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[Intervention Protocol]

Transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus

Irene C Kuo¹, Barbara S Hawkins², Mark Ren², Kristina B Lindsley³

¹Department of Ophthalmology, Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.

²Wilmer Eye Institute, The Johns Hopkins University School of Medicine, Baltimore, Maryland, USA. ³Life Sciences, Oncology, & Genomics, IBM Watson Health, Baltimore, Maryland, USA

Contact address: Irene C Kuo, Department of Ophthalmology, Wilmer Eye Institute, The Johns Hopkins University School of Medicine, 4924 Campbell Blvd #100, Baltimore, Maryland, 21236, USA. ickuo@jhmi.edu.

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ABSTRACT

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

The objective of this review is to assess the short-term and long-term effectiveness and safety of transepithelial CXL compared with epithelium-off CXL for progressive keratoconus.

BACKGROUND

Description of the condition

Keratoconus is a corneal condition that can cause loss of uncorrected and best-corrected visual acuity through ectasia (thinning) of the central or paracentral cornea, irregular corneal scarring, or corneal perforation. It is most commonly described as a corneal dystrophy but is influenced by environmental factors. The condition is bilateral but often asymmetric in severity (Rabinowitz 1998). Keratoconus is the most common corneal dystrophy; the prevalence in the Netherlands was recently estimated to be 1:375 (265 cases per 100,000, 95% confidence interval [CI]: 260 to 270) (Godefröoij 2017a), which is six times higher than the previous estimate of 1:2000 (Kennedy 1986). Analysis of data from 4.4 million individuals enrolled in the Netherlands' largest national health insurance provider showed an annual incidence of keratoconus of 1:7500 in the relevant age category (13.3 cases per 100 000, 95% CI: 11.6 to 15.2), which was also five to 10 times higher than previous population studies reported (Godefröoij 2017a). The reason for this increase is likely improved detection using corneal imaging.

Since the 1980s, when anterior corneal imaging devices became available, studies have reported keratoconus to be more prevalent in men than in women, although earlier studies based on clinical examination did not show gender association. In the study from the Netherlands, 60.6% of diagnosed patients were male, and the mean age at diagnosis was 28.3 years. In general, disease onset usually occurs in the second to fourth decade of life, which are periods of peak education attainment or career development in most developed countries. The condition is lifelong and sight-threatening. Therefore, keratoconus imposes a high economic burden on patients and caregivers (Rebenitsch 2011).

Studies from the United Kingdom have found that patients with India, Pakistan, and Bangladesh ethnicity have a higher prevalence of keratoconus compared with those from Northern Europe (Cozma 2005; Georgiou 2004; Pearson 2000). The differential disease burden surrounding gender, race, and ethnicity may arise from different diagnostic testing capabilities and different diagnostic criteria used in different populations over time.

Keratoconus is most commonly an isolated sporadic disorder. It has been reported to be associated with Down syndrome (Alio 2018; Rados 1948), and Leber congenital amaurosis (Elder 1994; Godel 1978), but is more often associated with atopy, wearing hard contact lenses, eye rubbing, and a positive family history of the disorder; in 13.5% of cases there is a family history of the disease (Zadnik 1998). The inheritance in these cases is thought to exhibit variable penetrance (Rabinowitz 1990). Therefore, both genetic and environmental factors probably contribute to the development of keratoconus.

Treatments like spectacles, contact lenses, intrastromal corneal ring segments, and corneal transplantation serve to improve vision but do not slow progression of disease, which corneal collagen crosslinking (CXL) purports to do.

Diagnosis

Aside from retinoscopic or slit-lamp biomicroscopic findings in longer-standing keratoconus (e.g. corneal iron ring, Vogt's striae, Munson's sign, evidence of previous corneal hydrops), earlier stages of keratoconus are evident using modern corneal imaging.

These devices include computer-assisted videophotokeratography or Scheimpflug imaging, which detects subtle abnormalities in topography of the anterior and posterior corneal surface, allowing detailed qualitative and quantitative analysis of corneal shape of the front and back surfaces. Placido-disc-based corneal topography provides tangential and axial dioptric power maps of the anterior corneal surface. Based on these maps, various topographic indices have been proposed for the diagnosis of preclinical (*forme fruste*) and clinical keratoconus, and the grading of disease severity. These image-based indices include asymmetry in dioptric power between inferior and superior hemispheres of the cornea, bow-tie asymmetry, and skewed astigmatic axes.

Newer Scheimpflug-based corneal tomography helps distinguish subclinical keratoconus and keratoconus from normal corneas by examination of anterior elevation and posterior elevation at the thinnest point, change in anterior elevation, change in posterior elevation, corneal thickness at the thinnest point, location of the thinnest point, pachymetric progression, and maximum keratometry (maximum curvature power of the whole anterior surface of the cornea, or "maximum K") (Cavas-Martínez 2016).

There is no universal method to diagnose keratoconus, especially *forme fruste* keratoconus. The best and safest method is to collect and analyze data using different modalities and to use established clinical parameters.

Pathogenesis

Corneal collagen fibrils are organized into bundles known as lamellae, of which there are about 300 in the central cornea and 500 in the peripheral cornea. Lamellae account for the biomechanical characteristics and strength of the normal cornea. Proteoglycans are an important component of the corneal stroma matrix. Biochemical and immunohistochemical studies of these proteoglycans show differences between normal and keratoconic corneas (Meek 2005; Raiskup-Wolf 2008). Corneal ectasia can develop in many different ways (e.g. fewer collagen lamellae than normal, fewer collagen fibrils per lamella, closer packing of collagen fibrils, or any combination of these). These conditions may arise from defects in the proteoglycans forming the extracellular matrix, destruction of previously formed components, an increased distensibility of corneal tissue causing sliding of collagen fibers or lamellae, or a combination of these mechanisms (Akhtar 2008; Hayes 2008).

Disease progression

Just as there are no definitive criteria for diagnosis of keratoconus, there are no definitive criteria for progression. Corneal changes apparent on slit-lamp biomicroscopic examination in overt cases of keratoconus are not always present to demonstrate evidence of progression; therefore, one cannot rely on clinical criteria alone. Increase in maximum keratometry (K) reading by 1 diopter (D) or more remains the most frequently reported index of disease progression (Caporossi 2010; Hersh 2011; Raiskup-Wolf 2008; Wittig-Silva 2008).

Other parameters used for disease progression include worsening of refractive or corneal astigmatism (a result of corneal ectasia that is progressing); change in uncorrected or corrected distance visual acuity, or both (O'Brart 2015; Poli 2015); and worsening of corneal topographical indices other than maximum K. These indices include simulated keratometry (SimK) or mean keratometry

(mean K) prior to CXL. When reviewing data for CXL submitted for approval, the US Food and Drug Administration defined keratoconus progression as exhibiting one or more of the following changes over 24 months: an increase of 1.00 D or greater in the “steepest keratometry measurement,” (i.e. also known as maximum cone apex curvature, “maximum K”; not to be confused with steepest central simulated keratometry, known as steep K or K2), an increase of 1.00 D or greater in manifest cylinder, and an increase of 0.50 D or greater in manifest refraction spherical equivalent. Other studies have defined progression as change occurring over the previous six- to 24-month period.

Therefore, the definition of “progressive keratoconus” varies in parameters examined, the amount of change in the parameters, and the length of time over which change is observed prior to CXL, ranging from 6 to 24 months. Terminology also varies; “maximum keratometry,” “apical keratometry,” and “cone apex keratometry,” “steepest keratometry,” or “maximum cone apex curvature” have been used interchangeably. In this review, we will not use the K max abbreviation to denote “maximum keratometry”, in order to avoid confusion with the maximum or steep simulated central keratometry (K2).

Description of the intervention

Corneal transplantation (keratoplasty) is performed in 10% to 20% of patients with keratoconus (Gordon 2006; Rabinowitz 1998; Tuft 1994). Although rare, keratoconus has been reported to recur in transplanted corneas (Abelson 1980). Recent studies strongly suggest that the introduction of CXL has reduced the need for corneal transplantation. In the three-year period after the introduction of CXL in the Netherlands (2012 to 2014), 25% fewer corneal transplants were performed than in the three-year period before its introduction (2005 to 2007) (Godefrooij 2016). At an institution in Norway, the frequency of keratoplasty was more than halved from 2013 to 2014 relative to 2005 to 2006, a decline attributed to the introduction of CXL (Sandvik 2015). Therefore, by halting or decreasing progression of keratoconus through corneal stiffening (Wollensak 2003a), CXL has the potential to decrease the number of keratoconus patients who undergo invasive procedures (lamellar or penetrating keratoplasties), with their attendant risks of rejection, endophthalmitis, and other infections.

CXL was first approved in Europe. The first patients with keratoconus to receive crosslinking were treated in Dresden, Germany; the CXL protocol developed by Seiler and colleagues in 1997 and used in clinical trials in Germany by 1998 is named the “Dresden Protocol” (Spoerl 1998; Spoerl 1999). It is an epithelium-off procedure and is the current standard worldwide, although some investigators are altering length of time of treatment and treatment protocols (Haberman 2018; Kymionis 2014; Kymionis 2017; Medeiros 2016; Price 2018b; Spadea 2018; Toker 2017).

The National Institute for Health and Care Excellence (NICE) in the UK produced interventional procedures guidance (IPG) for keratoconus in 2009, which was updated in 2013 to encompass keratectasia as well as keratoconus (NICE 2019). The Dresden Protocol was approved in 2016 by the Food and Drug Administration for use in the USA. It involves first de-epithelializing the central cornea (approximately 9 mm) and applying a solution of riboflavin-dextran (0.1% riboflavin-5-phosphate and 20% dextran T-500) as a photosensitizer to pre-treat the cornea, and then every five minutes for the duration of the 30-minute treatment with

ultraviolet A (UVA) 1 cm away from the cornea, using 370 nm UVA with an irradiance of 3 mW/cm. The NICE IPG acknowledges that “precise timings and treatment protocols vary”. Postoperatively, topical antibiotics and anti-inflammatory drops are normally prescribed, with topical steroids if necessary. In some cases, a bandage contact lens may also be used for a few days. The procedure is done on one eye at a time and may also be repeated if needed.

All of the seminal publications on CXL have described epithelium-off procedures. Transepithelial CXL is a (newer) alternative to the standard CXL procedure, in that the epithelium is kept intact during CXL. Theoretically, this technique is associated with avoidance of issues associated with removal of corneal epithelium such as delayed re-epithelialization and risk of microbial keratitis, reduction of pain, reduction of corneal haze, reduction of transient corneal edema, reduction of glare, and avoidance of corneal dehydration and thinning during epithelium-off CXL, thus allowing treatment of very thin, ectatic corneas (Caporossi 2012; Greenstein 2010; Hayes 2008; Hersh 2018; Mazzotta 2007; Wollensak 2009). Because the epithelium is a barrier to diffusion of riboflavin — a large molecule — into the corneal stroma, newer studies have described methods by which to circumvent this limitation through either iontophoresis (Bikbova 2016; Buzzonetti 2015) or chemical permeability enhancers like topical anesthetics and benzalkonium chloride, which Wollensak and colleagues were the first to describe (Koppen 2012; Vinciguerra 2016; Wollensak 2009).

How the intervention might work

Since Wollensak's publication of CXL in human trials in 2003, studies have supported the efficacy of epithelium-off corneal collagen crosslinking (O'Brart 2013; Poli 2015; Raiskup 2015; Wittig-Silva 2014). Natural crosslinking occurs in the cornea with age (Cartwright 2011); therapeutic CXL offers a much higher level of crosslinking beyond that which occurs with age. Seiler and colleagues found significant increases in stromal stress-strain measurements (i.e. corneal rigidity) in animal models following CXL treatment, which has been replicated in human trials (Wollensak 2003b). These trials have also shown an increase in the diameter of corneal collagen fibers, which likely contributes to decreased progression of ectasia. The resultant effect of CXL is increased resistance to both enzymatic digestion and thermal damage (Spoerl 2004a; Spoerl 2004b; Wollensak 2003b).

In short, it is theorized that CXL has an impact on keratoconus progression by strengthening and stabilizing the collagen lamellae, resulting in mechanical stiffening of the cornea. CXL may improve the patient's refractive error. It does so by reducing the irregular astigmatism caused by the biochemical instability of the cornea (Hersh 2017), and preventing the progression of corneal steepening; however, improvement is neither guaranteed nor significant for many patients. When the intervention is combined with intracorneal ring segments, the improvement in vision has been found to be greater than when using the segments alone (Chan 2007).

Transepithelial CXL differs from the standard CXL procedure in that the epithelium is kept intact during CXL. The reason the corneal epithelium is removed prior to standard CXL is to facilitate stromal absorption of riboflavin, a large molecule. Retention of the epithelium in CXL offers the putative advantages of faster healing, less patient discomfort, faster visual rehabilitation, and

less risk for corneal haze (Caporossi 2012; Greenstein 2010; Hayes 2008; Hersh 2018; Mazzotta 2007; Wollensak 2009). Haze seen with epithelium-off CXL generally does not occur in transepithelial CXL and is the result of keratocyte apoptosis and repopulation by myofibroblasts, leading to decreased corneal transparency and a clinically visible line demarcating the depth of the actual crosslinking effect (Kuo 1997; Mazzotta 2007; Seiler 2006; Wollensak 2007). In fact, some clinician researchers believe that aside from the main goal of stabilization of keratoconus, indicators of CXL effect are a visible demarcation line (that can appear as “haze”), a flattened keratometry, and reduced pachymetry (Doors 2009; Seiler 2006). In addition, transepithelial CXL may decrease the amount of corneal thinning that occurs during crosslinking (which can be substantial) and thus allow treatment of very thin, ectatic corneas, for which CXL might otherwise be precluded for fear of UVA damage to intraocular structure (Filippello 2012; Khairy 2014; Rosenblatt 2016; Spadea 2012).

Why it is important to do this review

The question remains which method of CXL is more effective and safe. Although epithelium-off CXL is more established than the transepithelial technique, an increasing number of studies of transepithelial CXL and comparison with epithelium-off CXL are being undertaken to evaluate their comparative effectiveness. It is unclear which technique better achieves the stated goal of CXL, which is to halt or slow progression of keratoconus (as defined in various ways). Furthermore, controversy surrounds the clinical effects of transepithelial CXL compared with epithelium-off corneal crosslinking for keratoconus (Al 2015; Kocak 2014; Leccisotti 2010; Magli 2013; Rossi 2015; Wen 2018). Research on rabbit eyes suggests that corneal biomechanical rigidity after transepithelial corneal crosslinking is 1/5 of that after epithelium-off procedures (Wollensak 2009). In addition, progression of keratoconus is not linear over time. Periods of stability can be interrupted by periods of progression. Because the rate of turnover of collagen and the extracellular matrix of the corneal stroma may be years or decades, long-term follow-up after CXL is essential to determine longevity of efficacy and to identify complications that may occur years after CXL (Caporossi 2013; Shalchi 2015; Soeters 2015; Stojanovic 2014; O’Brart 2015; Poli 2015; Raikup-Wolf 2008).

There are also uncertainties with regard to satisfaction, quality of life, and cost effectiveness of the two interventions. Eighty nine percent of approximately 500 CXL patients who responded to a survey at one center believed that CXL halted their disease progression by a median of 3.5 years after CXL (Price 2018a). Treatment at a younger age and at a mild stage of keratoconus was associated with higher satisfaction and perceived efficacy (Price 2018a), although objectively more patients with worse disease had improvement in visual acuity and corneal flattening (Greenstein 2013). Expectations of patients with advanced stages of keratoconus may exceed what CXL can deliver, leading to lower perceived efficacy (Price 2016). Researchers calculated that CXL for progressive keratoconus is cost-effective at a willingness-to-pay threshold of three times the gross domestic product (GDP) per capita. Cost effectiveness was influenced strongly by the assumption that CXL is effective for 10 years in the base-case scenario. The treatment would be extremely cost-effective if the effects last 15 years or more (Godefrooij 2017b; Leung 2017).

OBJECTIVES

The objective of this review is to assess the short-term and long-term effectiveness and safety of transepithelial CXL compared with epithelium-off CXL for progressive keratoconus.

METHODS

Criteria for considering studies for this review

Types of studies

We will only include data from randomized controlled trials (RCTs) that have compared transepithelial CXL with epithelium-off CXL. If such trials are not identified, we will accept quasi-randomized controlled trials (i.e. trials using quasi-random methods to allocate participants, such as alternation, date of birth, or case record number).

Types of participants

We will include studies of participants with progressive keratoconus. We will record information, when available, on participant characteristics (age, gender, age at onset), location of the cone, pre-operative severity of disease (if described in terms other than “progressive keratoconus”), and any comorbid conditions (Down syndrome). We will exclude studies of participants with corneal ectasia due to other reasons (e.g. ectasia status post laser in-situ keratomileusis). We will exclude studies that enrolled participants under age 14 (as the US Food and Drug Administration approval is for patients 14 years of age and over).

In most publications, progressive keratoconus is defined as one or more of the following: an increase of at least 1.00 D of steepest keratometry measurement (also known as maximum cone apex curvature, “maximum K”; not to be confused with steepest central simulated keratometry, known as steep K or K2); an increase of at least 1.00 D in manifest cylinder; or an increase of 0.5 D or more in manifest refraction spherical equivalent (MRSE) over the previous six- to 24-month period. The US Food and Drug Administration utilized these criteria when reviewing data for CXL submitted for approval but defined progression as change occurring over the previous 24-month period, which is much longer than most studies. Other criteria to be considered for progressive keratoconus are: 1.00 D or more increase in mean keratometry or in steepest central simulated keratometry (steep K or K2) in the previous six- to 24-month period (Sinhab 2014).

Examples of less conservative definitions of progressive keratoconus are as follows.

- An increase of at least 1.00 D in maximum K or central corneal astigmatism, over a six-month period (Cerman 2015)
- An increase of at least 0.5 D in maximum K, in steepest central simulated keratometry values (steep K or K2), in mean keratometry (the mean of steepest and flattest central simulated keratometry), and/or in topographic cylinder value over the previous six to 12 months (Soeters 2015)
- Reduced uncorrected distance visual acuity (UDVA) or corrected distance visual acuity (CDVA) by more than 1 line and/or worsening of refractive or corneal astigmatism, SimK, or maximum keratometry (Kmax) by 0.75 D over the 12 to 24 months prior to CXL (O’Brart 2015)

Types of interventions

We will include studies in which transepithelial CXL was compared with epithelium-off CXL. We will include studies in which different adjunctive therapy was used in both treatment arms. Riboflavin is a photosensitizer used in both methods of CXL. There may be chemical enhancers, such as benzalkonium chloride or topical anesthetic (proparacaine as well as the use of iontophoresis), to improve transepithelial stromal absorption of riboflavin.

Types of outcome measures

Critical outcomes

The critical outcome will be keratometry (K), a measurement of corneal curvature which is used to assess keratoconus progression. Because K is likely to be quantified in various ways in individual studies (e.g., maximum K vs. mean K), we will examine K both as a continuous outcome – change in maximum K from baseline; and as a categorical outcome – proportion of participants whose maximum K decreased by at least 2 diopters (indicating arrest or slowing of disease progression) and proportion of participants whose maximum K increased by at least 2 diopters from baseline (Asri 2011). The time points of interest will be 12 and 24 months after corneal CXL. We will use the data closest to these time points when available.

Important outcomes

We will consider the following important outcomes at 12 months or more after CXL. When there are multiple measurements after 12 months, we will use the measurement at the longest follow-up time point.

1. Visual acuity (best if visual acuity are recorded and analyzed as the number of Early Treatment of Diabetic Retinopathy Study letters read in logarithm of the minimum angle of resolution—logMAR units [ETDRS 1985](#))

- Mean change in corrected distance visual acuity (CDVA) from baseline
- Proportion of participants who gained 10 or more logMAR letters from baseline
- Proportion of participants who lost 10 or more logMAR letters from baseline

2. Patient questionnaire of subjective visual function parameters (e.g. photophobia, difficulty driving at night, difficult reading, diplopia, fluctuation in vision, glare, haloes, starbursts, dryness, pain, foreign body sensation), preferably as change from baseline

3. Costs of the interventions as reported in individual studies

Adverse outcomes

We will consider the following adverse outcomes at the longest follow-up time point:

Proportion of participants who have central corneal opacity or haze or scar; corneal sterile infiltrate; herpetic keratitis; non-healing or other epithelial defect lasting more than one week; eye pain or irritation; dry eye; photophobia; punctate keratitis; corneal inflammation; endothelial cell damage as indicated by decrease in endothelial cell density. Corneal stromolysis (“melt”) has been

described in the setting of CXL complicated by microbial infection or combined with excimer laser but not CXL alone to date.

Search methods for identification of studies

Electronic searches

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

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

Searching other resources

We will search the references of included studies for additional trials. We will not search conference abstracts for the purposes of this review as many eyes and vision conference abstracts are included in Embase.com, which will be searched as part of the electronic searches.

Data collection and analysis

Selection of studies

After duplicates are removed from the search results, two review authors will work independently to screen titles and abstracts of all records identified by the search using [Covidence](#). The review authors will classify each record as either relevant or not relevant for full-text review. Two review authors will independently assess the full-text copies of all records that they identified as relevant during title and abstract screening to determine eligibility for inclusion. We will identify and group reports from the same study to avoid extracting data from the same study for the same outcomes more than once. We will contact the trial report authors (and wait for two weeks) in an attempt to clarify any details necessary to make a complete assessment of eligibility. We will document reasons for exclusion for each study assessed as not eligible after review of the full-text reports. For reports in languages other than English, we first will attempt to screen for relevancy using Google Translate. If a clear decision cannot be made based on that translated version, we will consult with colleagues who are fluent in the language to determine eligibility. We will resolve all discrepancies between review authors by discussion at each stage of the screening process.

Data extraction and management

Two review authors, working independently, will extract data from included trials using [Covidence](#). We will extract the following information:

- study setting, countries where recruitment took place

- sample size, study duration and follow-up time, study design, analysis choice
- sources of funding, potential conflicts of interests
- characteristics of the participants (e.g. key inclusion/exclusion criteria), underlying conditions
- symptoms (pain, tearing/watery discharge, itching, foreign body sensation, and photophobia)
- clinical findings (chemosis, hyperemia, bulbar conjunctival injection, epithelial keratitis, subepithelial epithelial infiltrates)
- medical history (clinically suspected or laboratory confirmed epidemic keratoconjunctivitis)
- topical interventions (e.g. virustatic agents (cidofovir), antiseptic agents, immune modulators and suppressors (e.g. corticosteroid, interferon, cyclosporine A, tacrolimus)
- alternative medication, or placebo (no treatment)
- outcomes (e.g. domain, specific measurement, specific metric, method of aggregation, and the time frame), and quantitative results.

The two review authors will compare the extracted data and resolve any discrepancies by discussion. One review author will export data from [Covidence](#) into Review Manager 5 ([Review Manager 2014](#)), and a second author will verify the exported data.

Assessment of risk of bias in included studies

Two review authors will independently assess the risk of bias in each included study, following guidance described in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2017](#)). Specific items for consideration will include random sequence generation and allocation concealment (selection bias), masking of participants and study personnel (performance bias), masking of outcome assessors (detection bias), missing data and intention-to-treat analysis (attrition bias), selective outcome reporting (reporting bias), and other potential sources of bias. We will assign each item as having 'low risk of bias', 'high risk of bias' or, whenever the information provided is insufficient to make an assessment, 'unclear risk of bias'. We will document reasons for those assessments and resolve any discrepancies through discussion. We will present our assessments, for individual studies and overall, in the 'Risk of bias' summary figures.

Measures of treatment effect

We will use mean difference to assess the continuous outcomes, including change in maximum K, change in CDVA, change in patient questionnaire of subjective visual function parameters and costs.

We will use relative risk for dichotomous or categorical outcomes, including proportion of participants whose maximum K decreased by at least 2 diopters or increased by at least 2 diopters, proportion of participants who gained 10 or more logMAR letters, proportion who lost 10 or more logMAR letters, and proportion of participants who experienced adverse events.

Unit of analysis issues

We will determine whether each included study design specified intervention on one or both eyes from each participant and whether study investigators randomized at the participant level or at the eye level. We will extract estimates that properly accounted for the correlation of two eyes from the same participant when both eyes were treated in the study. Since certain medical treatments

have the potential to influence the outcome in the contralateral eye, we will exclude studies that adopted a paired design in our sensitivity analysis. In addition, keratoconus tends to have asymmetrical presentation, which would complicate paired design.

Dealing with missing data

Where data on included studies are unclear or incomplete, we will contact the authors via email. Should there be no response within two weeks, we will analyze the data using the best information available. We will not impute missing data. In the event that the quality of the available data prevents any meaningful analysis, we will omit the study from quantitative analyses and note this decision in the discussion.

Assessment of heterogeneity

We will assess clinical and methodological heterogeneity by examining participant characteristics and outcomes, carefully reviewing the study report(s), and taking into consideration potential risk of bias. We will assess forest plots and examine the I^2 value and its confidence interval. We will consider an I^2 value greater than 60% as indicative of substantial heterogeneity, suggesting that a meta-analysis may not be appropriate; however, we will give consideration to the consistency of the effect estimates. For example, if all estimates are in the same direction, we may report a meta-analysis even in the presence of substantial statistical heterogeneity; in this situation we will comment on the heterogeneity.

We anticipate that heterogeneity may be significant, arising from baseline patient characteristics (different definitions of "progressive keratoconus"), various techniques within the transepithelial and epithelium-off groups, and various outcome measures (the secondary outcomes reported likely will vary widely). Substantial heterogeneity may affect the overall strength of the evidence. We will examine comparisons between transepithelial and epithelium-off CXL techniques with subgroup analysis to explain observed heterogeneity when sufficient data are available.

Assessment of reporting biases

We will use funnel plots to assess small-study effects, which could be due to publication bias, where there are more than 10 trials included in a meta-analysis. We will judge selective reporting as part of the 'Risk of bias' assessment for each individual study.

Data synthesis

We will follow Chapter 9 of the *Cochrane Handbook* for data synthesis and analysis ([Deeks 2017](#)). We will provide a descriptive, qualitative synthesis of studies and their results for each outcome specified in [Types of outcome measures](#). We will use a random-effects model for quantitative syntheses when three or more studies report data for the same outcome.

Subgroup analysis and investigation of heterogeneity

We plan to perform subgroup analysis to account for the different protocols available for transepithelial CXL and for differences in types of participants. CXL protocols vary in type of riboflavin used, method of administration, how riboflavin saturation is assessed, and power and timing of UV light exposure. As new protocols

emerge for epithelium-off CXL, additional subgroup analyses also may be necessary.

As stated above, we will exclude trials that enrolled patients with corneal ectasia that is not keratoconus and did not report outcomes separately for keratoconus participants only.

Sensitivity analysis

We will conduct sensitivity analysis to determine the impact of paired-eye design and any post hoc decisions made during the review process. We will report results of any sensitivity analysis performed in a table or in the text of the review and discuss our interpretation of the effects on the overall findings of the review.

Summary of findings and assessment of the certainty of the evidence

We will present a 'Summary of findings' table for the comparison between transepithelial CXL versus epithelium-off CXL. The 'Summary of findings' table will include the following seven outcomes, assessed at 12 months after CXL.

1. The mean change in maximum K from baseline
2. The proportion of participants whose maximum K decreased by at least 2 diopters from baseline
3. The proportion of participants whose maximum K increased by at least 2 diopters from baseline

4. The mean change in CDVA from baseline
5. The proportion of participants who gained 10 or more logMAR letters from baseline
6. The proportion of participants who lost 10 or more logMAR letters from baseline
7. Adverse outcomes

We will use the GRADE approach to assess the overall certainty of evidence for each outcome. We initially will consider the design to confer a high certainty of evidence for each outcome and will downgrade certainty to moderate, low, or very low if there is evidence of high risk of bias, inconsistency, indirectness, imprecision, or publication bias.

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APPENDICES

Appendix 1. CENTRAL search strategy

```
#1 MeSH descriptor: [Keratoconus] explode all trees
#2 (keratocon* OR (conical NEAR/2 cornea*) OR (corneal NEAR/2 ectasia*) OR keratectas*)
#3 #1 OR #2
#4 MeSH descriptor: [Cross-Linking Reagents] explode all trees
#5 (cross link* or crosslink* or CXL)
#6 MeSH descriptor: [Collagen] explode all trees and with qualifier(s): [radiation effects - RE]
#7 Collagen
#8 MeSH descriptor: [Anti-Infective Agents] explode all trees
#9 (Anti Infective* or Antiinfective* or Antimicrobial* or Anti Microbial* or Microbicid*)
#10 MeSH descriptor: [Riboflavin] explode all trees
#11 (Riboflavin* or "Vitamin G" or "Vitamin B2" or "Vitamin B 2" or Beflavin or beflavine or flavaxin or hyrye or lactoflavin or lactoflavine or ovoflavin or pabriflan or riboflavine or ribovel or "83-88-5")
#12 MeSH descriptor: [Ultraviolet Therapy] explode all trees
#13 MeSH descriptor: [Ultraviolet Rays] explode all trees
#14 (Ultraviolet* or Ultra-Violet or UV Ray* or UV light* or "UV-A" or UVA or Actinotherap* or Actinic Ray*)
#15 MeSH descriptor: [Photosensitizing Agents] explode all trees
#16 Photosensitiz*
#17 MeSH descriptor: [Photochemotherapy] explode all trees
#18 (Photochemotherap* or Photodynamic*)
#19 MeSH descriptor: [Cornea] explode all trees and with qualifier(s): [radiation effects - RE]
#20 MeSH descriptor: [Cornea] explode all trees and with qualifier(s): [drug effects - DE]
#21 (chemical NEXT enhancer*) OR iontophor*
#22 {OR #4-#21}
#23 #3 AND #22
```

Appendix 2. MEDLINE Ovid search strategy

```
1. Randomized Controlled Trial.pt.
2. Controlled Clinical Trial.pt.
3. (randomized or randomised).ab,ti.
4. placebo.ab,ti.
5. drug therapy.fs.
6. randomly.ab,ti.
7. trial.ab,ti.
8. groups.ab,ti.
9. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10. exp animals/ not humans.sh.
11. 9 not 10
12. exp Keratoconus/
13. (keratocon* or (conical adj2 cornea*) or (corneal adj2 ectasia*) or keratectas*).tw.
14. 12 or 13
15. exp Cross-Linking Reagents/
```


16. (cross link* or crosslink* or CXL).tw.
17. exp Collagen/re [Radiation Effects]
18. Collagen.tw.
19. exp Anti-Infective Agents/
20. (Anti Infective* or Antiinfective* or Antimicrobial* or Anti Microbial* or Microbicid*).tw.
21. exp Riboflavin/
22. (Riboflavin* or "Vitamin G" or "Vitamin B2" or "Vitamin B 2" or Beflavin or beflavine or flavaxin or hyrye or lactoflavin or lactoflavine or oovoflavin or pabriflan or riboflavine or ribovel or "83-88-5").tw.
23. exp Ultraviolet Therapy/
24. exp Ultraviolet Rays/
25. (Ultraviolet* or Ultra-Violet or UV Ray* or UV light* or "UV-A" or UVA or Actinotherap* or Actinic Ray*).tw.
26. exp Photosensitizing Agents/
27. Photosensitiz*.tw.
28. exp Photochemotherapy/
29. (Photochemotherap* or Photodynamic*).tw.
30. exp Cornea/de, re [Drug Effects, Radiation Effects]
31. (chemical enhancer* or iontophor*).tw.
32. or/15-31
33. 14 and 32
34. 11 and 33

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

Appendix 3. Embase.com search strategy

- #1 'randomized controlled trial'/exp
- #2 'randomization'/exp
- #3 'double blind procedure'/exp
- #4 'single blind procedure'/exp
- #5 random*:ab,ti
- #6 #1 OR #2 OR #3 OR #4 OR #5
- #7 'animal'/exp OR 'animal experiment'/exp
- #8 'human'/exp
- #9 #7 AND #8
- #10 #7 NOT #9
- #11 #6 NOT #10
- #12 'clinical trial'/exp
- #13 (clin* NEAR/3 trial*):ab,ti
- #14 ((singl* OR doubl* OR trebl* OR tripl*) NEAR/3 (blind* OR mask*)):ab,ti
- #15 'placebo'/exp
- #16 placebo*:ab,ti
- #17 random*:ab,ti
- #18 'experimental design'/exp
- #19 'crossover procedure'/exp
- #20 'control group'/exp
- #21 'latin square design'/exp
- #22 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21
- #23 #22 NOT #10
- #24 #23 NOT #11
- #25 'comparative study'/exp
- #26 'evaluation'/exp
- #27 'prospective study'/exp
- #28 control*:ab,ti OR prospectiv*:ab,ti OR volunteer*:ab,ti
- #29 #25 OR #26 OR #27 OR #28
- #30 #29 NOT #10
- #31 #30 NOT (#11 OR #23)
- #32 #11 OR #24 OR #31
- #33 'keratoconus'/exp
- #34 (keratocon* OR (conical* NEAR/2 cornea*) OR (corneal* NEAR/2 ectasia*) OR keratectas*):ab,ti,kw
- #35 #33 OR #34
- #36 'cross linking reagent'/exp
- #37 ('cross link*' OR crosslink* OR cxl):ab,ti,kw

```
#38 'collagen'/exp
#39 collagen:ab,ti,kw
#40 'antiinfective agent'/exp
#41 ('anti infective*' OR antiinfective* OR antimicrobial* OR 'anti microbial*' OR microbicid*):ab,ti,kw
#42 'riboflavin'/exp
#43 (riboflavin* OR 'vitamin g' OR 'vitamin b2' OR 'vitamin b 2' OR beflavin OR beflavine OR flavaxin OR hyrye OR lactoflavin OR lactoflavine
OR ovoflavin OR pabriflan OR riboflavine OR ribovel OR '83-88-5'):ab,ti,kw,tn
#44 'ultraviolet phototherapy'/exp
#45 'ultraviolet radiation'/exp
#46 (ultraviolet* OR 'ultra violet' OR 'uv ray*' OR 'uv light*' OR 'uv-a' OR uva OR actinotherap* OR 'actinic ray*'):ab,ti,kw
#47 'photosensitizing agent'/exp
#48 photosensitiz*:ab,ti,kw
#49 'photochemotherapy'/exp
#50 (photochemotherap* OR photodynamic*):ab,ti,kw
#51 'cornea'/exp/dd_ae,dd_an,dd_cm,dd_it,dd_dt,dd_to
#52 ('chemical enhancer*' OR iontophor*):ab,ti,kw,tn
#53 #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52
#54 #35 AND #53
#55 #32 AND #54
```

Appendix 4. PubMed search strategy

```
1. ((randomized controlled trial[pt]) OR (controlled clinical trial[pt]) OR (randomised[tiab] OR randomized[tiab]) OR (placebo[tiab]) OR
(drug therapy[sh]) OR (randomly[tiab]) OR (trial[tiab]) OR (groups[tiab])) NOT (animals[mh] NOT humans[mh])
2. (keratocon*[tw] OR conical cornea*[tw] OR corneal ectasia*[tw] OR keratectas*[tw] NOT Medline[sb])
3. (cross link*[tw] OR crosslink*[tw] OR CXL[tw]) NOT Medline[sb]
4. Collagen[tw] NOT Medline[sb]
5. (Anti Infective*[tw] OR Antiinfective*[tw] OR Antimicrobial*[tw] OR Anti Microbial*[tw] OR Microbicid*[tw]) NOT Medline[sb]
6. (Riboflavin*[tw] OR "Vitamin G"[tw] OR "Vitamin B2"[tw] OR "Vitamin B 2"[tw] OR Beflavin[tw] OR beflavine[tw] OR flavaxin[tw] OR
hyrye[tw] OR lactoflavin[tw] OR lactoflavine[tw] OR ovoflavin[tw] OR pabriflan[tw] OR riboflavin[tw] OR ribovel[tw] OR "83-88-5"[tw]) NOT
Medline[sb]
7. (Ultraviolet*[tw] OR Ultra-Violet[tw] OR UV Ray*[tw] OR UV light*[tw] OR "UV-A"[tw] OR UVA[tw] OR Actinotherap*[tw] OR Actinic
Ray*[tw]) NOT Medline[sb]
8. Photosensitiz*[tw] NOT Medline[sb]
9. (Photochemotherap*[tw] OR Photodynamic*[tw]) NOT Medline[sb]
10. (chemical enhancer*[tw] OR iontophor*[tw]) NOT Medline[sb]
11. #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10
12. #2 AND #11
13. #1 AND #12
```

Appendix 5. LILACS search strategy

```
(keratocon$ OR "conical cornea" OR "corneal ectasia" OR keratectas$ OR MH:C11.204.627$ OR queratocon$ OR ceratocon$)
AND (MH:D27.720.470.410.210$ OR (cross link$) OR crosslink$ OR CXL OR MH:D05.750.078.280$ OR MH:D12.776.860.300.250$ OR
Collagen OR MH:D27.505.954.122$ OR (Anti Infective$) OR Antiinfective$ OR Antimicrobial$ OR (Anti Microbial$) OR Microbicid
$ OR Antiinfecciosos OR "Anti-Infeciosos" OR MH:D03.438.733.315.650$ OR MH:D03.494.507.650$ OR MH:D08.211.474.650$ OR
MH:D23.767.405.650$ OR Riboflavin$ OR "Vitamin G" OR "Vitamin B2" OR "Vitamin B 2" OR Beflavin OR beflavine OR
flavaxin OR hyrye OR lactoflavin OR lactoflavine OR ovoflavin OR pabriflan OR riboflavine OR ribovel OR "83-88-5" OR
MH:E02.774.945$ OR MH:G01.358.500.505.650.891$ OR MH:G01.590.540.891$ OR MH:G01.750.250.650.891$ OR MH:G01.750.750.659$ OR
MH:G01.750.770.578.891$ OR MH:G16.500.275.063.725.525.600$ OR MH:G16.500.750.775.525.600$ OR MH:N06.230.300.100.725.525.600$
OR MH:SP4.011.087.698.384.075.166.032$ OR MH:SP4.021.202.133.789$ OR Ultraviolet$ OR (Ultra Violet$) OR (UV Ray$) OR (UV light$)
OR "UV-A" OR UVA OR Actinotherap$ OR (Actinic Ray$) OR MH:D27.505.954.444.600$ OR MH:D27.505.954.600.710$ OR Photosensitiz$ OR
Fotosensibilizante$ OR Fotossensibilizante$ OR Photochemotherap$ OR Photodynamic$ OR MH:E02.186.500$ OR MH:E02.319.685$ OR
MH:E02.774.722$ OR Fotoquimioterap$ OR mh:"Cornea/DE" OR mh:"Cornea/RE" OR "chemical enhancer" OR "chemical enhancers" OR
iontophor$)
```

Appendix 6. ClinicalTrials.gov search strategy

```
keratoconus OR "conical cornea" OR "corneal ectasia" OR keratectasia
```

Appendix 7. WHO ICTRP search strategy

```
keratoconus OR "conical cornea" OR "corneal ectasia" OR keratectasia
```

Appendix 8. Data on study characteristics

Mandatory items		Optional items
Methods		
Study design	<ul style="list-style-type: none"> • Parallel-group RCT <i>i.e. people randomized to treatment</i> • Within-person RCT <i>i.e. eyes randomized to treatment</i> • Cluster-RCT <i>i.e. communities randomized to treatment</i> • Cross-over RCT • Other, specify 	Exclusions after randomization Losses to follow-up Number randomized/analyzed How were missing data handled? <i>e.g. available case analysis, imputation methods</i>
Eyes or	<ul style="list-style-type: none"> • One eye included in study, <i>specify how eye selected</i> 	
Unit of randomization/ unit of analysis	<ul style="list-style-type: none"> • Two eyes included in study, both eyes received same treatment, <i>briefly specify how analyzed (best/worst/average/both and adjusted for within person correlation/both and not adjusted for within person correlation) and specify if mixture one eye and two eye</i> • Two eyes included in study, eyes received different treatments, <i>specify if correct pair-matched analysis done</i> 	Reported power calculation (Y/N), <i>if yes, sample size and power</i> Unusual study design/issues
Participants		
Country		Setting
Total number of participants	<i>This information should be collected for total study population recruited into the study. If these data are only reported for the people who were followed up only, please indicate.</i>	Ethnic group
Number (%) of men and women		Equivalence of baseline characteristics (Y/N)
Average age and age range		
Inclusion criteria		
Exclusion criteria		
Interventions		
Intervention (n =)	<ul style="list-style-type: none"> • Number of people randomized to this group 	
Comparator (n =)	<ul style="list-style-type: none"> • Drug (or intervention) name 	
See Methodological Expectations of Cochrane Intervention Reviews (MECIR) 65 and 70	<ul style="list-style-type: none"> • Dose • Frequency • Route of administration 	
Outcomes		
Primary and secondary outcomes as defined in study reports	List outcomes Adverse events reported (Y/N)	Planned/actual length of follow up

(Continued)

See **MECIR R70**

Length of follow up and intervals at which outcomes assessed

CONTRIBUTIONS OF AUTHORS

Conception and design of study: ICK, KL

Drafting the review or commenting on it critically for intellectual content: ICK, KL, BSH, MR

Final approval of the document to be published: ICK, KL, BSH, MR

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ICK: no financial interests

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