.

Exclusion criteria included:

- Use of CXL combined with other treatments (CXL-plus)
- Studies that included patients with a history of corneal surgery and corneal pachymetry less than 300 μ m
- Use of riboflavin drops alone (as a sham control)
- Data from previously reported cases included in different articles
- Cohort studies, case-control studies, and studies that did not use a random method to prospectively assign participants to two groups
- Non-English language or non-human participants.

Primary and secondary outcomes selected by the review authors are described in Table 1. Outcomes were measured as the change in values between baseline and one-year follow-up. An expert reviewer advised that the maximum keratometry value (Kmax), best spectacle-corrected visual acuity (BSCVA) and refraction are particularly relevant outcomes.

Table 1: Outcome measure definitions, adapted from Kobashi and Rong (2017)

Outcome measure	Abbreviation	Unit	Definition
Primary			
Maximum keratometry value	Kmax	D	The steepest keratometry value obtained using topographies of a rotating Scheimpflug camera or computerised videokeratography
Thinnest corneal thickness	-	µm	The thickness of the thinnest point using ultrasound pachymetry
Best spectacle-corrected visual acuity*	BSCVA	logMAR	The visual acuity corrected by only glasses*
Uncorrected visual acuity	UCVA	logMAR	The visual acuity without correction
Secondary			
Spherical equivalent refraction	SE	D	The manifest subjective refraction of the SE
Cylindrical refraction	-	D	The manifest subjective refraction of the cylinder

D = diopter, logMAR = logarithm of the minimum angle of resolution.

*In this review, BSCVA also includes visual acuity corrected by contact lenses.

Meta-analyses were carried out unless there was evidence of significant heterogeneity ($I^2 > 50\%$). Where there were three or fewer studies, a fixed-effects model was used. A random-effects model was used if four or more studies were available. The weighted mean difference was used to compare intervention and control groups according to mean changes \pm standard deviation between baseline and one-year follow-up.

Five RCTs met the eligibility criteria and were included in this systematic review (table 2). A total of 289 eyes were included.

Table 2: Characteristics of trials evaluating CXL vs no treatment, adapted from Kobashi and Rong (2017).

First author (year)	Country	Number of eyes		Mean age (years)	Mean baseline Kmax (D)	Control design	Primary outcome measure(s)	Follow-up (months)*
		CXL	No treatment					
Greenstein (2011)	US	49	21	NR	60	Intra-patient	NR	12
Lang (2015)	Germany	15	14	30	47	Different patients	Kmax	36
O’Brart (2011)	UK	22	22	30	54	Intra-patient	NR	18
Seyedian (2015)	Iran	26	26	26	49	Intra-patient	Kmax, BSCVA, and Kmean	12
Wittig-Silva (2014)	Australia	46	41	26	53	Different patients	NR	36

*Where follow up was longer than 12 months, it is assumed that outcome data at 12 months was used.

BSCVA = Best Spectacle-Corrected Visual Acuity, CXL = Corneal cross-linking, D = diopter, Kmax = Maximum keratometry value, Kmean = Mean keratometry value, NR = not reported.

Summarised results of the meta-analyses are presented in table 3. For three of the outcome measures (Kmax, UCVA and SE), there was significant heterogeneity ($I^2 > 50\%$) in the size of the treatment effect: meta-analysis was not carried out for these outcomes.

Table 3: Summary of results of meta-analyses evaluating CXL vs no treatment, adapted from Kobashi and Rong (2017).

Outcome measure	IV Model	Number of eyes		Mean difference	95% CI	I^2	p value for overall effect
		CXL	Control				
Kmax (D)	Random	158	124	-	-	81%	-
Thinnest corneal thickness (μm)	Fixed	94	89	1.46	-2.77, 5.68	35%	0.50
BSCVA (logMAR)	Random	143	110	-0.09	-0.14, -0.04	0%	0.0005
UCVA (logMAR)	Fixed	117	84	-	-	57%	-
SE (D)	Fixed	94	89	-	-	66%	-
Cylindrical refraction (D)	Random	143	110	-0.25	-0.76, 0.26	46%	0.34

Where I^2 exceeded 50%, this was interpreted as indicating substantial statistical heterogeneity and therefore results were not pooled by the study authors.

BSCVA = Best spectacle-corrected visual acuity, CXL = Corneal cross-linking, D = diopter, I^2 = heterogeneity, IV = inverse variance, Kmax = maximum keratometry value, logMAR = logarithm of the minimum angle of resolution, SE = Spherical equivalent refraction, UCVA = Uncorrected visual acuity.

As shown in Figure 1, there was a statistically significant difference between groups in the change in BSCVA at one year (-0.09 logMAR; 95% CI -0.14, -0.04; $p = 0.0005$). Kobashi and Rong (2017) note that this is unlikely to reflect a clinically significant difference as this value “is less than a line on an eye chart and is within typical test-retest variability”. One expert reviewer suggested that if follow-up had continued for a longer period, this difference in the rate of deterioration had the potential to become substantial.

The change in thinnest corneal thickness did not differ significantly between groups (mean difference 1.46 μm ; 95% CI -2.77, 5.68; $p = 0.50$) (Figure 2). All of the included trials reported a reduction in maximum keratometry (Kmax) in favour of CXL (Figure 3). However Kobashi and Rong did not report an overall treatment effect for this measure due to a high degree of heterogeneity ($I^2 = 81\%$). Similarly, change in UCVA was not considered to be suitable for meta-analysis due to high levels of heterogeneity ($I^2 = 57\%$) (Figure 4). Forest plots for secondary outcomes (Figures 5 and 6) can be found in Appendix 4.

Kobashi and Rong (2017) noted that evidence was limited due to the small number of cases per trial, and the total number in the systematic review (289 eyes) as well as significant heterogeneity between the trials for some outcomes. All five trials were judged by the review authors as at low risk of bias for sequence generation and allocation concealment. There was a high risk of bias for blinding of study participants and personnel, and unclear blinding of outcome assessors. One study (Wittig-Silva 2014) was at risk of attrition bias. Kobashi and Rong (2017) also highlighted the possibility of publication bias, suggesting that those studies which showed no effect might not have been published.

Further considerations regarding the quality and relevance of the evidence include:

- Only one of the five trials included in the review included data from a UK context. Results achieved in other populations and health services may not be generalisable to the Welsh population.
- The definition of BSCVA in this review included use of contact lenses, which should not be considered as equivalent to spectacles (Expert reviewer)
- Although multiple meta-analyses were carried out to evaluate the four primary outcome measures and two secondary outcome measures, there is no evidence that the authors adjusted for multiplicity. Where multiple outcomes are tested for statistical significance without adjustment for this, there is a risk of an apparently statistically significant effect being artificially generated for at least one outcome measure.

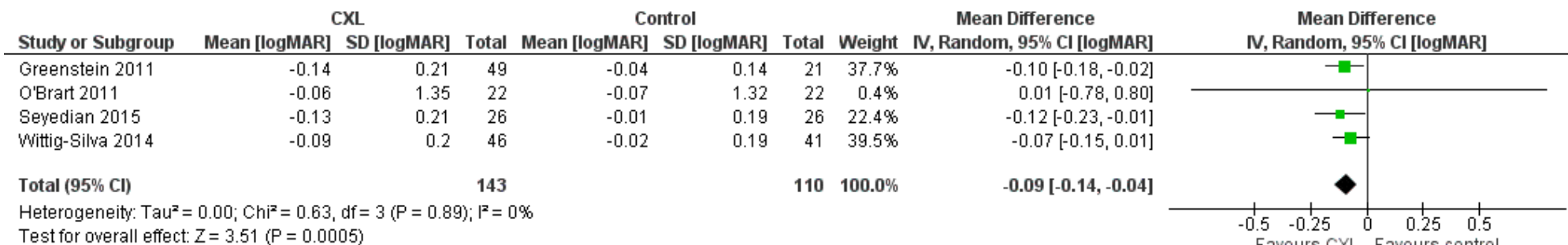


Figure 1. Change in BSCVA between CXL and control groups, adapted from Kobashi and Rong (2017).

BSCVA = Best spectacle-corrected visual acuity, CI = confidence interval, CXL = Corneal cross-linking, df = degrees of freedom, I² = heterogeneity, IV = inverse variance, logMAR = logarithm of the minimum angle of resolution, SD = standard deviation.

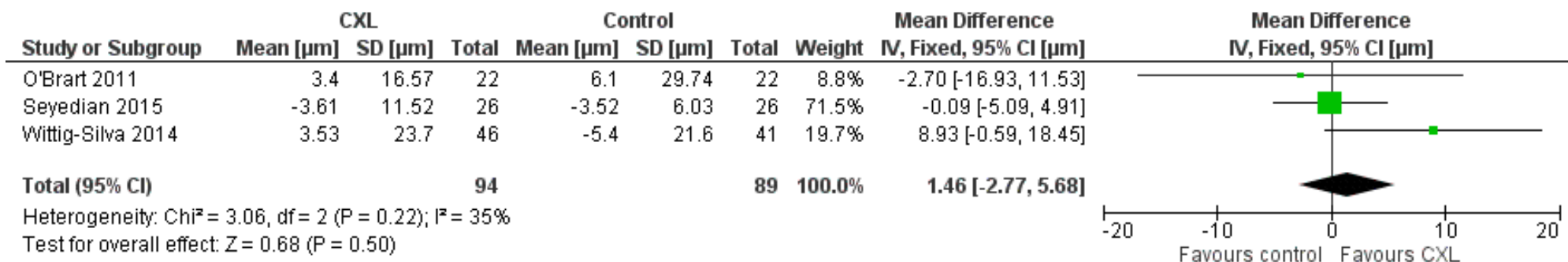


Figure 2. Change in thinnest corneal thickness between CXL and control groups, adapted from Kobashi and Rong (2017).

CI = confidence interval, CXL = Corneal cross-linking, df = degrees of freedom, I² = heterogeneity, IV = inverse variance, SD = standard deviation.

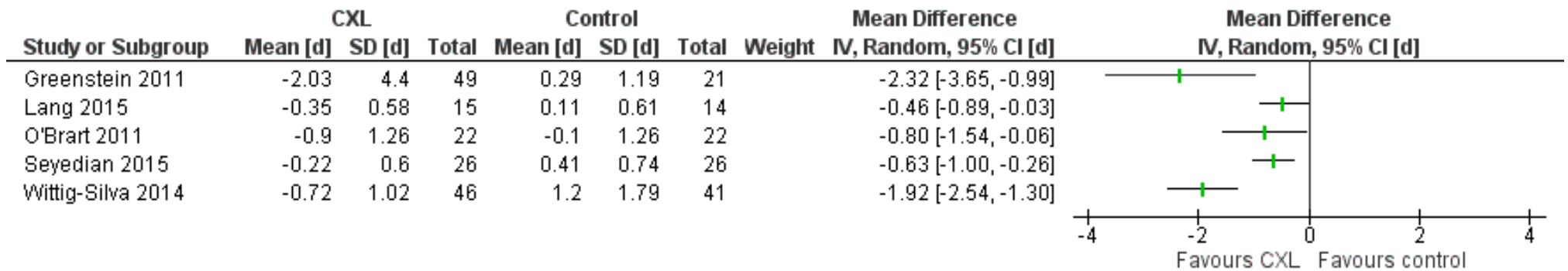


Figure 3. Change in maximum keratometry value (Kmax) between CXL and control groups, adapted from Kobashi and Rong (2017).

Heterogeneity: $\tau^2=0.35$, $\chi^2=20.53$, $df=4$ ($P=0.0004$); $I^2=81\%$. CI = confidence interval, CXL = Corneal cross-linking, d = diopter, df = degrees of freedom, I^2 = heterogeneity, IV = inverse variance, SD = standard deviation.

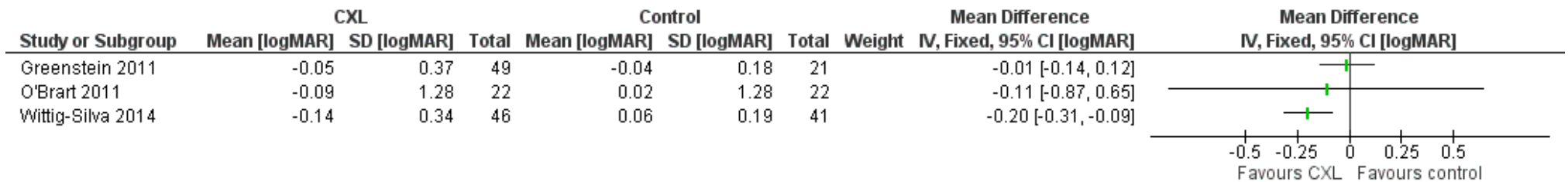


Figure 4. Change in UCVA between CXL and control groups, adapted from Kobashi and Rong (2017).

Heterogeneity: $\chi^2=4.67$, $df=2$ ($P=0.10$); $I^2=57\%$. CI = confidence interval, CXL = Corneal cross-linking, df = degrees of freedom, I^2 = heterogeneity, IV = inverse variance, logMAR = logarithm of the minimum angle of resolution, SD = standard deviation, UCVA = Uncorrected visual acuity.

4.2. Additional studies

As discussed in Section 3, randomised trials were considered eligible only if they were published after the search date of the systematic review by Kobashi and Rong (2017). No RCTs were identified that met this requirement, whilst also being directly relevant to the inclusion criteria (Appendix 1). One study (Kim 2016) compared CXL to no treatment, but only reported a single outcome (corneal densitometry) that was not considered to be relevant to this review. This study was part of a wider RCT of CXL in patients with progressive keratoconus: further results from this RCT have not been identified by this review and the timescale for their publication is not known. A second study by Rosenblat and Hersh (2016) treated keratoconus patients who were treated with CXL, but compared two different types of riboflavin. Since this study did not compare CXL to control/no treatment, it was judged as not relevant to this review.

To check whether any long-term observational studies could confirm a sustained treatment effect, a supplementary review was carried out by Health Technology Wales, focusing on studies with minimum follow-up duration of three years. The findings are reported in a supplementary report, which concluded that the long-term studies were not of sufficient quality to verify long-term effectiveness.

4.3. Ongoing trials

Four ongoing randomised clinical trials have some relevance to this work but have not yet reported findings. Some include children, and only one is expected to be followed up for more than one year (Registration reference: NCT02883478). Details of these trials can be found in Appendix 5.

5. Safety

Patient safety outcomes were not reported in the main systematic review (Kobashi and Rong 2017).

The NICE Interventional Procedural guidance for epithelium-off corneal cross linking for keratoconus noted that as CXL is a relatively new technique there were limited data available regarding the long-term risks and benefits of the procedure (NICE 2013). Risks associated with the procedure included some loss of vision in the treated eye as a result of haze, scarring, corneal surface shape irregularity or infection. NICE advised that the evidence on the safety and efficacy of epithelium-off CXL was adequate both in quantity and quality, and that this procedure could be carried out provided that normal arrangements are in place for clinical governance, consent and audit (NICE 2013).

Removal of the corneal epithelium may lead to postoperative discomfort for patients. Other patient safety issues were discussed in the RCTs summarised earlier in this report. Kim et al. (2016) reported the development of transient haze after CXL, although it was not thought to require specific treatment. Nordstom et al. (2017) reported that no corneal endothelial cell loss was seen after CXL procedures. In the RCT which compared two different types of riboflavin, the authors reported that no resulting effects on patient safety were observed (Rosenblat and Hersh 2016).

The FDA did not consider information on patient safety in the context of CXL as part of their approval of Riboflavin ophthalmic solution (FDA 2015). The evidence in support of this approval stated that the incidence of adverse events in the included trials was small, no deaths were reported and the most common ocular adverse reactions in any CXL-treated eye were corneal opacity (haze), punctate keratitis, corneal striate, corneal epithelium defect, eye pain, reduced visual acuity, and blurred vision. They advised that more long-term data was needed, but approved the treatment (FDA 2015). CXL became available to patients in the US in 2016 (FDA 2016).

6. Economic evaluation

6.1. Cost effectiveness

The systematic literature search identified three relevant publications reporting economic evidence. One was a Health Technology Assessment report published by the Australian Medical Services Advisory Committee (MSAC 2015) stating a proposed fee for CXL procedures of \$1,500 (converted and inflated to 2017 GBP: £739). The other two studies were cost-utility analyses based on decision-analytic modelling.

A Canadian study (Leung et al. 2017) used patient-level microsimulation over a lifetime horizon to calculate an ICER of CXL compared to conventional management of CAN\$9,090 (converted to 2017 GBP: £5,257) per quality-adjusted life year (QALY) gained.

The third publication was the focus of this economic assessment as it was most relevant to the decision problem in question. This was a modelling study conducted within the UK NHS (Salmon et al. 2015). This evaluation compared the cost-effectiveness of CXL to standard management, using a Markov model with five health states over a 25-year horizon. Progression of keratoconus was indicated using Amsler-Krumeich stages (AK I to IV, and grafted). The rate of progression was based on published epidemiological studies, and was assumed to be constant at 1.01 D per year for both eyes. After the initial diagnosis, the contralateral eye was assumed to start deteriorating 5 years later, commencing at AK stage 1. All diseased eyes in the model were then assumed to progress at the same rate for 10 years, or until they reach AK stage 3. Patients enter the model at age 21 years.

After initial assessment, people in the standard management group receive contact lens correction, with new contact lenses being provided every two years. Annually 1.3% of people in the model reach AK stage 4, at which stage CXL is contraindicated due to safety concerns and lack of efficacy; many of these patients undergo corneal transplantation. Following surgery, patients are invited to attend regular outpatient follow-up appointments. Systemic immunosuppression and monitoring of haematological parameters for three and a half years is assumed in 7.5% of these patients.

In the CXL group, initial keratometry provides an indication of the stage of progression. Eligible patients then undergo bilateral crosslinking, followed by further keratometry to assess efficacy. Contact lens correction is still required, with replacement lenses assumed to be supplied every two years. The model assumes that CXL stops progression without leading to disease improvement; after CXL visual acuity is assumed to remain constant over the remainder of the modelled time horizon. This is based on sustained mean improvements in corneal power and visual acuity benefit at 5-year follow-up in 12% of a cohort of patients with keratoconus (44/363) recruited in an observational study (Caporossi et al. 2010). Furthermore, 7.6% of modelled treatments are assumed to fail with subsequent retreatment. Adverse events were taken into consideration for corneal transplantation, but not for CXL.

No utility data were available to measure the impact of keratoconus on quality of life. Instead, an estimate was based on the expected visual acuity of each disease stage (according to mean visual acuity values measured in association with AK stages 1, 2, and 4 from a published study) and data from linear regression models based on the time trade-off (TTO) method. Costs were derived from the NHS National Tariff 2012-2013 discounted at 3.5%.

6.1.1. Results

The ICER reported by Salmon et al. (2015) is £3,174 per QALY gained with a probability of being cost-effective at the £20,000 and £30,000 willingness to pay thresholds of 79% and 85%, respectively. This ICER is sensitive to changes in the effect duration of CXL, rising to £33,263 per QALY gained if no further treatment benefit is assumed after five years.

6.1.2. Strengths and limitation of the economic analysis (Salmon et al. 2015)

- The study was well designed with a robust model, transparent methodology and costs derived from UK NHS tariffs.
- However, the study was limited by the lack of available data; estimations of efficacy depended on small, mostly single-centre, studies with a distinct lack of long-term follow-up to date. The assumption of no further progression after CXL over the model horizon of 25 years is based on 12% (n=44) of a cohort with available five-year follow-up data in an Italian study (Caporossi et al. 2010). These data showed a stabilisation in year two of follow-up, maintained until year five. However, the sample size was small and no follow-up data beyond five years were available. Furthermore, the sensitivity analysis showed a large effect on this assumption on the ICER resulting in £33,263 per QALY gained if no stable effect is assumed beyond year five. Cost-effectiveness of CXL is therefore highly dependent on the effect duration, which remains questionable.
- There is considerable uncertainty around the progression of disease in the contralateral eye. The model assumes disease starts in the contralateral eye after five years, following the same progression as the first eye. However, very little evidence was found to support or validate this assumption.
- No utility data were available to inform the model. Data manipulation and assumptions were required to estimate values associated with visual acuity, but it was not impossible to ascertain how realistic the utility values used in the model are.
- No source information was received to confirm the cost of the CXL procedure in Wales; the plausibility of the costs used in the model could not be verified without additional further information being provided.

6.1.3. Costs of CXL

The costs of CXL as reported in Salmon et al. (2015) are shown in table 7.

Table 7. Cost of CXL treatment for a single eye (Salmon et al. 2015)

CXL treatment	Cost (2012-2013)	Source
Procedure	£212	NICE OPCS 51.8
Riboflavin (1ml solution)	£75	Kestral Ophthalmics Ltd
4 outpatient visits	1 x initial (£115) 3 x follow-up (£67)	NHS national tariff 2012-2013
2 keratometry measurements	2 x £145	
Follow-up medication: acyclovir, chloramphenicol, fluorometholone, gabapentin, proxymetacaine, co-codamol	£35	
Total	£928	
Inflated to 2016-2017	£980	

The likelihood and plausibility of the accuracy of the reported ICER of £3,174 per QALY gained in the study by Salmon et al. (2015) depends upon the costs associated with the service.

It has been reported by a Welsh commissioner that the cost of CXL is £1,800 for both eyes when commissioned in Bristol (Expert reviewer). This is broadly consistent with the cost estimated in the Salmon et al. (2015) paper. It offers an estimated ICER of £3,063 per QALY gained, using their model (with permission of the authors).

The service which has been introduced in Wales may be marginally more costly than the charge for the service commissioned from Bristol. Using a representative cost for a Welsh service of £2,000 for two eyes would result in an ICER of £3,459 per QALY gained.

7. Organisational issues

The CXL procedure can be carried out as an outpatient procedure in a clean room with the use of topical anaesthesia. The length of the procedure is typically 60-90 minutes, including preparation, removal of the epithelium and application of dressings. Follow-up takes place at normal eye clinic appointments (Expert reviewers).

The procedure could be carried out in a normal clean room in approximately one hour, with follow up at normal eye clinics. However an operating microscope is needed and these are only found in operating theatres. Some of these are already operating at full capacity and an extra service would have an impact on resources. Introducing this procedure would require more clinic assessments, and therefore need more clinic rooms, nursing support, theatre time, space for the equipment and so on. In a few more complicated cases, such as patients with relevant co-morbidities, general anaesthesia would be required (Expert reviewers).

Expert reviewers felt that this was a relatively simple operation and could be learned by observing an experienced surgeon, visits to other units, or participating in training events.

At present there appear to be few NHS providers offering this treatment in Wales, and some patients are referred for treatment in England. The current geographical variation in service provision is likely to contribute to inequity of access.

Optometry Wales is the professional umbrella organisation representing all primary care optometrists, dispensing opticians and optometric practices across Wales. They strongly encouraged consideration of delivery of parts of this service through primary care. Reasons provided were:

- hospital eye services in Wales are 'crowded'
- rurality issues
- cost and resource savings
- Welsh Government commitment to move services into primary care.

Optometry Wales also referred to a report prepared by a Corneal Task and Finish Group, which proposed the development of a centralised corneal service for South Wales. CXL procedures were included amongst the proposed treatments to be provided by the service. No evidence specific to CXL was referenced other than the NICE Interventional Procedures guidance (NICE 2013).

8. Patient issues

If a patient has visual impairment to the extent that it has a substantial and long-term impact on day-to-day activities, they could be considered as having a disability. Disability is one of the protected characteristics of the Equality Act (2010).

9. Conclusions

- Evidence supporting the clinical effectiveness of the epithelium-off CXL procedure is limited in quantity and quality. In particular, there is limited evidence about outcomes in patients treated with CXL beyond one year of follow up. Long-term studies of the clinical effectiveness of CXL are needed, as has previously been highlighted (NICE 2013; FDA 2015; Kobashi and Rong 2017, Sykakis et al. 2015).
- A recent meta-analysis (Kobashi and Rong 2017) compared outcomes for eyes treated with epithelium-off CXL with those which received no treatment. The authors reported a statistically significant difference in favour of the CXL group for best spectacle-corrected visual acuity, one year after follow up (-0.09 logMAR; 95% CI -0.14, -0.04, $p = 0.0005$). The clinical significance of this small difference is uncertain in the long term.
- The same meta-analysis did not find any statistically significant differences between epithelium-off CXL and no treatment for the change in corneal thickness or cylindrical refraction (12 months follow up). It was not possible to reach conclusions for three other outcome measures (change in maximum keratometry value, uncorrected visual acuity or spherical equivalent refraction) due to significant heterogeneity between included studies. An earlier Cochrane review by Sykakis et al. (2015) reached similar conclusions to Kobashi and Rong about the effectiveness of CXL despite using a different approach to measure outcomes.
- A thorough evaluation of the safety of the use of riboflavin eye drops in treatments for keratoconus was undertaken by the FDA. A small number of adverse events was identified, mostly ocular reactions. NICE interventional procedures guidance (NICE 2013) concluded that the evidence supporting safety of standard epithelium-off CXL is sufficient in quantity and quality to allow its use under normal arrangements.
- The cost-effectiveness evidence for CXL is limited. A detailed and robust economic model was identified which suggests that there is a high likelihood that CXL is cost-effective. However, this conclusion was highly dependent on the clinical effectiveness and effect duration of CXL which has not been robustly demonstrated, especially beyond five years.
- The service currently being established in Wales is estimated to be marginally more costly (ICER of £3,459 per QALY gained) than the service provided in Bristol by referral (ICER of £3,063 per QALY gained).
- Provision of the service appears to be straightforward with respect to technology needs, patient pathways and staff training, once the necessary equipment is made available.

10. Further research

Research is recommended into the long-term clinical effectiveness and cost-effectiveness of epithelium-off CXL to treat adults with keratoconus compared with no treatment.

11. Contributors

The HTW staff and contract researchers involved in writing this report were:

- M Callaghan - main author and reviewer
- S Wilson - systematic literature searching
- T Winfield and B Sewell - economic appraisal
- R Poole - quality assurance and editing
- D Jarrom - quality assurance and editing
- K Facey - second abstract selection, editing and early project oversight
- S Myles - final project oversight.

The HTW Assessment Group advised on methodology throughout the scoping and development of the report.

A range of clinical experts from the UK provided material and commented on a draft of this report. Their views were documented and have been actioned accordingly. All contributions from reviewers were considered by HTW's Assessment Group. However, reviewers had no role in authorship or editorial control, and the views expressed are those of Health Technology Wales.

Review period

Two years after the date of publication, a high-level literature search will be undertaken to determine if there is new evidence that could alter the conclusions of this report. If so, the appraisal will be updated.

12. Glossary

ABMUHB	Abertawe Bro Morgannwg University Health Board
AK	Amsler-Krumeich (stage of keratoconus progression)
BSCVA	Best Spectacle-Corrected Visual Acuity
CI	Confidence Interval
CXL	Corneal Cross-Linking
CXL-plus	Corneal Cross-Linking used in combination with other procedures
FDA	Food and Drug Administration
HTA	Health Technology Assessment
HTW	Health Technology Wales
ICER	Incremental Cost-Effectiveness Ratio
ICRS	Intrastromal Corneal Ring Segments
IV	Inverse Variance
Kmax	Maximum keratometry value
Kmean	Mean keratometry value
NICE	National Institute for Health and Care Excellence
PICO	Population - Intervention - Comparators - Outcomes
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QALY	Quality-Adjusted Life Year
RCT	Randomised Controlled Trial
SD	Standard Deviation
SE	Spherical equivalent refraction
UCVA	Uncorrected Visual Acuity
UVA	Ultraviolet A

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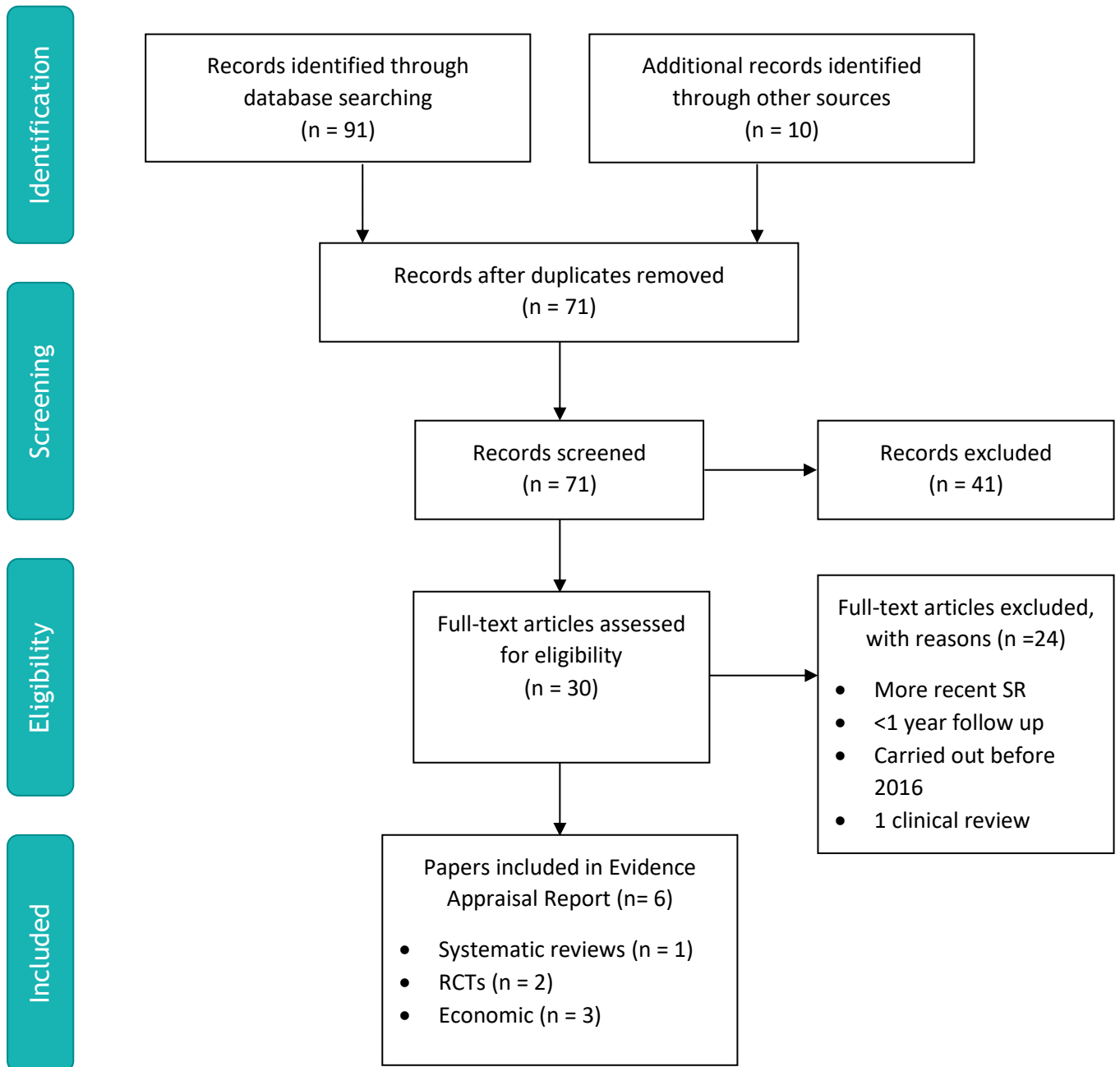
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Appendix 1. PICO framework

P (population)	Adults with keratoconus
I (intervention)	Epithelium-off corneal crosslinking (CXL)
C (comparator(s))	<ul style="list-style-type: none">• Accelerated CXL• Contact lenses• Glasses• No treatment
O (outcomes)	<ul style="list-style-type: none">• Changes in maximal keratometry• Corneal power/thickness• Uncorrected visual acuity• Health Related Quality of Life• Delay of disease progression• Adverse events
Training Needs	<ul style="list-style-type: none">• Ophthalmologists need to be trained to perform this procedure

Appendix 2 - PRISMA flow diagram outlining selection of papers for clinical and cost effectiveness (from 2000 - August 2017)



Appendix3. Summary of the systematic review by Sykakis et al. (2015)

In addition to the recent review by Kobashi and Rong (2017), the evidence search identified a Cochrane review (Sykakis 2015), the objective of which was to assess whether CXL is an effective and safe treatment for halting the progression of keratoconus compared to no treatment. The last search update was on 28 August 2014. The review looked for RCTs using any CXL protocol, but all the evidence identified (three studies; 219 eyes) used epithelium-off techniques. The quality of the evidence was all assessed as very low using GRADE criteria. The authors did not pool outcomes from individual trials, but the results presented suggest that whilst CXL may reduce the risk of disease progression over 12 months, effect size is very uncertain. The authors of the review concluded that there is a lack of evidence from RCTs that CXL is an effective treatment in halting the progression of keratoconus. No concerns with the methodological quality of this review were identified.

One further systematic review of RCTs (Li 2015) was identified, but had several methodological limitations: the review authors did not clearly define the types of control treatments included. No distinction was made between studies using no treatment or a sham control. The majority of pooled analyses had high ($I^2 > 75\%$) heterogeneity, possibly due to pooling of outcomes from trials using different types of control treatments. It was also unclear how the authors accounted for the different follow-up times used across trials. Finally, several subgroup and sensitivity analyses were conducted and used to draw conclusions, but it is not clear whether these were pre-planned.

Appendix 4. Results of meta-analyses for secondary outcomes as reported by Kobashi and Rong (2017)

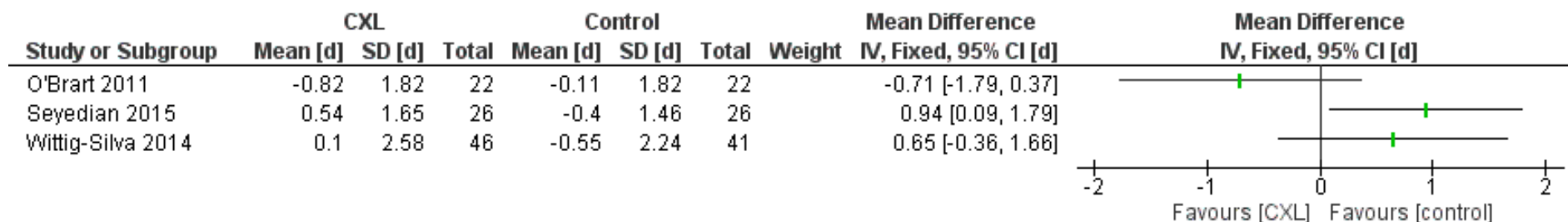


Figure 5. Change in the spherical equivalent refraction (d) between CXL and control groups, adapted from Kobashi and Rong (2017).

Heterogeneity: $\text{Chi}^2=5.89$, $\text{df}=2$ ($P=0.05$); $I^2=66\%$. CI = confidence interval, CXL = Corneal cross-linking, d = diopter, df = degrees of freedom, I^2 = heterogeneity, IV = inverse variance, SD = standard deviation.

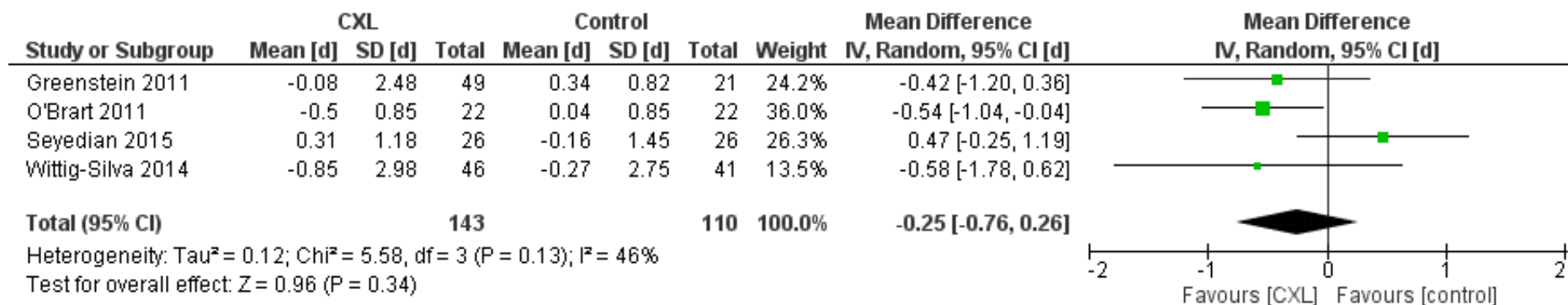


Figure 6. Change in the cylindrical refraction (d) between CXL and control groups, adapted from Kobashi and Rong (2017).

CI = confidence interval, CXL = Corneal cross-linking, d = diopter, df = degrees of freedom, I^2 = heterogeneity, IV = inverse variance, SD = standard deviation.

Appendix 3. Summary of ongoing randomised controlled trials

Study information	Status	Research question & outcome measures
<p>Registration: NCT01643226 https://clinicaltrials.gov/ct2/show/NCT01643226</p> <p>Country: US</p> <p>Target recruitment: 230 participants</p> <p>Max. follow-up: 12 months</p>	<p>Completed Sept 2016</p> <p>No Results posted Dec 2017</p>	<p>Safety and Efficacy Study of Corneal Collagen Cross-Linking in Eyes With Keratoconus.</p> <p>Population: Keratoconus, Age 12+ years</p> <p>Intervention: VibeX riboflavin solution</p> <p>Comparator: Placebo</p> <p>Primary Outcome Measure: Mean change in maximum keratometry between groups [Baseline to 6 months]</p> <p>Secondary Outcome Measure: Mean change in maximum keratometry between groups [Baseline to 12 months]</p>
<p>Registration: NCT02883478 https://clinicaltrials.gov/ct2/show/NCT02883478</p> <p>Country: Norway</p> <p>n = 40 participants</p> <p>Intended follow-up: 2 years</p>	<p>Started August 2012. Estimated completion date August 2016.</p> <p>Database entry not updated since August 2016.</p>	<p>Aimed to evaluate and compare different corneal parameters and clinical outcomes after CXL with conventional and accelerated UVA irradiation</p> <p>Population: Progressive Keratoconus, Age 18-30 years</p> <p>Intervention: CXL</p> <p>Comparator: Accelerated CXL</p> <p>Primary Outcome Measure: Change in maximum keratometry, BSCVA, UCVA, endothelial cell density (ECD) & depth of cross-linking</p> <p>Secondary Outcome Measure: Compare depth of crosslinking with ECD; compare depth of crosslinking with Kmax, BSCVA, and UCVA.</p>
<p>Registration: IRCT2015080723537N1 http://en.irct.ir/trial/20050</p> <p>Country: Iran</p> <p>Target recruitment: 72 participants</p> <p>Max. follow-up: 12 months</p>	<p>Unknown</p> <p>Anticipated recruitment end date August 2016. No further information.</p>	<p>Comparison of accelerated and conventional corneal collagen cross-linking for progressive keratoconus in visual acuity, topographic indices, endothelial cell density.</p> <p>Population: Progressive keratoconus, Age 12-35 years</p> <p>Intervention: Iontophoretic CXL</p> <p>Comparator: Standard CXL</p> <p>Primary Outcome Measure: Maximum keratometry [12 months]</p> <p>Secondary Outcome Measure: Minimum keratometry [3 months]</p>

Study information	Status	Research question & outcome measures
<p>Registration: NCT01868620 https://clinicaltrials.gov/show/NCT01868620 Country: France Target recruitment: 162 participants Max. follow-up: 12 months</p>	<p>Due to complete May 2017</p> <p>No results posted December 2017</p> <p>Trial information has not been updated since 2015</p>	<p>Iontophoretic CXL compared to standard CXL in progressive keratoconus (non-inferiority design)</p> <p>Population: Progressive keratoconus. Age 18+ years</p> <p>Intervention: Iontophoretic CXL</p> <p>Comparator: Standard CXL</p> <p>Primary Outcome Measure: Maximum keratometry [12 months]</p> <p>Secondary Outcome Measure: Minimum keratometry [3 months]</p>