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HTA Short Report

Title	Corneal collagen crosslinking for the treatment of progressive keratoconus
Authors	Meegan Vandepeer, Deanne Forel, JonHenry Jacobsen, Akwasi Ampofo, Ning Ma, Thomas Vreugdenburg Royal Australasian College of Surgeons

Bundesamt für Gesundheit
Sektion Health Technology Assessment
Schwarzenburgstrasse 157
CH-3003 Bern
Schweiz
Tel.: +41 58 462 92 30
E-mail: hta@bag.admin.ch

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Executive Summary

This report investigates the clinical efficacy, safety, costs and cost-utility associated with corneal collagen crosslinking (CXL) for treating progressive keratoconus. In addition, legal, social, ethical and organisational issues associated with the use of CXL are explored.

Clinical evaluation

Systematic literature searches were conducted in four biomedical databases (PubMed, Embase, Cochrane Library, CINAHL) to identify existing systematic review (SR) and randomised controlled trial (RCT) evidence addressing the research questions. The results in this executive summary are presented at longest follow-up due to the slow-progressing nature of the disease, and the fact that CXL aims to slow disease progression rather than improve symptoms.

CXL compared to sham or no treatment

The clinical efficacy of CXL compared to sham or no treatment was informed by RCTs. The safety of CXL was informed by 4 RCTs plus a SR of lower levels of evidence. There are risk of bias concerns in the RCTs relevant to both safety and efficacy related to incomplete data, randomisation, conflicts of interest and between-eye correlation. The systematic review of CXL safety was deemed to be of very low quality. The overall strength of evidence for the clinical efficacy outcomes was very low.

Compared to sham or no treatment, a significant difference was observed for uncorrected visual acuity (UCVA) (SMD -0.71, 95% CI -1.28, -0.14) and K_{max} (the maximum curvature in the central cornea) (MD -1.85 D, 95% CI -3.44, -0.25) in favour of CXL at longest follow-up (36 months). The weighted mean absolute changes indicate that K_{max} decreased over time relative to baseline for CXL, but slightly increased in the sham and no treatment group. Meta-analyses of best-corrected visual acuity (BCVA), K_{min} (the minimum curvature in the central cornea), K_{mean} (the average curvature in the central cornea), cylinder (the amount of astigmatism) and spherical equivalent (an estimate of the eyes refractive error) showed no significant difference between CXL and sham or no treatment at longest follow-up. One RCT reported on corneal transplant rates with none reported in the CXL arm (compared with 10% in the control arm), no RCT reported on quality of life.

Adverse events that can occur following CXL include keratitis, haze, sterile infiltrates, stromal oedema, golden striae, corneal scars, photophobia, increased lacrimation, dry eye, ocular irritation, blurred vision, ocular pain, corneal erosions, epithelial defects and corneal vascularisation. Haze, whilst generally only temporary, appears to be the most commonly reported event following CXL, with incidence rates of up to 100%; however, as safety was poorly reported no comment can be made as to how common these events are with any level of certainty.

In general, there is uncertainty with the evidence owing to the small size of many of the included studies, their variable definition of keratoconus progression – used as inclusion criteria in the trials – and the lack of validated parameters for measuring keratoconus progression. All of which make it difficult to draw conclusions to any degree of certainty.

Costs and cost-effectiveness

A Markov model was constructed to evaluate the comparative cost-utility of CXL over no treatment. Deterministic and probabilistic sensitivity analyses were used to quantify the impact of parameter uncertainties and to elicit key drivers of the model. The economic model was based on an existing model from the UK by Salmon (2015) The UK model was adapted to best reflect appropriate clinical findings and Swiss population; however, some of the input values and clinical assumptions from the Salmon model were used directly in the current evaluation due the lack of available information in the clinical evidence base. Over a 25-year time horizon, the base-case ICER was CHF 25,841 per QALY gained. Sensitivity analyses suggest the ICER is most sensitive to the efficacy of CXL, which was represented by the rate of CXL failure requiring repeat treatment. It is also sensitive to the utility difference between early disease status (AK stage 1) and a more advance status (AK stage 2). Most ICERs produced from all scenarios were below the hypothetical ICER threshold of CHF 100,000. Probabilistic sensitivity analyses showed 99.4% chance of CXL being cost-effective against the hypothetical threshold.

A budget impact analysis was undertaken to estimate the financial impact of publicly reimbursing CXL. In the base-case analysis, it was assumed that only a proportion (50%) of newly diagnosed keratoconus patients would receive CXL after reimbursement becomes available. It was estimated that CXL would cost CHF 573,346 in the first year (2021) and increase to CHF 584,865 (2025) as the total cost in Switzerland for all patients. However, when considering existing diagnosed patients who have not been able to receive CXL, the worst-case scenario would have the CXL costing over CHF 4.5 million in Switzerland in the first year (2021). This should be considered the ceiling of the financial impact subject to significant overestimation. The cost will taper down to the base-case level after 2 to 3 years of initial treatment backlog. When the initial patient loadings are cleared, the fourth and the fifth-year projections are in line with the base-case.

Legal, social, ethical and organisational issues

Children with keratoconus represent a vulnerable patient group, as the disease progresses faster, they are more likely to progress to advanced disease stages compared to adults, and have difficulties adhering to conservative treatments (such as spectacles and contact lenses); CXL may, from an ethical/social perspective, be more beneficial in this cohort. It is unclear whether utilisation

of healthcare resources (e.g. related to corneal transplants), will change if CXL is reimbursed.

Conclusion

CXL appears to have a beneficial effect on slowing keratoconus progression with respect to UCVA and K_{max}. A range of adverse events can occur following CXL based on moderate to low quality evidence. The most frequently reported adverse event was temporary corneal haze with incidences up to 100%; however, these results are subject to a high degree of uncertainty. CXL is likely to be a cost-effective treatment for keratoconus; however, there are still uncertainties regarding the applicability of the economic evaluation result to the Swiss context due to the use of inputs in the model that were not specific to the Swiss population.

Zusammenfassung

In diesem Bericht werden die klinische Wirksamkeit, Sicherheit, Kosten sowie das Kosten-Nutzen-Verhältnis des Crosslinkings der Hornhaut (CXL, Corneal Collagen Crosslinking) zur Behandlung des progressiven Keratokonus evaluiert. Zudem wird auf rechtliche, soziale, ethische und organisatorische Probleme im Zusammenhang mit CXL eingegangen.

Klinische Beurteilung

Systematische Literaturrecherchen wurden in vier biomedizinischen Datenbanken (PubMed, Embase, Cochrane Library, CINAHL) durchgeführt mit dem Ziel, vorhandene systematische Reviews (SR) und randomisierte kontrollierte Studien (RCT) zu den Forschungsfragen zu identifizieren. Die in dieser Zusammenfassung aufgeführten Ergebnisse werden bezugnehmend auf die längste Nachbeobachtungszeit präsentiert, da die Erkrankung langsam voranschreitet und CXL auf die Verlangsamung der Erkrankungsprogression und nicht auf Symptomlinderung abzielt.

CXL im Vergleich zur Scheinbehandlung oder zu keiner Behandlung

Die klinische Wirksamkeit von CXL im Vergleich zu einer Scheinbehandlung oder zu keiner Behandlung wurde mit RCT untersucht. Die Sicherheit von CXL wurde mittels vier RCT sowie einer SR mit niedrigerem Evidenzgrad überprüft. Bei den RCT zu Sicherheit und Wirksamkeit bestehen Bedenken hinsichtlich des Risikos für Bias im Zusammenhang mit unvollständigen Daten, Randomisierung, Interessenkonflikten und Korrelation zwischen den Augen. Die Qualität der systematischen Review zur Sicherheit von CXL wurde als sehr gering eingestuft. Die allgemeine Evidenzstärke der klinischen Wirksamkeitsergebnisse war sehr gering.

Im Vergleich zur Scheinbehandlung oder zu keiner Behandlung wurde bei der längsten Nachbeobachtungszeit (36 Monate) ein signifikanter Unterschied hinsichtlich der unkorrigierten Sehschärfe (UCVA) (SMD -0,71, 95 %-KI -1,28, -0,14) und K_{max} (maximale Krümmung in der zentralen Hornhaut) (MD -1,85 D, 95 %-KI -3,44, -0,25) zugunsten von CXL beobachtet. Die

gewichteten mittleren absoluten Veränderungen haben aufgezeigt, dass K_{max} im Verlauf der Zeit relativ zum Ausgangswert nach CXL abnahm, aber in den Gruppen, die die Scheinbehandlung oder keine Behandlung erhalten haben, leicht zunahm. Meta-Analysen der bestkorrigierten Sehschärfe (BCVA), K_{min} (minimale Krümmung in der zentralen Hornhaut), K_{mean} (durchschnittliche Krümmung in der zentralen Hornhaut), des Zylinders (Ausmass des Astigmatismus) sowie des sphärischen Äquivalents (eine Schätzung des Refraktionsfehlers der Augen) haben bei der längsten Nachbeobachtungszeit keinen signifikanten Unterschied zwischen CXL und Scheinbehandlung oder keiner Behandlung aufgezeigt. In einer RCT wurde die Häufigkeit von Hornhauttransplantationen untersucht, wobei im CXL-Arm von keiner Hornhauttransplantation berichtet wurde (gegenüber 10 % im Kontrollarm). Die Lebensqualität wurde in keiner der RCT untersucht.

Zu den unerwünschten Ereignissen, die nach CXL auftreten können, gehören Keratitis, Trübungen, sterile Infiltrate, Stromaödeme, Golden Striae, Vernarbungen der Hornhaut, Photophobie, vermehrter Tränenfluss, Augentrockenheit, Augenreizung, verschwommenes Sehen, Augenschmerzen, Hornhauterosionen, Epitheldefekte und Hornhautvaskularisation. Obwohl die Trübung im Allgemeinen nur vorübergehend bestand, scheint es sich hierbei um das am häufigsten berichtete unerwünschte Ereignis nach der Durchführung von CXL zu handeln, wobei die Inzidenzraten bei bis zu 100 Prozent lagen. Da über die Sicherheit jedoch nur unzureichend berichtet wurde, kann hinsichtlich der Häufigkeit dieser Ereignisse keine Aussage, die einen gewissen Grad an Sicherheit aufweisen würde, getroffen werden.

Im Allgemeinen besteht Unsicherheit hinsichtlich der Evidenz aufgrund der geringen Grösse vieler der eingeschlossenen Studien, ihrer variablen Definition von Progression des Keratokonus, die als Kriterium für den Einschluss in die Studien verwendet wurde, sowie dem Fehlen validierter Parameter zur Messung der Progression des Keratokonus. All dies macht es schwierig, Schlussfolgerungen mit einem gewissen Grad an Sicherheit zu ziehen.

Kosten und Kosteneffektivität

Zur Beurteilung des komparativen Kosten-Nutzen-Verhältnisses von CXL gegenüber keiner Behandlung wurde ein Markov-Modell konstruiert. Deterministische und probabilistische Sensitivitätsanalysen wurden verwendet, um die Auswirkungen von Parameterunsicherheiten zu quantifizieren und die wichtigsten Treiber des Modells zu ermitteln. Die Basis für das ökonomische Modell stellte ein bestehendes britisches Modell von Salmon (2015) dar. Dieses Modell wurde angepasst, um die entsprechenden klinischen Befunde auf die Schweizer Bevölkerung bestmöglich widerzuspiegeln. Aufgrund des Mangels an verfügbaren Informationen in der klinischen

Evidenzbasis wurden einige der Inputwerte und klinischen Annahmen aus dem Salmon-Modell direkt in der aktuellen Evaluation verwendet. Über einen Zeithorizont von 25 Jahren betrug die Basisfall-ICER 25 841 CHF pro gewonnenem QALY. Sensitivitätsanalysen legen nahe, dass die ICER am empfindlichsten auf die Wirksamkeit von CXL reagiert, die durch die Rate der gescheiterten CXL, welche eine Wiederholungsbehandlung erfordern, dargestellt wurde. Die ICER ist auch empfindlich gegenüber der Nutzendifferenz zwischen einem frühen Krankheitsstatus (AK-Stadium 1) und einem weiter fortgeschrittenen Status (AK-Stadium 2). Die meisten ICER aus allen Szenarien lagen unter der hypothetischen ICER-Schwelle von 100 000 CHF. Probabilistische Sensitivitätsanalysen zeigten eine Wahrscheinlichkeit von 99,4 %, dass CXL gegenüber dem hypothetischen Schwellenwert kosteneffektiv ist.

Eine Budget-Impact-Analyse wurde durchgeführt, um eine Schätzung der finanziellen Auswirkungen bei der Erstattung von CXL durch die obligatorische Krankenpflegeversicherung vorzunehmen. In der Basisfall-Analyse wurde angenommen, dass nur ein Teil (50 %) der neu diagnostizierten Keratokonus-Patienten CXL erhalten würde, nachdem die Kostenerstattung verfügbar geworden ist. Es wurde geschätzt, dass die Gesamtkosten für CXL für alle Patienten in der Schweiz im ersten Jahr (2021) 573 346 CHF betragen und auf 584 865 CHF (2025) ansteigen würden. Wenn jedoch die bereits diagnostizierten Patienten, die bisher kein CXL erhalten konnten, berücksichtigt werden, würden die Kosten für das CXL in der Schweiz im Worst Case Szenario im ersten Jahr (2021) bei über 4,5 Millionen CHF liegen. Dies sollte als Obergrenze für die finanziellen Auswirkungen betrachtet werden, die einer erheblichen Überschätzung unterliegen kann. Die Kosten werden sich nach 2 bis 3 Jahren der anfänglichen Aufholung des Behandlungsrückstandes auf das Basisfall-Niveau reduzieren. Nach der Bereinigung der anfänglichen Nachfrage durch die Patienten, stimmen die Projektionen für das vierte und fünfte Jahr mit dem Basisfall überein.

Rechtliche, soziale ethische und organisatorische Probleme

Kinder mit Keratokonus stellen eine vulnerable Patientengruppe dar, da die Erkrankung bei ihnen schneller fortschreitet, sie im Vergleich zu Erwachsenen eher fortgeschrittene Krankheitsstadien erreichen und Schwierigkeiten mit der Adhärenz an konservative Behandlungen (wie Brillen und Kontaktlinsen) haben. Aus ethischer/sozialer Sicht könnte CXL in dieser Kohorte einen grösseren Nutzen aufweisen. Es ist unklar, ob die Erstattung von CXL zu Veränderungen der Inanspruchnahme von Ressourcen im Gesundheitswesen (beispielsweise im Zusammenhang mit Hornhauttransplantationen) führen wird.

Fazit

CXL scheint eine positive Wirkung auf die Verlangsamung der Progression des Keratokonus

hinsichtlich UCVA und K_{max} zu haben. Ausgehend von der Evidenz, die eine mässige bis geringe Qualität aufweist, kann nach CXL eine Reihe von unerwünschten Ereignissen auftreten. Das am häufigsten berichtete unerwünschte Ereignis war eine vorübergehende Hornhauttrübung, wobei Inzidenzen von bis zu 100 % gemeldet wurden. Diese Ergebnisse sind jedoch mit einem hohen Mass an Unsicherheit behaftet. Es ist wahrscheinlich, dass CXL eine kosteneffektive Methode für die Behandlung des Keratokonus darstellt. Da im Modell Inputs verwendet wurden, die nicht spezifisch für die Schweizer Bevölkerung waren, bestehen jedoch immer noch Unsicherheiten hinsichtlich der Übertragbarkeit des Ergebnisses der ökonomischen Bewertung auf den Kontext der Schweiz.

Résumé

Ce rapport étudie l'efficacité clinique, la sécurité, les coûts et le rapport coût-utilité de la réticulation du collagène cornéen (corneal collagen crosslinking, CXL) comme traitement du kératocône progressif. Les questions juridiques, sociales, éthiques et organisationnelles liées à l'utilisation de ce traitement sont également examinées.

Évaluation clinique

Des recherches systématiques de la littérature ont été menées dans quatre bases de données biomédicales (PubMed, Embase, Cochrane Library et CINAHL) afin d'identifier les revues systématiques (RS) et les essais randomisés contrôlés (ERC) consacrés aux questions de recherche. Étant donné la progression lente de la maladie et le fait que la CXL vise à ralentir cette progression plutôt qu'à améliorer les symptômes, les résultats présentés dans ce résumé correspondent à la période de suivi la plus longue.

Comparaison entre la CXL et le traitement fictif ou l'absence de traitement

L'efficacité clinique de la CXL par rapport au traitement fictif ou à l'absence de traitement a été documentée par des ERC. Quatre ERC et une RS avec un niveau de preuve plus faible ont confirmé l'innocuité de la CXL. Des risques de biais ont été identifiés dans les ERC concernant à la fois la sécurité et l'efficacité. Ces craintes sont motivées par des données incomplètes, la randomisation, des conflits d'intérêts et la corrélation entre les yeux. La revue systématique de la sécurité de la CXL a été jugée de très faible qualité. La solidité globale des preuves pour les résultats concernant l'efficacité clinique était très faible.

Par rapport au traitement fictif ou à l'absence de traitement, une différence significative a été observée en faveur de la CXL concernant l'acuité visuelle non corrigée (AVNC) (DMS : -0,71, IC à 95 % : -1,28, -0,14) et la K_{max} (courbure maximale de la cornée centrale) (DM : -1,85 D, IC à 95 % : -3,44, -0,25) sur la période de suivi la plus longue (36 mois). Les changements absolus moyens

pondérés indiquent que la K_{max} a diminué au fil du temps par rapport à la base de référence pour la CXL, alors qu'elle a légèrement augmenté dans le groupe du traitement fictif et le groupe sans traitement. Les méta-analyses de la meilleure acuité visuelle corrigée (MAVC), de la K_{min} (courbure minimale de la cornée centrale), de la $K_{moyenne}$ (courbure moyenne de la cornée centrale), du cylindre (quantité d'astigmatisme) et de l'équivalent sphérique (estimation de l'erreur de réfraction) n'ont pas montré de différence significative entre la CXL et le traitement fictif ou l'absence de traitement pour la période de suivi la plus longue. Un ERC mentionne les taux de greffe cornéenne, aucune greffe n'ayant été signalée dans le bras expérimental (contre 10 % dans le bras témoin). Aucun ERC n'a porté sur la qualité de vie.

Les événements indésirables qui peuvent survenir à la suite d'une CXL sont notamment une kératite, une opacité cornéenne, des infiltrats stériles, un œdème stromal, des stries dorées, des cicatrices cornéennes, une photophobie, un larmoiement accru, une sécheresse oculaire, une irritation oculaire, une vision trouble, une douleur oculaire, des érosions cornéennes, des défauts épithéliaux et une vascularisation cornéenne. Bien qu'elle ne soit généralement que temporaire, l'opacité cornéenne ou haze semble être l'événement le plus fréquemment signalé après une CXL, avec des taux d'incidence allant jusqu'à 100 %. Étant donné la qualité insuffisante des indications relatives à la sécurité, la fréquence de ces événements ne peut pas être commentée avec certitude.

De manière générale, les preuves sont incertaines en raison de la petite taille d'un grand nombre d'études prises en compte, de leur définition variable de la progression du kératocône – utilisée comme critère d'inclusion dans les essais – et de l'absence de paramètres validés pour mesurer cette progression. Ces différents éléments font qu'il est difficile de tirer des conclusions avec un quelconque degré de certitude.

Coûts et rapport coût-efficacité

Un modèle de Markov a été construit pour évaluer le rapport coût-utilité de la CXL par rapport à l'absence de traitement. Des analyses de sensibilité déterministes et probabilistes ont été utilisées pour quantifier l'impact des incertitudes affectant les paramètres et pour identifier les facteurs clés du modèle. Le modèle économique a été fondé sur un modèle élaboré au Royaume-Uni par Salmon (2015). Des adaptations y ont été apportées pour refléter au mieux les résultats cliniques appropriés et la population suisse. Certaines valeurs d'entrée et certaines hypothèses cliniques du modèle de Salmon ont néanmoins été reprises directement pour la présente évaluation en raison du manque d'informations disponibles dans les preuves cliniques. Sur un horizon de 25 ans, le rapport coût-efficacité différentiel (ICER) par rapport au scénario de référence était de 25 841 francs par QALY gagnée. Les analyses de sensibilité suggèrent que l'ICER est plus sensible à l'efficacité de la CXL,

représentée par le taux d'échec de la CXL nécessitant de répéter le traitement. L'ICER est également sensible à la différence d'utilité entre le statut précoce de la maladie (stade 1 de la classification d'Amsler-Krumeich) et un statut plus avancé (stade 2). La plupart des ICER produits dans tous les scénarios étaient inférieurs au seuil hypothétique de 100 000 francs. Les analyses de sensibilité probabilistes ont montré que la CXL avait 99,4 % de chances de présenter un rapport coût-efficacité favorable par rapport au seuil hypothétique.

Une analyse d'impact budgétaire a été réalisée pour estimer l'incidence financière d'une prise en charge de la CXL. Dans l'analyse du scénario de référence, l'hypothèse retenue était qu'une part (50 %) seulement des patients atteints d'un kératocône nouvellement diagnostiqué seraient traités par CXL après la décision de prise en charge. Il a été estimé que les coûts de la CXL s'élèveraient à 573 346 francs la première année (2021) et augmenteraient à 584 865 francs (2025) pour l'ensemble des patients en Suisse. Si l'on prend également en considération les patients déjà diagnostiqués qui n'avaient pas pu être traités par CXL, le scénario le plus pessimiste serait un coût de plus de 4,5 millions de francs en Suisse la première année (2021). Ce chiffre doit être considéré comme le plafond de l'incidence financière et est sujet à une importante surestimation. Après une phase initiale de deux ou trois ans pour traiter les patients déjà diagnostiqués, le coût diminuera jusqu'au niveau du scénario de référence. Les projections pour la quatrième et la cinquième année sont conformes à ce scénario.

Questions juridiques, sociales, éthiques et organisationnelles

Les enfants atteints de kératocône représentent un groupe de patients vulnérables : la maladie progressant plus vite chez eux, ils risquent davantage que les adultes d'atteindre des stades avancés de la maladie ; ils ont par ailleurs des difficultés à adhérer aux traitements conservateurs (tels que le port de lunettes ou de lentilles de contact). D'un point de vue éthique et social, la CXL peut donc être plus bénéfique dans ce groupe. Il n'est pas certain qu'une prise en charge de la CXL modifie l'utilisation des ressources en soins de santé (en ce qui concerne les greffes cornéennes, p. ex.).

Conclusion

La CXL semble avoir un effet bénéfique en freinant la progression du kératocône du point de vue de l'AVNC et de la K_{max}. Sur la base de preuves de qualité moyenne à faible, il apparaît qu'une série d'événements indésirables peuvent survenir à la suite d'une CXL. L'événement indésirable le plus fréquemment signalé est l'opacité cornéenne temporaire, dont l'incidence peut atteindre 100 %. Ces résultats sont néanmoins entachés d'une grande incertitude. Il est probable que la CXL, en tant que traitement du kératocône, présente un rapport coût-efficacité favorable. En raison de l'utilisation

dans le modèle de valeurs d'entrée qui n'étaient pas spécifiques à la population suisse, des incertitudes subsistent néanmoins concernant l'applicabilité du résultat de l'évaluation économique au contexte suisse.

Executive summary

Il présente rapporto esamina l'efficacia clinica, la sicurezza, i costi e il rapporto costi-utilità legati al cross linking del collagene corneale (CXL) impiegato nel trattamento volto a contrastare l'evoluzione del cheratocono. Vengono inoltre analizzate questioni legali, sociali, etiche e organizzative relative all'impiego del CXL.

Valutazione clinica

Sono state condotte ricerche sistematiche in letteratura all'interno di quattro banche dati biomediche (PubMed, Embase, Cochrane Library, CINAHL) per identificare evidenze scientifiche derivanti da revisioni sistematiche (RS) e studi randomizzati controllati (RCT) relativi alle questioni che sono oggetto della ricerca. I risultati del presente executive summary derivano da un follow-up di lungo termine per via del fatto che la malattia progredisce lentamente e che il CXL mira a rallentarne l'evoluzione e non alleviarne la sintomatologia.

CXL confrontato con placebo o nessun trattamento

Grazie a RCT è stato possibile ottenere informazioni sull'efficacia clinica del CXL rispetto al placebo o a nessun trattamento. Quattro RCT e una RS che presenta un livello di evidenza scientifica inferiore hanno fornito informazioni sulla sicurezza del CXL. Desta preoccupazione il rischio di bias negli RCT rilevanti sia per la sicurezza che per l'efficacia legati all'incompletezza dei dati, alla randomizzazione, a conflitti di interessi e alla correlazione tra gli occhi. La qualità della revisione sistematica della sicurezza del CXL è stata ritenuta molto scarsa. La validità generale delle evidenze scientifiche per gli esiti relativi all'efficacia clinica era anch'essa molto scarsa.

Rispetto al placebo o a nessun trattamento, è stata osservata una significativa differenza per quanto concerne l'acuità visiva non corretta (UCVA) (SMD -0.71, 95 % CI -1.28, -0.14) e il K_{max} (la curvatura massima nell'area centrale della cornea) (MD -1.85 D, 95 % CI -3.44, -0.25) a favore del CXL nel follow-up di lungo termine (36 mesi). Le variazioni medie assolute ponderate indicano che il K_{max} diminuisce nel tempo rispetto al parametro di riferimento per il CXL, ma aumenta leggermente nei gruppi «placebo» e «nessun trattamento». Le meta-analisi della massima acuità visiva corretta (best-corrected visual acuity, BCVA), del K_{min} (curvatura minima nell'area centrale della cornea), del K_{mean} (curvatura media nell'area centrale della cornea), del cilindro (grado di astigmatismo) e dell'equivalente sferico (una stima dell'errore refrattivo degli occhi) non hanno evidenziato differenze significative tra CXL, placebo e non trattamento nel follow-up di lungo termine. Un RCT sui tassi di

trapianto di cornea ha indicato un tasso di trapianto nullo nel braccio CXL (rispetto a un tasso del 10 % nel braccio di controllo); in nessuno degli RCT è stata esaminata la qualità di vita.

Tra gli eventi avversi che possono verificarsi in seguito a un CXL si annoverano cheratite, opacità corneale, infiltrati sterili, edema stromale, striature giallo oro, cicatrici corneali, fotofobia, aumentata lacrimazione, secchezza oculare, irritazione oculare, visione offuscata, dolore oculare, erosioni corneali, difetti dell'epitelio e vascolarizzazione corneale. L'opacità corneale, sebbene sia in genere solamente temporanea, sembra essere l'evento più frequentemente segnalato in seguito al CXL, con tassi di incidenza fino al 100%; tuttavia, data la scarsità di dati disponibili sulla sicurezza non è possibile pronunciarsi con certezza sulla frequenza di questi eventi.

In genere sussistono incertezze sulle evidenze scientifiche a causa delle ridotte dimensioni di molti degli studi presi in considerazione, delle loro diverse definizioni dell'evoluzione del cheratocono, impiegate come criteri di inclusione nei trial, e della mancanza di parametri convalidati per misurare l'evoluzione del cheratocono. Tutto ciò rende difficile trarre conclusioni certe.

Costi e rapporto costi-utilità

È stato creato un modello di Markov per valutare il rapporto costi-efficacia del CXL rispetto a nessun trattamento. Sono state impiegate analisi di sensitività deterministiche e probabilistiche per quantificare l'impatto delle incertezze dei parametri e per far emergere gli elementi chiave del modello. Il modello economico si basava su un esistente modello britannico di Salmon (2015), adattato per rispecchiare al meglio i risultati clinici appropriati e la popolazione svizzera; tuttavia, alcuni valori di input e presupposti clinici del modello di Salmon sono stati impiegati direttamente nell'attuale valutazione a causa della mancanza di informazioni nella base di evidenze cliniche. In un orizzonte temporale superiore a 25 anni lo scenario di base ICER era di 25 841 franchi per QALY guadagnati. Le analisi sensitive suggeriscono che l'ICER dipende molto dall'efficacia del CXL, il che è stato rappresentato dal tasso di insuccesso di CXL per cui è stato necessario ripetere il trattamento. Esso varia inoltre in funzione della differenza di utilità tra uno stadio iniziale della malattia (1° grado della classificazione AK) e uno stadio più avanzato (2° grado della classificazione AK). La maggior parte degli ICER prodotti da tutti gli scenari erano inferiori alla soglia ipotetica dell'ICER di 100 000 franchi. Le analisi di sensitività probabilistica indicano che vi è un 99,4 % di possibilità che il CXL sia efficace in termini di costi rispetto alla soglia ipotetica.

È stata eseguita un'analisi dell'incidenza sul bilancio per valutare l'impatto finanziario del rimborso del CXL da parte degli enti pubblici. Nell'analisi dello scenario di base si è ipotizzato che solo una parte (il 50 %) dei pazienti con nuove diagnosi di cheratocono sia sottoposta a CXL in seguito all'introduzione dei rimborsi. Si è stimato che in Svizzera il CXL comporterebbe costi per un

ammontare di 573 346 franchi nel primo anno (2021) che aumenterebbero fino a 584 865 franchi (2025), intesi come costi totali in Svizzera per tutti i pazienti. Se tuttavia si considerano i pazienti cui è già stato diagnosticato il cheratocono e che non hanno potuto essere sottoposti al CXL, nella peggiore delle ipotesi, i costi in Svizzera sarebbero superiori a 4,5 milioni di franchi il primo anno (2021). Questo dovrebbe essere considerato il tetto dell'impatto finanziario, tenendo conto del fatto che si tratta di una sovrastima considerevole. I costi diminuiranno fino a raggiungere il livello dello scenario di base dopo due, tre anni in cui si dovrà inizialmente recuperare il ritardo sui trattamenti non effettuati finora. Trattati questi primi pazienti, le proiezioni per il quarto e il quinto anno sono in linea con lo scenario di base.

Questioni legali, sociali, etiche e organizzative

I bambini affetti da cheratocono costituiscono un gruppo di pazienti vulnerabile: dato che nel loro caso la malattia ha un'evoluzione più rapida vi sono maggiori probabilità che raggiunga stadi più avanzati rispetto agli adulti; i bambini hanno inoltre maggiori difficoltà a seguire trattamenti conservativi (ad es. occhiali o lenti a contatto). Il CXL potrebbe presentare maggiori benefici per questo gruppo da un punto di vista etico/sociale. Non è chiaro se il ricorso a risorse sanitarie (per es. legate ai trapianti di cornea) cambierà nel caso in cui il CXL venisse rimborsato.

Conclusioni

Il CXL sembra avere effetti benefici sul rallentamento dell'evoluzione del cheratocono per quanto attiene all'acuità visiva non corretta e al K_{max}. Una serie di eventi avversi può verificarsi in seguito al CXL stando a quanto riportato da evidenze scientifiche la cui qualità varia da scarsa a moderata. L'evento avverso più frequentemente segnalato è una temporanea opacità corneale con incidenze fino al 100 %; questi risultati presentano tuttavia un elevato grado di incertezza. È probabile che il CXL sia un trattamento efficace in termini di costi per il cheratocono ma sussistono ancora diverse incertezze per quanto concerne l'applicabilità del risultato della valutazione economica al contesto svizzero a causa dell'impiego all'interno del modello di input non specifici per la popolazione svizzera.

Table of contents

List of figures

List of tables

Abbreviations and acronyms

ACXL	Accelerated corneal collagen crosslinking
AK	Amsler-Krumeich classification
BCVA	Best corrected visual acuity
CAN	Canadian Dollar
CCT	Central corneal thickness
CDVA	Corrected distance visual acuity
CHF	Swiss Franc
CI	Confidence interval
CS	Case series
CXL	Corneal collagen crosslinking
DALK	Deep anterior lamellar keratoplasty
DRG	Diagnosis-Related Group
DSA	Deterministic sensitivity analysis
EUR	Euro
FOPH	Federal Office of Public health
GBP	Pound Sterling
GDP	Gross domestic product
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HAS	Haute Autorité de Santé
HTA	Health Technology Assessment
ICER	Incremental cost-effectiveness ratio
IQWIG	Institut für Qualität und Wirtchaftlichkeit im Gesundheitswesen
Kmax	Maximum keratometry
Kmean	Mean keratometry
Kmin	Minimum keratometry
K1	Flattest meridian keratometry
K2	Steep keratometry
MD	Mean difference
NA	Not applicable
NHS	National Health Service
NR	Not reported
NRC	Non-randomised comparative study
NS	Not significant
NT	No treatment

NUTH	Newcastle upon Tyne hospitals
RCT	Randomised controlled trial
PICO	Population, intervention, comparator, outcome
PK	Penetrating keratoplasty
PSA	Probabilistic sensitivity analysis
QALY	Quality-adjusted life year
SR	Systematic reviews
SMD	Standardised mean difference
TCT	Thinnest corneal thickness
UCVA	Uncorrected visual acuity
UK	United Kingdom
USD	United States Dollar
UVA	Ultraviolet light A
WTP	Willingness-to-pay threshold
YHEC	York Health Economics Consortium

Objective of the HTA short report

The objective of a health technology assessment (HTA) is to generate a focused assessment of various aspects of a health technology. The analytic methods applied to assess the value of using a health technology are described. The analytical process is comparative, systematic, transparent and involves multiple stakeholders. The domains covered in an HTA report include clinical efficacy and safety; costs, cost-effectiveness and budget impact; and legal, social, ethical and organisational issues. The purpose is to inform health policy and decision-making to promote an efficient, sustainable, equitable and high-quality health system. This report was commissioned as a short HTA project, meaning there was no formal scoping phase, and there is a greater reliance on including existing systematic review evidence where possible.

1 Policy question and context

Photochemical corneal collagen crosslinking (CXL) using riboflavin and ultraviolet A light (UVA) is a surgical procedure designed to halt the progression of keratoconus. The Federal Office of Public Health (FOPH) reviewed the procedure in 2008 and raised safety concerns based on case studies reporting serious complications such as keratitis and permanent corneal scarring.[1-5] As a result, the Department of Home Affairs decided to specifically list CXL using riboflavin and UVA as a procedure not required for reimbursement by the mandatory health insurance in the Health Insurance Benefits Ordinance Appendix 1.[6] Since then, reports from different European HTA agencies have concluded that CXL is a relatively safe and efficacious treatment for keratoconus. It has now been suggested that the Swiss FOPH, together with the Federal Medical Services Commission, should re-evaluate the procedure and, if appropriate, the Federal Department of Home Affairs should update the reimbursement decision in the Health Insurance Benefits Ordinance Appendix 1.

2 Medical background

The cornea is the clear dome-shaped front surface of the eye, laying directly over the iris and pupil.[7] Its function is to help refract (bend) and focus light rays onto the retina for vision.[8] Over time, normal eye pressure causes the round shape of a thinned cornea to become cone-shaped causing myopia and irregular astigmatism.[9] Keratoconus, also known as conical cornea, is a progressive, degenerative disease resulting from thinning and deformation of the central zone of the cornea.[7 8 10] These changes in shape can happen quickly or occur over several years and they can stop at any time or continue for decades. There is no way of predicting progression.[11] The level of visual impairment can be moderate to severe depending on the degree and location of the protrusion.[9 10] Keratoconus occurs bilaterally but is typically asymmetric in its development, with one eye more advanced than the other.[12] Onset is usually around puberty, although it can commence anywhere between the ages of 8 and 25, with progressive thinning and deformation of the cornea occurring until the third or fourth decade of life.[13 14] Keratoconus diagnosed in adolescence tends to be more aggressive.[14] The cause of keratoconus is unknown but thought to be multifactorial involving genetic, environmental and lifestyle factors.[15]

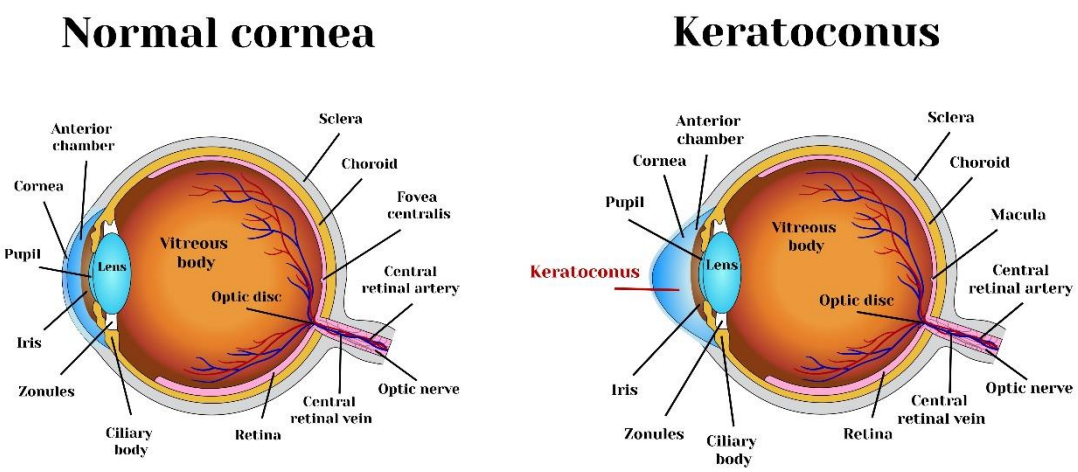

Figure 1 Cornea with and without keratoconus

Source: https://www.nvisioncenters.com/contacts/keratoconus-lenses/

The initial symptoms of keratoconus include blurring and distortion of vision. Frequent changes in glasses prescription may be required. As the disease progresses patients suffer from increased blurring and short-sightedness (myopia), light sensitivity, halos, and ghosting around light sources (making night driving dangerous).[10] More advanced keratoconus produces more severe visual distortion. Although uncommon, keratoconus may lead to hydrops formation and corneal opacity requiring surgical intervention.[9] The adverse effect of keratoconus on vision has a major impact on a patient's quality of life.[16]

The average incidence of keratoconus in Denmark from 2011 to 2015 was reported as 3.60 cases per 100,000 people whilst the prevalence, based on a National Patient Register from 1977 to 2015, was 44 cases per 100,000 people.[17] Incidence and prevalence have also been determined for the Netherlands based on a nationwide registry study of 4.4 million people. The study reported an annual incidence of 1:7,500 (13.3 cases per 100,000 people; 95% confidence interval [CI] 11.6–15.2) and an estimated prevalence of 1:375 (265 cases per 100,000; 95% CI: 260–270).[18] No peer-reviewed data could be found on the incidence or prevalence of keratoconus in the Swiss population. One grey literature source (Institute for Refractive and Ophthalmic Surgery (IROC)) reports that keratoconus occurs in 1 of every 2,000 people in Switzerland.[19]

Mandatory findings for a diagnosis of keratoconus are: abnormal corneal thickness distribution, abnormal posterior elevation and clinical non-inflammatory corneal thinning.[20] A diagnosis of early or subclinical keratoconus is based on the presence of posterior corneal elevation abnormalities as

determined from tomography measurements of posterior corneal curvature (Scheimpflug or optical coherence tomography).[20] Keratoconus is classified as an ectatic disease.[20] Ectatic disease is a group of non-inflammatory corneal conditions characterised by the progressive thinning and bulging of the cornea.[21] Ectatic disease may be iatrogenic or spontaneous.[21] Currently there are no consistent definitions of ectatic disease progression. Guidelines based on a consensus of ophthalmology experts from around the world state that ectasia progression is defined by a consistent change in at least two of the following parameters where the magnitude of the change is above the normal noise of the testing system:[20]

- *"Steepening of anterior corneal surface*
- *Steepening of posterior corneal surface*
- *Thinning and/or increasing rate of corneal thickness change from periphery to thinnest point"*

Although it is stated that changes to two of these parameters is a requirement to document progression, the magnitude of change is not provided.[20] The guidelines further note that although progression is often accompanied by a decrease in best corrected visual acuity (BCVA), a change in both uncorrected visual acuity (UCVA) and BCVA is not required to document progression.[20] They further state that studies correlating clinical findings such as BCVA with corneal topometric and tomographic parameters are needed.[20]

Treatment of keratoconus depends on its stage and the rate at which it is progressing. In the early stages, when it is mild, prescription glasses are all that is needed to correct vision.[8] The eyes and visual cortex of younger patients with keratoconus (up to 35–40 years of age) are capable of compensating for the multifocal images created by their irregular corneal surface. As such, these patients may have better visual acuity compared with older people with keratoconus. After 40 years of age, as the disease progresses and the cornea becomes more irregular, it becomes increasingly difficult to correct vision with glasses. At this time contact lenses are required (rigid, piggyback, hybrid or scleral).[8] The fitting of contact lenses becomes more challenging with increasing keratoconus severity, needing special designs to match the altered corneal shape and avoid rubbing resulting in corneal scars.[12] These treatments (glasses and contact lenses)) do not prevent progression of the condition, they only improve visual acuity. For some patients with advanced keratoconus, when extreme thinning or scarring is present and functional vision is no longer obtainable with contact lenses, a corneal transplant (keratoplasty) is required.[22]

3 Technology

3.1 Technology description

3.1.1 CXL

The surgical procedure under investigation is photochemical CXL using riboflavin and UVA light. The procedure uses photopolymerization to strengthen corneal tissue and is designed to halt the progression of keratoconus rather than reverse it.[23] When stimulated by UVA light, riboflavin (a photosensitiser) produces highly reactive oxygen species that interact with surrounding molecules to crosslink the chemical bonds of adjacent collagen fibrils within the stroma layer of the cornea.[23] Bonding of collagen strands across the cornea strengthens it to retain its shape and stabilise keratoconus.[8]

The traditional CXL procedure (known as the Dresden protocol), from here on in referred to as standard CXL, occurs in an outpatient setting and begins with the application of topical anaesthetic (typically proxymetacaine or oxybuprocaine followed by tetracaine; 1 drop each, up to 3 times over 2 minutes) to the cornea and placement of a lid speculum to keep the eyelids open.[23 24] Removal of the central 8–9 mm of the corneal epithelium (outermost layer of the cornea) then occurs using a dry cellulose sponge, blunt spatula or 20% alcohol solution.[23 25] Corneal pachymetry determines a baseline corneal thickness measurement followed by saturation of the eye with riboflavin. Treatment can only proceed when the thinnest point of the stroma (corneal layer beneath the epithelium) is ≥400 µm. In this case, riboflavin (0.1% iso-osmolar solution in 20% dextran [0.5% vitamin B2 ribvoflavin-5-phostate with T-500 20% dextran]) is applied to the corneal surface every 2 to 3 minutes for 30 minutes.[25] If stromal thickness measures <400 µm there is an increased risk the CXL procedure will damage the corneal endothelium or deeper ocular structures. In this case, hypo-osmolar riboflavin may be used (2 drops every 10 seconds) to swell the cornea to an appropriate thickness to facilitate CXL.[23 25] Slit lamp examination is then used to confirm riboflavin is present in the anterior chamber of the eye, indicating sufficient penetration into the corneal stroma.[23] Riboflavin saturation of the stroma enables UVA light absorption (to achieve crosslinking) whilst protecting the underlying corneal structures by preventing penetration of UVA light.[26]

Prior to the application of UVA light (the photoactivation stage), a sponge is placed over the limbus (the border of the cornea and surrounding sclera) to prevent damage of limbal stem cells.[23] UVA light is then applied to activate the riboflavin solution. UVA light (calibrated to 365 nm) providing an irradiance of 3 mW/cm^2 (total dose 5.4 J/cm^2) is placed 5 cm from the cornea and focused for 30 minutes on the area where the epithelium was removed.[23] Riboflavin instillation continues every three minutes, along with topical anaesthetic. Intermittent corneal pachymetry throughout the CXL procedure ensures that the

thinnest point of the stroma does not fall below 400 µm. If this occurs, additional hypo-osmolar riboflavin may be administered.[23]

Following the CXL procedure, broad-spectrum antibiotic drops (typically moxifloxacin) are applied to the cornea, which is then covered with a soft, long-term bandage contact lens.[23] Patients are discharged with a course of topical antibiotics and analgesics. Close monitoring for 3 to 7 days is required to ensure adequate epithelial healing and removal of the bandage contact lens.[27]

CXL is generally safe; however, minor postoperative complications can occur. These may include infection, scarring and corneal haze, all of which temporarily impair vision. Patients with corneal haze may experience glare, halos and mild blurriness in dim light. Most complications resolve within 12 months.[27]

Contraindications for CXL include thin corneas (350–400 µm), an active ocular disease other than keratoconus, herpes simplex keratitis, pregnancy, uncontrolled eye allergies, corneal scarring affecting vision, neurodermatitis or severe dry eye.[28] [29] These conditions increase the likelihood of adverse reactions to CXL or may lead to significant delay in epithelial healing.

Variations of this protocol now exist, including leaving the epithelium on (transepithelial CXL). Other common protocol variations relate to the delivery of UVA, including accelerated irradiation treatment, use of pulsed UVA light (compared with continuous light) and, more recently, customisation of UVA intensity. Other novel variations include the use of chemically altered riboflavin and regenerating agents to improve endothelial healing. The protocol variations most relevant to Swiss clinical practice as determined by a survey of Swiss ophthalmologists (see S***ection 6.2.2***) and with the largest body of evidence include accelerated CXL and transepithelial CXL.

3.1.2 Accelerated CXL

This protocol uses shorter UVA irradiation times than that of standard CXL by increasing irradiance intensity uniformly across the cornea so that the total energy levels achieved per treatment are the same as those of the original protocol. For example, instead of delivering UVA irradiance of 3 mW/cm^2 over 30 minutes, accelerated CXL may deliver 9 mW/cm^2 over 10 minutes, 18 mW/cm^2 over 5 minutes or 30 mW/cm^2 over 3 minutes.[30] Along with the improved comfort and tolerance of a shorter procedure (for patient and surgeon), the purported benefits of accelerated CXL include reduced corneal dehydration, intraoperative thinning and infection rates.[31]

3.1.3 Transepithelial CXL

Transepithelial CXL, also known as epithelium-on or epi-on CXL, uses the same principals as standard CXL without the initial removal of the surface epithelial cells of the cornea.[32] The challenge with transepithelial CXL is riboflavin absorption since the epithelium acts as a barrier to the underlying cornea. Methods to counteract this exist, including alternate riboflavin solutions (usually without Dextran) and the use of permeability enhancers.[33] Partial epithelium disruption may also be used to facilitate riboflavin absorption in transepithelial CXL. This involves the use of a corneal disruptor device which creates pockmarks in the epithelium without removing it.[34]

3.2 Alternative technologies

Currently there is no alternative technology to CXL that can slow or stop progression of keratoconus. The alternative technologies listed below are solely aimed at improving a patient's visual acuity.

3.3 Regulatory status/provider

Medical disciplines involved in crosslinking

In Switzerland CXL is performed by an ophthalmologist (personal communication (email); Swiss ophthalmologist, 28th August 2020).

Credentials, licensing, skills, training required for performing CXL

Other than being a qualified ophthalmologist, no formal accreditation or training is required to perform CXL in Switzerland (personal communication (email); Swiss ophthalmologist, 28th August 2020).

Regulatory status of CXL in Switzerland

Below is a list of some, but not all, of the UVA light source devices used for CXL that have the European CE Mark.[35-37] It is unclear which devices are used in Swiss practice.

- KXL System (Avedro Inc., USA)
- KXL II System (Avedro Inc. USA)
- Mosaic System (Avedro Inc., USA)
- LIGHTLink-CXL (LightMed Corporation, USA)
- The C-Eye Device (Emagine, Switzerland)
- CBM Vega XLink (Carleton Optical, UK)
- Opto Xlink (Optos, UK)
- UV-X™ 1000 (formerly IROC Innocross AG, Switzerland, now owned by Avedro Inc. USA)

- UV-X™ 2000 (IROC Innocross AG, Switzerland, now owned by Avedro Inc. USA)
- CCL-Vario (Peschke Meditrade, Switzerland)
- CCL-365 (Peschke Meditrade, Switerzland)

In addition to the device to perform the CXL, a riboflavin ophthalmic solution is required. Several riboflavin formulations have been CE marked (***Table 1***).[38 39] It is unclear which solutions are being used in Swiss practice. None of the solutions listed below could be found on the Swissmedic database.

Table 1 Riboflavin formulations with CE mark

Type	Trade Name	Manufacturer (country)
Riboflavin with dextran	MedioCROSS D	MedioHaus for Avedro (Germany)
	Ricrolin	Sooft italia (Italy)
	Collagex Isotonic	LightMed (USA)
	Innocross-R Isotonic	IROC Innocross (Switzerland)
Hypoosmolaric riboflavin	MedioCROSS H	MedioHaus for Avedro (Germany)
	Collagex Hypoosmolaric	LightMed (USA)
	Ribo-Ker*	EMAGINE (Switzerland)
	Innocross-R Hypotonic	IROC Innocross (Switzerland)
Transepithelial riboflavin	Paracel	MedioHaus for Avedro (Germany)
	MedioCROSS TE	MedioHaus for Avedro (Germany)
	Ricrolin TE	Sooft italia (Italy)
	Collagex TE	LightMed (USA)
	RiboCross TE	IROS (Italy)
Riboflavin with HPMC	VibeX Rapid	MedioHaus for Avedro (Germany)
	MedioCROSS M	MedioHaus for Avedro (Germany)
	Collagex Rapid	LightMed (USA)

Abbreviations
HPMC = hydroxypropyl methycellulose; **USA** = United States of America.
Notes
*Can be used with epithelium on and epithelium off corneal collagen crosslinking.

National coverage policy of CXL in Switzerland

CXL was evaluated by the Swiss FOPH in 2007. Following that evaluation, it was listed in the Health Insurance Benefits Ordinance Appendix 1 as a procedure that does not have to be reimbursed by the mandatory health insurance.

4 PICO

The PICO criteria for this evaluation were defined *a priori* in a research protocol, which was reviewed and approved by the FOPH.

4.1 PICO box

Table 2 Study selection criteria

P:	Patients with progressive keratoconus ***Subgroups:*** *Adult and paediatric patients*
I:	Corneal collagen crosslinking using riboflavin and UVA ***Subgroups:*** *accelerated UVA delivery and transepithelial crosslinking techniques* ***Exclusion****: concomitant surgical therapies*
C:	1. Sham procedure 2. No treatment 3. Standard treatment (*glasses, contact lenses or intrastromal ring segments)*

O:	**Clinical efficacy**
	• Change in visual acuity
	  ○ UCVA
	  ○ BCVA or BSCVA
	• Change in surrogate markers of disease progression
	  ○ Pachymetry (CCT and TCT)
	  ○ Topography (corneal curvature: K_{max}, K_{mean}, K_{min})
	  ○ Astigmatism
	• Quality of life
	• Corneal transplant rates
	Safety
	• Treatment-related adverse events

Abbreviations
BCVA = best corrected visual acuity**, BSCVA** = best spectacle-corrected visual acuity, **CTC** = central cornea thickness, **TCT** = thinnest corneal thickness, **UVA** = ultraviolet A light, **UCVA** = uncorrected visual acuity.

4.2 Population

The patient population is defined as patients with progressive keratoconus. There is no standardised definition of what constitutes progressive keratoconus. A global consensus guideline suggests patients must meet a consistent change in at least two of the following criteria to be diagnosed with ectasia:[20]

- *Steepening of the anterior corneal surface*
- *Steepening of the posterior corneal surface*
- *Thinning and/or an increase in the rate of corneal thickness change from the periphery to the thinnest point."*

The consensus guidelines further state that while these changes often result in alterations to BCVA or UCVA, changes in these parameters are not required to confirm a diagnosis of progressive keratoconus. It is unclear whether Swiss clinicians follow this definition of progressive keratoconus to determine which patients are eligible for CXL. In the absence of Swiss-specific information, the population will be left broad and include all patients with a diagnosis of progressive keratoconus.

Keratoconus in children is more complex owing the rate of progression and intolerance to conservative treatments.[40 41] Therefore, sub-group analysis evaluating the children and adolescents will be performed if there are suitable numbers of studies.

4.3 Intervention

The technology under investigation is photochemical CXL using riboflavin and UVA light. In addition to the standard CXL method, which involves removal of the epithelium and administration of riboflavin drops and UVA light at 3 mW/cm^2 for 30 minutes, there are several procedural variations including accelerated CXL and transepithelial CXL (see ***Section 3.1*** for further information). It is unclear which procedural variation is most commonly utilised in Switzerland and whether their safety and clinical efficacy differ.

As several CXL variations were identified in the initial literature search, a survey was sent to Swiss ophthalmologists to determine which variations are most commonly used in practice in order to prioritise the most relevant variations for evaluation. Ten ophthalmologists were contacted by the FOPH. It was agreed that accelerated and transepithelial CXL variants would be evaluated as these variations were the most commonly used by the respondents and had the largest evidence base.

Consequently, the HTA will first establish the overall clinical efficacy and safety of all CXL procedures (research question 1a), and then subsequently assess the clinical efficacy and safety of procedural variations (research question 1b).

4.4 Comparator

There are no other technologies that slow or stop the progression of keratoconus. Therefore, the comparators are sham and no-treatment. Sham procedures aimed to simulate the CXL procedure without the administration of UVA light treatment. Patients assigned to no-treatment continued to use glasses or contact lenses but received no medical technologies.

Aside from exposure to riboflavin or UVA light treatment, patients undergoing sham and no-treatments received similar treatments. Therefore, these patients were pooled together for the evaluation of clinical efficacy and safety outcomes if there was insufficient evidence to evaluate both separately.

4.5 Outcomes

4.5.1 Clinical efficacy outcomes

The aim of CXL is to halt progression of keratoconus, a type of ectasia. Currently there is no widely accepted, validated definition of ectasia progression.[20] Global consensus guidelines suggest that changes in at least two surrogate parameters are required (see ***Section 4.2***). No quantitative values regarding the degree of change in these parameters was given by these guidelines, only that a consistent change is required above the normal noise of the testing system.[20] The consensus guidelines further note that although progression is often accompanied by an increase in BCVA, a change in both uncorrected and BCVA is not required to document progression.[20]

For this HTA, CXL clinical efficacy was assessed based on changes in clinically relevant outcomes including visual acuity (uncorrected and best-corrected), change in surrogate markers of disease progression (pachymetry, topography and refractive errors [sphere, cylinder and spherical equivalent]) as well as quality of life and corneal transplant rates. These parameters were chosen as, excluding corneal transplant rates and quality of life, they have been typically used to determine progression.[38]

Visual acuity (BCVA and UCVA)

Visual acuity refers to the clarity of sharpness of vision.[42] It is measured by a test which requires patients to read letters on a standardised chart. Different standardised charts are available including the Snellen chart and the LogMAR (log of the minimum angle of resolution) chart. LogMAR charts are recognised as standard for clinical research and clinical trials of ophthalmic devices or drugs.[43] A LogMAR score of zero indicates standard vision, positive values indicate poor vision and negative values indicate good vision.[44] A minimal clinically important difference in visual acuity is 10 to 15 letters (0.2–0.3 log units).[45]

UCVA is the best visual acuity that can be achieved when measured without corrective aids (spectacles or contact lenses). BCVA is the best visual acuity that can be achieved when measured with corrective aids (spectacles or contact lenses). Sometimes BSCVA (best spectacle-corrected visual acuity) is reported. This refers to the best visual acuity that can be achieved when measured with the patient wearing spectacles.

Pachymetry (corneal thickness: thinnest and central)

As keratoconus results in progressive central thinning of the cornea, corneal thickness is used to diagnose keratoconus. The global consensus guidelines on keratoconus and ectatic disease note that change in corneal thickness is one of the parameters that can be used to document ectasia progression.[20]

Corneal pachymetry is the measurement of the thickness of the cornea in microns (µm). Measurements are typically taken at the centre of the cornea (central corneal thickness [CCT]) or at the thinnest location (thinnest corneal thickness [TCT]).[46]

Topography (corneal curvature, [K_{max}, K_{min}, K_{mean}])

In addition to progressive thinning, keratoconus also results in progressive steepening of the cornea. The global consensus guidelines on keratoconus and ectatic diseases note that change in the steepening of the corneal surface (either posterior or anterior) is a parameter that can be used to document ectasia progression.[20]

Corneal topography is an imaging technique that maps the shape and features of the corneal surface and is used to measure change in corneal steepness.[47]Typical corneal curvature measurements include K_{max} (maximum anterior corneal curvature), K_{min} (minimum anterior corneal curvature) and K_{mean} (mean anterior corneal curvature), all measured in dioptres (D). K_{max} is the most commonly used parameter to detect or document ectatic progression and is regularly used as an indicator of crosslinking efficacy.[48]

Refractive errors

Refractive errors cause blurred vision. Types of refractive errors include:

- myopia (near-sightedness): difficulty seeing distant objects clearly
- hyperopia (far-sightedness): difficulty seeing close objects clearly
- astigmatism: distorted vision resulting from an irregularly curved cornea[49]

Measures of refractive errors include sphere, cylinder and spherical equivalents. Sphere is a measure (in dioptres) of near- or far-sightedness. A plus sign (+) before the number indicates a person is farsighted; a minus (-) sign means a person is nearsighted.[50] The larger the number (negative or positive), the more near- or far-sighted a person is. Cylinder is a measure (in dioptres) of the degree of astigmatism. The larger the number (negative or positive), the greater the astigmatism.[50] Spherical equivalent is an estimate (measured in dioptres) of an eye's refractive error. It is calculated by adding one-half of the cylinder power to the sphere.[51] The higher the spherical equivalent, the higher the refractive error.

Quality of Life

The Beck Depression Inventory (BDI), State-Trait Anxiety Inventory (STAI) and Short Form-36 (SF-36) instruments have been previously implemented in studies investigating quality of life in keratoconus patients after collagen crosslinking.[52] Vision-related quality of life can be evaluated using the National Eye Institute Visual Function Questionnaire-25 (NEI-VFQ-25)[53] and the Vision and Quality of Life Index

(VisQoL) multi-attribute utility instrument.[54] Recently, a keratoconus end-point assessment questionnaire (KEPAQ) has also been developed and validated.[55]

Corneal transplant rates

CXL aims to slow the progression keratoconus, a disease that can result in the need for corneal transplant in later stages.[20] [56] Corneal transplant surgeries for keratoconus include penetrating keratoplasty and deep anterior lamellar keratoplasty. According to the global consensus guidelines on keratoconus and ectatic diseases, 21% to 60% of eligible keratoconus patients are offered a form of corneal transplant.[20]

4.5.2 Safety outcomes

Corneal crosslinking is a common procedure, but as with any surgical procedure, treatment-related adverse events arise.

Treatment-related adverse events

Possible CXL-related adverse events can include postoperative pain, infectious keratitis, stromal oedema, corneal opacity, sterile infiltrates, golden striae, haze, epithelial defects, corneal melting and corneal scarring.[57-59] These are all important safety outcomes.

4.6 Amendments to PICO from the protocol

The clinical efficacy outcome astigmatism was changed to refractive error (including cylinder, sphere and spherical equivalent) to more accurately reflect the reported results. In addition, the flattest meridian keratometry (K_1) and steepest meridian keratometry (K_2) were reported by some studies and have been included. These parameters are measured in dioptres.

5 HTA key questions

For the evaluation of the technology the following key questions covering central HTA domains—as designated by the EUnetHTA (European Network for Health Technology Assessment) Core Model (clinical efficacy; safety; costs; cost-effectiveness; budget impact; and legal, social, ethical and organisational aspects)—are addressed:

1a. What are the benefits and harms of CXL using riboflavin and UVA as a treatment for progressive keratoconus compared to sham or no treatment?

1b. If a benefit is found for using CXL to treat keratoconus, what are the benefits and harms of using different CXL variations (compared with standard protocol)?

2. How cost-effective is CXL using riboflavin and UVA as a treatment for progressive keratoconus compared to sham or no treatment?

3. What is the estimated yearly budget impact of CXL using riboflavin and UVA as a treatment for progressive keratoconus?

4. Are there social, legal, ethical and organisational considerations around the use of CXL using riboflavin and UVA as a treatment for progressive keratoconus?

6 Efficacy and safety

6.1 Summary statement clinical efficacy and safety

CXL appears to have a beneficial effect on both maximum corneal curvature (K_{max}) and visual acuity compared with no treatment. A range of adverse events can occur following CXL, the most common appears to be corneal haze. There is uncertainty regarding this finding owing to several limitations with the evidence. Key limitations include the variable definition of progressive keratoconus used by the studies as an inclusion criterion and the lack of validated parameters to define progression.

Based on the limited evidence, accelerated CXL and transepithelial CXL appear to have a similar effect to standard CXL, respectively. Where outcomes are significantly different, their direction of effect (in favour of the variant or standard CXL) is generally inconsistent. Adverse events are similar between the variants and standard CXL, with a tendency for improved perioperative comfort in favour of transepithelial CXL.

6.2 Methodology

6.2.1 Literature search

Databases and search strategy

A literature search for studies reporting the clinical efficacy and safety of CXL for the treatment of patients with progressive keratoconus was conducted in four biomedical databases (PubMed, Embase, Cochrane Library, CINAHL). York CRD and websites of HTA agencies were also searched to identify recent HTA reports on CXL. Searches were performed between the 14th to 22nd of April 2020.

Search terms consisted of a combination of key words and medical subject headings (MeSH) relating to keratoconus and CXL. The search strategy for each database is reported in ***Table 24***. All languages were screened by title and abstract, however, study selection was limited to English, French, German and Italian.

Other sources

A search for ongoing or unpublished clinical trials was conducted in three clinical trial databases (ClinicalTrals.gov, Cochrane Central Register of Controlled Trials, World Health Organization International Clinical Trials Registry Platform) (***Appendix C***). Grey literature searches were conducted on specialty websites (***Appendix A***).

Study selection

Study selection was performed independently by two authors. The authors reviewed records by title and abstracted and then full text. Title and abstract screening was performed using Rayyan software (Qatar Computing Research Institute).[60] Studies were included if they met the PICO criteria outlined in ***Section 4***.

In addition to the PICO criteria outlined in ***Section 4***, different levels of evidence were considered for the primary research question (i.e. CXL vs placebo/sham) and the secondary research question (i.e. CXL variants vs standard CXL). As this report was commissioned as a short HTA project, a pragmatic approach was taken to study selection whereby existing systematic reviews were included where possible.

6.2.2 Data analyses

Assessment of quality of evidence

Two independent researchers conducted the quality appraisal, including risk-of-bias assessment, with differences settled via consensus or an independent reviewer.

Study quality and risk of bias were assessed using different tools depending on trial design. RCTs were evaluated using the Cochrane Risk-of-Bias Tool (version 2.0).[61] Systematic reviews were appraised using the AMSTAR (measurement tool to assess systematic reviews) checklist (version 2).[62]

The overall quality of the estimated effect sizes were appraised according to the grading of recommendations, assessment, development and evaluations (GRADE) approach, which incorporates an assessment of risk of bias, indirectness, inconsistency, imprecision and publication bias.[63] The GRADE summary of findings tables summarise the overall strength of evidence associated with the seven most prioritised outcomes. Imprecision, risk of bias and inconsistency elements of the GRADE framework were scored according to the decision algorithm developed by Pollock (2016).[64]

Meta-analysis of continuous outcomes

Mixed-effect meta-regression models, incorporating time of follow-up as a covariate factor, were used to analyse the continuous efficacy outcomes in this report. This type of model considered not only the efficacy differences between the intervention (CXL) and the comparator (sham or no treatment) via random-effect models, but also compared the differences across time points via a fixed-effect model. As a result of using mixed-effect models, estimated heterogeneity was assumed to be the same at each timepoint (hence a single heterogeneity value for each analysis). This is considered appropriate as the data from the trial were produced by the same patients longitudinally. This approach was better than

running individual meta-analyses across different time points then pooling them together afterwards.[65] The limited number of studies available at each time point prevented the performance of a more complex longitudinal meta-analyses model to account for the time trend. Therefore, different time points were treated as nominal factors where the different gaps between time points were unaccounted for.

Scores measured at baseline were included in the meta-analyses as a separate subgroup as well as presented in the forest plots. This approach had the benefit of incorporating heterogeneities at baseline measurements, as well as demonstrating the consistency at baseline.

Outcomes (except for BCVA and UCVA) are presented as mean differences. Owing to the different way Hersch (2017a) reported BCVA and UCVA compared with the other studies, standardised mean differences have been analysed for these outcomes.[66]

For both question 1a and 1b the outcome BCVA refers to visual acuity corrected by either glasses or contact lenses. Whilst some studies did specify best spectacle-corrected visual acuity,[67-72] the data were pooled and all reported as BCVA owing to the small number of studies available. Similarly, where reported, best corrected distance visual acuity (BCDVA or CDVA)[66 73-81] results were pooled with BCVA and uncorrected distance visual acuity (UDVA)[66 69 76-81] results were pooled with UCVA.

The results of the meta-analyses with moderators were presented using forest plots, where the data at different time points were grouped and ranked by ascending order. Estimates of mean differences or standard mean differences (BCVA and UCVA) at each time point were illustrated by grey diamonds together with p values for significance levels. The omnibus heterogeneity estimates for the overall analysis were computed by the tau^2 and I^2 values (in percentages) and p value for the testing of significant heterogeneity. The impact of the moderator was also computed using a Chi^2 test with p value. Raw data at study level together with their weights in the meta-analyses were also plotted in forest plots.

For the surrogate markers, weighted absolute mean changes from baseline for the CXL and sham or no treatment groups were calculated for each outcome at each follow-up time point where at least two studies were available to indicate how the individual treatment groups changed over time (i.e. whether the surrogate markers increased or decreased relative to baseline measurements). This was not done for the visual acuity measures, as unlike the surrogate markers, these were combined using standardised mean differences.

Heterogeneity

Results of the meta-analysis were presented using forest plots for a visual representation of variability in reported effect sizes across studies. Heterogeneity and inconsistency were assessed statistically using the Chi^2 test ($p < 0.10$ representing significant heterogeneity) and the I^2 statistic for the meta-analysis of dichotomous outcomes, and tau^2 and I^2 for continuous outcomes. The thresholds for low,

moderate, substantial and considerable heterogeneity followed those proposed in the Cochrane handbook (I^2 0–40% might not be important; 30–60% moderate; 50–90% substantial; 75–100% considerable heterogeneity).[82] The importance of the I^2 result was dependent on the size and direction of the measured effect, and the strength of evidence for heterogeneity (i.e. chi^2 and tau^2).

Missing values

If standard deviations were not reported, they were calculated from standard errors or confidence intervals using the following formulas:

SD = standard error x √N

SD = √N x (upper limit – lower limit) / 3.92

Where studies only reported outcomes graphically, WebPlotDigitizer was used to generate numerical values.[83]

Trials that reported either absolute or percentage change from baseline that failed to report measures of variance were omitted from the meta-analyses but cited in the text to ensure transparency in reporting.

Narrative synthesis

Trials that did not provide enough data for inclusion in a meta- analysis (i.e. only reported values for the CXL arm and a p value noting whether the CXL and sham or no treatment arm differed significantly) were reported narratively.

Safety

For safety-related outcomes, the number of patients experiencing an event was reported, unless otherwise stated.

6.3 Search results

6.3.1 PRISMA flow diagram

Results from the systematic literature searches are presented in ***Figure 2***. Database searches and searches of HTA and relevant specialty websites yielded a total of 4,768 results. (Results from each database are listed in ***Appendix A***). After removal of 1,797 duplicate citations, 2,971 citations were reviewed by title and abstract. A total of 150 citations were reviewed by full text.

For the primary research question, no suitable systematic reviews were identified that evaluated efficacy outcomes for CXL versus sham or no treatment, and therefore primary RCTs were included and meta-

analysed. For safety outcomes, an existing systematic review was identified, and supplemented by the included RCT evidence.

For the secondary research question, existing systematic reviews were identified that evaluated safety and efficacy outcomes for CXL variants. In addition, primary RCTs that were not included in the existing systematic reviews, but met the inclusion criteria for the present review, were included and described narratively. De novo meta-analysis of all available RCTs addressing this research question was outside the scope of this review. Based on this revised approach 1 systematic review and 9 RCTs (reported across 10 publications) were included for research question 1a, and 2 systematic reviews and 12 RCTs were included for research question 1b. A comprehensive list of all excluded trials is listed in ***Appendix B.***

PRISMA diagrams were not provided for ethical, legal, social and organisational issues as the searches were conducted in both a systematic and non-systematic manner.

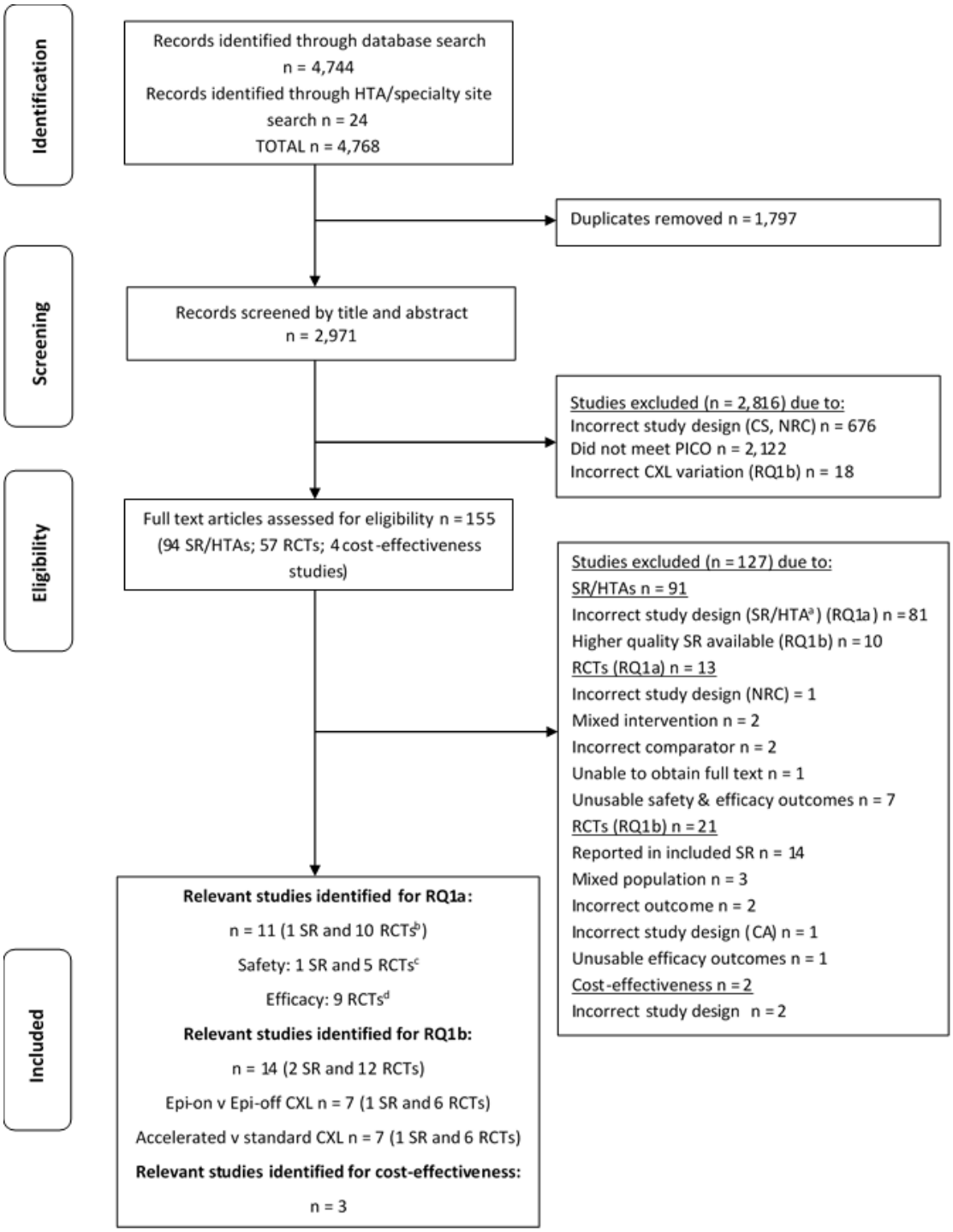

Figure 2 PRISMA flow chart for study selection

Abbreviations

CA = conference abstract, **CS** = case series, **CXL** = corneal collagen crosslinking, **HTA** = health technology assessment, **NRC** = non-randomised comparative study, **RCTs** = randomised controlled trial, **RQ1a** = research question 1a (i.e. What are the benefits and harms of CXL using riboflavin and UVA as a treatment for progressive keratoconus?), **RQ1b** = research question 1b (i.e. If a benefit is found for CXL to treat keratoconus, what are the benefits and harms of using different CXL variations compared with the standard protocol?), **SR** = systematic review.

Notes

a = Upon full text review it was apparent there were no SRs / HTAs that met our PICO criteria and had conducted high-quality analyses. As such, the decision was made to include RCT evidence only and to carry out de novo meta-analyses.
b = 10 publications reporting outcomes of 9 RCTs.
c = 5 publications reporting outcomes of 4 RCTs.
d = 9 publications reporting outcomes of 8 RCTs.

6.4 Research question 1a: What are the benefits and harms of CXL using riboflavin and UVA as a treatment for progressive keratoconus?

6.4.1 Characteristics of included studies

One systematic review[26] and 9 RCTs[66 68 70-72 84-88] were included for research question 1a. Detailed study profiles are presented in ***Appendix E, Table 34 and Table 35***.

Only RCTs comparing CXL with sham or no treatment in patients with keratoconus were included to inform the clinical efficacy of CXL. Expert opinion advised that safety complications resulting from CXL would not be significantly impacted by aetiology (i.e. keratoconus or other ectasias) (personal communication (email, Australian ophthalmologist, 9th June 2020). Consequently, it was deemed appropriate to include comparative safety outcomes from RCTs on patients with either keratoconus or post-refractive-surgery ectasia. As only comparative safety outcomes were included from these RCTs, the most recent and comprehensive systematic review informing on the safety of CXL from lower levels of evidence was also included to ensure all potential adverse events associated with CXL were identified.

Systematic review

The most recent and comprehensive review of safety data on CXL for progressive keratoconus was reported by Shalchi (2015).[26] This review aimed to compare the randomised evidence for epithelium-off versus transepithelial CXL techniques.[26] In the absence of sufficient evidence for this comparison, the authors chose to compare both techniques, separately, to no treatment. Case series that included greater than 20 patients and had a minimum follow-up of 12 months were also eligible for inclusion in the review. A systematic search identified a total of 45 studies reporting outcomes for epithelium-off CXL and 6 studies for transepithelial CXL. For the purposes of this short HTA, only those outcomes reported in the 45 epithelium-off studies were considered. These 45 studies comprised 3 RCTs, 2 non-randomised comparative studies and 40 case series. A total of 1 RCT and 1 non-randomised comparative study compared epithelium-off with transepithelial CXL (results are reported for the epithelium-off CXL arm only). The remaining RCTs and non-randomised study compared epithelium-off CXL with observation (sham or no treatment). Meta-analyses were not conducted. The review reported adverse event across 45 studies (approximately 2,033 eyes).

RCTs

Nine publications describing 8 RCTs were included for clinical efficacy[66 68 70-72 84 86-88] and 5 publications describing 4 RCTs were included to inform comparative safety.[66 72 85 87 88]

Wittig-Silva (2008)[88] and Wittig-Silva (2014)[72] reported results from the same RCT. Wittig-Silva (2008) reported the results of the first 66 eyes, while Wittig-Silva (2014) reported the result from the entire randomised population (94 eyes).

All RCTs performed CXL using the standard protocol involving epithelium removal and 30 minutes of UVA irradiation. The total number of eyes included in the RCTs ranged from 23[66 84] to 205.[66] Maximum follow-up ranged from 3[85] to 36 months.[72 87] It should be noted that some RCTs had longer follow-up, but comparative results were unavailable beyond 3 months.[66 85]

Six of the included RCTs reported age as an inclusion criteria for the trial.[66 68 71 72 84 85 88] Three stipulated an age range between 15–60 years,[68] 16–50 years[72 88] and 15–40 years.[71] The remaining 3 RCTs stipulated a minimum age of ≥14 years.[66 84 85] In general, the average age of patients in most of the RCTs was mid- to late-20s or early 30s.

In 4 RCTs, the comparator arm was no treatment,[70-72 86 88] in the remaining 5 RCTs the comparators were sham treatments.[66 68 84 85 87] In all but 1 of the 5 RCTs involving sham treatment, the epithelium was not removed.[84] In 4 of the 5 sham RCTs, riboflavin drops alone were used with no UV light treatment.[66 68 84 85] In 2 of these, the drops were applied every 2 minutes for 30 minutes,[66 85] and in another they were applied 4 times per day for a month.[68] The fourth study did not report duration of application.[84] In the fifth sham RCT, fluorescein eye drops were applied every 2 minutes for 30 minutes, plus radiation with visible blue light.[87]

Only 3 RCTs reported the patient's grade of keratoconus.[68 70 84] All 3 used the Amsler-Krumeich Classification[a] which stages keratoconus from I to IV, with stage IV being the worst. Patient stages ranged from I–III in the first RCT,[70] ≥ stage II in the second,[84] and stage II/III in the third.[68] A fourth RCT reported including patients with keratoconus at an early stage, which the authors defined as 'correction of refractive error possible with spectacles or contact lenses'.[87]

Six RCTs had an inclusion criterion of progressive keratoconus and provided a definition of disease progression. Definitions varied among studies. Four of these RCTs listed specified changes that had to have occurred over a given time, ranging from the previous 18 to 24 months.[66 70 84 87] The other 2 RCTs

[a] **Amsler-Krumeich Classification:** Stage I = eccentric steepening, myopia, induced astigmatism, or both < 5D, mean central K readings <48D; Stage II = myopia, induced astigmatism, or both from 5–8D, mean central K readings <53D, absence or scarring, corneal thickness >400µ; Stage III = myopia, induced astigmatism, or both from 8–10D, mean central K readings >53D, absence of scarring, corneal thickness 300–400µ; Stage IV, = refraction not measurable.

(1 reported in 2 publications) specified changes but did not provide a timeframe over which they had to have occurred.[71 72 88] Three RCTs provided no definition of progression.[68 85 86] In 3 of the RCTs that did provide a definition of progression, keratoconus could be deemed progressive if there was a loss in visual acuity alone (without change in any other parameters). The change in visual acuity required varied and included a reduction in UCVA or BCVA by 1 line,[70] loss of ≥2 lines of BCVA,[71] and a change in spectacle correction or contact lens parameters.[87]

The design of the RCTs varied. Three RCTs included one eye from each patient, with the eye being randomised to either CXL or the comparator.[66 85 87] One of these RCTs noted that the worst eye, or the one with greater progression or a steeper K value in case of equal progression, was included.[87] The other 2 RCTs did not state how eyes were chosen for inclusion.[66 85] Three RCTs included both eyes of all patients.[70 71 86] In 2 of these RCTs, one eye was randomly selected to receive CXL and the other eye served as the control.[70 71] In the third RCT involving both eyes, each eye was randomised to either CXL or the control group.[86] The remaining 3 RCTs used a mixture of one eye in some patients and both eyes in others.[68 72 84 88] In 2 of these RCTs in which both eyes were included, each eye was randomised separately.[72 84 88] In the third RCT the left eye underwent CXL and the right served as the control.[68]

The use of contact lenses can confound interpretation of CXL results as lens wear can affect topographic parameters.[89] Of the 8 RCTs included to inform the clinical efficacy of CXL, 5 noted that some of the patients wore contact lenses. One of these stated that patients with rigid contact lenses were asked to discontinue their use 3 weeks prior to examinations.[70] Another noted that patients were advised to discontinue wearing rigid contact lenses at least 3 weeks prior to the procedure and Pentacam imaging was only performed at least 3 weeks after discontinuation of lens wear. A third RCT noted that rigid lens wear was discontinued for a minimum of 2 weeks preoperatively, but did not mention whether contact lenses had to be removed for any period prior to postoperative evaluation. The RCT by Wittig-Silva, only mentioned contact lens use in the first publication, noting that the number of patients wearing rigid lenses was evenly distributed at baseline between groups and that patients removed their lenses the night before evaluation.[88] This study acknowledged that whilst the wearing of rigid, gas permeable contact lenses has the potential to alter corneal topography, the potential for contact lens wear to bias the findings of the study was small as there were similar numbers of wearers in both treatment groups. The second publication of this RCT (with longer follow-up and the full set of randomised patients) did not report whether contact lens wear remained even at baseline between the treatment groups.[72] The fifth study that reported contact lens use did not mention whether use was discontinued prior to evaluations, only that their use was not restricted.[87] This study further stated that a possible explanation for why only a few of the control patients maintained progression during the course of the trial was that, ‘the noise of the tomography system may render signs of progression impossible, especially in patients with higher

K-values or irregularities of the surface or after use of contact lenses'. Of the remaining 3 RCTs included for clinical efficacy, 2 made no mention of contact lens use,[84 86] whilst the third noted that their use was an exclusion criteria for the study.[68]

6.4.2 Risk of bias

Systematic review

The review by Shalchi (2015)[26] was appraised using AMSTAR[62] (summary of AMSTAR results can be found in ***Appendix E, Table 36***). The overall confidence in this systematic review was critically low as it failed in several domains. Therefore, it was uncertain whether the review accurately and comprehensively summarised the results from available studies.

RCTs

Risk of bias was appraised using the Cochrane Risk-of-Bias tool[61] and assessed on a per outcome basis (clinical efficacy and safety). Clinical efficacy was further delineated into visual acuity/refractive outcomes and topographic/pachymetry outcomes.

The risk of bias with randomisation (selection bias) was high or unclear for 6 studies.[68 70-72 86-88] The randomisation issues generally related to some studies including both eyes of all or some of the patients. This can lead to problems with between eye correlation. Overall, there was uncertainty regarding allocation concealment bias as it was not reported by most studies.

The studies by Wittig-Silva (2014)[72] and Hersh (2017a)[66] were deemed to have a high risk of performance bias because patients—aware of their treatment—were allowed to crossover to receive CXL. Wittig-Silva (2014)[72] reported that participants in their control group were offered compassionate CXL treatment from 6 months onwards if continuing and significant disease progression was noted during the study. Similarly, in the study by Hersh (2017a)[66] patients could crossover and receive CXL treatment after the 3-month follow-up examination.

Around half of the RCTs (those with longer follow-up ranging from 12–36 months) had high attrition bias.[66 71 72 87] Two studies with the highest losses to follow-up were those that allowed patients to crossover from the control group to receive CXL. Losses in the control groups in these studies were 46%[72] and 98%.[66] The high attrition bias in the RCTs by Wittig-Silva (2014)[72] and Hersh (2017a),[66] resulting from control patients being allowed to crossover to receive CXL, would negatively bias CXL because both of these studies used the last observation carried forward technique (before patients crossed over) to impute the missing data from these patients. Given that keratoconus is a disease of slow progression, if some patients crossed over at earlier time points the keratoconus in their control

eye was unlikely to have progressed, yet values for the different clinical efficacy parameters would have been carried through to the final follow-ups at 12 and 36 months.

Reporting bias was scored as unclear for all RCTs as most studies did not mention a protocol and thus there was no way of checking if their analyses followed a pre-defined plan. Whilst Hersh (2017a)[66] did report a study protocol, no link was provided to access the protocol so there was no way of checking if they adhered to it.

All studies were deemed to have a high or uncertain risk of bias in at least one other area. The study by Hersh (2017a)[66] was deemed to have a high risk of bias due to conflicts of interest. The study was funded by Avedro Inc., and most of the authors, including the primary author, were in some way connected to the company (consultant, equity owner, current or former employee). The study by Lang (2015)[87] was also funded by a company that make CXL devices; however, the authors noted no competing interests.

Another identified source of bias related to the use of contact lenses. Contact lenses, specifically rigid lenses, have the potential to alter refractive and topographic measurements.[70] Several studies were deemed to have an uncertain risk of bias in relation to this.[66 72 84 86 87] It is unclear whether the number of contact lens users was equivalent in treatment arms or whether patients were required to remove contact lenses for a reasonable length of time before evaluation so they did not affect measurements.

Five RCTs (6 publications) included both eyes in all or some of their included patients.[68 70-72 86 88] These were graded as having an uncertain risk of bias for 'other bias' because it appears that corrections to account for between-eye correlations were not undertaken in the statistical analyses of any of these studies.

There is an unclear risk of bias in all the RCTs regarding whether included patients were truly progressive. As mentioned, there is no evidence-based definition for what constitutes progressive keratoconus, only consensus guidelines.[20] Definitions of progressive keratoconus varied amongst those studies that provided one and used it in their inclusion criteria. Indeed, in the study by Lang (2015), the authors noted that only a few of the control patients maintained progression during the trial.[87] They explained that, according to the protocol, progression did not have to be proven by keratometry, it could be proven by a clinically significant change in refraction. Thus, they acknowledge there is a chance not all the patients had progressive keratoconus. Similarly, the RCT by O'Brart (2011) noted that only 14% per cent of the untreated eyes showed progression at 18 months.[70] Like the RCT by Lang (2015), progression, as defined by O'Brart (2011), did not have to be proven by keratometry but could be proven by a change in UCVA or BCVA. Including patients that were not truly progressive would result in a negative bias against CXL in RCTs.

Visual acuity and refractive outcomes

Seven RCTs (8 publications) reported visual acuity outcomes.[66 68 70-72 84 87 88] The risk-of-bias summary for visual acuity is reported in ***Figure 3*** and the risk-of-bias graph is presented in ***Figure 4***. In contrast to topography and pachymetry outcomes, which are objective, visual acuity and refractive errors involve subjective assessment. For this reason, all but two studies were graded as having a high risk of detection bias for these outcomes. The study by Sharma (2015)[84] was deemed to be at low risk of detection bias as the methods state it was a 'double blinded' trial and unlike the other RCTs with sham treatments, the patients in this study had epithelium removed, increasing the chance that they were blinded to their assignment. The study by Lang (2015)[87] was also deemed to be at low risk of detection bias as it noted that patients were not fully aware of their assignment to placebo or CXL and a second examiner took over after the fifth visit to ensure blinding of the assessor.

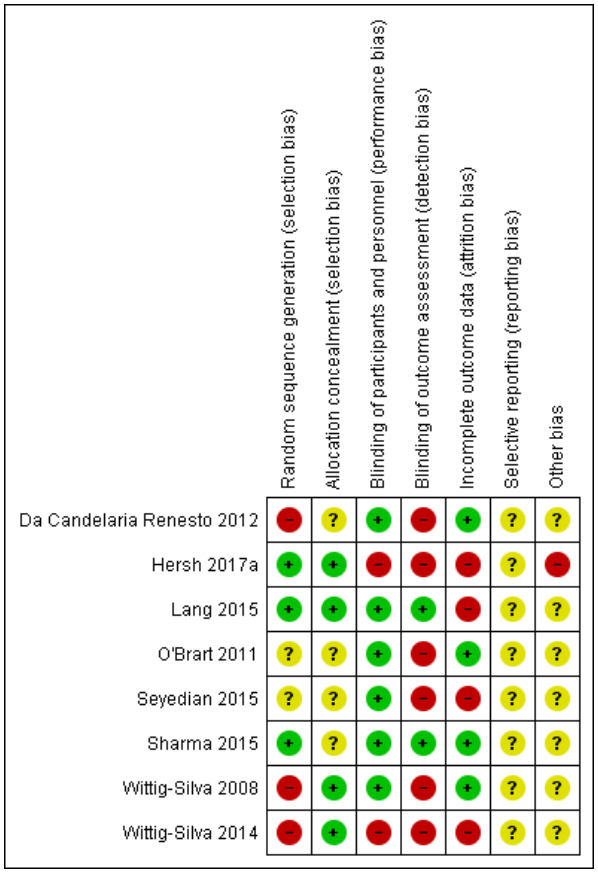

Figure 3 CXL vs no treatment/sham: risk-of-bias summary for visual acuity and refractive outcomes in the RCTs

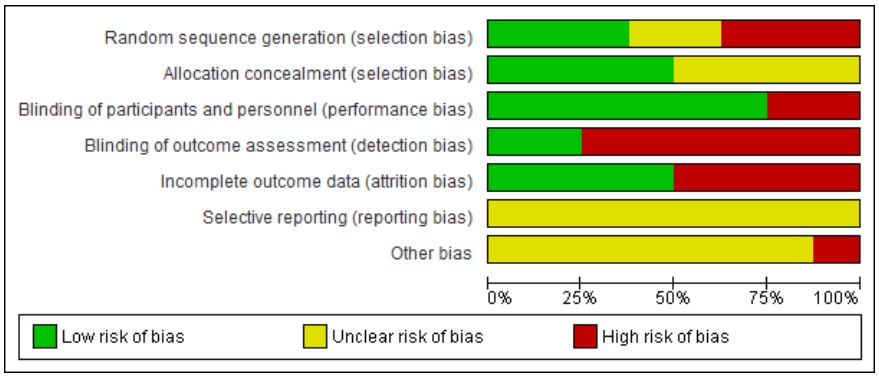

Figure 4 CXL vs no treatment/sham: risk-of-bias graphs assessing visual acuity and refractive outcomes in the RCTs

Topography and pachymetry

Eight RCTs (9 publications) reported topography/pachymetry outcomes. The risk-of-bias summary and the risk-of-bias graph are reported in ***Figure 5*** and ***Figure 6***, respectively.

Overall, the studies were deemed to be at low risk of outcome assessment bias and performance bias, despite only Lang (2015)[87] and Sharma (2015)[84] reporting any attempt to blind assessors and patients. Because topography/pachymetry outcomes are objective values reported by a device, they are unlikely to be affected by knowledge of intervention assignment by assessors.

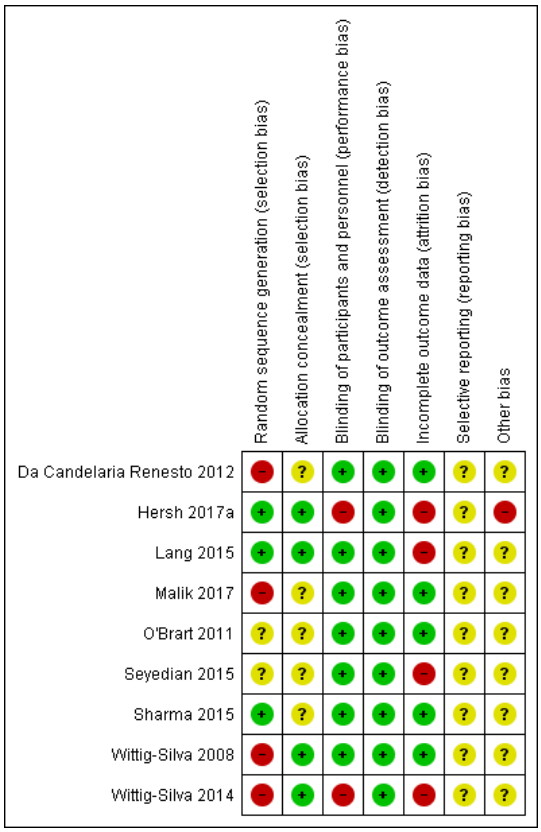

Figure 5 CXL vs no treatment/sham: risk-of-bias summary for topography and pachymetry outcomes in the RCTs

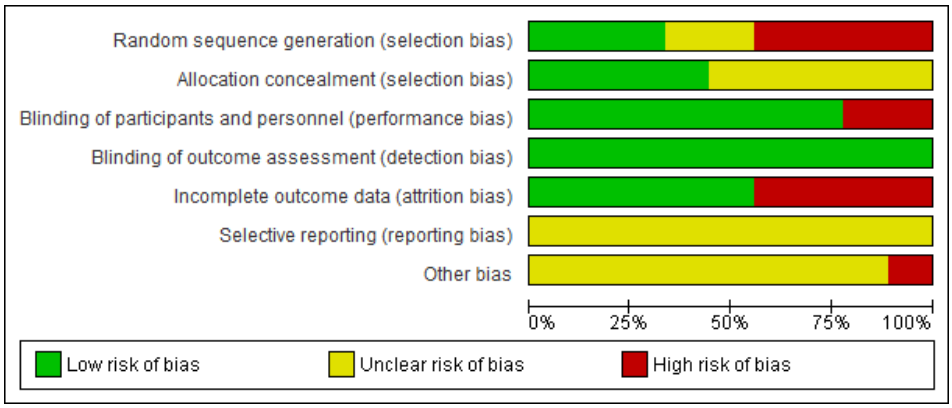

Figure 6 CXL vs no treatment/sham: risk-of-bias graphs assessing topography and pachymetry outcomes in the RCTs

Safety outcomes

Comparative safety was only reported in 4 RCTs (5 publications).[66 72 85 87 88] The risk-of-bias summary for safety outcomes are presented in ***Figure 7*** and the risk-of-bias graph is presented in ***Figure 8***.

One RCT included for safety, not clinical efficacy, is that by Hersh (2017b).[85] As previously mentioned, this study reported safety outcomes for patients with corneal ectasia resulting from refractive surgery. For the RCTs which reported topography/pachymetry outcomes, biases relating to randomisation allocation concealment and reporting were as reported previously. Biases relating to the other domains are discussed below.

In 2 of the 4 RCTs included for safety, a high risk of detection bias was detected. There was no mention of blinding in these RCTs and some of the reported safety outcomes were subjective (ocular pain, dry eye).[66 85] One RCT (2 publications) was deemed to have an unclear risk of detection bias because it failed to report whether the assessor of safety was blinded.[72 88]

Whilst the RCT by Hersh (2017a)[66] was deemed to have a high risk of performance and attrition bias for topography and visual acuity outcomes, bias for safety outcomes was low. This is because there were no losses to follow-up as safety outcomes were reported prior to patients crossing-over (unlike for visual acuity and topography outcomes).

The post-refractive-surgery ectasia study by Hersh (2017b)[85] had a high risk for 'other bias' because, as for Hersh (2017a),[66] the authors noted their study was funded by Avedro Inc. and several authors had links to the company (consultants or current/former employees).

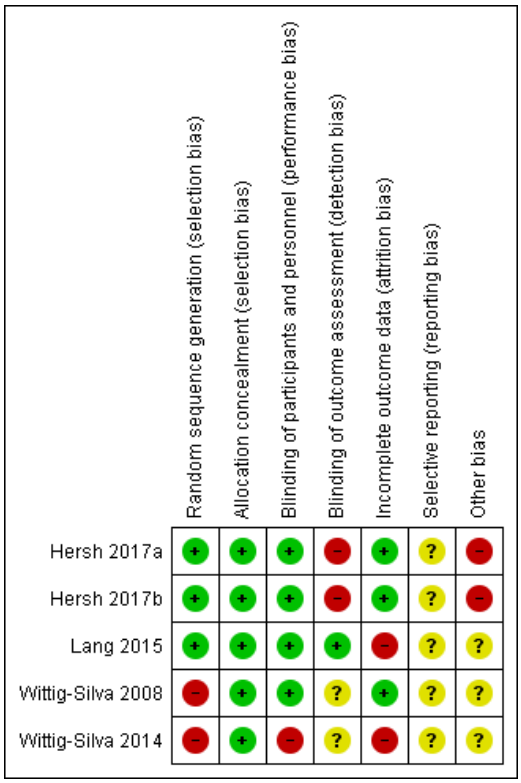

Figure 7 CXL vs no treatment/sham: risk-of-bias summary for safety outcomes in the RCTs

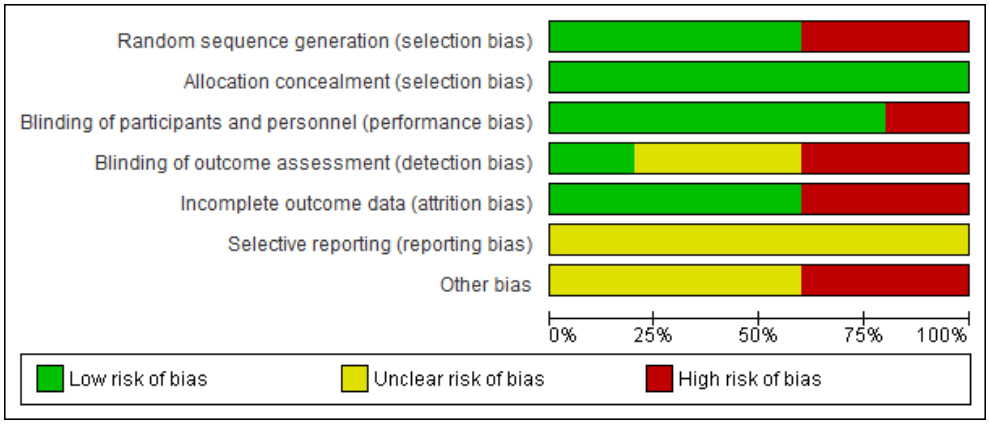

Figure 8 CXL vs no treatment/sham: risk-of-bias graph assessing safety outcomes in the RCTs

6.4.3 Findings: clinical efficacy

A summary of the main pooled clinical efficacy outcomes comparing CXL to sham or no treatment can be found in ***Appendix E*** (***Table 37***). Overall, there were statistically significant differences between CXL and sham or no treatment in K_{max}, BCVA and UCVA, however, it was unclear whether the results were clinically meaningful because values representing progression have not been validated and there are no consistent or clear evidence-based definitions of keratoconus progression.[48]

In addition, the weighted absolute mean changes from baseline for the CXL and sham or no treatment groups were examined to determine how the individual treatment groups changed over time (i.e. whether the surrogate markers increased or decreased relative to baseline measurements) (***Appendix E***, ***Table 38***). In brief, K_{max} was the only outcome which, on average, decreased in the CXL group over time and slightly increased in the no treatment group. The remaining outcomes were either assessed at one time point or had inconsistent effect directions within each treatment arm.

For additional information regarding each outcome, refer to the corresponding headings below.

Visual acuity

UCVA

Weighted absolute change in UCVA over time for CXL and sham or no treatment

Owing to the difference in units used to report UCVA between studies the values had to be standardised, hence weighted absolute changes were not calculated.

Standardised mean difference in UCVA between CXL and sham or no treatment

Three RCTs were included in the meta-analyses of UCVA[66 68 72] Statistically there was a significant difference between CXL and no treatment at all of these follow-up times (***Figure 9***). At the 1-month follow-up the difference favoured no treatment (MD 0.49; 95% CI 0.08, 0.89; p = 0.02); however, at all subsequent follow-up time points the significant difference was in favour of CXL (3 months: MD -0.41; 95% CI -0.81, 0.00; p = 0.05. 6 months: MD -0.57; 95% CI -1.05, -0.09; p = 0.02. 12 months: MD -0.88; 95% CI -1.25, -0.51; p <0.01. 24 months: MD -0.64; 95% CI -1.21, -0.07; p = 0.03. 36 months: MD -0.71; 95% CI -1.28, -0.14; p = 0.02). The tau^2 and I^2 statistics indicate moderate levels of heterogeneity and inconsistency. It should be noted that a significant difference was observed at baseline in favour of no treatment.

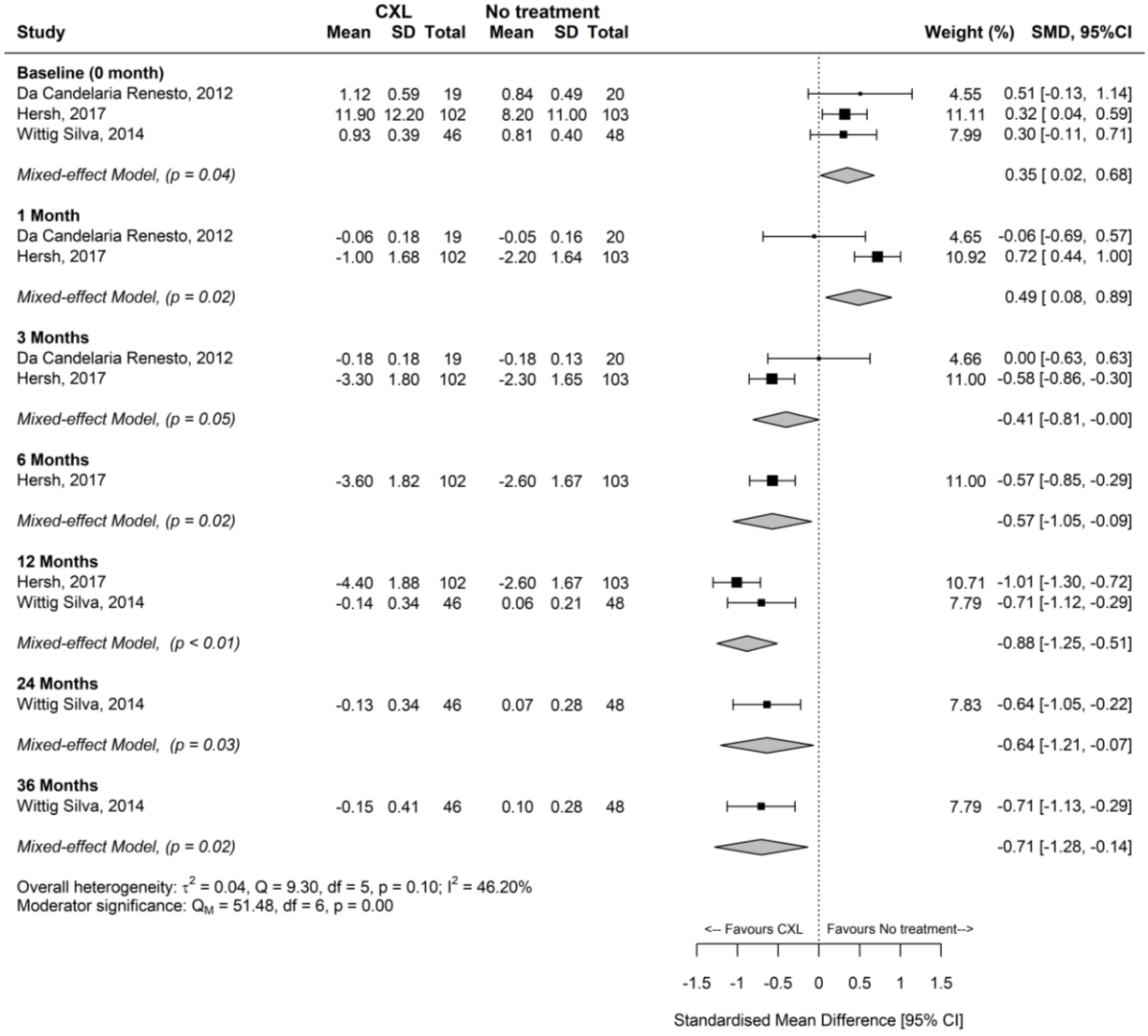

Figure 9 Standardised mean difference in UCVA for CXL compared with sham or no treatment (1 to 36 months)

Abbreviations
CI = confidence interval, **CXL** = corneal collagen crosslinking, **SMD** = standardised mean difference, **SD** = standard deviation.
Notes
Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

Results reported narratively

One RCT was not included in the meta-analyses due to missing data.

O'Brart (2011)[70] reported mean change in UCVA in both CXL and no treatment at 18 months (***Appendix E, Table 39***). The difference in mean change from baseline between CXL and no treatment was not significant (p = 0.2). Measures of variance were not reported.

BVCA

Weighted absolute change in BCVA over time for CXL and sham or no treatment

Owing to the different units used between studies reporting BCVA the values had to be standardised, hence weighted absolute changes were not calculated.

Standardised mean difference in BCVA between CXL and sham or no treatment

Five RCTs were included in the meta-analyses of BCVA.[66 68 71 72 87] Statistically, there was no difference between CXL and no treatment at 1 month (MD 0.97; 95% CI -0.02, 1.95; p = 0.06), 3 months (MD -0.35; 95% CI -1.34, 0.64; p = 0.49), 24 months (MD -0.24; 95% CI -1.61, 1.13; p = 0.73) or 36 months (MD 0.51; 95% CI -0.52, 1.53; p = 0.33) follow-up. A statistically significant difference was observed in favour of CXL at 6 months (MD -1.45; 95% CI -2.80, -0.11; p = 0.03) and 12 months (MD -0.96; 95% CI -1.76, -0.16; p = 0.02) (***Figure 10***). The tau^2 and I^2 statistics indicate considerable levels of heterogeneity and inconsistency.

Results reported narratively

One RCT was not included in the meta-analyses due to missing data.

O'Brart (2011)[70] reported mean change in BCVA in both CXL and untreated eyes at 18 months (***Appendix E, Table 40***). The difference between CXL and untreated eyes was not significant (p = 0.98). Measures of variance were not reported.

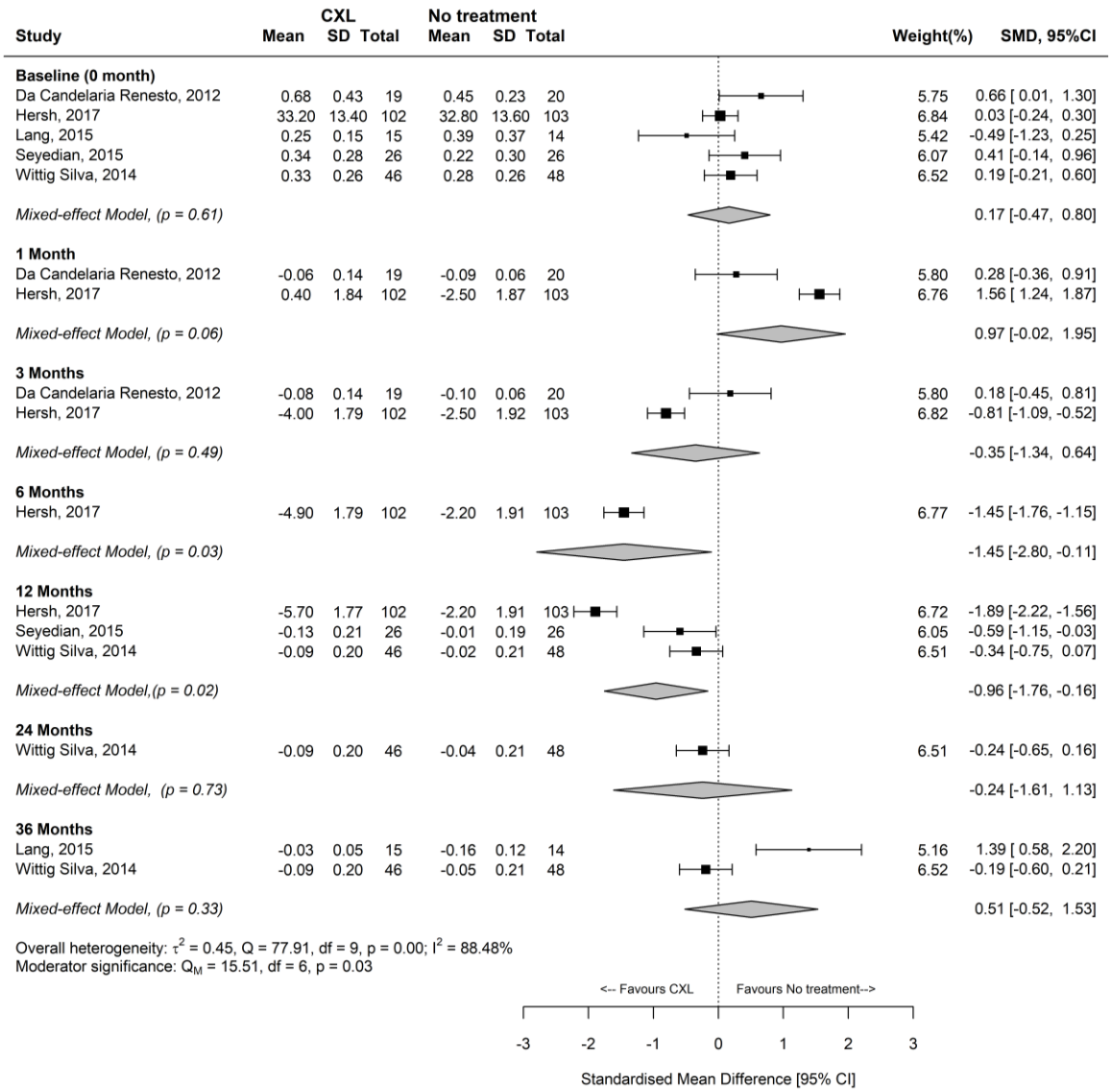

Figure 10 Standardised mean difference in BCVA for CXL compared with sham or untreated eyes (1 to 36 months)

Abbreviations

BCVA = best corrected visual acuity, **CI** = confidence interval, **CXL** = corneal collagen crosslinking, **SMD** = standardised mean difference, **SD** = standard deviation.

Notes

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

Pachymetry

TCT

Owing to a lack of data, a meta-analysis was not performed for TCT. Two RCTs reported the effects of CXL on TCT.[68 72] One RCT reported results up to 3 months follow-up, however, it is not discussed below owing to lack of statistical tests comparing CXL to no treatment.[68]

Wittig-Silva (2014)[72] compared mean change in TCT between CXL and no treatment up to 36 months follow-up using both ultrasound and Orbscan (Bausch & Lomb, Orbtek Inc., USA). A statistically significant difference in favour of untreated eyes was observed at 12 months with Orbscan only and at 36 months in favour of CXL with ultrasound only (***Appendix E, Table 41***).

CCT

Owing to a lack of data, a meta-analysis was not performed on CCT. The effects of CXL on CCT was reported by four RCTs.[68 70 71 87] One RCT reported results up to 3 months follow-up, however, it is not discussed below owing to lack of statistical tests comparing CXL to no treatment.[68]

Seyedian (2015)[71] compared the change in CCT measured using ultrasound and Pentacam between CXL and no treatment at 12 months follow-up and reported no significant difference with either device (***Appendix E, Table 42***).

O'Brart (2011)[70] compared mean change in CCT from baseline to 18 months follow-up between CXL and no treatment and reported no significant difference (***Appendix E, Table 43***). Measures of variance were not reported.

Lang (2015)[87] compared CCT at baseline and a mean of 36 months follow-up between CXL and sham treated eyes. No significant differences were observed (***Appendix E, Table 44***).

Topography

K_{max}

Weighted absolute change in K_{max} over time for CXL and sham or no treatment

The absolute weighted mean change for K_{max} at 3, 6, 12 and 36 months follow-up was negative for CXL, denoting a decrease in maximum corneal curvature relative to baseline (***Appendix E, Table 38***). Conversely, the absolute weighted mean change for K_{max} for the no treatment group at these follow-up time points was positive, indicating that, on average, maximum corneal curvature was increasing relative to baseline.

Mean difference in K_{max} for CXL and sham or no treatment

Four RCTs (5 publications) were included in the meta-analysis of K_{max} [66 71 72 87 88] Apart from the 3-month time point, there were statistically significant differences between CXL and sham or no treatment at all other follow-up points (***Figure 11***). A statistically significant difference in favour of no treatment was observed at 1 month (MD 2.50; 95% CI 0.49, 4.51; p = 0.01) whilst a statistically significant difference in favour of CXL was found at 6 months (MD -1.80; 95% CI -3.51, -0.08; p = 0.04), 12 months (MD -1.71; 95% CI -2.89, -0.54; p = 0.004), 24 months (MD -2.66, 95% CI -4.78, -0.54; p = 0.01) and 36 months (MD -1.85; 95% CI -3.44, -0.25; p = 0.02). The tau^2 and I^2 statistics indicate considerable levels of heterogeneity and inconsistency for K_{max}.

Results reported narratively

One RCT was not included in the meta-analyses due to missing data. Sharma (2015)[84] reported K_{max} outcomes at 1 week and at 1, 3 and 6 months. Compared to the sham group, K_{max} in the CXL group was significantly less at 3 months follow-up (by 2.1 ± SD 1.1 D; p = 0.03) and 6 months follow-up (by 2.8 ± 1.3 D; p = 0.01). Sharma (2015)[84] reported K_{max} outcomes at 1 week and at 1, 3 and 6 months. Compared to the sham group, K_{max} in the CXL group was significantly less at 3 months follow-up (by 2.1 ± SD 1.1 D; p = 0.03) and 6 months follow-up (by 2.8 ± 1.3 D; p = 0.01).

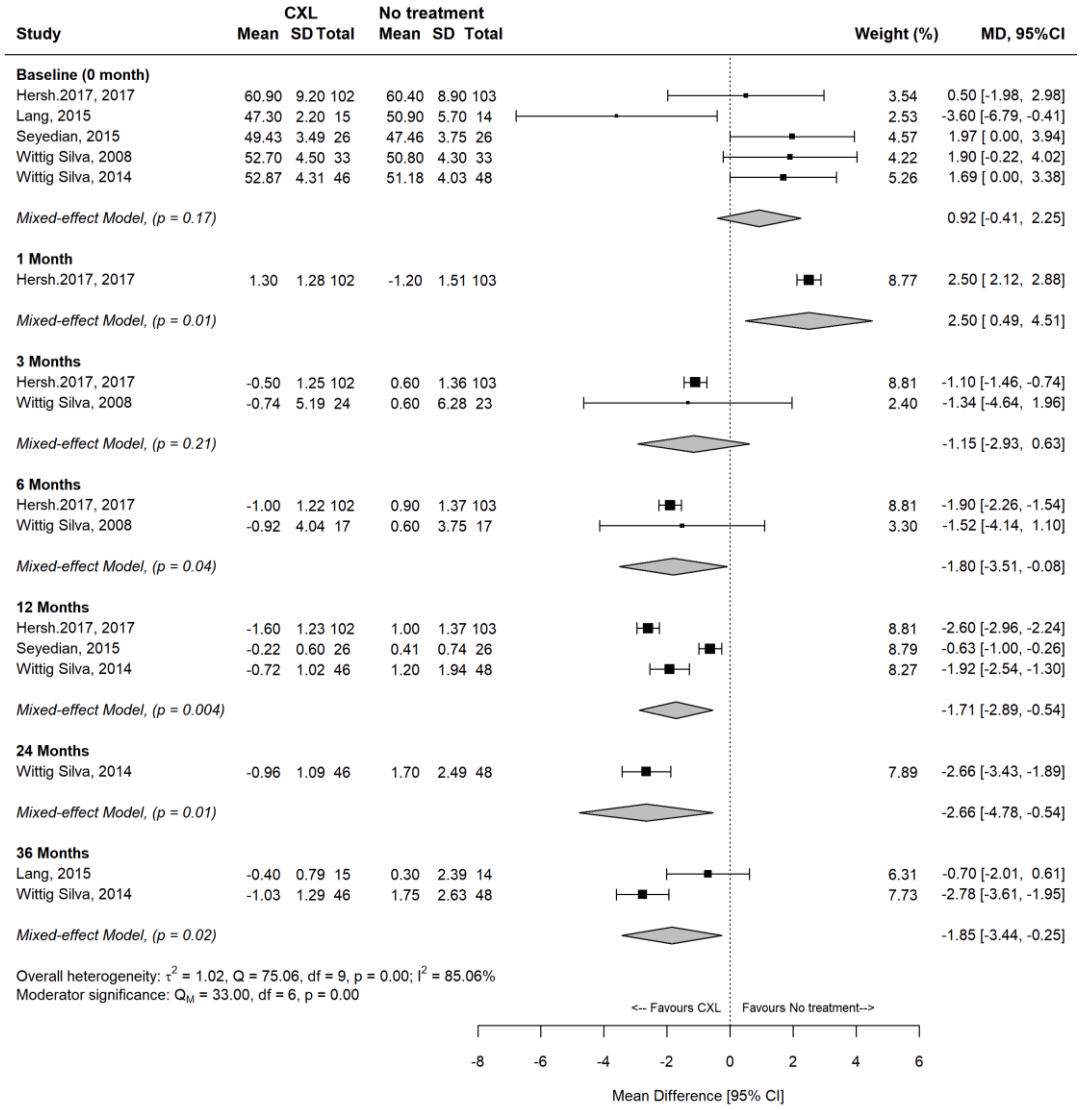

Figure 11 Mean difference in K_{max} for CXL compared to sham or no treatment (1 to 36 months)

Abbreviations
CI = confidence interval, **CXL** = corneal collagen crosslinking, **MD** = mean difference, **SD** = standard deviation.
Notes
Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

K_{mean}

Weighted absolute change in K_{mean} over time for CXL and sham or no treatment

For K_{mean}, 3 months was the only follow-up for which data was available from at least 2 studies.[68 86] The absolute weighted mean change at 3 months follow-up was negative for the CXL group, indicating a reduction in mean corneal curvature from baseline, and positive for the no-treatment group, indicating an increase in mean corneal curvature from baseline (***Appendix E, Table 38***).

Mean difference in K_{mean} between CXL and sham or no treatment

The meta-analysis of K_{mean} included three RCTs.[68 71 86] Statistically, there was no difference between CXL and sham or no treatment at 1 month (MD 0.17; 95% CI -3.40, 3.74; p = 0.93), 3 months (MD -2.14; 95% CI -4.63, 0.35; p = 0.09) or 12 months (MD -0.50; 95% CI -3.93, 2.93; p = 0.77) follow-up (***Figure 12***). The tau^2 and I^2 statistics indicate considerable levels of heterogeneity and inconsistency.

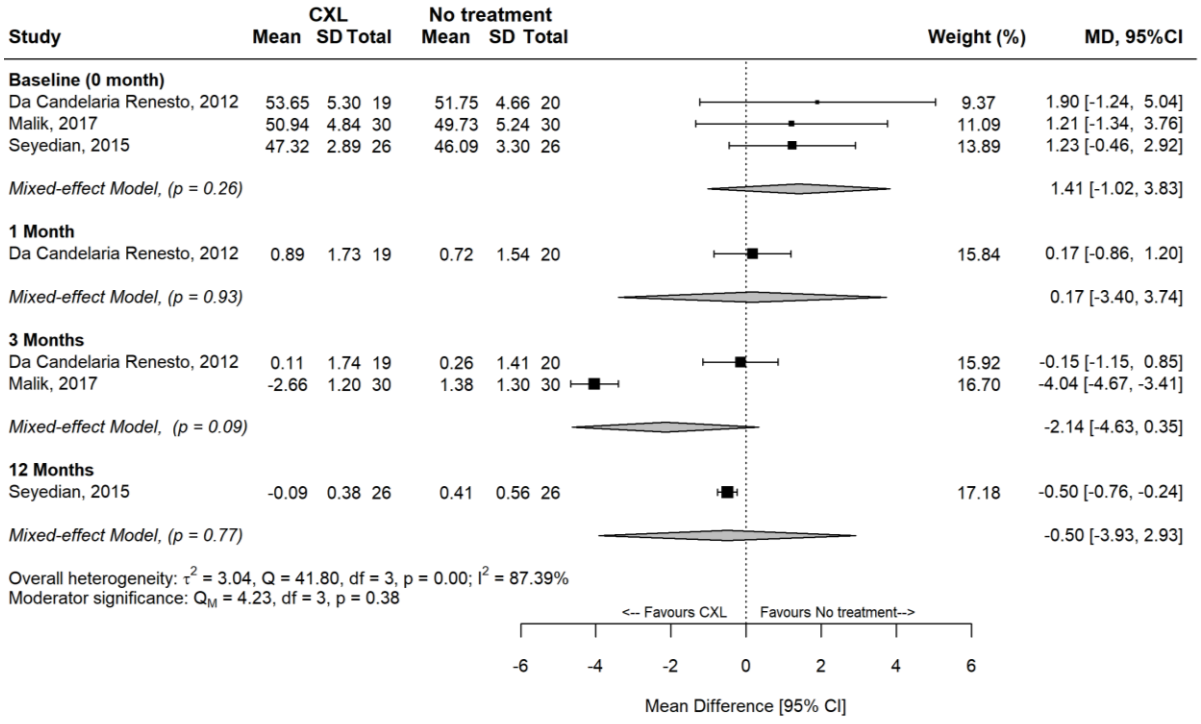

Figure 12 Mean difference in K_{mean} for CXL compared to sham or no treatment (1 to 12 months)

Abbreviations
CI = confidence interval, **CXL** = corneal collagen crosslinking, **MD** = mean difference, **SD** = standard deviation.
Notes
Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

K_{min}

Weighted absolute change in K_{min} over time for CXL and sham or no treatment

For K_{min}, 36 months was the only follow-up time for which data was available from at least two studies.[72 87] The absolute weighted mean change at this time point was negative for CXL, indicating a reduction in minimum corneal curvature from baseline, and positive for the no treatment group, indicating an increase in minimum corneal curvature from baseline (***Appendix E, Table 38***).

Mean difference in K_{min} between CXL and sham or no treatment

The meta-analysis of K_{min} included three RCTs[72 84 87] There was no statistically significant difference between CXL and sham or no treatment at any follow-up point (6 months: MD 0.00; 95% CI -2.77, 2.77; p = 1.00. 12 months: MD -1.08; 95% CI -3.83, 1.67; p = 0.44. 24 months: MD -1.83; 95% CI -4.62, 0.96; p = 0.20. 36 months: MD -1.11; 95% CI -3.12, 0.89; p = 0.28) (***Figure 13***). The tau^2 and I^2 statistics indicate considerable levels of heterogeneity and inconsistency.

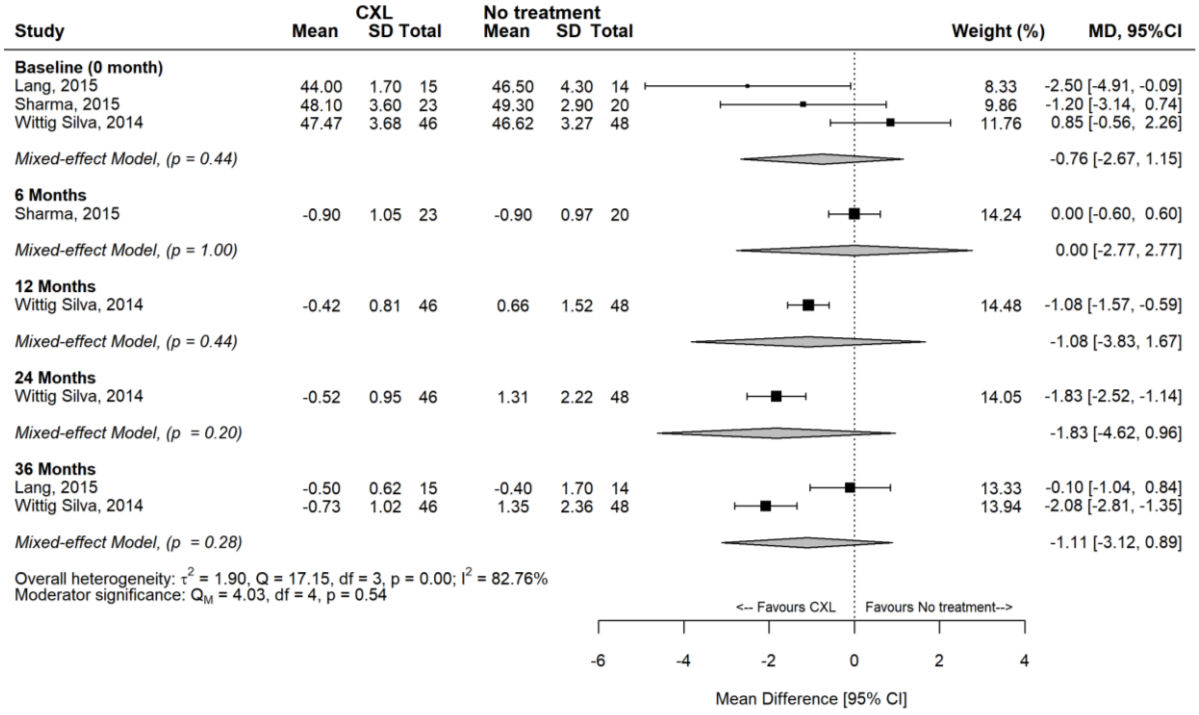

Figure 13 Mean difference in K_{min} for CXL compared to sham or no treatment (6 to 36 months)

Abbreviations
CI = confidence interval, **CXL** = corneal collagen crosslinking, **MD** = mean difference, **SD** = standard deviation.
Notes
Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

K_1 and K_2

One RCT reported K1 and K2 at 1 and 3 months follow-up; however, it did not conduct any statistical comparison of CXL to no treatment.[68]

Refractive errors

Cylinder

Weighted absolute change in cylinder over time for CXL and sham or no treatment

For cylinder, 12 months was the only follow-up time for which data was available from at least two studies. The absolute weighted mean change at this time point was negative for both the CXL and sham or no treatment groups, indicating astigmatism was worsening in both arms (***Appendix E, Table 38***).

Mean difference in cylinder between CXL and sham or no treatment

The meta-analysis of cylinder included three RCTs[68 71 72] The difference between the CXL and no treatment groups was not statistically significant at any follow-up point (1 month: MD -0.23; 95% CI -1.08, 0.62; p = 0.60. 3 months: MD -0.13; 95% CI -0.98, 0.72; p = 0.76. 12 months: MD 0.10; 95% CI -0.76, 0.96; p = 0.83. 24 months: MD -0.10; 95% CI -1.68, 1.48; p = 0.90. 36 months: MD 0.27; 95% CI -1.32, 1.86; p = 0.74). The tau^2 and I^2 statistics indicate moderate levels of heterogeneity and inconsistency (***Figure 14***).

Results reported narratively

Two RCTs were not included in the meta-analyses due to missing data.

Sharma (2015)[84] recorded cylinder from 1 week to 6 months in CXL- and sham-treated eyes. A significant difference between CXL and sham treatment was observed at 6 months in favour of CXL (p = 0.01) (***Appendix E, Table 45***).

O'Brart (2011)[70] reported the mean change in cylinder at 18 months follow-up in CXL and untreated eyes and found no significant difference between the two (p = 0.9) (***Appendix E, Table 46***).

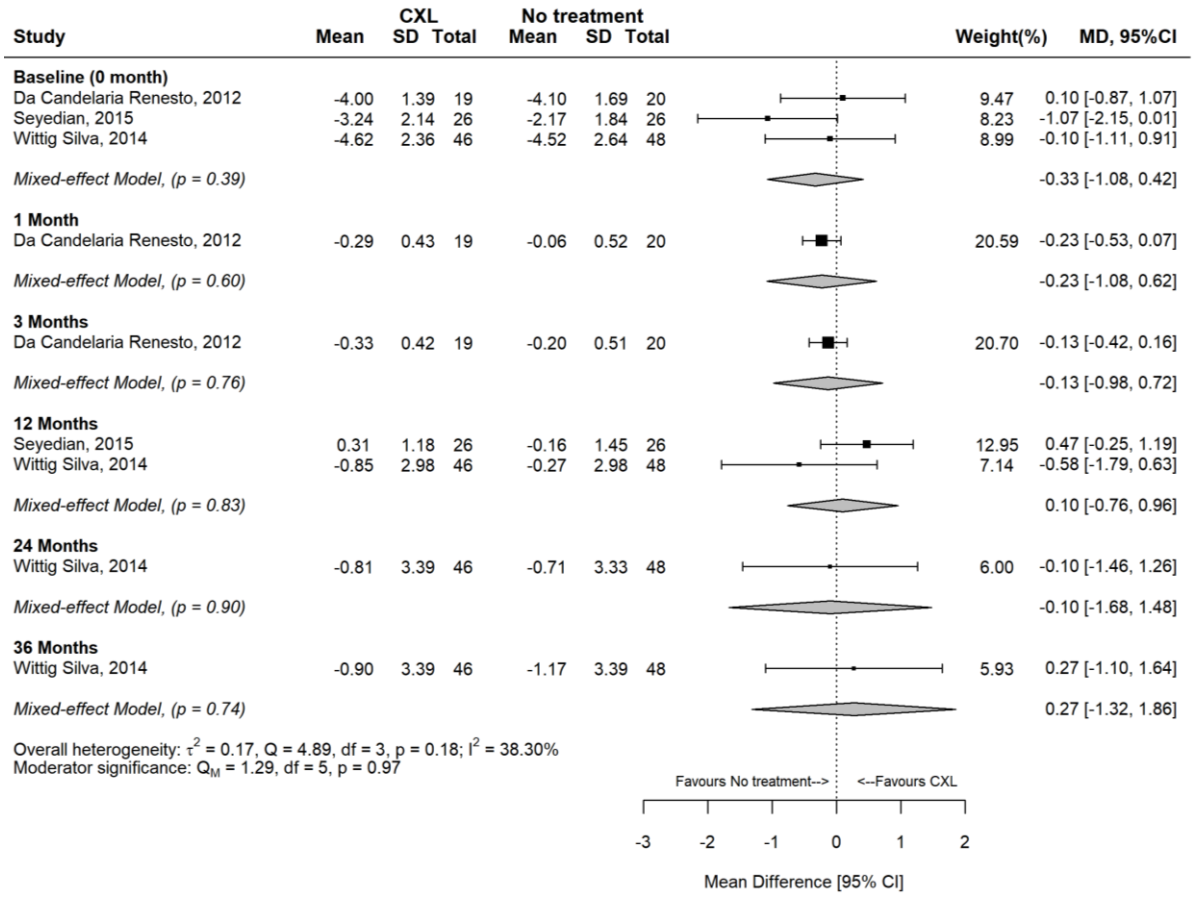

Figure 14 Mean difference in cylinder for CXL compared to sham or no treatment (1 to 36 months)

Abbreviations
CI = confidence interval, **CXL** = corneal collagen crosslinking, **MD** = mean difference, **SD** = standard deviation.
Notes
Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

Spherical equivalent

Weighted absolute change in spherical equivalent over time for CXL and sham or no treatment

For spherical equivalent, data was available from at least two studies at 1, 3 and 12 months. For the CXL group, the absolute weighted mean changes were negative at 1 month, indicating a worsening of spherical equivalent, and positive at 3 and 12 months, indicating an improvement in spherical equivalent. Conversely, the spherical equivalent for the no treatment group slightly improved at 1 and 3 months and then worsened at 12 months (***Appendix E, Table 38***).

Mean difference in spherical equivalent between CXL and sham or no treatment

The meta-analysis of spherical equivalent included four RCTs.[66 68 71 72] Statistically, there was no significant difference in spherical equivalent between CXL and no treatment at any follow-up time point (1 month: MD -0.27; 95% CI -0.87, 0.32; p = 0.37. 3 months: MD -0.07; 95% CI -0.66, 0.52; p = 0.81. 6

months: MD -0.10; 95% CI -0.83, 0.63; p = 0.79. 12 months: MD 0.30; 95% CI -0.24, 0.85; p = 0.28. 24 months: MD 0.52; 95% CI -0.77, 1.81; p = 0.43. 36 months: MD 0.18; 95% CI -1.17, 1.53; p = 0.79) (***Figure 15***). The tau^2 and I^2 statistics indicate moderate levels of heterogeneity and inconsistency.

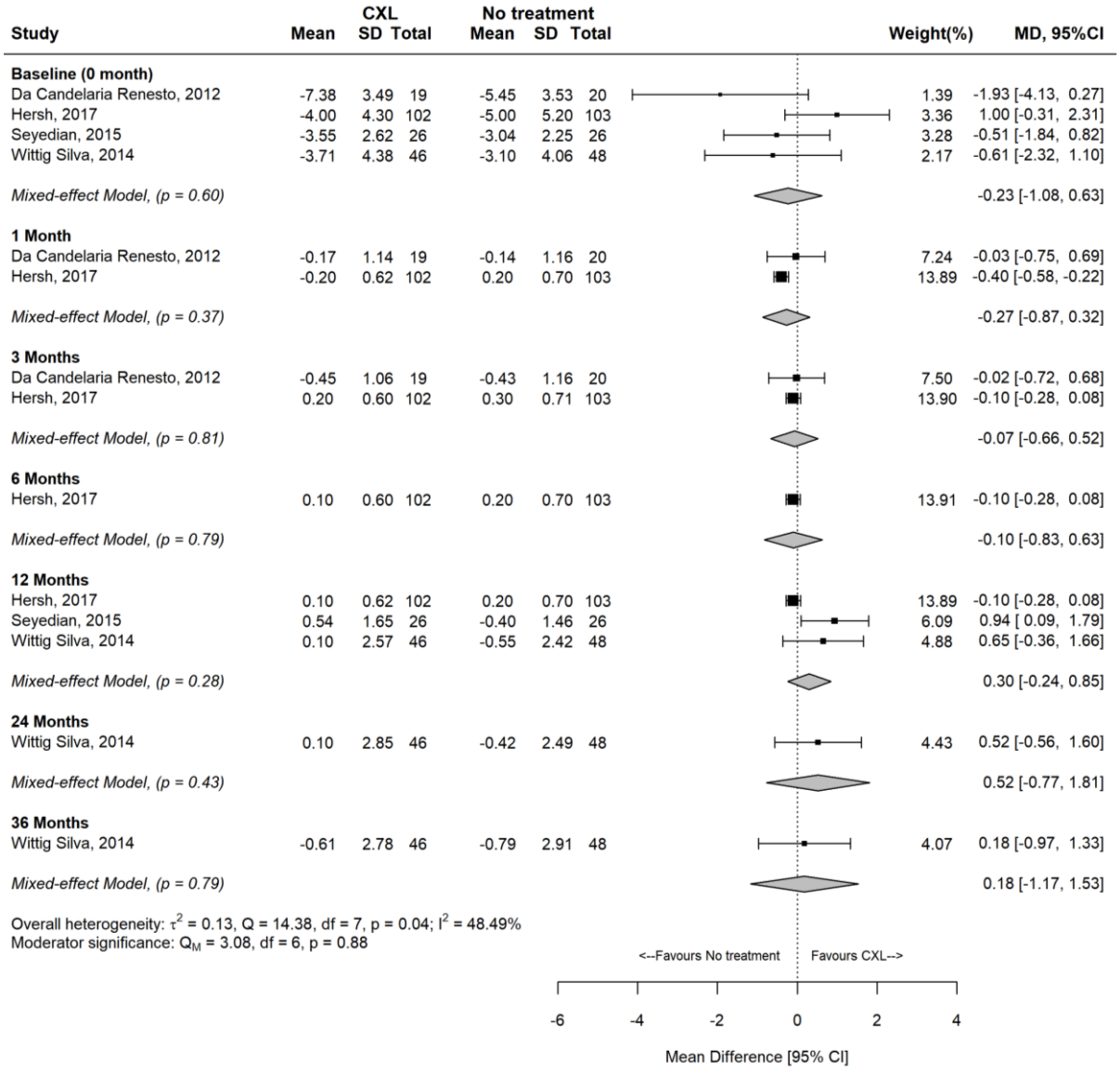

Figure 15 Mean difference in spherical equivalent for CXL compared to sham or no treatment (1 to 36 months)

Abbreviations

CI = confidence interval, **CXL** = corneal collagen crosslinking, **MD** = mean difference, **SD** = standard deviation.

Notes

Horizontal and vertical bars around the estimate (black square) depict the bounds of the confidence intervals.

Results reported narratively

One RCT was not included in the meta-analyses due to missing data.

O'Brart (2011)[70] reported mean change in spherical equivalent in both CXL and untreated eyes at 18 months (***Appendix E, Table 47***). The difference in mean change between the CXL and untreated eyes was not significant (p = 0.2). Measures of variance were not reported.

Sphere

Owing to a lack of data, a meta-analysis was not performed on sphere. Two RCTs reported changes in sphere.[68 72] One RCT reported results up to 3 months follow-up, however, it is not discussed below owing to lack of statistical tests comparing CXL to no treatment. [68] Wittig-Silva (2014)[72] compared mean change in sphere between CXL and no treatment. There was no statistically significant difference between the two groups at any follow-up (***Appendix E, Table 48***).

Corneal transplant rates

Only one study reported corneal transplant rates. Wittig-Silva (2014) reported that five eyes (10%) from the control group underwent corneal transplantation during the 36 month follow-up.[72]

6.4.4 Findings: safety

Systematic review

The systematic review by Shalchi (2015)[26] included 45 studies and provided a narrative report of safety. Rates of adverse events were not provided by the review, nor did they comment on their severity. The following events were reported. A summary of the adverse events reported by Shalchi (2015)[26] can be found in ***Appendix E, Table 49***.

Failure to re-epithelise

Nine studies reported data on failure to re-epithelise. In a combined total of 326 eyes there were no cases of failure to re-epithelise. Two of these studies stated that failure to re-epithelise was measured at 1 week postoperatively. The remaining studies did not specify when re-epithelisation was assessed. These patients were followed for 12 to 26 months.

Stromal oedema

Stromal oedema was reported by 7 studies (approximately 365 eyes). Stromal oedema in an RCT (20 eyes) was 1.68% at 12 months[b]. Across the remaining 6 studies (345 eyes) the median percentage of eyes with stromal oedema was 17.5% (range 0–70%). Follow-up ranged from 6 weeks to 36 months.

Sterile infiltrates

Six studies reported on sterile infiltrates, 5 of which reported a numerical outcome. One study noted 'seen in very few eyes' and resolution with use of topical steroids. Of the 5 studies providing a numerical outcome, the median percentage of eyes with sterile infiltrate was 2.5% (5/203 eyes, range 0–4%). None of these studies specified the time point at which this adverse event was assessed. Latest follow-up in these studies ranged from 12 to 36 months.

Golden striae

Only 2 studies reported on golden striae; 1 reported golden striae in 43.5% (12/28) of eyes at 12 months, the other reported an incidence rate of 62% (25/40 eyes) at an unspecified time point. The latest follow-up in that study was 24 months.

Stromal haze

Of 45 studies, 12 reported on stromal haze, 11 of which reported data as a percentage for approximately 675 eyes. The median percentage of eyes with stromal haze in these 11 studies was 9.8% (range 0–100%). The twelfth study reported on haze used its own grading system, therefore rates were unable to be determined.

Seven studies reported the time point at which haze was assessed. In one case series, 4.8% (5/104) of eyes reported haze at 3 months, which decreased to 1.9% (2/104) and 1.5% (1/64) of eyes by 6 and 12 months, respectively. Similarly, another case series reported a decrease in haze over time, with 9% (4/44) of eyes experiencing haze within the first 3 months and 2% (1/44) after 6 months. Two studies reported the incidence of haze only within the first 3 months, with findings of 9.8% (4/44) and 100% (46/46) of eyes. At 6 months, 1 study reported 100% haze in its population (24/24 eyes). Two studies reported reduced rates at 12 months of 8.6% (14/163 eyes) and 12.7% (4/28 eyes). Like sterile infiltrates, haze was reported to be responsive to topical steroid treatment.

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[b] As the total number of eyes at latest follow-up was 20, it is unclear how the authors determined the stromal oedema to be 1.68% as this would equate to 0.34 eyes.

Corneal scar formation

Five studies, with follow-up ranging from 1 to 24 months, reported on corneal scar formation (total of 345 eyes). The median percentage of eyes with corneal scar formation was 0% (range 0–6%).

Microbial keratitis

Microbial keratitis was reported by 7 studies, 6 of which reported data as a percentage (from a total of 335 eyes). The median percentage of eyes with microbial keratitis in these 6 studies was 0% (range 0–3%). The remaining study did not report infection data specifically for eyes with keratoconus.

RCT

Four RCTs (described in 5 publications) compared safety outcomes of CXL to no treatment or sham.[66 72 85 87 88] All of these RCTs used the standard 'epithelium-off' protocol for CXL. Three RCTs used a sham intervention and one used no treatment.

Comparative results were reported in at least 1 of 4 four RCTs for bacterial keratitis, peripheral corneal vascularisation, sub-epithelial infiltrates, haze, corneal erosions, ocular pain, need for subsequent surgery, blurred vision, photophobia, conjunctival hyperaemia, ocular irritation, dry eye, striae and increased lacrimation (***Appendix E, Table 50***). Maximum duration of follow-up ranged from 12 to 36 months. It should be noted that for the RCTs by Hersh only adverse events occurring in more than 5% of patients after CXL were reported.[66 85]

Outcomes reported across three RCTs

Keratitis

Three RCTs reported comparative results for keratitis.[66 85 87] In 2 RCTs, punctate keratitis occurred in 3 – 8% of patients in the sham group and 20 – 25% in the CXL group at 3 months.[66 85] Statistical comparisons were not reported. In another RCT, there were no reported cases of any type of keratitisin both groups by 36 months.[87]

In one of these RCTs,[66] one patient, originally assigned to the control group, developed ulcerative keratitis (which was considered a severe complication) 3 days after receiving CXL. This was treated with antimicrobials and resolved.

Haze

Three RCTs reported comparative results for haze.[66 85 87] One RCT noted there was a statistical difference in haze, with more haze in the CXL group compared with the sham group at 36 months (100% vs 29%, p <0.01).[87] In 2 other RCTs the CXL group reported a statistically significant higher percentage of haze compared to the sham group at 3 months follow-up (57–68% compared to 4–8%, respectively, p = 0.02).[66 85]

Regarding the effect of corneal haze on visual acuity, 1 RCT simply reported that haze did not impair visual acuity.[87] The 2 other RCTs found that outcomes of BCVA and UCVA varied in the 7 patients with persistent haze at 12 months. Of these patients, 5 experienced an improvement in UCVA (of 3 to 14 letters) and 2 experienced no change. For BCVA, 5 experienced an improvement (of 4 to 30 letters) and 2 experienced a decrease (of 5 to 10 letters).[66 85]

Epithelial defects

Three RCTs reported comparative results for epithelial defects.[66 85 87] In each, a greater percentage of CXL eyes had defects compared to the sham treated eyes (100% vs 21%[87]; 23% vs 1%[66]; 26% vs 3%[85]). No statistical comparisons were provided. One of the RCTs attributed the epithelial defects reported in the sham treatment to drying of the ocular surface despite intensive eye drop application.[87] Another RCT reported one patient with irregular epithelium on postoperative day 5 that was ongoing at one year (graded as mild) and a 5-letter improvement in CDVA.[66]

Corneal striae

Corneal striae were reported in 3 RCTs.[66 85 88] In 2 of these, striae were observed in both the CXL and sham treated patients at 3 months [66 85] The percentage of patients with striae was higher in CXL treated patients (24% vs 12%) in one study[66] whilst in the other, which included post-refractive-surgery ectasia patients, a similar percentage of patients had striae in the CXL and sham arms (9% and 7%,

respectively); these differences were not statistically significant (p = 0.20).[85] The third study did not report the number of patients with striae but noted that striae were most prominent at 1 to 3 months after CXL and progressively less marked with subsequent follow-up.[88] Unlike the other RCTs, no striae were observed in the control eyes.

Outcomes reported across two RCTs

Ocular pain, blurred vision, photophobia, ocular irritation, dry eye and increased lacrimation were reported by RCTs comparing CXL to sham with 3-month follow-up.[66] [85] No statistical comparisons of these events were conducted by either study. Dry eye, ocular irritation and blurred vision were observed in both CXL eyes and sham eyes in both studies, although they were consistently observed in a greater percentage of CXL eyes. Increased lacrimation and ocular pain were observed in the sham eyes in only one RCT, whereas they were observed in the CXL eyes in both RCTs. Photophobia was only observed in CXL eyes in both RCTs that reported it.

Outcomes reported in a single RCT

Subepithelial infiltrates, corneal erosions and need for subsequent surgery

One RCT reported comparative results for subepithelial infiltrates, corneal erosions and need for subsequent surgery.[87] During a follow-up averaging 36 months no subepithelial infiltrates and no requirement for subsequent surgery were observed in either the CXL or sham treated eyes; however, significantly more corneal erosions were observed in CXL treated eyes (93% vs 21%; p <0.01).

Peripheral corneal vascularisation

Peripheral corneal vascularisation was reported by one RCT, occurring in the CXL treated and untreated eyes of the same patient three years after CXL treatment.[72] The authors noted that they thought the event was unrelated to CXL and that the patient also had acne rosacea.

Conjunctival hyperaemia

Conjunctival hyperaemia was reported by one RCT with a 3-month follow-up.[66] It was observed in both CXL and sham eyes, but occurred in a greater percentage of CXL eyes

1

6.5 Research question 1b: If a benefit is found for CXL to treat keratoconus, what are the benefits and harms of using different CXL variations (compared with the standard protocol)?

To address this research question, two CXL variations were compared to standard CXL: accelerated CXL and transepithelial CXL. These variations were selected based on their relevance to Swiss clinical practice and an extensive evidence base. Study characteristics and results are reported per variation below. A list of studies identified for other CXL variations (not included below) can be found in ***Appendix D***.

6.5.1 Characteristics of included studies

Accelerated CXL versus standard CXL

The systematic review and meta-analysis conducted by Kobashi (2020)[69] was the most recent and most complete available for this variation so it was selected for inclusion. This review included RCTs with a minimum of 12 months follow-up of patients with progressive keratoconus undergoing accelerated CXL (defined as UVA intensity ≥9mW/cm^2 delivered over 10 minutes or less) compared with standard CXL (UVA delivered at 3mW/cm^2 for 30 minutes). The review included 6 RCTs and reported outcomes in a total of 379 eyes.[69] Three accelerated CXL protocols were used in the included RCTs: UVA intensity of 30mW/cm^2 for 3 or 4 minutes (n = 3), UVA intensity of 18mW/cm^2 for 5 minutes (n = 1) and UVA intensity of 9mW/cm^2 for 10 minutes (n = 2).

All included studies had a high risk of bias (according to appraisal by the authors of the systematic review) owing to the lack of blinding. The meta-analyses conducted in the review were limited by the small number of included studies/included eyes for some outcomes, heterogeneity amongst the included studies and the lack of long-term evidence. The quality of this systematic review was assessed using the AMSTAR tool[62] and is summarised in ***Appendix E, Table 53***.

RCTs identified by our search and not included in the systematic review by Kobashi (2020)[69] were also eligible for inclusion. Six were included.[75-78 90 91]

Two accelerated CXL protocols were used in the additional four included RCTs: UVA intensity of 30mW/cm^2 for 3 or 4 minutes (n = 2)[78 90] and UVA intensity of 18mW/cm^2 for 5 minutes (n = 2).[75 91] The quality of these RCTs was assessed using the Cochrane Risk-of-Bias tool[61] and summarised in in the next section.

The 6 RCTs reported outcomes in a total of 509 eyes, 102 of which had their earlier outcomes reported in Kobashi (2020).[69] As such, the total evidence base for this variation, consisting of 7 publications

reporting on 10 RCTs, comprised 786 eyes. Across the included studies, follow-up ranged from 6 to 48 months. Further study details can be found in ***Appendix E, Table 51***.

Transepithelial CXL versus standard CXL

The systematic review with meta-analysis conducted by Zhang (2018)[81] was the most recent and complete available for this variation and as such was selected for inclusion. This review included RCTs of patients (mean age >18 years) diagnosed with progressive keratoconus, comparing standard (epithelium-off) CXL with transepithelial CXL (including iontophoresis-assisted techniques). The review included a total of 6 RCTs and reported outcomes in a total of 344 eyes.[81] The transepithelial protocols used in the included studies generally used the same UVA intensity and duration as used in standard CXL, with the exception of 2 studies[67 79] that utilised an accelerated protocol (9–10mW/cm^2 for 9–10 minutes). All the included studies utilised the standard CXL protocol in the comparator arm, except for 1, which used the same accelerated protocol as its intervention group.[67] One study employed iontophoresis.[79]

The authors assigned each included study a Jadad Score for quality, where 0 indicated very poor quality and 5 indicated rigorous quality.[81] Study quality ranged from poor to moderate. Limitations of the meta-analysis carried out by Zhang (2018) include the pooling of outcomes across time points, the small number of included studies/included eyes for some outcomes, heterogeneity between the included studies, and publication bias.[81] The quality of this systematic review was assessed using the AMSTAR tool[62] and is summarised in ***Appendix E, Table 53***.

RCTs identified by our search and not included in the systematic review by Zhang (2018) were also assessed for eligibility for inclusion. A total of 6 publications were ultimately included.[67 73 74 79 80 92] Of these, 1 provided longer-term (24 month) follow-up for RCTs already included in the review by Zhang (2018).[79] The transepithelial CXL protocols used in these studies generally consisted of a standard CXL protocol. One RCT used an epithelium disruptor[67] and another removed the precorneal mucin layer from the central cornea.[79] The same 2 RCTs used an accelerated UVA delivery protocol (9–10mW/cm^2 for 9–10 minutes).[67 79] The standard CXL protocol used in the included RCTs removed 7mm to 10mm of the central cornea. They were performed according to the standard protocol, with the exception of an RCT that used an accelerated UVA delivery.[67] The quality of these RCTs was assessed using the Cochrane Risk-of-Bias tool[61] and summarised in the next section.

The new publications reported outcomes in a total of 324 eyes, 34 of which had their earlier outcomes reported in Zhang (2018). As such, the total evidence base for this variation, consisting of 6 publications reporting on 11 RCTs, comprised 634 eyes. Across the included studies, follow-up ranged from 6 to 36 months. Further study details can be found in ***Appendix E, Table 52***.

6.5.2 Risk of bias

Systematic reviews

Systematic reviews by Kobashi (2020)[69] and Zhang (2018)[81] were appraised with the AMSTAR tool[62] (***Appendix E, Table 53***). Both studies assessed risk of bias of their included studies. Neither study considered their risk of bias findings whilst making conclusions and recommendations or reported conflicts of interests among their included studies. Thus, by AMSTAR assessment, both systematic reviews are low quality.

RCTs

Accelerated CXL compared with standard CXL

The risk of bias of the RCTs comparing accelerated with standard CXL was assessed on a per outcome basis (clinical efficacy and safety). Clinical efficacy was further delineated into visual acuity outcomes and topographic/pachymetry outcomes.

With respect to randomisation, 4 of the 6 RCTs were deemed to have an unclear risk of bias.[75-77 91] Reasons for this classification included not stating how randomisation was performed or incorrect randomisation. Two RCTs were deemed to have a high risk of bias with regards to randomisation as they randomised patients to receive the intervention / control in both eyes (in some[90] or all[78] of the patient cohort). Five RCTs were deemed to have unclear risk of allocation concealment bias owing to a lack of reporting.[75 76 78 90 91]

In general, the RCTs had a low risk of performance bias. The RCT by Choi (2017)[90] was graded as having unclear risk as this study noted losses to follow-up but it was unclear how many, from what treatment or what the reasons were. The RCT by Hagem (2019)[76] was also deemed to have an unclear risk of performance bias because the reason for withdrawal from several patients in the accelerated CXL treatment group was not reported. Because the patients were not blinded, it was unknown whether knowledge of their intervention may have contributed to their withdrawal.

Half of the RCTs had a high risk of bias related to incomplete outcome data.[76 77 90] As noted above for performance bias, the study by Choi (2017)[90] was scored as having an unclear risk of incomplete outcome data as it was unclear how many losses there were.

Reporting bias was deemed unclear for all 6 RCTs. Although 3 RCTs[75 76 78] did report having a protocol, there was no link to the protocol so no way of checking whether the analyses conducted were those that had been planned.

All 6 RCTs were deemed as having an unclear risk of bias relating to at least one other area not captured by the risk-of-bias tool. One area of unclear risk of bias identified in all but 1 RCT was the use of contact lenses, which can affect some outcomes such as topography readings. The RCT by Hagem (2019)[76] was the only one to mention contact lens use, noting that patients were required to remove them 1 week prior to evaluation. The other 5 RCTs made no mention of whether patients wore contact lenses.[75 77 78 90 91]

A second area of unclear bias identified in some RCTs was correction for between-eye correlation when both eyes of patients were included. Three RCTs included both eyes from each patient and made no mention of correction for between-eye correlation.[75 77 78] The RCTs that included one, or mainly one, eye per patient were also scored as having an unclear risk for 'other bias' as it was not clear how the one eye was selected.[76 90] In the RCT by Razmjoo (2017)[91] it was not clear whether they used one or both eyes of each patient as they did not mention the number of eyes in the study, only the number of patients, thus this RCT was also scored as unclear risk in 'other bias'.

Visual acuity and refractive outcomes

All 6 RCTs comparing accelerated to standard CXL reported visual acuity outcomes. The risk-of-bias summary for visual acuity is reported in ***Figure 16*** and the risk-of-bias graph for these outcomes is presented in ***Figure 17***.

The RCTs by Eissa (2019) and Hashemi (2020) were deemed to be at low risk of detection bias as they stated that patients were blinded.[75 77] The study by Iqbal (2020) was scored as having unclear risk of detection bias because although there was no mention of blinding, the patients were children, so possibly unlikely to understand the intervention they had been assigned, even if told.[78] The other 3 studies were deemed to be at high risk of bias for safety as there was no mention of blinding of patients or assessors and visual acuity outcomes involve a degree of subjective assessment.[76 90 91]

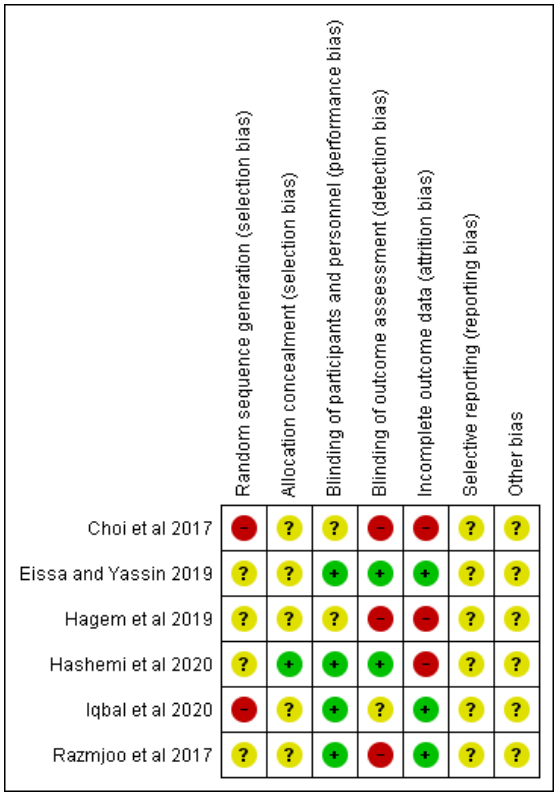

Figure 16 Accelerated vs standard CXL: risk-of-bias summary for visual acuity and refractive outcomes in the RCTs

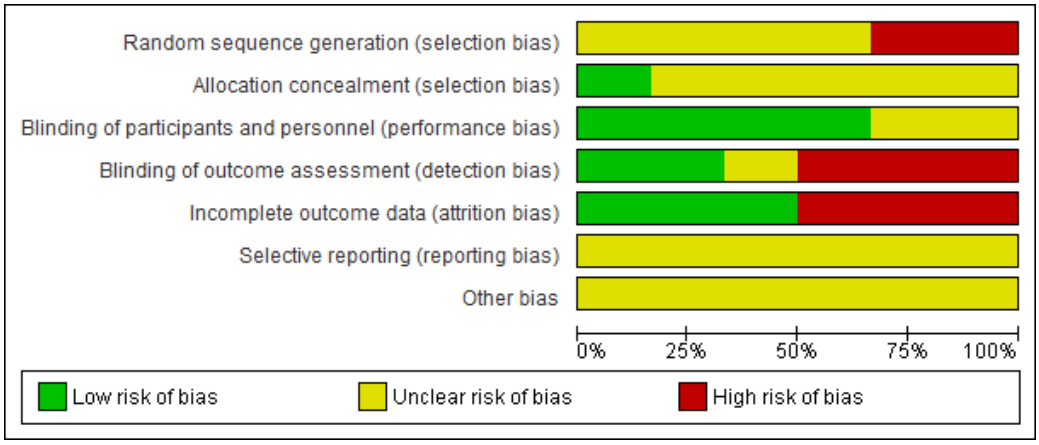

Figure 17 Accelerated vs standard CXL: risk-of-bias graph assessing visual acuity and refractive outcomes in the RCTs

Topography and pachymetry

All 6 RCTs comparing accelerated to standard CXL reported topography and/or pachymetry outcomes.[75-78 90 91] The risk-of-bias summary for topography and pachymetry outcomes are reported in ***Figure 18*** and the risk-of-bias graph for these outcomes is presented in ***Figure 19***.

As topography and pachymetry values are generated by a device, all RCTs were deemed as having a low risk of outcome assessment for these parameters, despite the RCT by Eissa (2019)[75] being the only one to mention blinding of assessors.

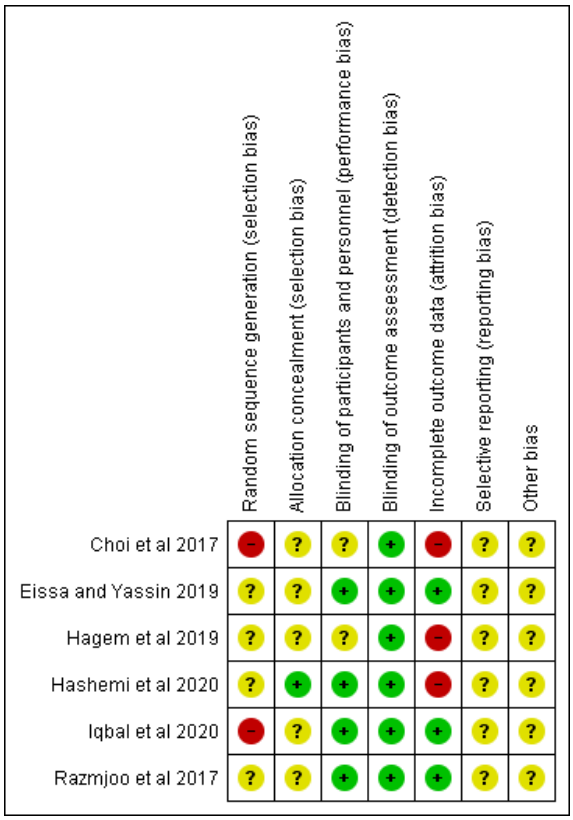

Figure 18 Accelerated vs standard CXL: risk-of-bias summary for topography and pachymetry outcomes in the RCTs

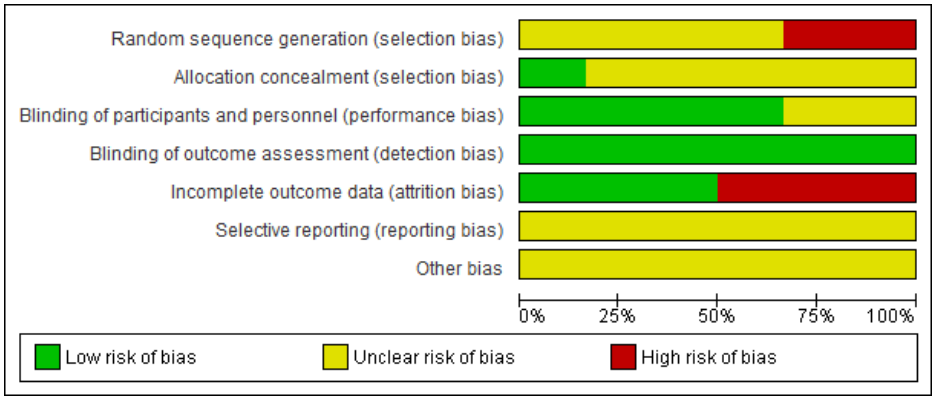

Figure 19 Accelerated vs standard CXL: risk-of-bias graph assessing topography and pachymetry outcomes in the RCTs

Safety outcomes

Four of the 6 RCTs reported on safety.[75-78] The risk-of-bias summary for safety outcomes is reported in ***Figure 20*** and the risk-of-bias graph for these outcomes is presented in ***Figure 21***.

The study by Eissa (2019) was deemed to be at low risk of detection bias as it stated that postoperative examiners and patients were blinded at all times.[75] The other 3 studies were deemed to be at high risk of detection bias as there was no mention of blinding of assessors and some safety outcomes involve a degree of subjective assessment.[76-78]

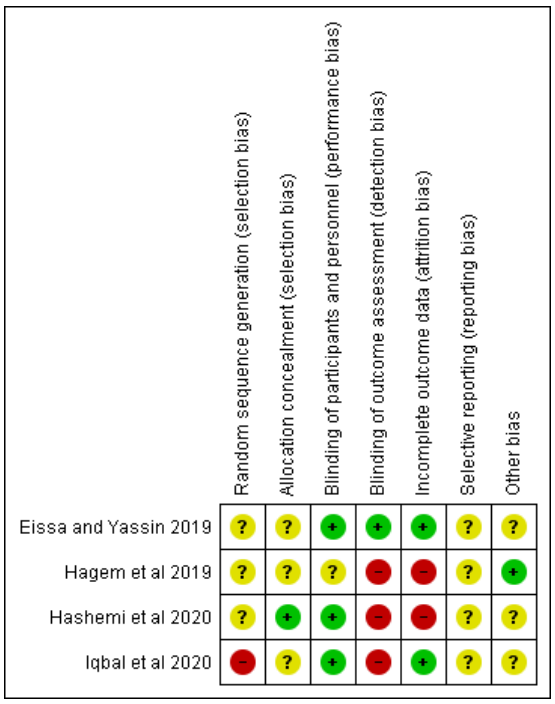

Figure 20 Accelerated vs standard CXL: risk-of-bias summary for safety outcomes in the RCTs

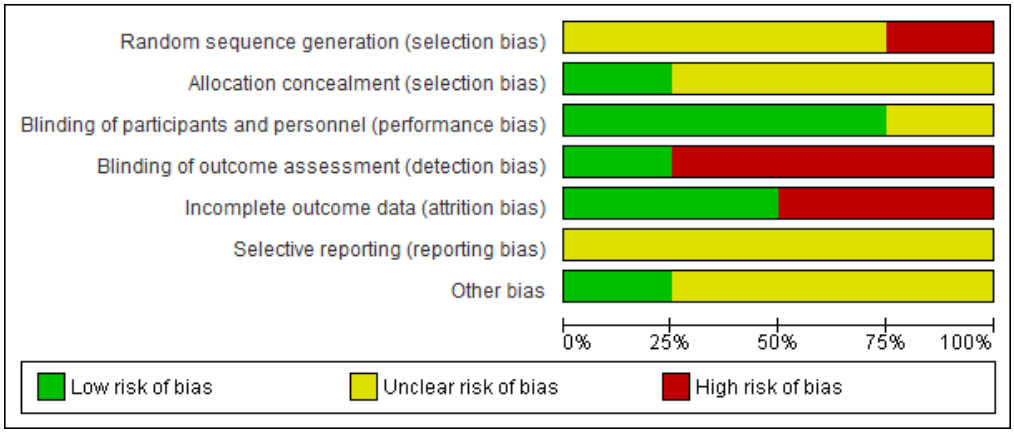

Figure 21 Accelerated vs standard CXL: risk-of-bias graph assessing safety outcomes in the RCTs

Transepithelial CXL compared with standard CXL

The risk of bias of the RCTs comparing transepithelial with standard CXL was assessed on a per outcome basis (clinical efficacy and safety). Clinical efficacy was further delineated into visual acuity outcomes and topographic/pachymetry outcomes.

Two RCTs had a high risk of randomisation bias as they did not describe their randomisation process.[67 92] Three RCTs were deemed to have an unclear risk of randomisation bias because they did not use computer-generated randomisation but there were no differences in baseline characteristics between the treatment groups.[74 79 80] Four RCTs had an unclear risk of allocation bias[67 74 79 80] and 1 RCT had a high risk of allocation bias[92] owing to a lack of reporting.

The study by Cifariello (2018) was deemed as having a high risk of performance bias as it was a non-blinded study (although this was reported transparently).[92] Similarly, Al Zubi (2019) was deemed to be at high risk of bias as no mention was made of blinding.[74] Bamdad (2020) discussed blinding of patients and the clinician recording the outcomes; however, any blinding of carers and individuals administering the intervention was unreported and thus assumed absent.[67] Furthermore, the authors did not identify who recorded the outcomes. If this were to be the same person who delivered the procedure, blinding would be compromised resulting in a high risk of bias. This lack of transparency gave unclear selection and reporting bias.[67]

Two RCTs were deemed to have high risk of attrition bias[74 92] and 2 RCTs were deemed to have an unclear risk.[67 80] Al Zubi (2019) and Cifariello (2018) did not provide any information concerning blinding or missing data (drop-outs).[74 92] Reporting bias was determined as unclear for all of the RCTs due to the lack of a predefined statistical analysis protocol.

With regards to 'other' bias, the RCTs were generally lacking in describing participant use of contact lenses prior to measuring outcomes, providing conflict of interest statements, and reporting between-eye correlation analyses. One RCT reported that contact lens use was halted 3 weeks prior to baseline measurements, surgery and follow-up appointments; however, other bias sources were present resulting in an overall 'unclear' score for the other bias domain.[79] Stojanovic (2014) was the only RCT to receive a low 'other' bias score.[80] The study reported limiting contact lens use prior to recording outcomes and surgery, had a conflict of interest statement, and included only one eye per participant.

Visual acuity and refractive outcomes

In studies where there was no blinding, detection bias was deemed as high for these outcomes. This was the case for all RCTs,[73 74 79 80 92] excluding Bamdad (2020)[67]. For the risk-of-bias summary see ***Figure 22*** and for the risk-of-bias graph see ***Figure 23***.

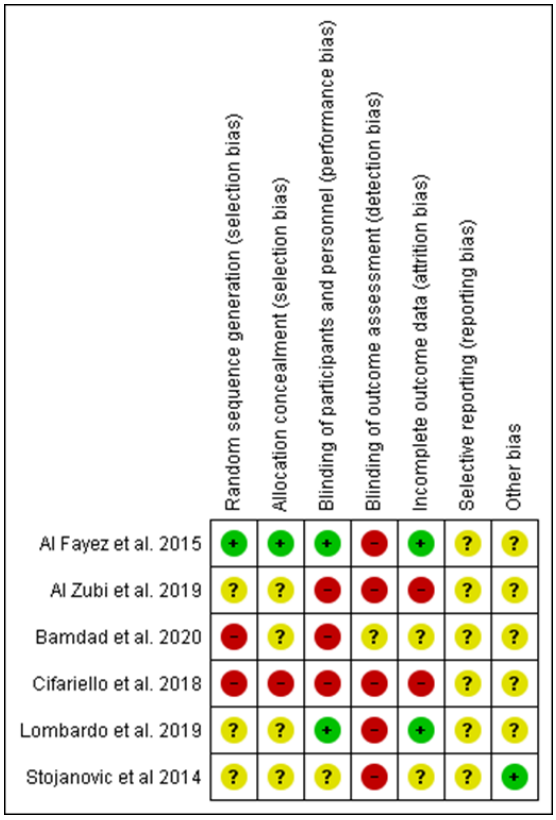

Figure 22 Transepithelial vs standard CXL: risk-of-bias summary for visual acuity and refractive outcomes in the RCTs

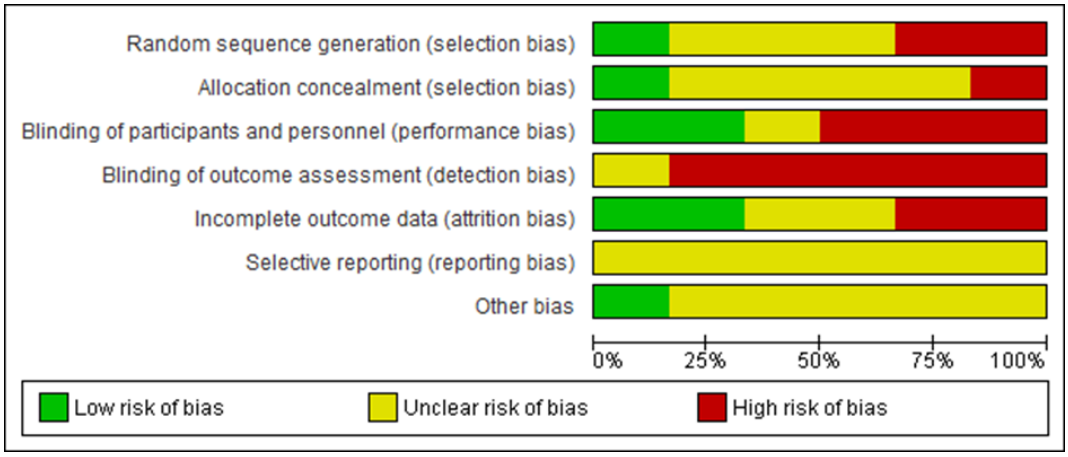

Figure 23 Transepithelial vs standard CXL: risk-of-bias graph assessing visual acuity and refractive outcomes in the RCTs

Topography and pachymetry

The risk of bias for the 6 included RCTs looking at topography and pachymetry of transepithelial CXL was generally unclear or low.[67 73 74 79 80 92] All studies were considered to have a low risk of detection bias because these outcomes are measured by a device and thus are objective measurements. For the risk-of-bias summary see ***Figure 24*** and for the risk-of-bias graph see ***Figure 25***.

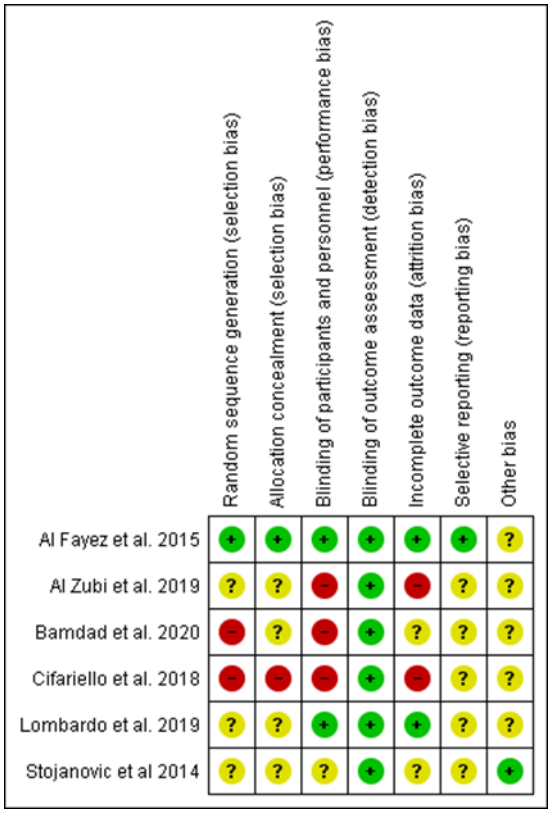

Figure 24 Transepithelial vs standard CXL: risk-of-bias summary for topography and pachymetry outcomes in the RCTs

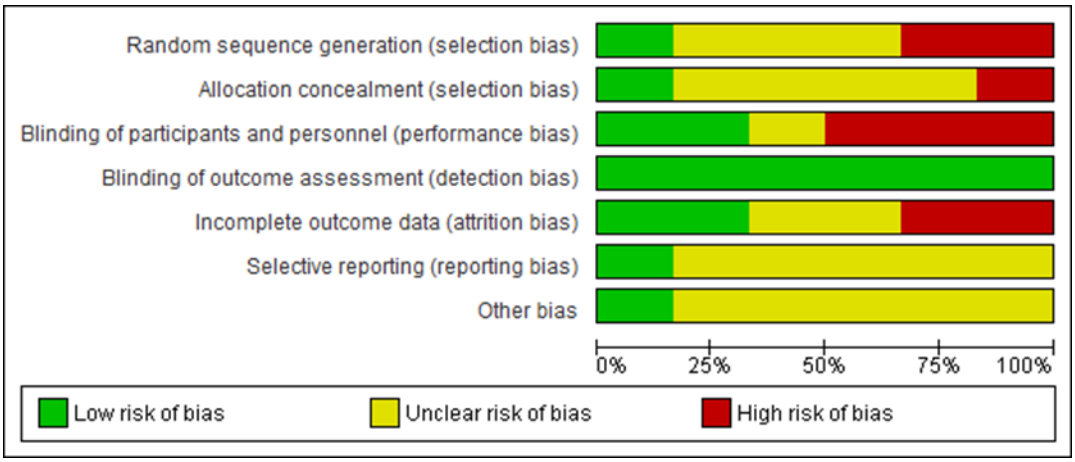

Figure 25 Transepithelial vs standard CXL: risk-of-bias graph assessing topography and pachymetry outcomes in the RCTs

Safety outcomes

Risk of bias in studies reporting comparative safety was similar to risk of bias for the visual acuity outcomes. Bias risk was elevated in several areas by missing data and subjective reporting of discomfort. Unblinded studies—both patients and outcome assessors—are likely to influence subjectively reported outcomes. For the risk-of-bias summary see ***Figure 26*** and for the risk-of-bias graph see ***Figure 27***.

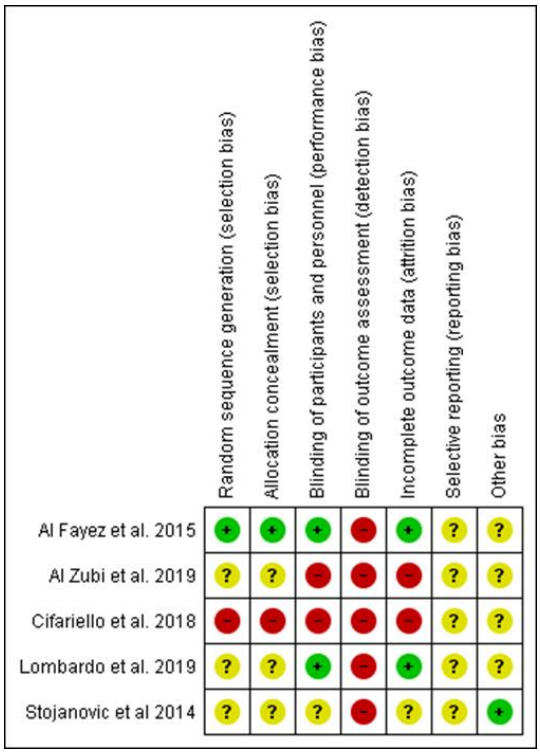

Figure 26 Transepithelial vs standard CXL: risk-of-bias summary for safety outcomes in the RCTs

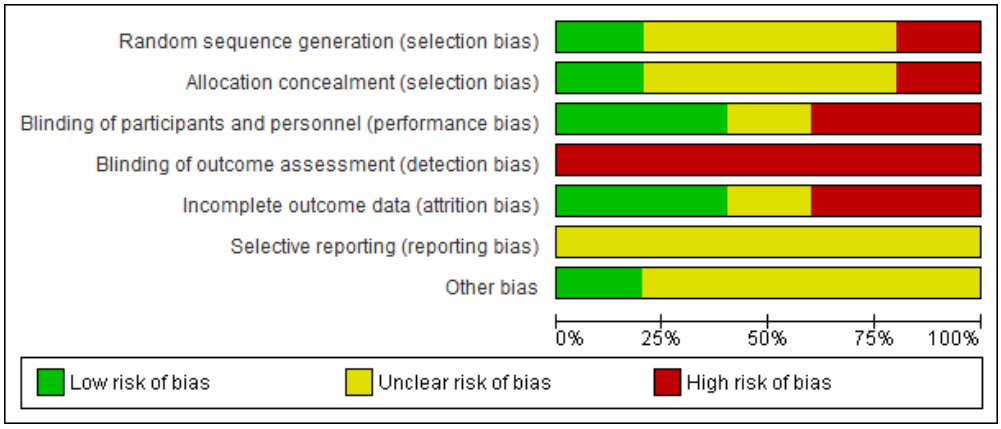

Figure 27 Transepithelial vs standard CXL: risk-of-bias graph assessing safety outcomes in the RCTs

6.5.3 Findings: clinical efficacy

Accelerated CXL versus standard CXL

A summary of the efficacy findings for the studies included for this comparison can be found in ***Appendix E, Table 54*.**

Visual acuity

Systematic review

In the meta-analysis by Kobashi (2020),[69] UCVA was not significantly different between accelerated and standard CXL (MD: -0.01; 95% CI -0.13, 0.11; p = 0.88). BCVA significantly improved with standard CXL treatment; however, the weighted mean difference in BCVA was very small (MD -0.02; 95% CI -0.03, -0.01; p <0.0001). Given that the minimum clinically important difference for visual acuity is 10 to 15 letters,[45] this finding is not clinically meaningful. Heterogeneity between studies was moderate for UCVA (I^2 = 56%) and low for BCVA (I^2 = 0%).

RCTs

Visual acuity (either BCVA and/or UCVA) was reported by all six RCTs. Findings varied, with 4 of the 6 RCTs that reported on BCVA finding no significant difference between accelerated and standard CXL at 6 to 48 months follow-up,[76 77 90 91] and 2 of the 4 RCTs that reported on UCVA finding no significant differences at 24 to 48 months follow-up.[76 77]

Two of the 6 RCTs did report significant differences between standard and accelerated CXL for both UCVA and UCVA.[75 78] In one of these studies, visual acuity outcomes fluctuated between no difference and a statistically significant difference in favour of standard CXL at follow-up time points of 6, 12 and 24 months (***Appendix E, Table 55***).[78] In the other, a significant improvement in visual acuity in favour of accelerated CXL occurred at 12, 24 and 36 months (***Appendix E, Table 56***).[75]

Pachymetry

Systematic review

Kobashi (2020) meta-analysed CCT at 12 months and found no statistical difference between standard and accelerated CXL (MD 7.41; 95% CI -0.29, 15.11; p = 0.06). Heterogeneity between studies was low (I^2 = 0%).[69]

RCTs

Two RCTs reported CCT following accelerated and standard CXL. Both found no difference between the variants at 12, 24, 36 and 48 months.[75 77]

Three RCTs reported TCT following CXL.[77 78 91] Two found no difference between the groups at 6 or 48 months,[77 91] while the other reported improved TCT following accelerated CXL at 6, 12 and 24 months (***Appendix E, Table 57***).[78]

Topography

Systematic review

Kobashi (2020) meta-analysed K_{max} only and found no significant difference between standard and accelerated CXL at 12 months (MD -0.45; 95% CI -1.08, 0.17; p = 0.15). There was high heterogeneity between studies (I^2 = 92%).[69]

RCTs

K_{max}

K_{max} scores were reported by all six RCTs. Two RCTs reported no significant difference in K_{max} between standard and accelerated CXL; one reporting at 6 months[91] and the other at 24 months follow-up.[76] Eissa (2019)[75] reported statistically lower K_{max} scores at 12, 24 and 36 months follow-up for accelerated CXL (***Appendix E, Table 58***). Iqbal (2020)[78] reported no significant difference at 6 or 12 months follow-up but found a significant difference at 24 months in favour of standard CXL (***Appendix E, Table 58***). Choi (2017)[90] measured K_{max} at 6 months follow-up using a Pentacam and auto kerato-refractometer, reporting a significant difference with the Pentacam in favour of standard CXL but no difference with the auto kerato-refractometer (***Appendix E, Table 58***). Hashemi (2020)[77] measured K_{max} in the anterior and posterior cornea, reporting three K_{max} scores: anterior 3 mm, anterior 8 mm, and posterior. At 48 months, anterior 3 mm and 8 mm K_{max} favoured standard CXL. Posterior K_{max} was not significantly different between the variants (***Appendix E, Table 59***). Subgroup analyses found the significant difference in anterior (3 mm and 8 mm) K_{max} was only applicable for peripheral keratoconus.

The RCT by Iqbal (2020)[78] also described keratoconus progression (defined as K_{max} progression >1D). In this study, 5 eyes (5.4%) progressed in the accelerated CXL group compared with no eyes in the standard CXL group. Progression in eyes having undergone accelerated CXL occurred at 12 months (2 eyes) and 24 months (3 eyes). The treatment success rate (i.e. percentage of eyes with no deterioration of K_{max}) at 24 months was higher for standard CXL compared with accelerated CXL (100% vs 94.6%).

K_{mean}

Two RCTs reported K_{mean}, one of which found a significant difference between the variants at 6 months in favour of standard CXL when measurements were taken using a Pentacam (mean change standard CXL -0.44 ± 0.63 D; mean change accelerated CXL 0.11 ± 0.5; p = 0.019 D) but not with an auto kerato-refractometer.[90] The other RCT reported no difference in K_{mean} between the variants at 24 months.[76]

K_{min}

Two RCTs reported on K_{min}. Hashemi (2020)[77] reported K_{min} for the anterior (3 mm) and posterior cornea, neither of which was significantly different between the variants at 48 months. The other RCT reported K_{min} at 6 months, again finding no difference between accelerated and standard CXL.[90]

K_1 and K_2

Two RCTs reported on K_1 and K_2 at 6- and 24-months follow-up. No differences were found in either study at either follow-up time.[76 91]

Refractive errors

Systematic review

Kobashi (2020) meta-analysed cylinder and SE at 12 months. For cylinder there was a significant difference in favour of accelerated CXL (MD: 0.15; 95%CI: 0.05, 0.26; p = 0.005). For SE there was no difference between the variants (MD -0.04; 95% CI -0.74, 0.65; p = 0.91). Heterogeneity was low for cylinder (I^2 = 0%) and moderate to high for SE (I^2 = 59%).

RCTs

Three RCTs reported on sphere[78 90 91] and 4 on cylinder and SE.[77 78 90 91] Two RCTs reporting all 3 outcomes at 6 months found no differences between standard and accelerated CXL.[90 91] An RCT reporting only on cylinder and SE at 48 months follow-up, also reported no significant difference between the variants.[77]

One RCT reported varied findings for sphere, cylinder and SE that fluctuated between no significant difference and a preference for standard CXL over time. There was a significant difference in favour of standard CXL for all three parameters at 24 months (***Appendix E, Table 60***).[78]

Transepithelial CXL versus standard CXL

A summary of the efficacy findings for the studies included for this comparison can be found in**,** ***Appendix E, Table 61*****.**

Visual acuity

All the included studies reported visual acuity outcomes (UCVA and/or CDVA).[67 73 74 79-81 92]

Systematic review

The systematic review by Zhang (2018) reported no significant difference between transepithelial and standard CXL for both UCVA (MD -0.00; 95% CI -0.11, 0.10; p = 0.94) and BCVA (MD -0.04; 95% CI -

0.09, 0.02; p = 0.20). Heterogeneity between studies was moderate for UCVA (I^2 = 56%) and BCVA (I^2 = 69%).[81]

RCTs

For UCVA (reported in 4 of 6 RCTs), there was generally no difference between the variants at 6 and 24 months follow-up.[67 73 79 80] One RCT reporting UCVA beyond 12 months found a significant improvement for standard CXL at 12, 24 and 36 months follow-up (***Appendix E, Table 62***).[73]

In all six RCTs reporting BCVA, no differences were seen between transepithelial and standard CXL from 6 to 36 months,[67 73 74 79 80] with the exception of 1 RCT that found a difference in favour of standard CXL at 24 months (p = 0.01)[92]. In this study, BCVA improved from 0.36 ± 0.14 logMAR to 0.22 ± 0.12 logMAR in the standard CXL group compared with 0.32 ± 0.16 logMAR to 0.27 ±0.13 logMAR in the transepithelial group.[92]

Pachymetry

Corneal thickness was reported in all the included studies, as either mean corneal thickness, CCT or TCT.[67 73 74 79-81 92]

Systematic review

The systematic review by Zhang (2018), which meta-analysed CCT, favoured standard CXL (MD 4.53; 95% CI 0.42, 8.64; p = 0.03). Heterogeneity between studies was low (I^2 = 0%).[81]

RCTs

One RCT reported a significant improvement in TCT in favour of transepithelial CXL at 6 months (p = 0.0001) (***Appendix E, Table 63***).[67]

Conversely, all the RCTs found no difference in CCT (1 RCT at 6 months,[74] 1 RCT at 12 months[74] and 1 RCT at 24 months[79]), MCT (1 RCT at 24 months[92]), 'corneal thickness' (1 RCT at 36 months[73]) or 'pachymetry' (1 RCT at 1, 6 and 12 months[80]) between transepithelial and standard CXL.

Topography

Topography outcomes (maximum and mean keratometry scores, and K_1 and K_2) were reported in all the included studies.[67 73 74 79-81 92]

Systematic review

Zhang (2018) meta-analysed K_{mean}, K_1 and K_2. K_{mean} outcomes favoured standard CXL (MD 0.79; 95% CI: 0.04; 1.53; p = 0.04), while there was no difference for K_1 (MD 0.15; 95% CI -0.54, 0.85; p = 0.67) and K_2 (MD 0.70; 95% CI -0.02, 1.41; p = 0.06). Heterogeneity between studies was low for all 3 outcomes (I^2 = 0%).[81]

RCTs

Three RCTs reported K_{mean} outcomes, which were not significantly different at 3 to 24 months follow-up.[67 74 92] Two other RCTs reported K_1 and K_2, for which there was no difference between transepithelial and standard CXL at 1, 6 and 12 months follow-up,[80 92] but a preference towards standard CXL at 24 months[92] (p = 0.01 for K_1 and K_2) (***Appendix E, Table 64***). Three RCTs reported K_{max}.[73 79 80] Two reported no differences between the variants; one reporting at 24 months follow-up and the other at 1-12 months follow-up. months.[79 80]The third RCT reported no difference at 3 and 6 months but a significant difference in favour of standard CXL at 12 to 36 months[73] (***Appendix E, Table 65***).

Refractive errors

Six of the included studies reported refractive outcomes (cylinder and/or SE).[67 73 74 79-81]

Systematic review

The systematic review by Zhang (2018) meta-analysed SE and found no difference between transepithelial and standard CXL (MD 0.15; 95% CI -0.18, 0.49; p = 0.37). Between-study heterogeneity was low (I^2 = 0%).[81]

RCTs

Similarly, the remaining five RCTs found no differences between the variants for cylinder (two RCTs at 1, 3, 6 and 12 months[74 80]) or SE (four RCTs at 1, 3, 6, 12, and 24 months[67 74 79 80]). Al Fayez (2015) reported 'refraction' was not significantly different at 36 months.[73]

6.5.4 Findings: safety

Accelerated CXL versus standard CXL

The systematic review and 4 of the additional RCTs reported safety outcomes, none of which were statistically analysed.[69 75-78] Kobashi reported the number of adverse events occurring in 2 of its included RCTs; the others did not report safety outcomes. Adverse events included haze and delayed epithelial healing. At 12 months, the incidence of these was similar for accelerated CXL and standard CXL.

Three of the additional RCTs reported no complications after either accelerated or standard CXL.[75-77] The RCT by Iqbal (2019) reported a higher incidence of complications (photophobia, pain, watery eyes, delayed healing, persistent epithelial healing, corneal stromal opacity and haze) following standard CXL compared with accelerated CXL (statistical significance was not evaluated).

A summary of the safety outcomes reported for accelerated CXL versus standard CXL can be found in ***Appendix E***, ***Table 66***.

Transepithelial CXL versus standard CXL

The systematic review and 4 of the additional RCTs reported safety outcomes.[73 74 80 81 92] Zhang (2018) narratively summarised the adverse events reported in 4 of its included RCTs but no statistical analyses were conducted.[81] Fewer postoperative complications were reported in patients who underwent transepithelial CXL compared with standard CXL. Complications included stromal oedema (observed up to 7 days post-procedure), herpes simplex keratitis, sterile infiltrate, delayed epithelial healing, tearing, photophobia, pain and long-term corneal haze. These complications generally resolved during follow-up and none of the RCTs included in the review by Zhang (2018) reported any patient requiring keratoplasty.[81]

Two RCTs statistically analysed intraoperative comfort[73] and pain outcomes[80] following CXL. Al Fayez (2015) reported significantly less intraoperative discomfort in the transepithelial CXL group (2 versus 4 on a pain scale 1–5; $p = 0.0035$).[73] Stojanovic (2014) reported no significant difference in pain scores for transepithelial CXL and standard CXL but a significantly longer duration of pain in the standard CXL group (33.9 hours versus 11.6 hours; $p = 0.000$).[80]

The remaining 2 RCTs did not statistically analyse their safety outcomes.[74 92] Al Zubi (2019) reported no complications in the transepithelial CXL group. In the standard CXL group they noted the occurrence of stromal haze (early postoperative period until 3–4 months follow-up in four eyes), and photophobia and pain (first 2 postoperative days in the 'majority' of patients).[74] Cifariello (2018) reported similar complication rates for haze, Vogt's striae and follicular conjunctivitis between transepithelial and standard CXL.[92]

A summary of the safety outcomes reported for transepithelial CXL versus standard CXL can be found in ***Appendix E***, ***Table 67***.

6.6 Applicability of evidence base to Switzerland

Applicability refers to the generalisability of the clinical trials to the Swiss context. It involves comparing patient demographics and clinical characteristics in the RCTs to what generally occurs in Swiss practice. There is no data describing the demographics of patients in Switzerland with keratoconus who are undergoing this procedure.

6.6.1 Included studies

For research question 1a, the 9 included RCTs for safety and efficacy were from a range of countries including the UK,[70] India,[84] the USA,[66 85] Pakistan,[86] Germany,[87] Iran,[71] Australia[72 88] and Brazil.[68] The systematic review included for safety did not report the countries of the included studies.[26] For research question 1b, RCTs were included from Norway,[76 80] Italy,[79 92] Iran,[67 77 91] Saudi Arabia,[73] South Korea,[90] Jordan[74] and Egypt.[75 78] The systematic reviews for question 1b included RCTs from some of the previously mentioned countries, as well as the Netherlands and Russia. Owing to differences in population demographics and healthcare systems the applicability of the studies from India, Pakistan, Iran, Saudi Arabia, South Korea, Jordan, Egypt, Russia and Brazil to the Swiss population is uncertain.

All included RCTs for research question 1a performed CXL using the standard protocol involving epithelium removal and 30 minutes of UVA irradiation. Feedback from a survey of 10 Swiss ophthalmologists, conducted by the FOPH for this HTA report, revealed that the 9 who were performing CXL used different variations including transepithelial, accelerated, pulsed light and customised intensity of UV light delivery.

All but 1 of the included RCTs (for research question 1a) reported age as an inclusion or exclusion criterion for entry into the trial. Three stipulated an age range: 15–60 years,[68] 16–50 years[72 88] and 15–40 years.[71] Another 3 RCTs stipulated a minimum age of ≥14 years old.[66 84 85] One RCT noted an exclusion of patients <12 years of age[87] and another excluded patients <18 years of age. In general, the mean age of patients in the RCTs was mid- to late-20s to early-30s; however, in 1 RCT, included for safety only, the mean age of patients was early-40s whilst in another 2 RCTs it was early-20s.[84 86] For research question 1b, age was used as an inclusion criterion in one of the included systematic reviews[81] and half of the additional RCTs.[67 74 75 77 78 92] Two RCTs included a paediatric population,[75 78] three included patients aged from 15 to 40[67 77 92] and two included patients aged 18 and over.[74 81] Several Swiss eye clinic websites were searched to see if they reported the age of patients acceptable for treatment with CXL. One noted it performed CXL in patients aged from 6 to 60 years.[93]

For research question 1a, 6 of the 9 RCTs had progressive keratoconus as a trial inclusion criterion and provided a definition of this.[66 70-72 84 87 88] Similarly for research question 1b, both systematic reviews and 11 of 12 RCTs had progressive keratoconus as an inclusion criterion.[67 69 73 74 76-81 90-92] For both research questions, the definitions of progression varied both in the parameters specified and the timeframe over which changes had to have occurred. Across the research questions, one study specified changes that had to have occurred over the preceding 3 months,[91] 1 study specified a timeframe of 6 months,[92] 1 study specified a timeframe of 3 to 12 months,[76] 1 specified 6 months or greater,[74] 5 studies specified 12 months[67 69 73 79 80] and 4 studies specified 18 to 24 months.[66 70 84 87] The remaining studies specified changes but did not provide a timeframe over which they had to have occurred.[71 72 77 78 81 88 90] For 4 of

the RCTs, keratoconus was deemed progressive if there was a loss in visual acuity. Definitions for this varied and included a reduction in uncorrected or best spectacle-corrected visual acuity by 1 line,[67 70] loss of ≥2 lines of best spectacle-corrected visual acuity[71] and 'a clinically significant change in refraction' defined as a change in spectacle correction or contact lens parameters.[87] No information could be found on how Swiss ophthalmologists assess progression in their patients for determining those eligible for CXL. It is possible they follow the consensus guidelines, which were published after the commencement of many of the RCTs informing this report.

Corneal thickness was used as an inclusion or exclusion criteria in most of the RCTs included for research question 1a and 1b.[66 68 70-78 80 84 85 87 88 91] In 12 RCTs, patients were required to have a corneal thickness of ≥400 µm,[68 70-75 77 78 80 84 88 91] in 1 RCT patients had to have a corneal thickness of >360 µm,[76] in 2 RCTs patients had to have a corneal thickness of ≥300 µm[66 85] and in 1 RCT the corneal thickness had to be >450 µm.[87] The website of one Swiss eye clinic noted that the clinic can perform CXL on thin corneas but did not state thickness.[93]

6.7 GRADE summary of findings

The following tables summarise the key findings for the three comparisons reported by the meta-analyses conducted for this review (i.e. CXL compared to sham or no treatment), and reported in the existing systematic reviews (i.e. standard CXL compared to accelerated and transepithelial CXL).[69 81] Evidence that was summarised in the report narratively are not represented in the GRADE tables, due to the risk of mis-interpreting unweighted ranges of reported values.

Per the GRADE approach, seven key outcomes are reported in the summary of findings tables for each comparison.[63] These outcomes are reflected in the PICO criteria in ***Section 5***. For measures of topography, K_{max} has been prioritised for inclusion in the summary tables, followed by K_{mean} and K_{min} where K_{max} was not reported. Outcomes are reported at the longest follow-up reported, due to the slow-progressing nature of the disease. Safety outcomes could not be summarised due to highly varied reporting in the primary studies. Quality of life outcomes are not reported in the tables, as none of the included studies measured this outcome.

The certainty of evidence supporting an outcome, as scored according to the GRADE approach, is defined into the following categories:[63]

- **High certainty**: We are very confident that the true effect lies close to that of the estimate of the effect.
- **Moderate certainty**: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
- **Low certainty**: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
- **Very low certainty**: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Table 3 GRADE summary of findings table, CXL compared to sham or no treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with sham or no treatment	Risk with corneal collagen crosslinking				
Uncorrected visual acuity follow up: 36 months	-	SMD **0.71 SD lower** (1.28 lower to 0.14 lower)	-	94 (1 RCT)	⨁◯◯◯ VERY LOW [a,c]	A SMD of 0.71 represents a moderate improvement in visual acuity favouring CXL.
Best corrected visual acuity follow up: 36 months	-	SMD **0.51 SD more** (0.52 fewer to 1.53 more)	-	123 (2 RCTs)	⨁◯◯◯ VERY LOW [a,c,d]	The results indicate no significant difference between CXL and sham or no treatment.
Central corneal thickness (CCT) follow up: 36 months	The mean central corneal thickness was **467.3** µm	MD **18.1 µm lower** (56.64 lower to 20.44 higher)	-	29 (1 RCT)	⨁◯◯◯ VERY LOW [b,c]	The results indicate no significant difference between CXL and sham or no treatment.
K_{max} follow up: mean 36 months	The mean K_{max} was **52.5** dioptres	MD **1.85 dioptres lower** (3.44 lower to 0.25 lower)	-	123 (2 RCTs)	⨁◯◯◯ VERY LOW [a,b,c]	The results indicate a significant difference favouring CXL; the clinical significance of this finding is unclear.
Spherical equivalent follow up: 36 months	The mean spherical equivalent was **-3.89** dioptres	MD **0.18 dioptres higher** (-1.17 lower to 1.53 higher)	-	94 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	The results indicate no significant difference between CXL and sham or no treatment.
Cylinder follow up: 36 months	The mean cylinder was **-5.7** dioptres	MD **0.27 dioptres higher** (-1.32 lower to 1.86 higher)	-	94 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	The results indicate no significant difference between CXL and sham or no treatment.
Treatment-related adverse events	Data not useable		-	-	-	Adverse events were not pooled due to varied reporting in the primary studies. See the text in the report for a narrative summary of specific treatment-related adverse events.

Abbreviations

CI: Confidence interval; **SMD**: Standardised mean difference; **MD**: Mean difference

Notes

***The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

a. The unblinded study by Wittig-Silva allowed control patients to undergo CXL if continuing and significant disease progression was noted during the study from 6 months onwards. The data from these patients were then imputed using the last observation carried forward technique. The use of data from control patients lost prior to 12 months would result in a bias against CXL given keratoconus is a slowly progressive disease and patients are unlikely to have progressed prior to 12 months. Also, the study by Wittig-Silva included both eyes from some patients, although it is unclear how many. Where both eyes were included from a patients they were randomised separately, meaning a patient could potentially have both eyes randomised to the control or to CXL. This is a concern owing to between eye correlation effects.

b. This is a surrogate marker that has not been validated as an indicator of keratoconus progression and has been scored down for indirectness.

c. The analysis was downgraded due to low precision (total sample size <200).[64]

d. There was high heterogeneity between studies included in this analysis (I^2 > 75%).[64]

Table 4 GRADE summary of findings table, accelerated compared to standard CXL

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard corneal collagen crosslinking	Risk with accelerated CXL				
Best corrected visual acuity follow up: range 12 months to 18 months	The mean best corrected visual acuity was **0.27** logMAR	**0.02 logMAR lower** (0.03 lower to 0.01 lower)	-	329 (5 RCTs)	⨁⨁◯◯ LOW [a,b]	The results indicate a small statistically significant difference in favour of standard CXL; the clinical significance of this finding is unclear.
Uncorrected visual acuity follow up: range 12 months to 18 months	The mean uncorrected visual acuity was **0.73** logMAR	MD **0.01 logMAR lower** (0.13 lower to 0.11 higher)	-	260 (4 RCTs)	⨁⨁◯◯ LOW [c,b]	The results indicate no significant difference between standard CXL and accelerated CXL.
K_{max} follow up: range 12 months to 18 months	The mean K_{max} was **50.86** dioptres	MD **0.45 dioptres lower** (1.08 lower to 0.17 higher)	-	354 (6 RCTs)	⨁◯◯◯ VERY LOW [d,b]	The results indicate no significant difference between standard CXL and accelerated CXL.
Central corneal thickness follow up: 12 months	The mean central corneal thickness was **468.37** µm	MD **7.41 µm higher** (0.29 lower to 15.11 higher)	-	99 (3 RCTs)	⨁◯◯◯ VERY LOW [b,e,f]	The results indicate no significant difference between standard CXL and accelerated CXL.
Spherical equivalent follow up: range 6 months to 12 months	The mean spherical equivalent was **-2.84** dioptres	MD **0.04 dioptres lower** (0.74 lower to 0.65 higher)	-	143 (3 RCTs)	⨁◯◯◯ VERY LOW [b,f,g]	The results indicate no significant difference between standard CXL and accelerated CXL.
Cylindrical refraction follow up: range 6 months to 12 months	The mean cylindrical refraction was **-4.21** dioptres	MD **0.15 dioptres higher** (0.05 higher to 0.26 higher)	-	227 (3 RCTs)	⨁⨁◯◯ LOW [b,h]	The results indicate a statistically significant difference in favour of accelerated CXL; the clinical significance of this finding is unclear.
Safety	Data not useable			(6 RCTs)	-	Adverse events were not pooled due to varied reporting in the primary studies. See the text in the report for a narrative summary of specific treatment-related adverse events.

Abbreviations

CI: Confidence interval; **MD**: Mean difference

Notes

a. None of the included RCTs masked participants, three had high reporting bias, selection bias was high for 1 RCT and unclear for 3 RCTs.

b. The majority of RCTs were conducted in countries not applicable to Switzerland. Inclusion criteria for each study NR.

c. None of the included RCTs masked participants, two had high reporting bias, selection bias was high for 1 RCT and unclear for 2 RCTs.

d. None of the included RCTs masked participants, four had high reporting bias, selection bias was high for 1 RCT and unclear for 3 RCTs.

e. None of the included RCTs masked participants, two had high reporting bias.

f. The analysis was downgraded due to low precision (total sample size <200).[64]

g. None of the included RCTs masked participants, all of the RCTs had high reporting bias.

h. None of the included RCTs masked participants, two had high reporting bias, selection bias was high for 1 RCT and unclear for 1 RCT.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

†Findings from meta-analyses of outcome results at 12 months are reported throughout this table.

Source

Kobashi (2020)[69]

Table 5 GRADE summary of findings table, transepithelial compared to standard CXL

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard CXL	Risk with transepithelial CXL				
Uncorrected visual acuity follow up: range 12 months to 24 months	The mean uncorrected visual acuity was **0.69** logMAR	MD **0 logMAR** (0.11 lower to 0.1 higher)	-	264 (4 RCTs)	⨁⨁⨁⨁ HIGH [a]	The results indicate no significant difference between standard CXL and transepithelial CXL.
Best corrected visual acuity follow up: range 6 months to 24 months	The mean best corrected visual acuity was **0.24** logMAR	MD **0.04 logMAR lower** (0.09 lower to 0.02 higher)	-	304 (5 RCTs)	⨁⨁⨁◯ MODERATE [b]	The results indicate no significant difference between standard CXL and transepithelial CXL.
Central corneal thickness follow up: 6 months to 24 months	The mean central corneal thickness was **465.40** µm	MD **4.53 µm higher** (0.42 higher to 8.64 higher)	-	304 (5 RCTs)	⨁⨁⨁◯ MODERATE [b,c]	The results indicate a statistically significant difference in favour of standard CXL; the clinical significance of this finding is unclear.
K_{mean} follow up: range 6 months to 24 months	The mean K_{mean} was **46.04** dioptres	MD **0.79 dioptres higher** (0.04 higher to 1.53 higher)	-	209 (3 RCTs)	⨁⨁⨁◯ MODERATE [c,d]	The results indicate a statistically significant difference in favour of standard CXL; the clinical significance of this finding is unclear.
Spherical Equivalent follow up: range 6 months to 12 months	The mean spherical Equivalent was **1.84** dioptres	MD **0.15 dioptres higher** (0.18 lower to 0.49 higher)	-	155 (4 RCTs)	⨁⨁◯◯ LOW [a,c]	The results indicate no significant difference between standard CXL and transepithelial CXL.
Cylinder follow up: range 6 months to 12 months	The mean cylinder was **4.36** dioptres	MD **0.07 dioptres lower** (0.63 lower to 0.49 higher)	-	60 (2 RCTs)	⨁◯◯◯ VERY LOW [c]	The results indicate no significant difference between standard CXL and transepithelial CXL.
Safety	Data not useable		-	-	-	Adverse events were not pooled due to varied reporting in the primary studies. See the text in the report for a narrative summary of specific treatment-related adverse events.

Abbreviations

CI: Confidence interval; **MD**: Mean difference

Notes

a. Of the four RCTs meta-analysed, one was low quality and the others were moderate (n = 1) or high (n = 2).

b. Of the five RCTs meta-analysed, one was low quality and the others were moderate (n = 2) or high (n = 2).

c. Surrogate marker that has not been validated as a indicator of keratoconus progression.

d. Of the three RCTs meta-analysed, one was low quality and the other two were moderate quality.

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

Source

Zhang (2018)[81]

7 Costs, Cost-effectiveness and Budget Impact

7.1 Summary Statement Costs, Cost-Effectiveness, and Budget Impact

A Markov model was developed to evaluate the cost-utility of CXL compared to no treatment. In the base case, the model produced an incremental cost-effectiveness ratio (ICER) value of CHF 25,841 per additional quality-adjusted life year (QALY) gained, indicating CXL is costing more compared to no treatment (incremental cost of CHF 8,161.43). The ICER result is below the hypothetical threshold of CHF 100,000, and significantly lower than the 2019 gross domestic product (GDP) per capita, estimated at CHF 78,890. Key drivers of the model included the clinical efficacy of CXL and utilities at different disease stage. Results of all the one-way deterministic sensitivity analyses are substantially below the hypothetical ICER threshold of CHF 100,000. Moreover, the two-way sensitivity analysis found the usage of CXL to be cost-effective even with some scenarios above the hypothetical threshold of CHF 100,000. A probabilistic sensitivity analysis is also conducted, and the result shows that CXL has a 99.4% probability of being cost-effective against the threshold. However, the interpretation of these results should be done with caution, given the use of input values which were not specific to Swiss population.

A budget impact analysis was performed to estimate the financial impact of insurance reimbursement of CXL in Switzerland from 2021 to 2025. The total cost of CXL for all patients in Switzerland is estimated in the base-case to be CHF 573,346 in the first year and moderately increased to CHF 584,865 five years later. However, this projection is sensitive to patient volumes, and is considered to be uncertain due to the lack of information around the number of patients in the country who would receive the treatment if it should be listed. If there were up to 50% of existing patients waiting to receive CXL for insurance access, the CXL would cost over CHF 4.5 million in the first year and gradually taper base-case level after two to three years. However, this surge is unlikely to happen, and this estimate should be regarded as the worst-case scenario.

7.2 Methods

The economic evaluation for this HTA was developed using a stepwise approach. Firstly, existing published models were identified and reviewed. Modelling techniques, assumptions and other evaluation specifications (e.g. countries and evaluation perspectives) were investigated and compared to provide a comprehensive understanding to guide the model development. The clinical evidence from this HTA was then reviewed, and issues around the applicability and translation of the clinical evidence

to the economic evaluation were investigated. Possible gaps between availability of clinical data and requirements for the economic evaluation were clearly identified and these gaps were bridged when limitations were found. Key modelling techniques, specifications and relevant assumptions are described in detail in the following subsections (***Section 7.2.1***).

7.2.1 Overview of the economic model

Review of Existing Economic Studies

Three studies relevant to the PICO were identified in the systematic literature searches (See PRISMA Chart in ***Section 7.3.1***). The methodology and relevance of each study to the current model is summarised in ***Table 6***.

The study by Godefrooij (2017)[94] performed a Markov cohort study by examining the cost-effectiveness of CXL compared to no treatment within the context of the Netherlands. The model assumed keratoconus as a bilateral disease with independent progression for each eye with or without CXL. Patients in the model had a starting age of 22 years and progressed at a one-yearly cycle with a life-time horizon. CXL was assumed to have a 10-year stabilising effect with keratoconus progressing as if untreated thereafter. The study found CXL to be cost-effective compared to no treatment using the 2016 GDP per capita of the Netherlands as a threshold. The study reported the base-case ICER to be EUR 54,384 per QALY gained. The ICER result reduced to EUR 10,149 per QALY gained when CXL was assumed to have a lifelong stabilising effect.

A Canadian study by Leung (2017)[95] examined the cost-effectiveness of CXL compared to conventional management with keratoplasty. The study performed a microsimulation model and included patients with progressive keratoconus. Although the model allows both eyes of patients to have different progression trajectories in both arms, the disease progression was dealt with differently between the CXL and comparator arms. In the CXL arm, both eyes were treated at diagnosis, whereas in the conventional management arm, the second eye would experience a 5-year delay in diagnosis. Patients had a starting age of 25 years and progressed at a one-monthly cycle with a lifelong time horizon. The study found CXL to be cost-effective at an estimated ICER of CAN 9,090 per QALY gained.

A UK study by Salmon (2015)[96] performed a Markov cohort model comparing CXL to no treatment.[96] The model also assumed independent disease progression between the two eyes with or without CXL. The model included patients with progressive keratoconus with a starting age of 21 years and progressed at a four-weekly cycle. Costs and utilities of the treatment arms were accumulated over a 25-year horizon. The study found CXL to be cost-effective with an estimated ICER of GBP 3,174 per QALY gained.

It is worth noting that the included economic studies made specific assumptions regarding the quality of life measure. Direct measures of quality of life for patients with keratoconus or treated with CXL are absent. Mapping from other existing studies was therefore used to derive quality of life inputs.

Table 6 Overview of existing, relevant economic evaluations of CXL

Study Country	Comparisons	Key modelling approach and parameters	Base-case ICER	Sensitivity analysis Key driver of the model	Conclusion	Limitation
Godefrooij (2017) [94] Netherland	CXL versus no treatment	• Markov cohort model with visual acuity and keratoplasty as health states • Starting age of 22 years in a 1-yearly cycle over lifelong time horizon up to 100 years of age • Eyes are modelled independently • CXL stabilises keratoconus progression for 10 years and progresses as if untreated thereafter • Utilities are based on visual acuity	EUR 54,384/QALY (2017 Euro value)	**DSA and PSA** Key driver (ranked by impact): • CXL stabilisation effect, • discount rates, • initial disease severity, • healthcare costs and CXL cost.	CXL is cost-effective at the 2016 GDP per capita of the Netherlands.	Bilateral treatment of patients
Leung (2017) [95] Canada	CXL versus no treatment	• Microsimulation model with CXL and keratoplasty treatment as health states • Starting age of 25 years in a 1-monthly cycle over lifelong time horizon up to 110 years of age • Eyes are modelled independently in the control arm but jointly in the CXL arm • CXL stabilises keratoconus progression for 10 years and progresses as if untreated thereafter • Utilities are based on visual acuity	CAN 9,090/QALY (2017 Canadian dollar value)	**DSA** Key driver (ranked by impact): • Utility variations, CXL costs, • healthcare costs and • Keratoconus stabilisation effect	CXL is cost-effective within a Willingness-To-Pay thresholds of CAN 20,000 and CAN 100,000/QALY	Bilateral treatment of CXL patients

Study Country	Comparisons	Key modelling approach and parameters	Base-case ICER	Sensitivity analysis Key driver of the model	Conclusion	Limitation
Salmon et al. [96]	CXL versus no treatment	• Markov cohort model with AK stages and keratoplasty as health states • starting age of 21 years in 4-week cycle length over 25-year time horizon • Eyes modelled independently • CXL stabilises keratoconus progression with 7.6% failure rate • Utilities are based on visual acuity	£3,174/QALY (2015 GBP value)	**DSA and PSA** Key driver (ranked by impact): • CXL efficacy, • utility of severe disease, initial disease severity	CXL is cost-effective at the UK ICER threshold.	Lack of available data on CXL efficacy and disease progression rates

Abbreviations
AK = Amsler–Krumeich, **CAN** = Canadian Dollar, **CXL** = corneal collagen crosslinking, **DSA** = Deterministic sensitivity analyses, **EUR** = Euro, **QALYs** = Quality-adjusted life years, **QBP** = Pound Sterling, **GDP** = Gross domestic product, **PSA** = Probabilistic sensitivity analyses.

Applicability of clinical evidence

The construction of the economic model required clinical data and information regarding the disease status of patients in Switzerland. Further, data and findings from the clinical sections needed to be assessed against the Swiss context to make sure they were applicable. However, we found that there were issues regarding how the results of the clinical investigation could be applied to inform the construction of the economic model. This led to the situation where quantitative results (e.g. results of meta-analyses and other numeric results) were not directly useable as input values in the economic model, and most inputs were therefore sourced independently from the clinical section. The source of specific model inputs and their applicability to the Swiss context are addressed in ***Section 7.3*** and relevant input parameters have been tested via sensitivity analyses. Despite sourcing model inputs and using assumptions based on studies outside of the clinical evidence base, the data used to populate the model were generally in favour of CXL, which were in line with the outcome of the clinical review.

This section firstly highlights the gap and discrepancies between the clinical findings and what was needed to populate the economic model, and then discusses the solutions that have been implemented to bridge the gap and allow the economic model to be performed to address the cost-effectiveness of CXL in the Swiss context.

Evidence gap between the clinical and economic evaluation

In general, the extracted or synthesised data in the clinical efficacy section of this HTA had limited or uncertain applicability to the Swiss context. A few key discrepancies are summarised below:

- There was no information available on the characteristics of Swiss patients undergoing CXL for keratoconus. Therefore, it was unknown whether the population demographic characteristics in the clinical evidence base is applicable to the Swiss context.
- The eight RCTs included in the clinical efficacy section of the report varied in how they defined keratoconus progression, a criterion which they used for inclusion of patients into their trials. It is possible that some of the patients in two RCTs, which used visual acuity as one of the possible determinants of progression, may not have been progressive.[70 87] However, in the economic model, it has been assumed that all patients would progress at a certain rate overtime, and CXL will only be able to slow the progression for a finite amount of time.
- There was no information available on the disease status of Swiss patients undergoing CXL for keratoconus. Therefore, it was unclear whether the CXL recipients studied in the RCTs was similar or representative of Swiss patients. The disease status of the patients in the RCTs was generally not reported. Specifically, only three out of the eight RCTs reported the patients' grade of keratoconus, with all three using the Amsler-Krumeich (AK) classification.[68 70 84] One noted

that the patients' stage ranged from AK classification I to III,[70] the second reported ≥ stage II[84] and the third noted stage II/III.[68] Of the three RCTs that reported AK classification the effect of CXL on change in AK stages was not reported.

- Quality of life was not reported in the evidence included in this report. The information regarding the impact of CXL on quality of life, specific to the Swiss population, is therefore unavailable. Therefore, relevant utility mappings were sourced from other literature to provide the model inputs. Sensitivity analyses were undertaken to address any uncertainties regarding the use of utility mapping.

Strategies to resolve the applicability issues

In the absence of better alternatives, the model adopted most of the approaches and assumptions in the published model by Salmon (2015)[96] Rather than imposing subjective and arbitrary assumptions or adjustments to the clinical inputs to fit the model, the peer-reviewed published model was deemed comparatively more reliable. Despite the limitations around the clinical data applicability as outlined above, a few assumptions in the model were adopted to construct and evaluate the economic model. They were generally in line with the findings from the clinical section regarding the safety and efficacy of CXL.

- To adopt the AK classification to represent the health states in the model was considered appropriate. The studies reported changes in parameters relating to the anterior corneal surface (e.g. K_{mean}, CCT) which aligns with AK classification system.[68 70-72 86 87] Further, the model assumption that patients with AK classification stage IV would not receive CXL was deemed reasonable because patients with AK classification IV have corneal scarring, which is a contraindication for CXL.[97] This is universal to patients in any jurisdiction.
- The assumption that keratoconus is a slowly progressive disease and patients can only get worse with time, not improve, is supported by the literature.[98 99] Similarly, the assumption that keratoconus is a bilateral yet asymmetric disease, with eyes progressing independently is also supported by the literature.[98] Both of these assumptions are universal to keratoconus patients, hence applicable to the Swiss context.
- A Swiss study reported a failure rate of 7.6% after CXL, as measured by the percentage of eyes with continued progression.[100] This has been incorporated into the model as the key efficacy driver of the CXL clinical benefit.
- Data from ***Section 6.4.4*** and ***Section 6.5.4*** showed that patients with keratoconus are not at risk of having elevated mortality hence general population mortality is applicable for these

patients. This allowed the current economic model to use general Swiss mortality data to describe the background death rate for patients over the modelling time horizon.

- Whilst a range of adverse events may occur following CXL as reported in ***Section 6.4.4*** and ***Section 6.5.4***, they were generally mild. None of the evidence on either the standard CXL technique or CXL variants reported mortality.

Overview of the economic model

Based on the discussion above, it was considered appropriate to use the Salmon[96] model structure for the current assessment. Key modelling information is summarised and presented in ***Table 7***.

Table 7 Overview of the modelling methodology and key data sources

Model feature	Specification in Salmon model	Current model
Perspective	UK NHS	Payer perspective
Patients population	Patients with progressive keratoconus	Patients with early stage and progressive keratoconus
Intervention	CXL using riboflavin and ultraviolet A	No change
Comparator	No treatment	No change
Model type	Cost-utility analysis	No change
Basic modelling profile	Markov cohort model with 4-week cycle length over 25-year time horizon	No change
Choice of health states	Health states based on AK classification with each eye modelled individually	No change
Outcomes	QALYs	No change
Discounting	3.5% for the base-case 6% in a sensitivity analysis	3% in the base case 0% and 6% in a sensitivity analysis
Start age	21 years	11 years
CXL benefit	CXL assumed to halt progression for 10 years	No change
Utility data	Utility data mapped from visual acuity data onto AK stage classifications	No change
Background mortality	UK life table	Swiss life table
Adverse events	No adverse event assumed with CXL, but glaucoma and cataract were associated with keratoplasty	No change
Standard of care	All patients in CXL and no treatment arms had contact lenses	No change
Disease progression	Based on dioptre changes with constant rate over specific period (see section 8.3.1 for more detail)	No change
Sources of inputs	Trials, published studies, NHS National Tariff	Trials, published studies, Swiss DRG costs, inputs from clinicians
Sensitivity analysis	Both DSA and PSA	No change

Abbreviations
AK = Amsler–Krumeich, **CXL** = corneal collagen crosslinking, **DRG** = Diagnosis-Related Groups, **DSA** = deterministic sensitivity analysis, **NHS** = National Health Service, **PSA** = probabilistic sensitivity analysis, **QALYs** = quality-adjusted life years.

7.2.2 Key structural and modelling assumptions

This section primarily discusses the key model structure and the associated assumptions behind the construction of the current model, including a clear indication of which modelling assumptions were evidence-based. Variables to be tested via sensitivity analyses to investigate and minimise the uncertainties of this evaluation are also provided.

The choice of health states

As the economic model was undertaken using a Markov modelling approach, a set of health states were chosen to represent key disease progression milestones, where relevant costs and utility values could be accrued during the process. The model used the AK classification to represent the severity of keratoconus disease,[101] with the four AK stages plus keratoplasty and death used as the health states for the evaluation. In the model, 40% of patients were assumed to start from AK sage 1, and 60% start from AK stage 2.[96 102] The schematic illustration of how the health states interact with each other is provided in ***Figure 28.***

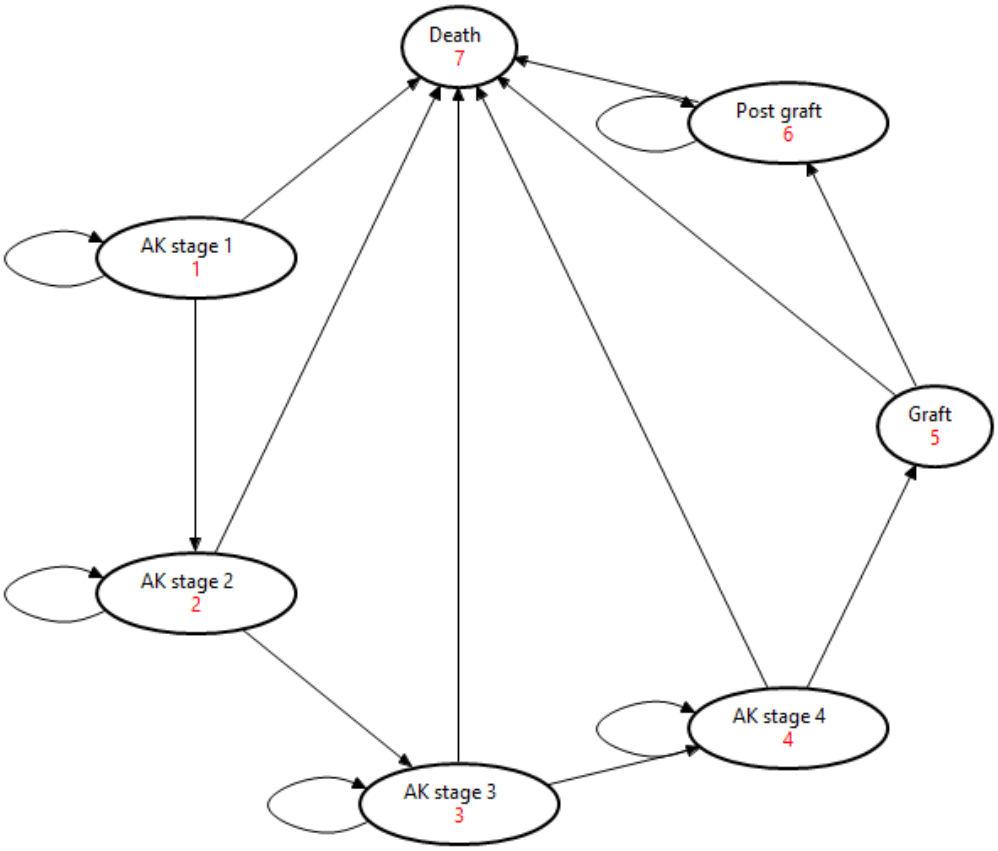

Figure 28 Simplified Health states in the model

It should be noted that the AK classification was not investigated as an independent efficacy outcome in the clinical evidence review section. The AK classification is a composite outcome that covers a range of patient-related and surrogate outcomes, including visual acuity measures (corrected or uncorrected) and keratometric parameters (e.g. K values, corneal thickness).[101] This composite outcome was considered to better reflect real-life clinical situations and was more practical when modelling disease progression. Further, most of the outcomes considered by the AK classification system were a part of the PICO and extensively investigated in the clinical section. To rely solely on any single outcome (e.g. via visual acuity) may not be appropriate.

Following Salmon (2015),[96] the current study modelled each eye separately. This was considered necessary and reasonable since keratoconus is a bilateral but asymmetrically progressing disease. Different eyes can have different progression baselines and experience different progression rates. This diversity in disease progression between the two eyes of one patient may result in different levels of treatment for each eye to achieve appropriate disease management. Furthermore, the likelihood of keratoplasty—the endpoint of disease progression—depends on eye-specific progression. Modelling the evaluation by considering the two eyes separately seemed to be a reasonable choice. The economic study from Canada[95] modelled keratoconus as a bilateral disease with bilateral treatment of the eye. This assumption limits the possibility of keratoconus affecting a single eye as observed in the Salmon model.[96]

Key clinical assumptions

A range of assumptions were made during the construction of the model. Most of these assumptions were based on non-RCT studies and other lower levels of evidence, and an understanding of how keratoconus progresses over time, gained through a review of the current evidence-base and other studies sourced during the evaluation process. However, some assumptions were made to ensure model functionality due to the lack of available evidence. These assumptions may have introduced uncertainty into the estimates, and were hence subjected to sensitivity analyses. In general, key assumptions were made to construct the basic model structure in four key areas:

1. Single-step transition through AK classes

Keratoconus is a slow, progressive disease, and changes to the cornea (e.g. bulging and thinning) are irreversible.[103] As outlined above, the AK classification system was used in this model-based health economic evaluation to represent progression of keratoconus over time. Being a composite measure, the AK classification has the advantage of utilising both patient-related outcomes (e.g. visual acuity changes) and corneal parameters (e.g. keratometry values) to define the stage of disease. Given the nature of these outcomes, it was considered reasonable for the model to assume that patients would not improve upon their AK stage over time—the only possible change being worsening of the disease.

Further, CXL treatment would only halt disease progression, not reverse the AK class to a better stage.[104]

Following Salmon (2015)[96] and Leung (2017),[95] the model has also taken a relatively short cycle length (4 weeks). Transition probabilities for patients to progress through AK stages were derived based on data from the literature.[105] In this HTA, it was assumed that, in a four-week cycle, patients could progress only one stage further in disease status during a one-step transition, where transition probabilities between non-adjacent AK stages were set to zero.

These two major assumptions define the basis of the disease progression pattern in the model. As they were based on a relatively robust clinical understanding of the disease, they are not subject to any sensitivity analyses to test the variability of their impact.

2. Independent bilateral progression with a 5-year delay for the better eye

It is understood that keratoconus is a bilateral but asymmetrically progressing eye disease. Patients who develop this condition in one eye are likely to experience the same disease in the other eye later in life,[106-108] although it is unclear how the onset of disease in one eye impacts the other. Disease progression in the better eye is often slow, but there have been cases reported whereby the better eye develops disease and deteriorates relatively quickly.[109] Due to the limited information available and following Salmon (2015),[96] the model assumed the two eyes progress independently but in a similar pattern; thus, the model assumed that keratoconus progresses at a relatively stable rate, as represented by constant transition probabilities over time, and that there was no interaction between the two eyes regardless of their disease status. Furthermore, the model assumed a typical patient could have a five-year delay before disease progression in the second eye (non-progressed).[96 110] Lastly, the model assumed that disease progression was likely to stabilise, reaching AK stage 3 at a low rate.. Small proportion of patients (0.12% in the CXL arm and 1.5% in the no treatment arm) progress further to AK4, with fewer patients eventually receiving keratoplasty as the final treatment.[105 111]

3. Only patients with AK stage 4 to receive keratoplasty

The use of keratoplasty to treat keratoconus is relatively rare and is often only considered for advanced keratoconus patients.[112] It requires the cornea to be significantly damaged due to advanced keratoconus. The model assumed that only AK stage 4 patients would eventually receive the corneal transplant procedure due to severe disease progression.[105 111] AK stage 4 patients have very high keratometry values (mean >55.0 dioptres) with possible central corneal scarring and extreme corneal thinning (<300 µm).[113] This assumption was considered reasonable and is not subject to further sensitivity analysis.

In current clinical settings, two major corneal grafting techniques are available: penetrating keratoplasty (PK) and deep anterior lamellar keratoplasty (DALK).[114] The latter is a partial thickness graft where the innermost layer of the cornea is reserved. This technique can reduce the chance of graft rejection due to preservation of the endothelium.[115] In recent years, DALK has become more routinely practiced compared to conventional PK;[116] however, the cost of DALK in Swiss health system could not be obtained. In general, the cost of DALK is greater (up to 50% more) than the conventional PK technique due to the former's longer procedure.[115] Thus, a conservative assumption was made to consider only PK in the base case of the current model. In addition, due to the infrequency of keratoplasty in the Swiss health system, the weight split between the two techniques may not be reliably derived. Therefore, the cost of keratoplasty was tested as a varying input parameter via a sensitivity analysis.

4. No additional impact to general population mortality

The associated treatments of keratoconus are relatively safe. Patients are unlikely to die from the disease or from the application of any treatment. There has been no reported increase in mortality and death is not considered a relevant outcome in the evidence base.[117] For this reason, age-specific Swiss population life table is used in the current model.[49] The current model uses a reasonably long-time horizon (25 years) across a relatively large life spectrum, therefore it would be reasonable to consider background mortality to be sufficient to account for all-cause death during the modelling process.

7.3 Modelling inputs for the economic evaluation

The modelling input parameters have been broadly categorised into three groups:

- parameters associated with clinical outcomes
- parameters associated with costs
- parameters associated with utility values as the result of disease

These three categories are discussed separately to report how input parameters were sourced, derived and implemented in the current model. Utilisation of these model parameters was also compared with the Salmon model, on which this evaluation has been based. Appropriate adaptations and modifications from the Salmon model were made specifically for this economic evaluation to ensure the current evaluation was relevant to the clinical evidence base identified and the Swiss health system.

7.3.1 Input parameters associated with safety and efficacy of CXL

Transition probabilities – keratoconus progression

AK classifications were used to represent the severity of keratoconus disease and thereby represent key health states in the model.[101] Transitions across different health states (i.e. AK stages and

keratoplasty) followed a set of clinical assumptions and rules outlined above. The likelihood of patients transiting from one state to another for both the CXL and no treatment arms was derived by converting clinical data, such as rate of disease progression, to probabilities.

Baseline transition probabilities for CXL and no treatment arms in the model were based on epidemiological studies, which were retrospective and observational in nature.[105] [111] Disease progression was quantified by a worsening of the corneal shape (measured in dioptres). Following Salmon (2015), the base case model used an annual progression rate of 1.01% in each eye for ten years and a reduction to 0.2% annual progression rate after ten years in both treatment arms.[105] [111] Keratoplasty was assumed to affect 1.3% of patients and as mentioned, was only for patients in AK stage 4. These values were converted to transition probabilities to describe the likelihood of patients migrating from AK stage I to II, and so on, in each cycle. Rates and the converted transition probabilities for the base case in the model are presented in ***Table 8.*** The transition probability of the CXL arm accounted for the failure rate of the CXL treatment procedure, which has been estimated to be 7.6% retreatment after the initial treatment.[100]

Table 8 Baseline rate to transition probability conversions

Clinical efficacy outcome	Rate	Converted probabilities baseline	Converted probabilities – CXL
High progression	1.01%[105]	0.0748	0.0059
Low progression	0.2%[105] [111]	0.0153	0.0012
Rate of keratoplasty	1.3%[110]	0.001	0.001

Abbreviations
CXL = corneal collagen crosslinking.
Notes
CXL was assumed to have a failure rate of 7.6%, which was compounded upon the baseline probability to produce CXL-arm value. Rates were annual whereas converted probabilities were monthly.

Despite using the epidemiological data to derive the transition probabilities, the setup of transition matrices in the current model involved some further assumptions.

1) Keratoconus is a bilateral but asymmetrical disease affecting both eyes. The current model evaluated keratoconus progression for individual eyes, assuming they progressed independently. The progression probabilities produced above are for a single eye only. The model assumed that keratoconus patients would experience disease progression for the worst eye first and the other (better) eye would start to progress independently at the same rate after five years. This made the Markov model non-time homogeneous, so two separate matrices were produced to capture how patients would transition across different states in the first five and then the following five years. In the absence of better clinical data informing alternative approaches, the assumption regarding the progression of both eyes was considered appropriate in the current evaluation.

2) The model also assumed that disease status would start to stabilise after ten years, where the progression would slow down to a lower level (i.e. 0.2% or 0.00153 in probability). Therefore, this resulted in an additional transition matrix being generated in the model to account for patients' progression 10 years after receiving CXL or no treatment.

The transition probabilities due to the efficacy of CXL compared to no treatment were implemented with the two key efficacy outcomes: progression halting and CXL treatment failure. The Salmon model proposed that CXL could effectively halt disease progression such that patients would be able to maintain their corneal profile and retain acceptable visual acuity post treatment.[118] On the other hand, patients could also experience CXL treatment failure, whereby no benefits were brought to those patients when CXL failed and they essentially received no treatment.

It was estimated that the treatment failure rate was approximately 7.6% among all CXL procedures.[100] This rate was similarly converted to transition probabilities and applied across assumptions 1) and 2) above to derive the three transition probability matrix counterparts for the CXL arm. The conversion is reported in ***Table 8*** above where the rate is directly compounded to the transition probability to reflect the increment benefit CXL would bring to patients. When the failure rate was lower or close to zero, patients would have smaller probability to progress, which reflects greater clinical benefit of CXL in terms of reducing progression.

Three similar transition matrices were also produced for the CXL arm. For illustrative purposes, only the transition matrices between AK stages in the first five years are provided in ***Table 9***. The full transition matrices are further calculated to include rate of keratoplasty as well as background mortalities.

Table 9 Transition probabilities first 5 years for patients without keratoplasty

No treatment arm					
From \ To	**AK1**	**AK2**	**AK3**	**AK4**	**Total**
AK1	0.9252	0.0748	0.0000	0.0000	1.0000
AK2	0.0000	0.9252	0.0748	0.0000	1.0000
AK3	0.0000	0.0000	0.9847	0.0153	1.0000
AK4	0.0000	0.0000	0.0000	1.0000	1.0000
CXL arm					
From \ To	**AK1**	**AK2**	**AK3**	**AK4**	**Total**
AK1	0.9941	0.0059	0.0000	0.0000	1.0000
AK2	0.0000	0.9941	0.0059	0.0000	1.0000
AK3	0.0000	0.0000	0.9988	0.0012	1.0000
AK4	0.0000	0.0000	0.0000	1.0000	1.0000

Abbreviations
AK = Amsler-Krumeich classification.
Notes
This table only describes the AK Classification transitions where all probabilities are conditioned on non-keratoplasty and alive patients.

Transition probabilities – background mortality

Keratoconus is not considered a life-threatening disease and CXL treatment poses no further risk to life, therefore the general population background mortality was considered sufficient to capture the risk of death over the time horizon of the model. The Salmon model was evaluated under the UK NHS perspective, so the UK life table was used for background mortality. It should be noted that the Salmon model only used three mortality data points (i.e. gender-weighted mortality of 0.0038%, 0.0040% and 0.0057% at age 21, 15 and 30, respectively) despite availability of age-specific mortality values from 0 to 100 years in the UK life table. This was due to inherent software (Excel) limitations on dynamic indexing. Since the risk of death at different ages is not homogenous, realisation of age-specific death probability transitions would require 25 different transition matrices for each arm (50 in total), which was impractical for model construction. As patients in this evaluation are relatively young, this approach—although not ideal—was not expected to significantly impact the model.

The economic evaluation for this HTA was to be considered in the context of Switzerland so the life table for the general Swiss population was applied to the calculations.[119] The life table presents data in five-year groups so age-specific mortality was linearly interpolated to fill the gaps. The life table was provided in the model calculation sheet in Excel and then applied in TreeAge for implementation. As TreeAge is

more flexible in terms of dynamic indexing, the linearly interpolated mortalities are applied appropriately to match patient gender and age.

Performance of keratoplasty

Keratoconus can progress to cause significant vision impairment. CXL is not performed for advanced keratoconus (AK stage 4) due to limited efficacy and potential safety concerns.[72] It was further assumed that only patients with advanced disease may receive keratoplasty. The current model assumed an annual rate of 1.3% for the proportion of AK4 patients undergoing keratoplasty.[110] It should be noted that the application of CXL treatment would not alter the probability of keratoplasty, but only delay it owing to its efficacy in halting disease progression. Therefore, the keratoplasty rate was universally applied across both arms at AK stage 4. Under the above assumptions and calculation, a 0.1% probability of keratoplasty was used in the model to allow AK4 patients to transition to a keratoplasty health state where treatment costs and utilities are accumulated. Post-keratoplasty health states are also included to capture possible utility values and costs incurred from ongoing keratoplasty maintenance. The Salmon model also assumed a keratoplasty repeat procedure at 20 years.

Using the calculations and assumptions above, a total of six transition matrices were generated to model disease progression for both the treatment and comparator arms. Although largely replicating the Salmon model, the current evaluation was implemented using TreeAge where the calculations are largely hidden in the background. (The Salmon model was implemented in Excel, where the transition matrices must be physically produced and are thus visibly represented in the spreadsheet. Patient progression pathways and associated Markov trace were also directly available for examination.)

A clear representation of transition matrices could be helpful for reviewers of this report to observe the model design and to facilitate understanding of how patients progress over the model time horizon. The six transition matrices in the current model are relatively sparse, with probabilities concentrated around the diagonal of the matrices, therefore a summary has been produced (***Table 10***) to outline the basic structure of these matrices and to illustrate how patients are transitioned from one health state to another.

Table 10 Overview of transition matrices used in the current model

Transition Matrices	Intervention: CXL treatment	Comparator: No treatment
Year 0 to 4	P (<AK3) = 0.0059 P (AK3–4) = 0.0012 P (AK4–PK) = 0.0010 P (all 2nd eye) = 0 P (death) = Swiss age-specific mortality P (diagonal) = 1 – (the sum above) All other transitions set to 0	P (<AK3) = 0.0748 P (AK3–4) = 0.0153 P (AK4–PK) = 0.0010 P (all 2nd eye) = 0 P (death) = Swiss age-specific mortality P (diagonal) = 1 – (the sum above) All other transitions set to 0
Year 5 to 9	P (<AK3) = 0.0059 P (AK3–4) = 0.0012 P (AK4–PK) = 0.001 P (all 2nd eye) = P (all 1st eye) P (death) = Swiss age-specific mortality P (diagonal) = complementary of sum above All other transitions set to 0	P (<AK3) = 0.0748 P (AK3–4) = 0.0153 P (AK4–PK) = 0.001 P (all 2nd-eye) = P (all 1st eye) P (death) = Swiss age-specific mortality P (diagonal) = complementary of sum above All other transitions set to 0
Year 10 onwards	P (all progression slow) = 0.0012 P (all 2nd eye) = P (all 1st eye) P (death) = Swiss age-specific mortality P (diagonal) = 1 – (the sum above) All other transitions set to 0	P (all progression slow) = 0.0153 P (all 2nd eye) = P(all 1st eye) P (death) = Swiss age-specific mortality P (diagonal) = 1 – (the sum above) All other transitions set to 0

Abbreviations
AK = Amsler-Krumeich classification, **CXL** = corneal collagen crosslinking, **PK** = penetrating keratoplasty. **P** = probability.

The transition probabilities described in ***Table 10*** are nominal items that may represent several transition probabilities in the matrices. For example, P <AK3 represents all possible transitions for a single eye from AK1 to AK2 or AK2 to AK3. Further, these transition probabilities were applied to both eyes, whereas second eye progression was assumed to be impossible in the first five years, hence P (all 2nd eye) = 0. The probabilities at matrices diagonals represent all possible self-transitions for disease status, keratoplasty recipients, or death.

Adverse events due to keratoplasty

The Salmon model assumed that adverse events associated with CXL were likely to be minor and transient,[96 100] and so did not consider any possible clinical effects or costs associated with CXL adverse event management. In the model for this HTA, two types of adverse events associated with keratoplasty were considered: cataract and glaucoma. Prevalence rates of patients experiencing these events are documented in ***Table 11***.

Table 11 Adverse events involved in the current model

Adverse event	Estimated proportion	Source of estimations
Cataract	3.23%	Lim (2000). Penetrating keratoplasty for keratoconus: visual outcome and success. *Ophthalmology* 107(6): 1125–1131.
Glaucoma	20%	

The adverse event rate of cataract and the glaucoma for keratoplasty patients were extrapolated over the time horizon of the model based on a published study.[120] Then relevant costs were applied only once at about the 20th year (259th cycle) to account for the cost of post-keratoplasty adverse events.

7.3.2 Inputs associated with costs of the management of keratoconus

The cost inputs in the current model are based on four categories: CXL costs, cost of standard care, cost of keratoplasty and adverse event management costs. The cost items used in the current model are provided below in ***Table 12.***

Table 12 Costs associated with CXL treatment

Cost items	Total cost (in CHF)	Source
CXL	2,300	Swiss clinic published price[19]
Keratoplasty	11,166	Swiss DRG C04Z
Adverse event: Cataracts or glaucoma	4,100	Swiss DRG C64Z
Special lenses for cataract surgery	500	FOPH, personal communications 9th October 2020
Scleral lenses (single)	450	FOPH, personal communications 9th October 2020
Lenses routine check	95	https://eyeness.ch/unsere-preise/
Initial lenses adjustment cost	600	https://eyeness.ch/unsere-preise/
Other maintenance care	300	https://eyeness.ch/unsere-preise/

Abbreviations
CXL = corneal collagen crosslinking, **DRG** = Diagnosis-Related Groups, **FOPH** = Federal Office of Public Health.
Notes
Keratoplasty cost is for outpatient treatment. Cost for special lenses for cataract surgery is an average of range between CHF 300 and 700. This is same for Scleral lenses (CHF 400 - 500) and initial lenses adjustment cost (CHF 500 – 700).

Costs of CXL

CXL is not currently reimbursed through mandatory health insurance, so all procedures are paid by patients out-of-pocket. One private clinic has published the cost of CXL as a commercial price, and this price is further verified (FOPH, personal communications 3rd September 2020). The clinic can perform the CXL procedure at CHF 2,300 per eye, and it is a flat fee to cover all medications and ongoing follow-ups.

It should be noted that the commercial price of CHF 2,300 does not include diagnosis procedures using keratometry. However, the costs associated with diagnosing of keratoconus would be incurred

regardless of whether CXL is used, and was hence deemed irrelevant for this model. Therefore, they are not included in the cost calculations.

Standard of care

The cost of contact lenses was also considered in the current model as part of the standard of care, and they are incurred in both the treatment and the comparator arms. Patients are provided with scleral lenses initially and are to be replaced every 12 to 18 months. The lenses are estimated to cost CHF 450 (with possible variation ranged from CHF 400 to 500) and with adjustment of the lenses estimated to be CHF 600 (with possible variation ranged from CHF 500 to 700). These costs were provided by the FOPH in consultation with clinicians (FOPH, personal communication, 9th October). A routine examination of the lenses is performed every 6 to 12 months at a cost of CHF 95. Additionally, patients spend CHF 300 every year to maintain the product.

Cost of keratoplasty

The keratoplasty procedure can be performed in either inpatient or outpatient setting. In the model base-case, the cost of keratoplasty is sourced from the Swiss DRG by assuming all procedures are performed in hospitals. Keratoplasty is estimated to cost, on average, CHF 11,166, which is an aggregate of preoperative, procedure and follow-up costs for each patient cohort in the model. This cost is only repeated in instances of a repeat keratoplasty.

The TARMED position (08.2300) and the associated costs for keratoplasty was also identified. The cost expressed as tax points is around CHF 800, which is significantly less than the DRG value. This is because the cost from the TARMED item only provides the procedure cost by itself where the associated medical services and follow-ups are unknown. Therefore, this prevents the model to use the outpatient costs. Also, to fully capture the cost of keratoplasty in the Swiss health system, the weighting for the inpatient and outpatient split would also be required.

Nonetheless, due to the insignificant keratoplasty rate in the progression pathway of keratoconus patients, the variations in the procedure cost was not expected to have significant impact on the model result. This was later confirmed in the univariate sensitivity analyses where the results were provided in Section 8.4.2. Therefore, the current assumption and cost was considered adequate for the model.

Cost of adverse event management

In the current model, CXL was not associated with any substantial adverse events, as those adverse events were relatively transient, minor and with low costs. Hence there was no impact of adverse events on cost and utilities of patients treated with CXL.

The keratoplasty procedure is, however, associated with adverse events. Cataract and glaucoma were considered for patients treated with this procedure in the current model. Treatment for both cataract and glaucoma procedures are coded under one DRG code and are estimated to cost CHF 4,100. Additional estimated cost of CHF 500 (CHF 300-700) are incurred for special lenses needed in the treatment procedure. All costs are discounted at an annual rate of 3% and varied in a sensitivity analysis.

7.3.3 Inputs associated with patients' quality of life

Direct utility measures of keratoconus are currently unavailable. Existing economic evaluation studies derive utility data using expected visual acuity measures, regression inferences from visual acuity data and expert consensus when visual acuity data is absent.[94-96] Godefrooij (2017)[94] derived utility weights from visual acuity data from the Collaborative Longitudinal Evaluation in Keratoconus cohort study,[121] whereas Leung (2017) used data from studies on expected visual acuity and expert consensus when such information were absent.[122-124] In the Salmon study, utility values of AK health states 1,2 and 4 were mapped from visual acuity data.[125] Visual acuity for AK stage 3 was inferred from weighted regression estimates of the existing visual acuity data for AK stages 1,2 and 4. The inference was then used to map utility value for AK stage 3. In the Salmon study, patients who underwent keratoplasty were assumed to have same utility values as patients without keratoconus if the procedure was done in the worse-seeing eye. The graft procedure conferred a postoperative VA of 0.1 logMAR if undertaken in the better seeing eye.[126] Utility data were assumed to be same for the CXL and control arms but varied by health states. The utility values used in the three studies are presented in ***Table 13.***

Table 13 Reported QALYs gained in key studies comparing CXL to no treatment

Health states provided in the published study	QALYs Gained
Leung (2017) [95]	
Keratoconus with contact lenses or spectacles	0.841
Graft (reversible vision loss due to minor complication)	0.770
Graft (successful)	0.873
Graft (rejection)	0.770
Graft (irreversible vision loss due to major complication)	0.607
CXL with contact lenses or spectacles	0.841
CXL (vision loss due to minor complication)	0.770
CXL (successful)	0.873
CXL (rejection)	0.770
Salmon (2015) [96]	
N	0.920
1	0.852
2	0.800
3	0.770
4	0.749

Health states provided in the published study	QALYs Gained
Graft (in better-seeing eye)	0.870
Graft (in worse-seeing eye)	0.920
Godefrooij (2017) [94]	
Good	0.85
Medium	0.83
Bad	0.81
Graft & Good Visual Acuity	0.84
Graft & Medium Visual Acuity	0.82
Graft & Bad Visual Acuity	0.69
Bilateral Graft	0.81

Abbreviations
CXL = corneal collagen crosslinking, **QALYs** = quality-adjusted life years.

Following Salmon (2015),[96] patients with bilateral disease were assigned utility values to the better-seeing eye. This was because visual function in the better-seeing eye was assumed to be highly correlated with utility.[125] Patients with unilateral disease were assigned utility values to the worse-seeing eye.[125] This approach was different from the Leung and Godefrooij studies, where utilities of the better-seeing eye were used in the calculation of QALYs.[94 95] The two studies considered keratoconus to be a bilateral disease from the start of the model. It is therefore not surprising to observe different utility values for the Salmon study and the two other studies. QALYs are discounted at an annual rate of 3% in the base case model.

It is important to note that utility and transition probabilities values were assumed to be same for paediatric and adult patients, as the paediatric-specific utility values were not available.

7.3.4 Sensitivity Analyses

Uncertainties in the assumptions and inputs in the model were addressed using deterministic and probabilistic sensitivity analyses (PSAs). Deterministic sensitivity analyses were done by varying a range of uncertain inputs separately; procedure costs, health utilities, discount rates, retreatment of CXL procedure, time horizon, initial cohort in health states, keratoplasty rates, progression rates and bilateral rates. The results of these analyses were tabulated and presented as tornado diagrams to identify major drivers in the model. PSAs was considered by simultaneously varying input parameters to address uncertainties. Results were presented in a cost-effectiveness acceptability curve and cost-effectiveness plane to compare against various hypothetical ICER thresholds. Variables subject to DSAs are summarised in ***Table 14***.

Table 14 Variables subject to DSA and PSA

Input category	Variable	Base-case value	Uncertainty range	Distribution
Cost	CXL cost	2,300	± 10%	Gamma α = 100 λ = 0.04
	Cataract surgery cost	4,600	4,443 to 4756	Gamma α = 3.33 λ = 7.24
	Scleral lenses	545	CHF 400 to 500	Gamma α = 100 λ = 0.18
	Cost of keratoplasty	11,165	± 10%	Gamma α = 2.89 λ = 2.58E-04
Effectiveness	Progression rate of the first (worse) eye	1.01%	0% to 2%	Gamma α = 10.74 λ = 10.63
	Progression rate of the subsequent (better) eye	1.01%	0% to 2%	Gamma α = 10.74 λ = 10.63
	CXL efficacy rate	7.6%	0% to 100%	Beta α = 5.85 β = 71.17
	Proportion of patients receive a CXL repeat in 5 years	7.6%	0% to 100%	Beta α = 90.54 β = 12.49
	Keratoplasty rate	1.3%	0% to 2%	
Utility	AK stage 1 utility same as AK stage 2	0.852	0.80	Beta α = 2.12 β = 0.37
	AK stage 2 utility same as AK stage 3	0.80	0.77	Beta α = 1.84 β = 0.46
Others	Discount rate	3%	0% and 6%	
	Cohort entering the model	AK1 = 40% AK2 = 60%	AK1 = 0% to 100%	Beta α = 3.35 β = 5.02
	Time horizon	25 years	100 years	
	Proportion of bilateral cases	0.8787	0 to 1	Beta α = 85.82 β = 11.15

Abbreviations

AK = Amsler-Krumeich classification, **CXL** = corneal collagen crosslinking.

Notes

Keratoplasty cost is for outpatient treatment. Cost for special lenses for cataract surgery is an average of range between CHF 300 and 700. This is same for Scleral lenses (CHF 400 - 500) and initial lenses adjustment cost (CHF 500 – 700).

7.4 Results of the economic evaluation

The economic evaluation results are first presented with a base-case scenario. Input parameters with uncertainties were tested firstly via univariate sensitivity analysis, to investigate their impact and the robustness of the assumptions. Probabilistic sensitivity analyses were also performed to allow uncertain variables to vary simultaneously to derive the likelihood of CXL being cost-effective.

7.4.1 Model base-case results

Base-case results of the model are presented in terms of the ICER. The results of the ICER are outlined in ***Table 15.***

Table 15 Incremental cost-effectiveness ratio of CXL vs No treatment

	Cost (CHF)	Incremental cost (CHF)	Effectiveness (QALYs gained)	Incremental effectiveness	ICER (CHF per QALY gained)
No treatment	19,013.16		15.233		
CXL	27,174.58	8,161.43	15.549	0.316	25,841

Abbreviations
CXL = corneal collagen crosslinking, **ICER** = incremental cost-effectiveness ratio, **QALYs** = quality-adjusted life years.

CXL was estimated to be more costly than no treatment with an incremental cost of CHF 8,161 over the 25-year time horizon. The total costs of no treatment and CXL were estimated to be CHF 19,013 and 27,174 with corresponding QALYs of no treatment and CXL estimated to be 15.233 and 15.549 respectively. This implies that the patient cohort in the CXL arm were expected to gain an additional 0.316 QALYs gained over the 25-year time horizon. The base case ICER comparing CXL to no treatment was estimated to be CHF 25,840 per additional QALY gained, which was less than the hypothetical willingness-to-pay of CHF 100,000 and the 2019 GDP per capita of CHF 78,890.51 (constant 2010 USD).

7.4.2 Deterministic sensitivity analyses

The sensitivity of the results to different model assumptions was explored in univariate deterministic sensitivity analysis. CXL and keratoplasty costs were varied by ±10% and scleral lenses cost was varied between CHF 400 and CHF 500. Discount rates were varied from 0% to 6%, with eye progression annual rates varying from 0 to 2% for the first eye, and 0.2% to 0.5% for the second eye. The proportion of patients with AK stage 1 at the start of the model were varied between 0 and 1 and probability of bilateral disease varied between 0 and 1. CXL treatment efficacy was also tested with CXL assumed to be effective (0 retreated) or not effective (all retreated) over the time horizon. Utility estimates were also varied. Utility for patients with AK stage 1 in the second eye was equated to AK stage 2 in the second eye. Utility for patients with unilateral disease was equated to patients with bilateral disease. Results

are presented as ICER, incremental cost and incremental QALYs in ***Figure 29***, ***Figure 30*** and ***Figure 31*** (DSA).

The ICER estimate was most strongly affected by changes in retreatment of CXL within five years, the proportion of patients in AK stage 1, the proportion of patients with bilateral disease, discount rates and time horizon. A higher retreatment rate for CXL increased the ICER to CHF 78,482/QALY but a lower rate decreases the ICER to CHF 24,270/QALY. This means that the efficacy rate of CXL has a major impact on the result. The ICER increased when patients started from higher stage other than AK stage 1, higher discount rates, and reduction in utility for AK stage 1. Nonetheless, all the ICERs in the univariate sensitivity analyses were cost-effective given they were less than the hypothetical willingness-to-pay threshold of CHF 100,000/QALY and the 2019 GDP per capita for Switzerland.

Costs were mostly influenced by changes in the CXL retreatment rate within five years, the CXL procedure cost, discount rates and the proportion of bilateral cases. The cost of lenses, progression rates and keratoplasty rates did not have any impact on the incremental cost. QALYs, on the other hand, were impacted by the changes in the time horizon, patient proportion in AK stage 1 at the start of the model, discount rates, CXL retreatment within five years, proportion of bilateral cases and utilities. Graft rate and CXL retreatment after five years had no impact on incremental QALYs. Therefore, the non-influential variables were omitted from the tornado diagrams.

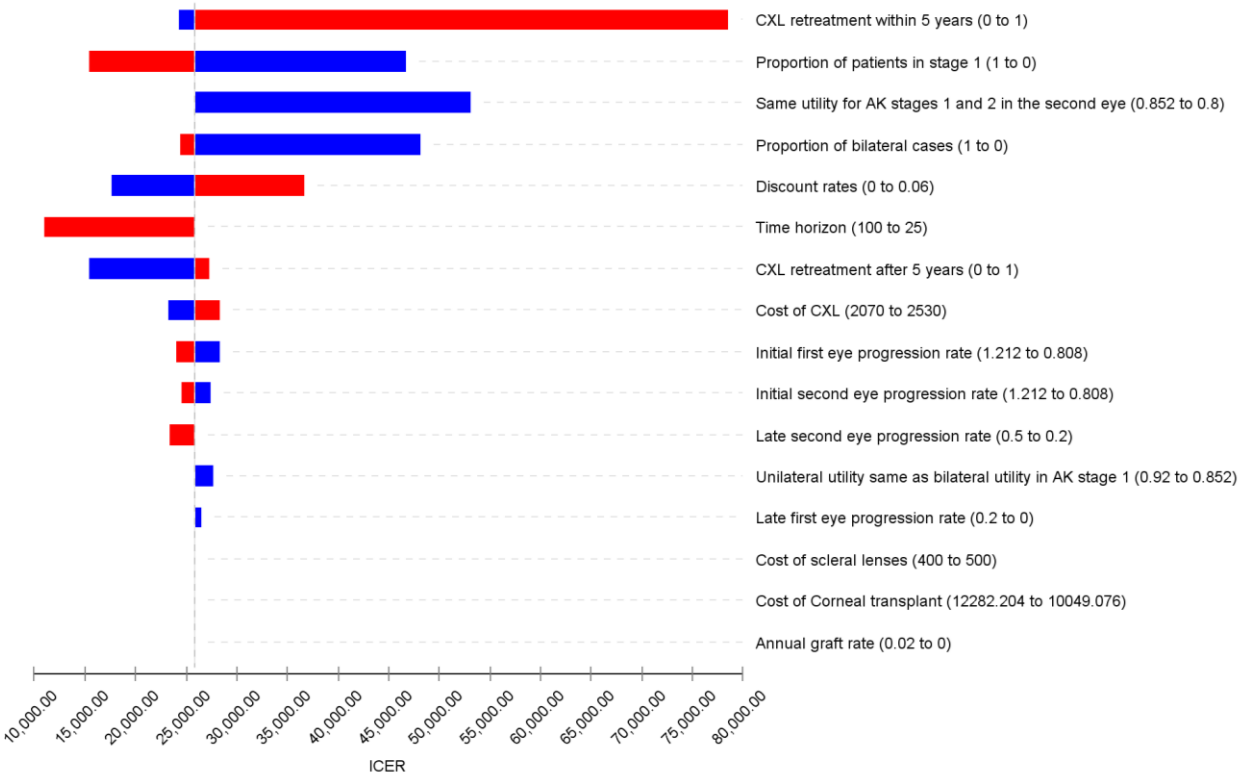

Figure 29 DSA results over parameter uncertainties against ICER

Notes: Right of the base-case ICER (dotted vertical line) indicates an increase, whereas left indicates a decrease in ICER. Red and blue bars indicate higher and lower values of inputs respectively.

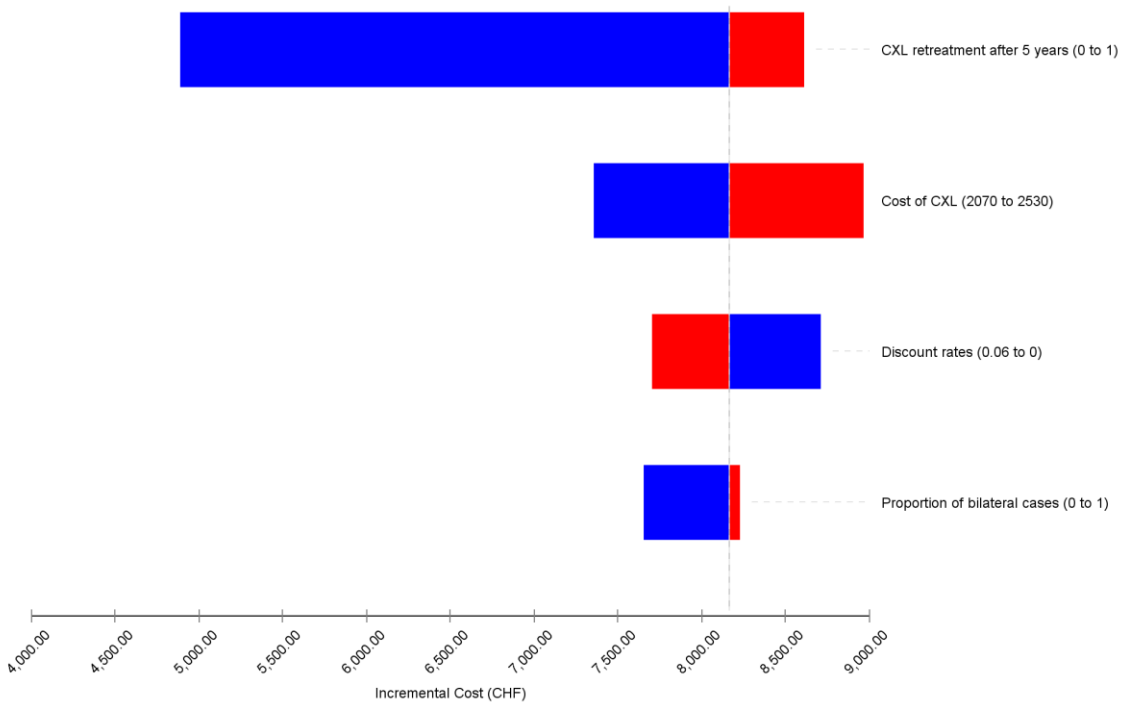

Figure 30 DSA results over parameter uncertainties against incremental costs

Notes: Right of the base-case incremental cost indicates higher incremental cost (more costly CXL), whereas the left indicates lower incremental cost (less costly CXL). Red and blue bars indicate higher and lower values of variables respectively.

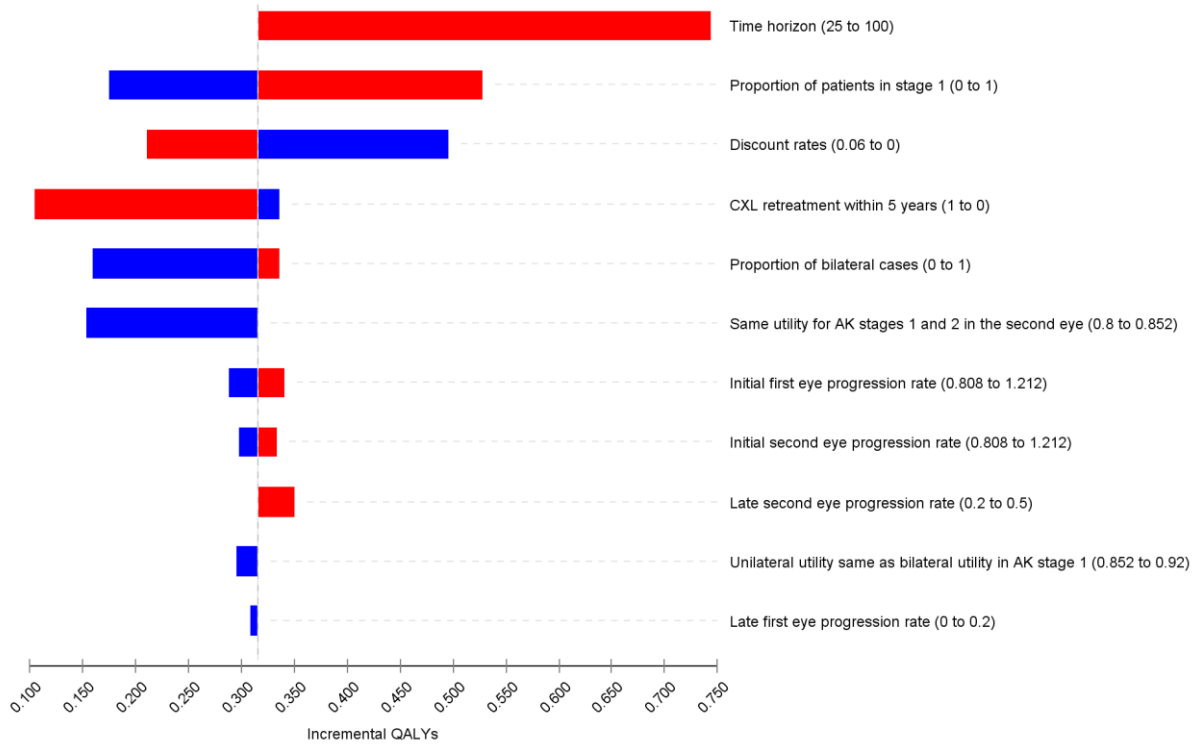

Figure 31 DSA results over parameter uncertainties against incremental utility gain

Notes: Right of the base-case incremental QALY indicates a higher incremental effect (more effective CXL), whereas the left indicates lower incremental effect (less effective CXL). Red and blue bars indicate higher and lower values of variables respectively.

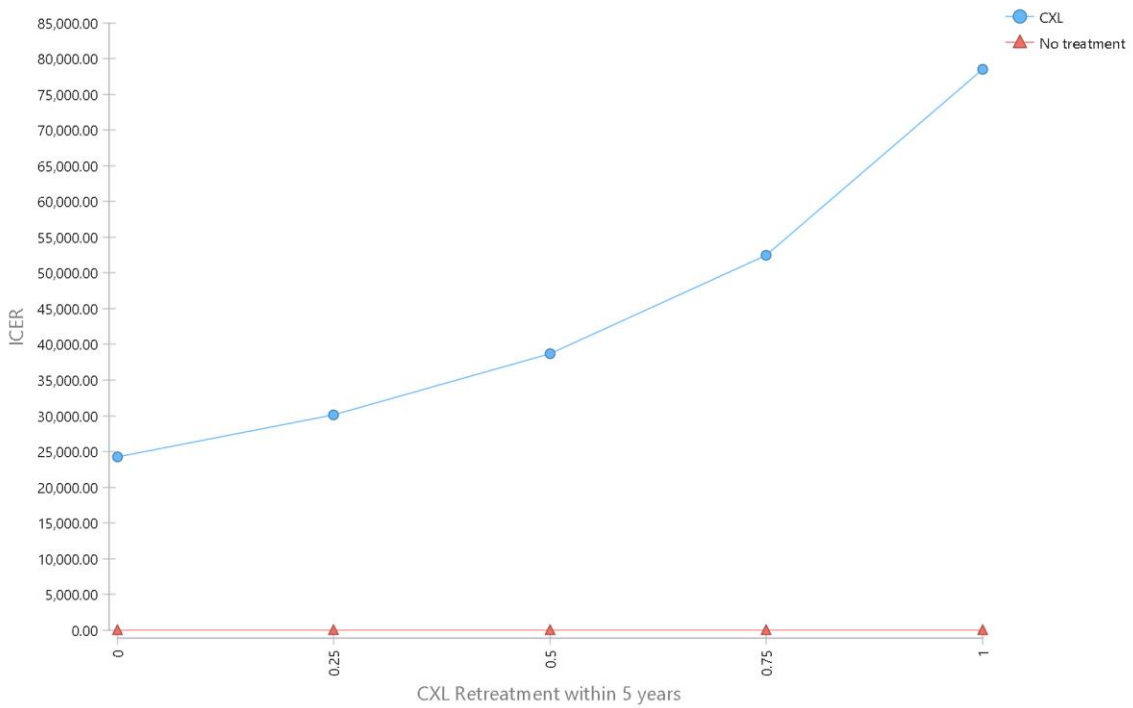

Figure 32 CXL retreatment within 5 years

The retreatment rates within five years had the highest impact on the ICER. Costs and QALYs varied given a change in the variable. A closer look at this variable and corresponding ICER thresholds (***Figure 32***) shows that, beyond a 50% rate of CXL retreatment, the ICER increases steeply.

7.4.3 Two-way sensitivity analyses

Univariate DSA can inform the most impactful variable in the model but may not be sufficient to address scenarios when more than one uncertain variable which could change at the same time. Scenario analyses were conducted to examine the impact of bivariate uncertainties against the base-case ICER. In the univariate case, CXL retreatment within five years (efficacy rate) had the most impact on the model. This input is varied with other inputs to examine their impact to the cost-effectiveness result. Different retreatment rate within five years was tested against eye progression rates, patient proportions and utility values. ICERs significantly different from the base case and hypothetical WTP thresholds were presented for different scenarios of the inputs in ***Table 16***. ICER values were highlighted in dark grey if they were over the hypothetical CHF 100,000 threshold.

In a scenario where most patients start the model with severe disease stage (i.e. 0% patients starting at AK stage 1), the ICER increases in all scenarios compared to the base-case result (Panel A). This is expected given that patients enter the model at a severe disease stage would accumulate higher costs. In contrast, when all patients start at a less severe disease (i.e. all 100% patients starting at AK stage 1), the ICER is reduced. The worst-case scenario occurs when assuming all patients starting from a

more severe disease with a 75% probability of CXL retreatment within five years. In a scenario of high CXL retreatment and low progression rates in the first eye (Panel C), the ICER is higher than the base case. However, the best-case scenario is when there is no retreatment of the eye, even with a 2% progression rate in the first eye. The ICER will be higher than the base case in a scenario where utility for AK stage 1 patients is low and retreatment is done for all patients (Panel B). Additionally, the ICER will be high in a low AK stage 1 utility value and no progression in the first eye (Panel D).In other inputs, the best scenario is when no patient has a CXL retreatment within five years should all patient start the model with a bilateral disease (ICER = 22,970), and worst scenario will be when all patients are retreated even with unilateral disease (ICER = 101,269). Across all the results of the two-way sensitivity analysis, over 80% of the results produced the ICER values lower than the hypothetical threshold of CHF 100,000. Therefore, the two-way sensitivity analyses demonstrated that CXL is still likely to be cost-effective. On the other hand, some of the results in the worst-case scenarios also produced ICER values greater than that hypothetical CHF 100,000 threshold.

Table 16 Two-way sensitivity analyses (CHF)

Panel A		Proportion in AK stage 1				
		0	0.25	0.5	0.75	1
CXL retreatment within 5 years	0	42,528	28,926	21,918	17,645	14,767
	0.25	59,401	36,942	26,809	21,040	17,315
	0.5	92,079	49,424	33,780	25,660	20,688
	0.75	**183,553**	71,665	44,527	32,299	25,341
Panel B		AK stage 1 utility same as AK stage 2				
		0.8	0.813	0.826	0.839	0.852
CXL retreatment within 5 years	0	50,871	39,930	32,862	27,920	24,270
	0.25	59,365	47,765	39,958	34,344	30,113
	0.5	72,313	59,399	50,398	43,766	38,677
	0.75	93,605	78,269	67,250	58,951	52,475
Panel C		First eye progression rate (%)				
		0	0.5	1	1.5	2
CXL retreatment within 5 years	0	61,053	32,388	24,370	20,735	18,738
	0.25	85,988	40,891	30,240	25,750	23,443
	0.5	**135,896**	53,999	38,848	32,947	30,104
	0.75	**285,668**	76,928	52,732	44,181	40,308
Panel D		First eye progression rate (%)				
		0	0.5	1	1.5	2
AK stage 1 utility same as AK stage 2	0.8	**362,299**	76,891	53,344	45,834	42,909
	0.813	**172,707**	58,924	42,204	36,128	33,369
	0.826	**113,377**	47,763	34,913	29,814	27,299
	0.839	84,387	40,157	29,770	25,378	23,097
	0.852	67,203	34,640	25,948	22,092	20,017

Note: All ICER values are in Swiss Francs (CHF)

7.4.4 Probabilistic sensitivity analyses

Inputs were specified as distributions (described in ***Table 14***) for CXL and no treatment. The results of 10,000 iterations for the PSA is plotted in the cost-effectiveness plane demonstrated in ***Figure 33.*** Using a hypothetical willingness-to-pay (WTP) threshold of CHF 100,000/QALY, each iteration has been plotted against WTP threshold where results below the threshold are plotted in green and results above are in red. There was a 99.4% probability that CXL is cost-effective when compared to no treatment. The cost-effectiveness acceptability curve (***Figure 34***) shows CXL to be cost-effective beyond a WTP threshold of CHF 30,000, which is 2 times less the 2019 GDP per capita of 78,890 (constant 2010 USD).[127] When compared to the willingness-to-pay thresholds of CHF 38,000 (GBP 30,000) in the UK, there is 90.5% probability that CXL is cost effective relative to no treatment.[128]

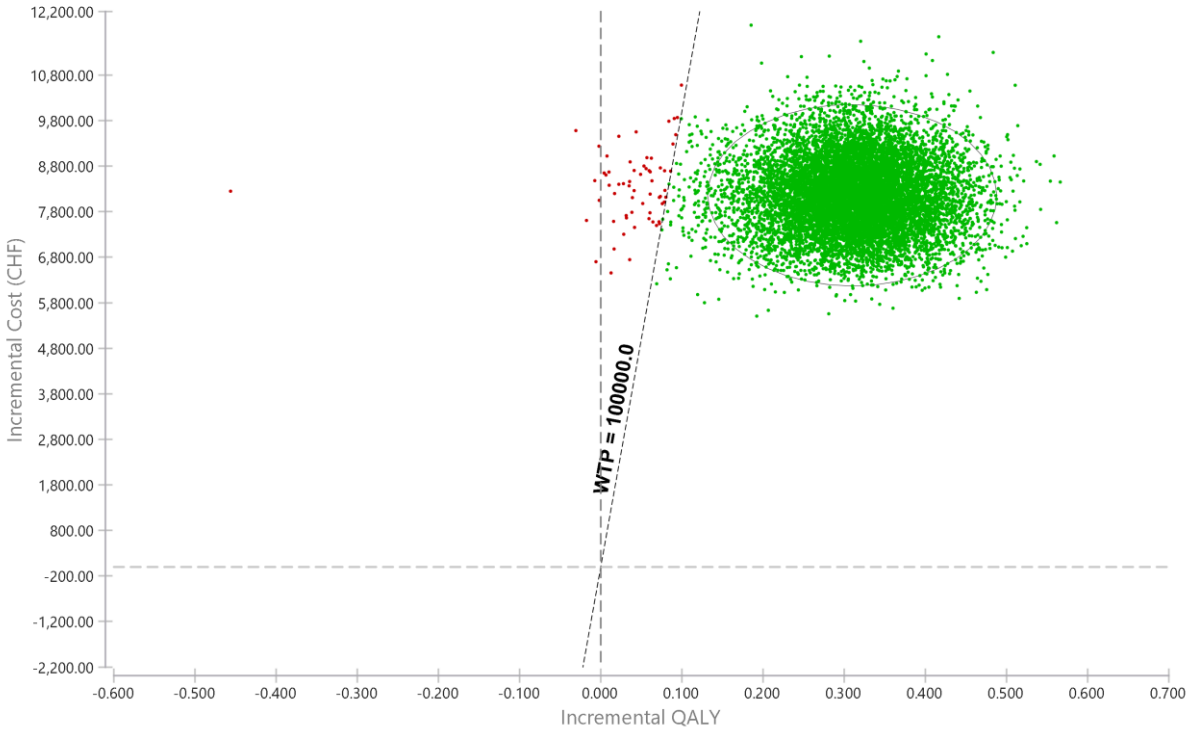

Figure 33 Cost-effectiveness scatter plot of CXL and no treatment

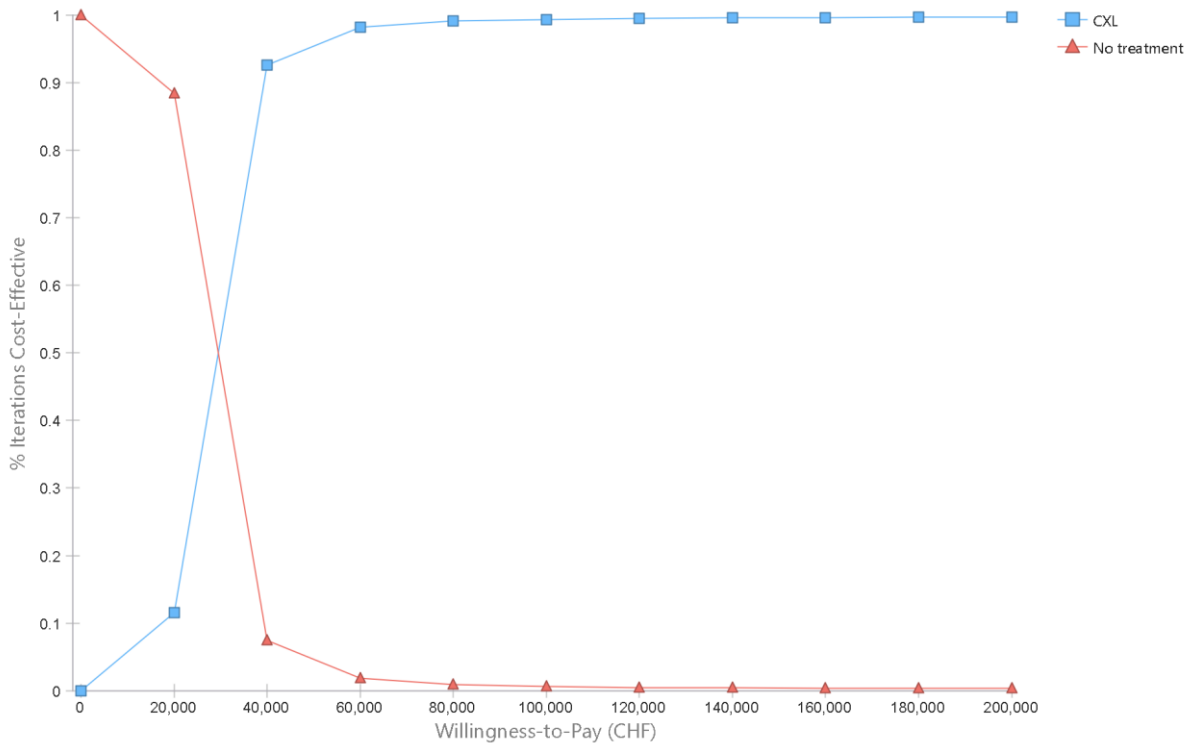

Figure 34 Cost-effectiveness acceptability curve

7.5 Budget impact analysis

The financial implications of allowing insurance reimbursement to cover CXL for keratoconus was examined using budget impact analysis from the payer perspective. An epidemiological approach was used as the primary method to estimate the number of patients. As no treatment was the comparator, the cost of CXL was the sole source of financial burden to be reimbursed by insurance.

7.5.1 Patient population estimates

The direct size of the population of keratoconus patients in Switzerland is unavailable because the occurrence of the disease has not been surveyed by any registries in the country. Therefore, prevalence and incidence of keratoconus in the Swiss population were estimated using epidemiological data from other jurisdictions. A range of values were examined to best estimate the size of the keratoconus population and the size of the patient cohort who would receive CXL.

Estimating the patient population size starts from the projection of the general population in Switzerland. Using the population trajectory from the past five years, the quadratic trend produced a growing population from over 8.7 million in 2021 to approximately 8.9 million in 2025 (***Figure 35***).

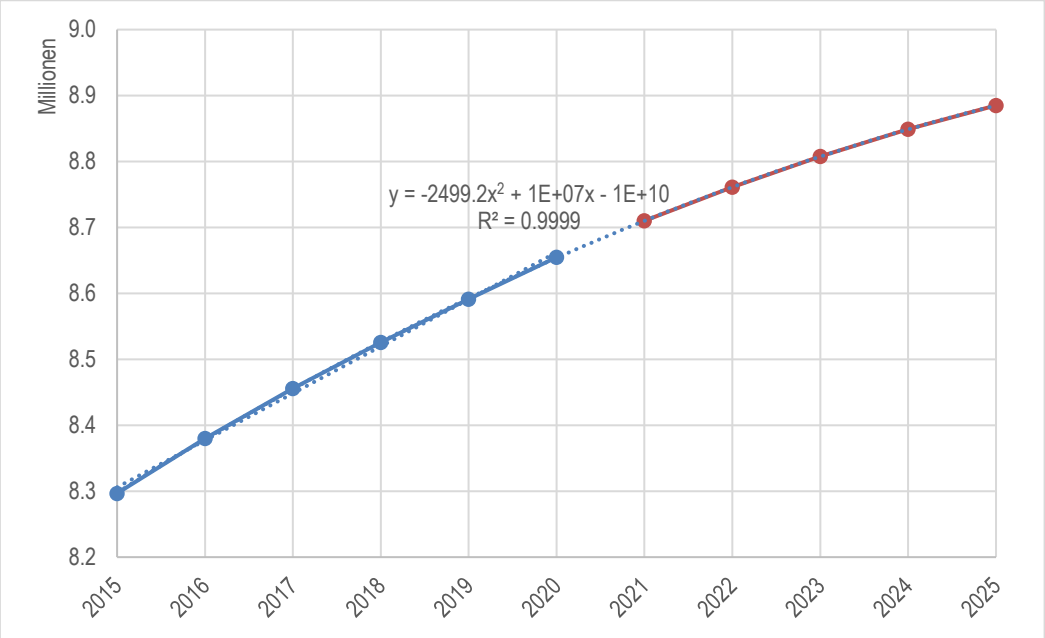

Figure 35 Population size trajectory from 2021 to 2025

Searches in both peer-reviewed databases and grey literature were conducted to identify epidemiological studies to estimate number of patients with keratoconus. The targeted search showed that the prevalence and the incidence of keratoconus vary significantly, with different countries at different times reporting highly variable results. The prevalence of the disease ranged from over 200 per 100,000[129] to fewer than 10 per 100,000.[130] One Swiss clinic reported that the prevalence of keratoconus in the country is approximately 1 in every 2000 patients.[19] This data was not verified but is in line with the European general prevalence in general such as in Finland[131] or Denmark,[17] hence it was used in the base-case estimate. The disease prevalence data ranked from the highest to the lowest sourced from published articles are tabulated below in ***Table 17***.

As CXL does not require ongoing treatment, eligible individuals will receive the procedure only once. Effectiveness persists for a relatively long period until a repeat procedure is required due to lapse of the effects. The time horizon of the lapsed effects is much greater than five years, which was beyond the consideration of the current budgetary analysis. As a result, newly diagnosed patients would be potentially eligible for CXL and the procedure cost only needs to be considered once over the five-year projection.

In contrast to the prevalence estimates, the incidence data was relatively consistent across different countries. A range of different incidence rates were identified as shown in ***Table 17.*** The Denmark data was used in the base-case calculation.

Table 17 Prevalence and incidence of keratoconus across different countries and time

Prevalence estimate per 100,000	Incidence estimate per 100,000	Country and time of article published
267	Not reported	Israel, 2011[129]
55	2	The US, 1986[132]
50	Not reported	Switzerland, 2020†
44	3.6	Denmark, 2019[17]
30	1.5	Finland, 1986[131]
9	Not reported	Japan, 1985[133]
7	2	Macedonia, 2009[130]

Notes
† = this estimate was provided by the Swiss clinic, the Institute for Refractive and Ophthalmic Surgery, and the data was not referenced.

Although both incidence and prevalence data were sourced to estimate the number of keratoconus patients who could potentially receive CXL, only the incidence data was used to estimate the financial implication of CXL as the base-case. This decision was based on two major factors: 1) among keratoconus patients considered by the prevalence calculation it was unclear how many have already received CXL treatment, and who therefore would not need the procedure to be paid by mandatory health insurance. Feedback from a clinician (Prof Claude Kaufmann, personal communication on 2 November) indicated that clinics were not expecting a significant uptake of CXL due to insurance reimbursement becoming available[3]. This indicated that a substantial proportion of keratoconus patients would have received CXL paid for out-of-pocket; 2) prevalence estimates would include patients at all stages of the disease, even though a proportion of patients would be ineligible for CXL due to old age, advanced progression or other contraindications, or by personal choice. Therefore, the use of prevalence data to project keratoconus patient numbers and derive cost impact was considered unreliable. The prevalence information was used in sensitivity analyses to test the boundaries of the financial implications. This is discussed in detail in ***Section 7.5.5***.

The incidence estimates encompass all patients at various disease stages at diagnosis, which means not all patients would receive CXL due to the keratoconus diagnosis. There has been no reliable estimate to derive the actual number of eligible patients who could receive CXL. Therefore, assumptions were made to test various proportions of patient incidence as CXL recipients. The base-case assumption was 50% with a high and low proportion tested via sensitivity analyses.

[3] Many patients would already have had the treatment and paid out of pocket.

The estimate must also consider the possibility of bilateral disease status. One study (published in 1986) reported that unilateral keratoconus occurred in 41% of patients and bilateral disease in 59% of patients at the time of the diagnosis.[132] Therefore, eligible patient numbers were multiplied by a coefficient of 1.59 (assuming 59% of patients receiving CXL in both eyes) to compute the number of CXL procedures occurring each year. The base-case estimates were calculated and are presented in ***Table 18***. More detailed calculation procedures are available in the Excel sheet.

Table 18 Patient number estimates for keratoconus

Year	2021	2022	2023	2024	2025	Calculation	Reference
Switzerland population	8,710,028	8,761,274	8,807,521	8,848,770	8,885,020	A	Swiss Federal Office of Statistics
Keratoconus incidence	314	315	317	319	320	B = A × 0.0036%	Denmark data[17]
Patients treated	157	158	159	159	160	C = B × 50%	assumption
Number of eyes treated	249	251	252	253	254	D = C × 1.59	study by Kennedy and Dyer[132]

7.5.2 Costs of CXL

Since the CXL procedure has not been reimbursed by health insurance in Switzerland, a universal cost position for CXL is not yet available. The cost of CXL was provided by one clinic at CHF 2,300.[19] This cost was confirmed by four additional clinics that were contacted by the FOPH (personal communication with FOPH, 9th October 2020). This was a flat fee to treat one eye for one patient including all possible costs of follow-up clinical visits and medication use. Adverse events would incur an additional cost, but the associated event rates are relatively low with relatively low-cost treatment involved. Furthermore, the rate estimates of those events are subject to great uncertainties, as was reported in ***Section 7***, so inclusion of those costs may not be informative. Thus, the figure of CHF 2,300 was used as the single cost input to calculate the budgetary impact of CXL. The result of the calculation is presented in ***Table 19***. As CXL costs may vary in real clinical settings, this estimate was subject to sensitivity analyses with 10% variations up and down (see ***Section 7.5.5***).

Table 19 Financial implication of CXL public reimbursement

Year	2021	2022	2023	2024	2025	Calculation	Reference
Number of eyes treated	249	251	252	253	254	A	row D of ***Table 18***
Cost of CXL	**CHF 573,346**	**CHF 576,720**	**CHF 579,764**	**CHF 582,479**	**CHF 584,865**	B = A × 2,300	calculated

Abbreviations
CXL = corneal collagen crosslinking, **CHF** = Swiss Franc

The base-case estimate shows that CXL reimbursement will cost slightly above CHF 573,000 in the first year (2021) and increase to approximately CHF 585,000 in the fifth year. The increase is entirely driven by background population growth.

7.5.3 Costs of keratoplasty

In this budget impact analysis, the cost of keratoplasty was not considered relevant, and therefore was not incorporated into the calculation. Keratoplasty is performed only when keratoconus patients are in the advanced stage of disease when all other options have been exhausted. In theory, patients will eventually progress to the advanced stage and keratoplasty would be performed regardless of CXL treatment. Under this scenario, CXL would not fundamentally impact the use or cost of keratoplasty, but only delay the timing of such costs occurring. Furthermore, since these budgetary estimates are short-term (five years; 2021–2025) and the immediate benefits brought by CXL regarding keratoplasty delay or avoidance are long-term (10 years or more), the financial benefits of delaying keratoplasty would not be immediately observable. Therefore, significant fluctuations in keratoplasty surgery numbers and associated costs are not expected. Patients considering keratoplasty within the horizon of the 5-year budgetary projection would be unlikely to cancel or avoid the surgery, and procedures scheduled in the next five years are unlikely to be impacted by CXL treatment.

7.5.4 Overall budget impact for CXL reimbursement

The overall financial impact to the Swiss health system of providing reimbursement for CXL was solely driven by the number of patients (or eyes) to be treated with CXL plus the CXL treatment cost (see ***Section 7.5.2***, ***Table 19***, above for further detail).

7.5.5 Sensitivity analyses

A range of sensitivity analyses were undertaken to test how different assumptions could impact the financial estimates of CXL reimbursement. The assumptions tested and the results appear in ***Table 20***.

Table 20 Sensitivity analysis over different uncertain variables

Tested variable	Assumptions of values varied	2021	2022	2023	2024	2025
Base-case estimate		CHF 573,346	CHF 576,720	CHF 579,764	CHF 582,479	CHF 584,865
CXL load (base case = 50%)	High = 70%	CHF 802,685	CHF 807,407	CHF 811,669	CHF 815,471	CHF 818,811
	Low = 25%	**CHF 286,673**	CHF 288,360	CHF 289,882	CHF 291,240	CHF 292,433
Include Prevalence	Low = 15%	CHF 1,767,818	CHF 1,173,955	CHF 1,177,000	CHF 582,479	CHF 584,865
	Medium = 25%	CHF 2,564,132	CHF 1,572,113	CHF 1,575,157	CHF 582,479	CHF 584,865
	High = 50%	**CHF 4,554,918**	CHF 2,567,505	CHF 2,570,550	CHF 582,479	CHF 584,865
	Medium 1st uptake	CHF 1,568,739	CHF 2,069,809	CHF 2,072,853	CHF 582,479	CHF 584,865
Bilateral progression (BC = 1.59)	High coefficient = 1.71	CHF 615,897	CHF 619,520	CHF 622,790	CHF 625,707	CHF 628,270
	Low coefficient = 1.47	CHF 530,796	CHF 533,919	CHF 536,737	CHF 539,251	CHF 541,460
CXL cost (base case = CHF 2,300)	10% up = CHF 2,530	CHF 630,681	CHF 634,392	CHF 637,740	CHF 640,727	CHF 643,352
	10% down = CHF 2,070	CHF 516,012	CHF 519,048	CHF 521,787	CHF 524,231	CHF 526,379

Abbreviations
CXL = corneal collagen crosslinking, **CHF** = Swiss franc
Notes
Highlighted figures indicate total lowest and highest financial impacts from budget projections using varying modelling inputs

While the Excel sheet provides more options to allow multiple variables to vary simultaneously, a selection of sensitivity analyses is presented here, most of them being one-way. It should be noted that incorporation of the prevalence data required additional assumptions besides the rate itself, that is:

- Prevalence data was only used in the first year (2021) and the rest of the estimates from 2022 onwards were based on incidence data.
- The financial model assumes that not *all* existing patients diagnosed with keratoconus will receive CXL. The basic scenario of CXL uptake for existing patients was assumed at a medium level of 25%. Higher (50%) and lower (15%) eligibility levels were also explored.
- The procedure load was assumed to be spread over a 3-year period, with a basic scenario of 50% of existing keratoconus patients receiving CXL in the first year (2021), and the remaining patients having CXL over the following 2 years (25% in 2022 and 25% in 2023). This assumption was also varied during the sensitivity analysis to a medium first-year uptake of 25% and 37.5% of existing keratoconus patients receiving CXL in 2022 and 37.5% in 2023.

Varying these inputs could significantly change the budget projection. In the first year, the total financial impact can be as low as CHF 287,000 or as high as CHF 4.5 million or more (15-fold difference). These significant variabilities were primarily driven by uncertain estimates of the potential volume of patients and CXL procedures. In the absence of more accurate estimates, the financial implication of providing reimbursement for CXL remains uncertain.

8 Legal, social and ethical issues

8.1 Summary statement legal, social and ethical issues

No information was identified relating to potential legal issues associated with reimbursing CXL.

Patients generally held positive perceptions of CXL and contact lenses. Patients believed crosslinking stopped or slowed the progression of keratoconus, however, patients also noted their vision had not improved or had worsened following the procedure.

Children represent an at-risk group because they often present with a more advanced stage of keratoconus and are often non-compliant with conservative treatments.

8.2 Methods

Literature identified from systematic and non-systematic searches was used to address legal, social and ethical issues. The search terms used for the systematic search are outlined in ***Appendix A***, ***Section 14.1***, ***Table 29*** to ***Table 31***. The non-systematic search involved targeted searches of Google and PubMed using the following terms: access, autonomy, benefits, burden, keratoconus, crosslinking, harm, satisfaction and perception. The non-systematic searches were conducted by a single reviewer who identified an additional six studies. A PRISMA chart is not provided owing to the use of systematic and non-systematic searches. Results of the literature searches were summarised using narrative synthesis.

8.3 Evidence table

There were no studies evaluating legal issues. Thirteen studies were included in the assessment of social and ethical issues (***Table 21***). These studies consisted of primary (k = 8) and secondary (k = 5) research. The primary research studies were mostly survey studies evaluating patient perception and satisfaction with CXL or contact lenses (k = 8) and quality of life (k = 5) of patients with keratoconus. The studies were performed in the North America (k = 3) or Europe (k = 5). Secondary research studies were literature reviews exploring keratoconus or the use of CXL in children.

Table 21 Characteristics of included studies for social and ethical issues

Study; country	Indication; sample size	Design; follow-up; setting	Interview/survey topics
Bergmanson 2016[134] USA	Patients with keratoconus using scleral contact lenses n = 284	Prospective case series NR University eye institute	Patient satisfaction of contact lenses
Buzzonetti 2020[135] Italy	NA	Literature review	CXL use in vulnerable patient groups
Jordan-Jones 2010[136] USA	NA	Literature review	CXL use in vulnerable patient groups
Aydin Kurna 2014[53] Turkey	Patients with keratoconus or health controls n = 60	Survey NR Fatih Sultan Mehmet Education and Research Hospital	Patients with keratoconus quality of life
Kymes 2008[137] USA	Patients with keratoconus n = 1,166	Survey 7 years NR	Patients with keratoconus quality of life
Moschos 2018[138] Greece	Patients with keratoconus n = 56	Survey NR University hospital	Patients with keratoconus quality of life
Mukhtar 2018[40] USA	NA	Literature review	CXL use in vulnerable patient groups
Olivo-Payne 2019[41] Mexico	NA	Literature review	CXL use in vulnerable patient groups
Panthier 2020[139] France	Patients with keratoconus n = 101	Survey NR Hôtel-Dieu Hospital	Patients with keratoconus quality of life
Price 2018[140] USA	Patients treated with Dresden protocol or accelerated epithelium-off CXL n = 448	Prospective case series Median 3.5 years Electronic survey	Patient perception and satisfaction of CXL
Shorter 2020[141] USA	Patients with keratoconus using contact lenses n = 422	Prospective case series NR National Keratoconus Foundation	Patient satisfaction
Saunier 2017[142] France	Patients with keratoconus n = 550	Survey NR Private and public practice	Patients with keratoconus quality of life
Woodhouse 2018[143] UK	NA	Literature review	Patients with keratoconus quality of life

Abbreviations
CXL = corneal collagen crosslinking, **n** = number of patients, **NA** = not applicable, **NR** = not reported, **UK** = United Kingdom, **USA** = United States of America.

8.4 Legal results

No legal issues were identified from systematic and non-systematic searches.

8.5 Social results

8.5.1 Patient perception and satisfaction

There was limited information regarding patient perception of CXL. In one study, 83% of patients believed CXL halted progression of keratoconus; however, patients subsequently reported that their vision had not improved or had worsened. Patients who were younger, male and had mild keratoconus were more likely to perceive the treatment as efficacious compared to those who were older, female and had severe keratoconus. There was no difference in perceived effectiveness between patients who had undergone standard or accelerated CXL. Most patients were broadly satisfied with CXL and would recommend the procedure to a friend with a similar eye condition.[140]

When considering keratoconus treatments more broadly, adult patients were more satisfied with scleral contact lenses than gas-permeable lenses.[134 141] This was due to a reduction in visual symptoms (halos and sunbursts) and reduced movement of the lens – collectively improving vision and comfort. There was no difference in the average cost or difficulty in applying or removing contact lenses.[141] Similar findings were observed in children, with scleral contact lenses causing less itching, tearing, and light sensitivity compared to gas-permeable lenses. In contrast to adults; however, visual acuity improved following gas-permeable lenses.[136]

8.5.2 Vulnerable patient groups

There was limited literature addressing the use of CXL in vulnerable patient groups; therefore, the results were expanded to include all keratoconus patients. Children with keratoconus are more likely to present with an advanced stage of the disease and exhibit faster progression compared to adults, suggesting they are a vulnerable patient group.[40 41]

The management of keratoconus in children is complex. Conservative approaches such as contact lenses or glasses are often poorly tolerated in children, they do not confer sufficient visual acuity and do not prevent progression of the disease. Further, non-compliance concerns and constant eye-rubbing limits the utilisation of other interventions such as intracorneal ring segments.[41] Thus, paediatric patients require more invasive treatments to successfully manage the condition. However, while paediatric patients may require more invasive treatments, there is limited randomised evidence for CXL in children. Given that the pathogenesis of keratoconus differs slightly in children compared to adults, it is important to highlight to parents/caregivers that the clinical efficacy of CXL may differ because existing RCTs were

performed in adults.[41] In spite of the lack of RCT evidence, it may be appropriate nevertheless to consider collagen treatment at an early stage in children owing to the faster disease progression and limited clinical efficacy with conservative treatments.[135]

8.6 Ethical results

8.6.1 Burden of disease

Keratoconus is a progressive disease leading to significant visual impairment. It is generally diagnosed in young adults, although onset may occur during childhood. As previously mentioned, keratoconus results in increased blurring, myopia, light sensitivity, halos and ghosting around light sources. As disease progresses, visual distortion worsens; however, it is unlikely patients will become blind.

Owing to the early onset of the disease, the impact on quality of life can be substantial.[137] Patients report difficulties across all life stages. For example, patients with keratoconus reported problems during schooling years[142] due to difficulties with reading.[143] During adulthood, patients with keratoconus reported feeling confined to their job and noted adjustments had been made to their position to facilitate ongoing employment. Some patients with keratoconus also reported the need for caregivers to perform daily tasks.[142] As the disease progresses and individuals become more visually impaired, there is a greater loss of independence and reliance on caregivers, and consequently quality of life is further reduced.[139]

Keratoconus impairs other dimensions of an individual's life, for example, patients reported lower general health, more ocular pain and mental health problems, and reduced near and peripheral vision, which hampers driving ability.[53] Importantly, depressive disorders and anxiety are directly associated with keratoconus, further impeding quality of life.[138]

8.6.2 Perceived benefits and harms of CXL

Avoidance or minimisation of harm is a key ethical concern when considering an intervention. In this context, harm included adverse physical and psychological consequences of CXL.

Non-maleficence: a norm of avoiding causation of harm

It is unclear whether CXL had an equivalent or inferior safety profile to sham as the studies were not powered for safety and statistical comparisons were not reported (***see Section 7***). There was an increased incidence of keratitis, haze, epithelial defects and corneal striae following CXL compared to sham or no treatment. When reported, adverse events were generally mild. However, the adverse events long-term impact was less certain, with studies reporting an improvement or no change to UCVA following the event.

When considering CXL variants, the incidence of adverse events was generally similar between accelerated and standard CXL procedures (see ***Section 6.5.4***). However, there were fewer intraoperative (e.g. discomfort and pain) and postoperative complications following transepithelial CXL compared to standard CXL. This reduction in adverse events probably relates to differences between the procedures—during standard CXL, corneal epithelial cells are removed, likely increasing discomfort. Again, for analyses involving accelerated and transepithelial CXL compared to standard CXL, the statistical difference was infrequently reported, so it is unclear whether the groups differed.

Beneficence: a group of norms for providing benefits and balancing benefits against risks and costs

The goal of CXL is to prevent progression of keratoconus and preserve an individual's sight.[23] The results from ***Section 6.4.3*** indicate CXL improved some markers of visual acuity and keratoconus progression (UCVA and K_{max}, respectively); however, there were limited to no differences for the remaining topography, pachymetry or refractive error outcomes. No studies evaluated quality of life or corneal transplant rates. Therefore, the extent to which CXL improves vision and quality of life relative to sham and no treatment is uncertain and, consequently, the risk/benefit of CXL is also uncertain.

For CXL variants, there was limited information to determine whether accelerated and transepithelial CXL improved visual acuity and markers of keratoconus progression relative to standard CXL (see ***Section 6.5.3***). Given the safety profile of accelerated CXL was broadly similar to standard CXL, the risk/benefit of the procedures is likely similar. However, patients undergoing transepithelial CXL reported fewer intraoperative and postoperative complications compared to standard CXL, suggesting the risk/benefit likely favours transepithelial CXL.

9 Organisational issues

9.1 Summary statement organisational issues

There was limited literature addressing organisational issues associated with CXL. In Norway[13] and the Netherlands,[144] the implementation of collagen crosslinking reduced the number of patients undergoing corneal transplantations over a 1- to 2-year period. In Canada however, there was no change in the number of patients undergoing corneal transplants at 8 years post-implementation.[116]

Use of resources such as glasses or contact lenses is unlikely to change following CXL.

CXL reduced subjective measures of dependency, suggesting caregiver burden may be alleviated following the procedure in patients with less severe keratoconus. There was no difference in dependency in more severe patients.

9.2 Methods

Literature identified from systematic and non-systematic searches was used to address organisational issues. The search terms used for the systematic search are outlined in in ***Appendix A***, ***Section 14.1***, ***Table 32***. The non-systematic search involved targeted searches of Google and PubMed using the following terms: keratoconus, corneal transplant, keratoplasty, crosslinking, resource, trends in treatment and utilisation. The non-systematic searches were conducted by a single reviewer who identified two additional studies. A PRISMA chart was not provided owing to the use of systematic and non-systematic searches. Results of the literature searches were summarised using narrative synthesis.

9.3 Evidence table

Eight studies evaluating organisational issues associated with CXL were identified (***Table 22***).[13 52 116 144-149] The studies consisted of prospective (k = 4) and retrospective research (k = 4).

Prospective studies were performed in India, Greece and Turkey, and consequently their applicability to the Swiss context is uncertain. Two prospective studies evaluated use of contact lenses in patients with keratoconus following crosslinking over a 6- and 12-month period. Two studies evaluated patient quality of life 6 and 36 months post-CXL. The sample size of prospective studies ranged from 14 to 63 patients.

The retrospective research evaluated medical databases from Canada, Germany, the Netherlands and Norway, analysing trends in corneal transplantation following implementation of crosslinking. These studies are more applicable to the Swiss context than is the prospective research, owing to perceived

similarities in population demographics and healthcare systems. The duration of follow-up ranged from 2 years (over two study periods) to 18 years. The number of procedures ranged from 386 to 31,943.

Table 22 Characteristics of included studies for organisational issues

Study; country	Indication; sample size	Design; follow-up; setting	Interview/survey topics
Cingu 2015[52] Turkey	Patients undergoing CXL n = 33	Prospective case series 12 months University hospital	Quality of life post-CXL
Godefrooij 2016[144] The Netherlands	Patients undergoing corneal transplantation or CXL n = 851	Retrospective registry 2005–2007, 2012–2014 Dutch National Organ Transplant Registry	Use of CXL and corneal transplants over time
Labiris 2012/2013[145 146] Greece	Patients undergoing CXL or CXL with photorefractive keratectomy n = 63	Prospective non-randomised 36 months Eye Institute of Thrace	Quality of life post-CXL
Sandvik 2015[13] Norway	Patients undergoing corneal transplantation or CXL n = 386	Retrospective registry 2005–2006, 2013–2014 Oslo University Hospital	Use of CXL and corneal transplants over time
Singh 2018[148] India	Patients with keratoconus n = 14	Prospective case series 6 months Guru Nanak Eye Centre	Resource use following CXL
Sklar 2019[116] Canada	Patients undergoing corneal transplantation or CXL n = 31,943 grafts	Retrospective registry 1998–2016 Eye Bank of Canada	Use of CXL and corneal transplants over time
Röck 2018[147] Germany	Patients undergoing corneal transplantation n = 1,185	Retrospective registry 2004–2015 University hospital	Use of corneal transplants over time
Ünlü 2017[149] Turkey	Patients with keratoconus unable to tolerate lenses n = 30	Prospective case series 6 months University hospital	Resource use following CXL

Abbreviations
CXL = corneal collagen crosslinking, **n** = number of patients/corneal transplants.

9.4 Organisational results

9.4.1 Resource utilisation and CXL

Since the introduction of CXL, the number of patients undergoing corneal transplantation for keratoconus decreased by 25% in the Netherlands[144] and by 28.8% in Norway.[13] The demographics of patients who received corneal transplants was mostly similar pre- and post-implementation. However, patients had more severe keratoconus, suggesting corneal transplants were being performed in patients who were refractory to crosslinking.[13]

Likewise, in Germany from 2004 to 2015, the number of patients undergoing keratoplasty for keratoconus decreased, although it was unclear whether this was solely attributable to increased uptake of CXL.[147]

In Canada, the proportion of keratoconus patients undergoing corneal transplants decreased from 2008 (CXL introduction) to 2016; however, the absolute number of transplants was unchanged. The authors postulated the discrepancy was attributable to the increase in population size, funding for transplants, number of surgeons performing the procedure and a shift to performing endothelial keratoplasties. Further, the increased efficacy of contact lenses and the absence of long-term data for CXL may have underscored the lack of change in the total number of corneal transplants.[116]

In one study, stage I keratoconus patients who underwent CXL with topography-guided photorefractive keratectomy reported improvements in the dependency, role limitations and driving domains of the National Eye Institute Visual Function Questionnaire (NCI-VFQ). Similarly, patients who underwent CXL without keratectomy reported improvements in the dependency and mental health domains suggesting both procedures may decrease caregiver burden owing to reduced levels of dependency.[145] [146] However, for more severe patients, one study reported no improvement in dependency and driving domains of the NCI-VFQ.[52]

CXL does not reverse keratoconus, thus patients will still require contact lenses or glasses to correct for vision impairments, suggesting the need for these resources will not change post-procedure. Further, crosslinking may increase contact lens use because patients report improved fit and less lens intolerance following the procedure.[148] [149]

10 Additional issues

Clinical practice position statements and guidelines

No position statements on the use of CXL were identified. A preferred practice pattern guideline on corneal ectasia by the American Academy of Ophthalmologists reported the following in their highlighted findings and recommendations for care: “Corneal crosslinking (CXL) reduces the risk of progressive ectasia in patients with keratoconus (particularly in its early stages) and stabilizes the cornea. It also stabilizes cases of corneal ectasia occurring after keratorefractive surgery.[150]

Developmental trends

The evidence used to assess clinical efficacy of CXL for keratoconus compared with sham or no treatment in this report used the standard protocol, also referred to as the Dresden protocol, which includes UVA at 3 mW/cm^2 of energy for 30 minutes. Several variations to this protocol have been developed and are being assessed in clinical trials. The two with the largest evidence bases—accelerated and transepithelial—were evaluated in this report. One of the requirements of both the standard protocol and current variations such as accelerated and transepithelial CXL, is that the cornea is of a minimum thickness, generally ≥400 µm. The reason for this is to protect the cornea. If the cornea is too thin, there is the risk that the UV light might penetrate too deep and damage the endothelial cells at the base of the cornea.[93] The ELZA Institute in Switzerland is developing new techniques aimed at tailoring the CXL procedure to individual corneal thickness with the hope of treating corneas thinner than 300 µm without swelling the cornea first.[93]

In addition to developments in CXL technique, there are also advancements in the technology used to deliver CXL, such as customised or topography-guided CXL. The Mosaic System marketed by Avedro (Avedro Inc. Massachusetts, USA) combines an eye tracker with an adjustable UVA light device that irradiates the cornea in customised patterns, delivering greater energy levels to where greater stiffening is required.[151 152] Another recent development in CXL technology is the C-EYE device (EMAGine, Zug, Switzerland). This device enables ophthalmologists to perform CXL at the slit lamp instead of the operating room.[37]

It should be noted, in addition to research aimed at broadening the scope of patients eligible for CXL treatment, research is also being conducted to broaden the scope of ophthalmic diseases that can be treated with CXL, such as keratitis and corneal oedema.[153]

The use of CXL is an area of ongoing research, both with respect to the way it is used to treat keratoconus and its usefulness in treating other eye disorders. These advancements in the delivery of CXL, and the potential broadening of the patient population eligible for CXL, may potentially change the clinical efficacy and/or safety profile of the procedure for keratoconus.

11 Discussion

The objective of this HTA was to evaluate the clinical and economic effectiveness of CXL, and to consider the social, legal, ethical and organisational issues associated with its use.

To address the clinical efficacy of CXL a systematic search of published literature was undertaken. A total of eight RCTs described in nine publications were included to inform efficacy, and four RCTs described in five publications were included to inform safety. In addition, as safety can be under-reported in RCTs, the most recent and comprehensive systematic review on the safety of CXL that included lower levels of evidence was also included. The studies varied with respect to eligibility requirements, length of follow-up and risk of bias. The overall strength of the evidence, as evaluated using the GRADE approach, was very low.

The second objective of this HTA was to compare clinical efficacy between standard CXL and variants of this procedure (accelerated and transepithelial CXL). The clinical efficacy and safety of each of these CXL variants were informed by one systematic review and six RCTs. The overall quality of the evidence comparing the variants to standard CXL ranged from low to very low for accelerated CXL, and high to low for transepithelial CXL.

11.1 Findings of the clinical evaluation

CXL vs sham or no treatment

For clinical efficacy outcomes, there were statistically significant differences in favour of CXL for markers of cornea curvature (K_{max}) and visual acuity (UCVA and BCVA); the clinical relevance of which is not known. The favourable effect of CXL on K_{max} and UCVA persisted to 36 months, however, the favourable effect on BCVA was only observed from 6 to 12 months post-procedure. It should be noted that the results for BCVA and BSCVA were combined, which whilst not ideal, was necessary due the low number of studies. For the remaining pachymetry and refractive error outcomes, there were minimal differences.

Common adverse events reported in the systematic review and/or RCTs included keratitis, haze, stromal oedema and golden striae. When reported, the adverse events were mostly mild and self-limiting. As safety was poorly reported no comment can be made on how common these adverse events are following CXL with any certainty. The incidence of adverse events was generally higher in the CXL group than the sham or no-treatment groups. However, the statistical difference was not reported by most RCTs, so it is uncertain whether the groups differed. There were no quality of life outcomes reported.

CXL variations vs standard CXL

The systematic review[69] and RCTs[69 75-78 90 91] found significant differences between standard and accelerated CXL in some markers of visual acuity and refractive error. However, the direction of effect

was inconsistent with changes in BCVA favouring accelerated CXL and changes in cylinder, sphere and SE favouring standard CXL. Thus, it is unclear whether accelerated CXL improved vision more than standard CXL.

When compared to standard CXL, it was uncertain whether transepithelial CXL improved markers of visual acuity and topography when considering the systematic review[81] and RCTs[67 73 74 79 80 92].The time points assessed varied for each outcome as did the direction of effect. Therefore, it was uncertain whether transepithelial CXL produced sustained improvement in all outcomes.

The safety of both CXL variants was generally similar to standard CXL. Noting, the incidence of perioperative discomfort and post-operative complications were potentially higher following standard CXL compared with transepithelial CXL owing to the more invasive nature of the procedure (i.e. removal of the epithelium). However, the absence of statistical information limits this conclusion.

11.2 Comparison to previous HTA reports

A total of five HTAs comparing CXL to no treatment,[24 154-157] and one HTA comparing standard CXL to accelerated and transepithelial CXL were identified (***Appendix F***).[156]

The findings of the HTAs comparing CXL to no treatment were generally congruent with the current report. Three HTAs also reported a favourable effect of CXL on K_{max}.[24 155 157] Findings for visual acuity were mixed. Some HTAs reported significant improvement in UCVA[154 156 157] following CXL and other HTAs reported significant improvement in BCVA.[24 155] The variations likely reflect the different RCTs included in each of the HTAs. Other clinical efficacy outcomes reported by one or more of the HTAs included astigmatism, pachymetry, SE, TCT and cylinder with the results consistent with the current HTA. As for this report, the HTAs noted a range of adverse effects following CXL, however, the authors noted they were generally transient and resolved over time.

For the CXL variations, the results of the current HTA are similar to IQWIG (2016). Specifically, IQWIG (2016) reported transepithelial CXL improved BCVA relative to standard CXL, however, they noted there were no differences in UCVA between transepithelial (or accelerated) CXL and standard CXL.[156] With respect to safety, IQWIG (2016) reported similar adverse events for standard and accelerated CXL but a slight reduction in postoperative pain for transepithelial CXL.[156]

11.3 Quality and applicability of evidence

According to the GRADE summary of findings tables, the quality of the reported outcomes for research question 1a was very low. For research question 1b, the quality of the reported outcomes was very low to low for the comparison of accelerated CXL versus standard CXL, and very low to high for the comparison of transepithelial CXL versus standard CXL. Common sources of downgrading related to

imprecision due to small sample sizes, indirectness due to surrogate outcome measures, and risk of bias concerns relating to blinding, randomisation and losses to follow-up.

Patient attrition, and concerns with the randomisation and blinding procedures (for visual acuity and refractive error outcomes) were common sources of bias in the RCTs. A high risk-of-bias was noted for several studies because some control patients received CXL prior to the final follow-up and their data was subsequently imputed using the last observation carried forward technique. Including the values from the crossed-over patients may bias the clinical efficacy results against CXL and contribute to the heterogeneity in the meta-analyses. It was also uncertain whether the use of contact lenses was similar between the treatment groups and whether patients were required to remove contact lenses before eye evaluations in some studies. This may confound the assessment of topography and visual acuity outcomes. Lastly, the between eye correlation was not corrected for in several studies, again biasing the results.

The small number of patients and limited follow-up likely added to the heterogeneity in the analyses. The short follow-up is particularly problematic for keratoconus trials given it is a slow progressive disease. The control patients may not have progressed in trials with short follow-up, biasing the results against CXL. The inconsistent definition of progressive keratoconus also served as a potential source of heterogeneity. For example, some studies defined progressive keratoconus based on changes to visual acuity and/or refraction alone. The lack of a standardised definition may have resulted in the inclusion of patients who were at different disease stages.

The applicability of the evidence to the Swiss population is unclear because there was limited literature addressing how Swiss ophthalmologists determine keratoconus progression, whether their definition aligns with those used by the RCTs and whether the CXL procedure in the RCTs were in accordance with Swiss practice. Furthermore, the included studies were performed in Asia, Australia, Europe and South America and it was unclear how applicable these countries are to Switzerland. The applicability concern is furthered because there is evidence suggesting ethnic differences in the frequency and severity of keratoconus.[158]

The clinical interpretation of the evidence is limited by the absence of evidence-based guidelines on a standardised method to document keratoconus progression. The parameters included in this report are those that have been most commonly used to determine progression.[38] However, there is conjecture in the literature regarding which parameters should be used to measure progression and what quantitative changes are required. K_{max}, the steepest anterior corneal curvature, is the most commonly used parameter to detect or document progression[47 159] and is often used as an indicator to assess effectiveness of crosslinking; however, it has been suggested that it fails to reflect the degree of ectasia, ignores the contribution of the posterior cornea to progression, and that marked ectactic progression

can occur without change or reduction in K_{max}.[159] One study reports that K_{max}, CCT and TCT are all problematic indices for the follow-up of keratoconus in terms of repeatability.[160] Visual performance is said to be influenced by many factors such as tear film and lens irregularities, and has been found to be a poor parameter for diagnosing keratoconus progression.[38] Quality of life outcomes were not reported in any of the included studies. The lack of validated parameters to document progression adds to the uncertainty of the evidence.

11.4 Findings and limitations of the economic analyses

The findings from the cost-utility analysis show that CXL is cost-effective in the treatment of keratoconus. When compared to no intervention, CXL has an ICER of CHF 25,841/QALY over the 25-year time horizon. The possibility of a CXL retreatment increases the cost of the procedure in general, thereby increasing the ICER. This unilateral uncertainty did not capture uncertainties in other inputs that may vary along with CXL retreatment rate. Thus, in a scenario of a high retreatment rate and high patient proportion with severe disease stage, the ICER will be 7 times higher than the base case and 1.8 times higher than the hypothetical WTP. However, these scenarios of CXL retreatment are a worst case given the low failure rate of the procedure in clinical practice. Though better than the one-way sensitivity analysis, the two-way sensitivity analysis may not capture simultaneous uncertainties in more than two inputs. The probabilistic sensitivity analysis showed that CXL is still cost-effective in treating keratoconus. At the hypothetical WTP threshold of CHF 100,000, the procedure is 99% cost-effective.

In comparison to the two published models from European countries, the base case result of the current model (CHF 25,841) under the context of Switzerland is higher than the UK model but lower than the Netherlands model. The model by Salmon (2015) estimated an ICER of GBP 3,174/QALY in 2015, which is equivalent to approximately CHF 4,687 in 2015.[96] The model by Godefrooij (2017) estimated an ICER of EUR 54,384/QALY, which is equivalent to CHF 63,586 in 2017.

The economic evaluation has several limitations and uncertainties. Studies in the clinical evidence base did not provide useful information around patient disease status and the progression of keratoconus. Also, it was uncertain whether the patients in the clinical trials in the evidence base were representative of the Swiss patient population. This led to the situation where the review results from the clinical sections (e.g. the output of meta-analyses) could not be directly utilised to inform the model structure and to populate the inputs for the model. Consequently, the current economic evaluation was performed by adapting a published model. Although costs and some general patient characteristics (e.g. background mortality) were adapted during the model fitting, a large proportion of the modelling assumptions and inputs were still inherited from the existing study. These adaptations have a possibility of impacting on the findings of this current study.

Additionally, the absence of data on paediatric patients meant that paediatric patients were assumed to progress and have same QALY values as adults. This may impact the results and has the possibility of biasing the results. The limitation on QALYs, however, is offset by the challenges around the reporting of quality of life values by children or adult. Children and adolescents are unlikely to understand the process of collecting such information and may have difficulty expressing their quality of life on a scale. Adults may report utility data for children, which in itself maybe biased given the possible deviation from the exact measure for the child.[161] The use of any of such information has the possibility of impacting the result.

The budget impact analysis was significantly limited by the uncertainty over the number of patients in Switzerland when CXL is reimbursed through insurance. In the absence of reliable epidemiological data of keratoconus in Switzerland, incidence from other jurisdictions in European countries is borrowed. Further, it is unclear how many existing keratoconus patients would be treated CXL when the reimbursement becomes accessible. It was assumed that only a proportion of newly diagnosed patients would access CXL in the base-case, and the scenario involving treatment existing patients were considered in sensitivity analyses to be the ceiling of the financial impact.

11.5 Legal, social, ethical and organisational issues

There were limited legal and social issues associated with CXL. When considering vulnerable patient groups, children represent an at-risk group. Keratoconus progresses more quickly in children and they present with a more advanced disease stage and are often less tolerant to conservative treatments compared to adults. To preserve visual acuity, earlier and more intensive interventions are warranted in this patient group. Earlier intervention is beneficial for the preservation of sight; however, the lack of long-term RCTs in children mean the applicability of the clinical efficacy and safety findings for CXL performed on adults is unclear. A search of clinical trials databases identified only one ongoing clinical trial in paediatric patients (ISRCTN17303768) It is unclear whether this trial will address these concerns.

It was unclear whether CXL modifies healthcare resource use following the procedure. Analysis of hospital registries noted the number of patients undergoing corneal transplantation reduced following implementation of CXL in the Netherlands and Norway, reinforcing the notion that CXL slows or stops keratoconus progression.[23] In Canada; however, there was no difference to the number of corneal transplants. The authors postulated the lack of change was due to increases in population size, funding for transplants and number of surgeons performing the procedure, and a shift to endothelial keratoplasties, rather than a lack of efficacy of CXL. Likewise, it is unclear whether CXL affects the use of conservative treatments such as spectacles or contact lenses.

12 Conclusions

The findings from the clinical evaluation suggest a positive benefit of CXL compared with sham or no treatment. CXL had a statistically significant favourable effect on clinical and surrogate measures of keratoconus progression (including K_{max} and visual acuity). The clinical relevance of these changes and their impact on QoL are unknown, as well as the effect of the other outcomes which were not significantly different. Whether these improvements translate to a slowing in the rate of keratoconus progression is unclear as currently there are no evidence-based guidelines documenting which parameters should be measured to document progression and what quantitative changes in those parameters are indicative of progression. It should also be taken into consideration that this finding was based on evidence deemed generally to be of low quality.

With regards to the CXL variants (accelerated and transepithelial CXL), most clinical efficacy outcomes did not significantly differ when compared with standard CXL. For accelerated CXL the evidence varied; however, there were generally no differences seen for K_{mean}, K_{min}, K_1 or K_2. The evidence for transepithelial CXL was more consistent and where a significant difference was found it was generally in favour of standard CXL.

Adverse events following CXL (standard, accelerated or transepithelial protocols) can include stromal oedema, sterile infiltrates, golden striae, stromal haze, corneal scar, keratitis, epithelial defects, peripheral corneal vascularisation, conjunctival hyperaemia, ocular pain, blurred vision, photophobia, ocular irritation, dry eye and increased lacrimation. The most common adverse event was corneal haze (reported incidence up to 100% in some studies). Perioperative discomfort and adverse event rates tended to be lower for transepithelial CXL, which is to be expected given it is less invasive than standard protocols. Statistical analyses comparing the safety of CXL to sham or no treatment and comparing different CXL variants are lacking; therefore, it is not possible to make conclusions with regards to safety.

The economic evaluation showed that CXL was cost-effective compared to no treatment for keratoconus patients. This outcome is most sensitive to the efficacy of CXL, but results from all the sensitivity analyses were substantially lower than the hypothetical ICER threshold. The effect of reduced corneal transplant rates, due to CXL, on resource utilisation may not be seen for some time.

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14 Appendices

14.1 Appendix A: Source of literature (databases and websites)

Table 23 Databases searched and number of search results (without study type filters)

Source	Location	Search results Inception–14/15 April 2020
PubMed	https://www.ncbi.nlm.nih.gov	1,637
Embase	https://www.embase.com/	2,040
The Cochrane Library (inc. CENTRAL)	https://www.cochranelibrary.com/	591
CINAHL	https://www.ebscohost.com/nursing/products/cinahl-databases/cinahl-complete	460
York CRD (inc. HTA, NHS EED, DARE)	https://www.crd.york.ac.uk/CRDWeb/	16
Econlit	https://www.aeaweb.org/econlit/	0
	Total	4,744

Table 24 Database search terms and results

Number	Query	Results PubMed Searched 14 April 2020	Results Embase Searched 15 April 2020	Cochrane library Searched 15 April 2020	CINAHL searched 15 April 2020	York CRD searched 22 April 2020
1	Keratoconus (mh)	5,220	8,295	211	829	22
2	Keratocon* (tw)	13,388	16,569	1,437	1,904	34
3	Ectasia (tw)	16,956	7,527	161	893	8
4	Thin* cornea (tw)	3,465	187	262	314	0
5	Refractive instab* (tw)	11	14	17	12	0
6	Irregular astigmatism (tw)	840	803	81	107	1
7	Ectatic cornea* (tw)	60	32	25	56	1
8	Cornea* ectasi* (tw)	1,113	797	94	257	3
9	Keratectasia (tw)	251	323	18	34	0
10	Conical cornea (tw)	7,139	14	9	6	0
11	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	32,569	23,888	1,785	2,971	42
12	UV crosslink* (tw)	615	722	55	14	1
13	Corneal crosslink* (tw)	241	390	321	132	3
14	Corneal collagen crosslink* (tw)	276	430	216	93	3
15	Photochemical crosslink* (tw)	100	123	7	6	0
16	UV riboflavin crosslink* (tw)	2	4	38	7	0
17	Ultraviolet crosslink* (tw)	46	61	140	59	0
18	Collagen crosslink* (tw)	1,113	1,713	1,078	371	4
19	Cross link* (tw)	85,716	119,459	91,140	17,220	36
20	Crosslink* (tw)	32,548	42,409	1,948	978	13

Number	Query	Results PubMed Searched 14 April 2020	Results Embase Searched 15 April 2020	Cochrane library Searched 15 April 2020	CINAHL searched 15 April 2020	York CRD searched 22 April 2020
21	Vitamin B2 (tw)	19,646	1,583	280	678	2
22	Riboflavin (tw)	18,632	18,712	939	1,497	18
23	CXL (tw)	1,211	1,521	197	230	10
24	CCL (tw)	5,894	5,583	185	431	3
25	KXL (tw)	27	60	11	9	0
26	C3-R (tw)	95	180	7	2	0
27	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26	134,316	158,992	354,229	20,027	59
28	11 AND 27	1,637	2,040	591	460	16

Table 25 EconLit search terms and results

Number	Query	Results Searched 16 June 2020
1	Keratoconus (mh)	NA
2	Keratocon* (tw)	0
3	Ectasia (tw)	0
4	Thin* cornea (tw)	53
5	Refractive instab* (tw)	0
6	Irregular astigmatism (tw)	0
7	Ectatic cornea* (tw)	0
8	Cornea* ectasi* (tw)	0
9	Keratectasia (tw)	0
10	Conical cornea (tw)	0
11	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10	53
12	UV crosslink* (tw)	0
13	Corneal crosslink* (tw)	0
14	Corneal collagen crosslink* (tw)	0
15	Photochemical crosslink* (tw)	0
16	UV riboflavin crosslink* (tw)	0
17	Ultraviolet crosslink* (tw)	0
18	Collagen crosslink* (tw)	0
19	Cross link* (tw)	9,064
20	Crosslink* (tw)	3
21	Vitamin B2 (tw)	3
22	Riboflavin (tw)	10

23	CXL (tw)	2
24	CCL (tw)	20
25	KXL (tw)	0
26	C3-R (tw)	0
27	12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26	9,100
28	11 AND 27	0

Table 26 Specialty websites and results

Specialty websites	Link	Results
American Academy of Ophthalmology	https://www.aao.org/	2
American Association for Pediatric Ophthalmology and Strabismus	https://aapos.org/home	0
American Ophthalmological Society	http://www.aosonline.org/	0
American Society of Ophthalmic Plastic and Reconstructive Surgery	https://www.asoprs.org/	0
Anglo-Spanish Ophthalmological Society	https://www.asos.bio/	0
Austrian Ophthalmological Society	https://www.augen.at/	0
Association For Research in Vision and Ophthalmology (ARVO)	https://www.arvo.org/	0
Canadian Ophthalmological Society	http://www.cos-sco.ca/	0
Centre for Eye Research Australia	https://www.cera.org.au/community/your-eye-health/keratoconus/	0
Cornea Society	https://www.corneasociety.org/	0
Croatian Ophthalmological and Optometric Society	https://www.hood.com.hr/	0
Czech Ophthalmological Society	http://www.oftalmologie.com/content/homepage	0
Danish Ophthalmological Society	http://www.dansk-oftalmologisk-selskab.dk/	0
European Board of Ophthalmology	https://www.ebo-online.org/	0
European Contact Lens Society of Ophthalmologists (ECLSO)	https://www.eclso.eu/	0
European Paediatric Ophthalmological Society (EPOS)	https://www.epos-focus.org/	0
European Society of Cornea and Ocular Surface Disease Specialists	http://eucornea.org/	0
European Society of Ophthalmic Plastic and Reconstructive Surgery	https://www.esoprs.eu/	0

Specialty websites	Link	Results
European Society of Ophthalmology	https://soevision.org/	0
European Union of Medical Specialists (U.E.M.S.) Section of Ophthalmology	https://www.uems-ophtalmologie.org/	0
Eye Bank Association of America (EBAA)	https://restoresight.org/	0
Finnish Ophthalmological Society	http://www.silmalaakariyhdistys.fi/	0
French Society of Ophthalmology	https://www.sfo.asso.fr/	0
German Ophthalmological Society (DOG)	https://www.dog.org/	0
German-Speaking Society for Intraocular Lens Implantation and Refractive Surgery	http://www.dgii.org/de/	0
Global Alliance of Eye Bank Associations	http://www.gaeba.org/	0
International Society of Geographic and Epidemiologic Ophthalmology (ISGEO)	http://iceh.lshtm.ac.uk/isgeo/	0
International Council of Ophthalmology	http://www.icoph.org/	0
International Keratoconus Academy	http://www.keratoconusacademy.com/	0
International Pediatric Ophthalmology & Strabismus Council	https://iposc.org/	0
International Society for Eye Research	http://www.iser.org/	0
International Society for Low Vision Research and Rehabilitation	http://www.islrr.org/	0
International Society for Ophthalmic Pathology	http://www.isop-new.com/	0
Iranian Society of Ophthalmology	http://www.irso.org/	0
Irish College of Ophthalmologists	https://www.eyedoctors.ie/	0
Israel Ophthalmology Society	https://www.ophthalmology.org.il/	0
Israel Society for Vision and Eye Research	http://isver.org.il/?lang=en	0
Italian Society of Ophthalmology	https://www.sedesoi.com/	0
Japanese Ophthalmological Society	http://www.nichigan.or.jp/index.jsp	0
Keratoconus Australia	https://www.keratoconus.org.au/	0
National Keratoconus Foundation	https://www.nkcf.org/	0
National Union of Ophthalmologists of France	https://www.snof.org/	0
Netherlands Ophthalmological Society	https://www.oogheelkunde.org/	0
North American Neuro-Ophthalmology Society	https://www.nanosweb.org/i4a/pages/index.cfm?pageid=1	0

Specialty websites	Link	Results
Pacific Eye Care Society (PacEYES)	http://www.paceyes.org/home	0
Pan-American Association of Ophthalmology	https://paao.org/	0
Royal Australian and New Zealand College of Ophthalmologists	https://ranzco.edu/	0
Singapore Society of Ophthalmology	http://www.ssophth.org/	0
Spanish Society of Ophthalmology	https://www.oftalmoseo.com/	0
Swedish Ophthalmological Society	https://swedeye.org/	0
Swiss Academy of Ophthalmology	https://www.saoo.ch/en/	0
Swiss Society of Ophthalmology	https://www.sog-sso.ch/startseite.html	0
Tear Film & Ocular Surface Society	https://www.tearfilm.org/	0
The Belgian Ophthalmic Associations	http://www.ophthalmologia.be/page.php?edi_id=842	0
The Eye and Contact Lens Association (ECLA)	https://www.clao.org/	0
The International Agency for the Prevention of Blindness	https://www.iapb.org/	0
The Royal College of Ophthalmologists	https://www.rcophth.ac.uk/	1

Table 27 HTA websites and results

HTA Websites	Hyperlink	Results
International		
National Information Centre of Health Services Research and Health Care Technology (NICHSR)	https://www.nlm.nih.gov/hsrph.html	0
National Library of Medicine Health Services/Technology Assessment Texts (HSTAT)	https://www.ncbi.nlm.nih.gov/books/NBK16710/	0
International Information Network on New and Emerging Health Technologies (EuroScan International Network)	https://www.euroscan-network.global/index.php/en/47-public-features/761-database-home	0
Australia and New Zealand		
Adelaide Health Technology Assessment (AHTA)	https://www.adelaide.edu.au/ahta/pubs/	0
Centre for Clinical Effectiveness, Monash University	http://monashhealth.org/health-professionals/cce/	0
Centre for Health Economics, Monash University	https://www.monash.edu/business/che	0
National Health and Medical Research Council	https://www.nhmrc.gov.au/	0
Australian Safety and Efficacy Register of New Interventional Procedures—Surgical (ASERNIP-S)	https://www.surgeons.org/research-audit/research-evaluation-inc-asernips	0
Health Technology Reference Group (HTRG)	https://www.coaghealthcouncil.gov.au/AHMAC/Health-Technology-Reference-Group	0

HTA Websites	Hyperlink	Results
Medical Services Advisory Committee (MSAC)	http://www.msac.gov.au/	1
Austria		
Institute of Technology Assessment/HTA unit	https://www.oeaw.ac.at/ita/publikationen/	0
Ludwig Boltzmann Institute for Health Technology Assessment (LBI-HTA)	https://hta.lbg.ac.at/page/publikationen/en	1
Gesunheit Österreich GmbH (GOG)	http://www.goeg.at	0
Hauptverband der Österreichischen Sozialversicherungsträger (HVB)	http://www.sozialversicherung.at	0
University for Health Sciences, Medical Informatics and Technology	https://www.umit.at	0
Argentina		
Institute for Clinical Effectiveness and Health Policy (IECS)	http://www.iecs.org.ar	0
Belgium		
Scientific Institute of Public Health (IPH)	https://www.wiv-isp.be/en	0
Belgian Health Care Knowledge Centre (KCE)	http://kce.fgov.be	1
Rijksinstituut voor Ziekte- en Invaliditeitsverzekering (RIZIV-INAMI)	https://www.inami.fgov.be/	0
Bulgaria		
National Center of Public Health Analyses (NCPHA)	http://ncpha.government.bg/index.php?lang=en	0
Brazil		
National Committee for Technology Incorporation (CONITEC)	http://conitec.gov.br/en/	0
Canada		
Institute of Health Economics (IHE)	http://www.ihe.ca	0
Institut National d'Excellence en Santé et en Services (INESSS)	https://www.inesss.qc.ca/en/home.html	0
The Canadian Agency for Drugs and Technologies in Health (CADTH)	http://www.cadth.ca/	5
The Canadian Association for Health Services and Policy Research (CAHSPR)	https://www.cahspr.ca/	0
Centre for Health Economics and Policy Analysis (CHEPA), McMaster University	http://www.chepa.org/	0
Centre for Health Services and Policy Research (CAHSPR), University of British Columbia	http://www.chspr.ubc.ca/	0
Institute for Clinical and Evaluative Studies (ICES)	http://www.ices.on.ca/	0
Saskatchewan Health Quality Council (Canada)	http://www.hqc.sk.ca/	0
Evidence Development and Standards Branch (HQO)	http://www.hqontario.ca	1
Croatia		
Croatian Health Insurance Fund (CHIF)	https://www.hzzo.hr	0
Croatian Institute of Public Health (CIPH)	https://www.hzjz.hr/english/	0
Colombia		
Instituto de Evaluación Tecnológica en Salud (IETS)	http://www.iets.org.co	0
Cyprus		

HTA Websites	Hyperlink	Results
Republic of Cyprus Pharmaceutical Services	https://www.moh.gov.cy/moh/phs/phs.nsf/dmlindex_en/dmlindex_en?opendocument	0
Czech Republic		
Ministry of Health Czech Republic (MoH Czech)	http://www.mzcr.cz/en/Info.aspx?aspxerrorpath=/en/default.aspx	0
State Institute for Drug Control (SUKL)	https://www.sukl.eu	0
Denmark		
Danish National Institute of Public Health	https://www.sdu.dk/en/sif/forskning	0
Social & Health Services and Labour Market (DEFACTUM)	http://www.defactum.net	0
Estonia		
Institute of Family Medicine and Public Health (UTA)	https://www.tervis.ut.ee	0
Finland		
National Institute for Health and Welfare (THL)	https://www.thl.fi	0
Finnish Coordinating Center for Health Technology Assessment (FinCCHTA)	https://www.ppshp.fi/Tutkimus-ja-opetus/FinCCHTA/Sivut/HTA-julkaisuja.aspx	2
Finnish Medicines Agency (FIMEA)	http://www.fimea.fi	0
France		
French National Authority for Health (Haute Autorité de Santé; HAS)	http://www.has-sante.fr/	1
Comité d'Evaluation et de Diffusion des Innovations Technologiques (CEDIT)	http://cedit.aphp.fr/	0
Germany		
German Institute for Medical Documentation and Information (DIMDI)	https://www.dimdi.de/	0
Institute for Quality and Efficiency in Health Care (IQWiG)	http://www.iqwig.de	2
Federal Joint Committee (Gemeinsamer Bundesausschuss; G-BA)	https://www.g-ba.de/english/	0
Greece		
Institute of Pharmaceutical Research and Technology (IFET)	http://www.ifet.gr/english_site/	0
National and Kapodistrian University of Athens (EKAPTY-NKUA)	http://en.phs.uoa.gr/	0
National Evaluation Centre of Quality and Technology in S.A-EKAPTY	http://www.ekapty.gr/	0
National Organization for Medicines (EOF)	http://www.eof.gr	0
National Organisation for Healthcare Provision (EOPYY)	http://www.eopyy.gov.gr	0
Onassis Cardiac Surgery Centre (OCSC)	http://www.onasseio.gr/	0
Hungary		
Health Services Management Training Center (SU)	http://www.semmelweis.hu/emk/en/	0
National Institute of Pharmacy and Nutrition (NIPN)	http://www.ogyei.gov.hu/main_page/	0
Ireland		
Health Information and Quality Authority (HIQA)	http://www.hiqa.ie	0
National Centre for Pharmacoeconomics, St James Hospital (NCPE)	http://www.ncpe.ie	0

HTA Websites	Hyperlink	Results
Italy		
Agenzia Sanitaria e Sociale Regionale (ASSR)	http://www.inahta.org/members/assr/	0
Centro Regionale Unico sul Farmaca del Veneta (CRUF/AOUIVR)	http://www.ospedaleuniverona.it/ecm/home	0
Italian Medicines Agency (AIFA)	http://www.agenziafarmaco.gov.it	0
National Agency for Regional Health services (Agenas)	http://www.agenas.it	0
Regione Del Veneto – Area Sanita E' Sociale (Veneto/CRUF)	https://www.regione.veneto.it/web/sanita	0
Regione Emilia-Romagna (RER)	http://www.regione.emilia-romagna.it/	0
Sede del Ministro – Ministero della salute (DGFDM IT)	http://www.salute.gov.it	0
Unita di Valutazione Technology Assessment (UVTA/AOP)	http://www.sanita.padova.it	0
Kazakhstan		
Ministry of Public Health of the Republic of Kazakhstan, Republican Centre for Health Development (RCHD)	http://www.rcrz.kz	0
Korea		
National Evidence-based healthcare Collaborating Agency (NECA)	www.neca.re.kr/eng	0
Latvia		
National Health Service (NVD)	http://www.vmnvd.gov.lv/	0
Lithuania		
The Institute of Hygiene (HI)	http://www.hi.lt	0
State Health Care Accreditation Agency (VASPVT)	http://www.vaspvt.gov.lt	0
Luxembourg		
Inspection Générale de la Sécurité Sociale (IGSS), Cellule d'Expertise Médicale (CEM)	http://www.mss.public.lu/publications/index.html	0
Malaysia		
Health Technology Assessment Section, Ministry of Health Malaysia (MaHTAS)	http://www.moh.gov.my	0
Malta		
Directorate for Pharmaceutical Affairs (DPA/MoH Malta)	http://www.health.gov.mt/en/pharmaceutical/Pages/pharmaceutical-affairs.aspx	0
Mexico		
Centro Nacional de Excelencia Tecnológica en Salud (CENETEC)	www.cenetec.gob.mx	0
the Netherlands		
Erasmus Universiteit Rotterdam (EUR)	http://www.eur.nl/	0
Health Council of the Netherlands (Gezondheidsraad)	https://www.gezondheidsraad.nl/	0
the Netherlands Organisation for Health Research and Development (ZonMw)	http://www.zonmw.nl	0
Zorginstituut Nederland (ZIN)	https://www.zorginstituutnederland.nl/	1
Utrecht University (UU)	http://www.uu.nl	0
Norway		

HTA Websites	Hyperlink	Results
The Norwegian Institute of Public Health (NIPHNO)	http://www.fhi.no/	0
Norwegian Directorate of Health (Hdir)	http://helsedirektoratet.no/english	0
Norwegian Medicines Agency (NOMA)	http://www.legemiddelverket.no	0
Poland		
Agency for Health Technology Assessment and Tariff System (AOTMiT)	http://www.aotm.gov.pl	0
Portugal		
Administração Central do Sistema de Saúde, I.P. (ACSS IP)	http://www.acss.min-saude.pt	0
National Authority of Medicines and Health Products (INFARMED)	http://www.infarmed.pt	0
Republic of China, Taiwan		0
Center for Drug Evaluation (CDE)	http://www.cde.org.tw	0
Romania		
Babes-bolayi University, Cluj School of Public Health (UBB)	http://publichealth.ro/	0
Institutu National De Sanatate Publica (INSP/NIPHB)	https://www.insp.gov.ro/	0
National School of Public Health, Management and Professional Development (NSPHMPDB)	http://www.snspms.ro	0
Singapore		
Agency for Care Effectiveness (ACE)	http://www.ace-hta.gov.sg/	0
Slovakia		
Comenius University in Bratslava (UniBA FOF)	https://uniba.sk/en/	0
Ministry of Health of the Slovak Republic (MoH Slovak Republic)	http://www.health.gov.sk	0
Slovenia		
Ministry of Health of the Republic of Slovenia (MoH Slovenia)	http://www.mz.gov.si/en/	0
Public Agency of the Republic of Slovenia for Medical Products and Medical Devices (JAZMP)	http://www.jazmp.si/en/	0
South Africa		
Charlotte Maxeke Research Consortium (CMeRC)	http://www.cmerc.org	0
Spain		
Agencia Española de Medicamentos y Productos Sanitarios (AEMPS)	http://www.aemps.gob.es	0
Agencia de Evaluación de Tecnologias Sanitarias, Instituto de Salud “Carlos III”I / Health Technology Assessment Agency (AETS)	http://publicaciones.isciii.es/	0
Agency for Health Quality and Assessment of Catalonia (AQuAS)	http://aquas.gencat.cat	0
Andalusian HTA Agency	http://www.aetsa.org/	0
Basque Foundation for Health Innovation and Research (BIOEF)	http://www.bioef.org/	0
Basque Office for Health Technology Assessment (OSTEBA)	http://www.euskadi.eus/web01-a2ikeost/en/	0
Evaluation and Planning Unit – Directorate of the Canary Islands Health Service (SESCS)	https://funcanis.es/	0

HTA Websites	Hyperlink	Results
Fundación Canaria de Investigación Sanitaria (Funcanis)	http://www.funcanis.org/	0
Fundacion Profesor Novoa Santos (AVALIA FNS)	http://www.fundacionprofesornovoasantos.org/es/	0
Fundación Pública Andaluza Progreso y Salud (FPS)	http://www.juntadeandalucia.es/fundacionprogresoysalud/	0
Galician Agency for Health Technology Assessment (AVALIA-T)	http://acis.sergas.es	0
Health Sciences Institute in Aragon (IACS)	http://www.iacs.es/	0
The Instituto De Salud Carlos III (AETS-ISCIIIS)	https://eng.isciii.es/eng.isciii.es/Paginas/Inicio.html	0
Sweden		
Center for Medical Health Technology Assessment	http://www.cmt.liu.se/?l=en&sc=true	0
Dental and Pharmaceutical Benefits Agency (TLV)	http://www.tlv.se	0
Medical Products Agency (MPA)	http://www.lakemedelsverket.se	0
Swedish Council on Technology Assessment in Health Care (SBU)	http://www.sbu.se/en/	0
Switzerland		
Swiss Federal Office of Public Health (SFOPH)	http://www.bag.admin.ch/hta	0
Swiss Network on Health Technology Assessment (SNHTA)	http://www.snhta.ch/	0
Tunisia		
INEAS – National Authority for Assessment and Accreditation in Healthcare, TUNISIA	http://www.ineas.tn/fr	0
United Kingdom		
All Wales Therapeutics and Toxicity Centre (AWTTC)	http://awttc.org	0
Healthcare Improvement Scotland (HIS)	http://www.healthcareimprovementscotland.org	0
National Health Service Health Technology Assessment (UK)/National Coordinating Centre for Health Technology Assessment (NCCHTA)	https://www.nihr.ac.uk/	0
NHS Quality Improvement Scotland	http://www.nhshealthquality.org/	0
National Institute for Clinical Excellence (NICE)	http://www.nice.org.uk/	5
Health Technology Wales (HTW)	http://www.healthtechnology.wales	1
National Institute for Health Research (NIHR), including HTA programme	http://www.nets.nihr.ac.uk/programmes/hta	0
United States of America		
Agency for Healthcare Research and Quality (AHRQ)	https://www.ahrq.gov/research/findings/index.html	0
Harvard School of Public Health	http://www.hsph.harvard.edu/	0
Institute for Clinical and Economic Review (ICER)	http://www.icer-review.org/	0
Institute for Clinical Systems Improvement (ICSI)	http://www.icsi.org	0
Minnesota Department of Health (US)	http://www.health.state.mn.us/	0
Office of Health Technology Assessment Archive (US)	http://ota.fas.org/	0
U.S. Blue Cross / Blue Shield Association Technology Evaluation Center (Tec)	https://www.bcbs.com/news/press-releases/blue-cross-blue-shield-association-launches-evidence-street-website-streamline	0
Veteran's Affairs Research and Development	http://www.research.va.gov/default.cfm	0

HTA Websites	Hyperlink	Results
Technology Assessment Program (US)		
Uruguay		
Health Assessment Division, Ministry of Public Health, (HAD)	http://www.msp.gub.uy	0

Table 28 Clinical trial registries and results

Clinical trial registries	Search Inception–September 2020
ClinicalTrials.gov	120
Cochrane Central Register of Controlled Trials	182
WHO International Clinical Trials Registry Platform (ICTRP)	74

Additional legal, social, ethical and organisational searches

Table 29 Search strings for legal issues (17 or 28 September 2020)

Number	Query	PubMed	Embase
1	Personal autonomy [mh]	17,089	14,154
2	Human rights [mh]	143,262	264,334
3	Human rights [tiab]	10,496	9,578
4	Rights to human [mh]	433,567	8
5	Human rights abuses [mh]	1,383	2,942
6	Patient rights [mh]	78,146	164,725
7	“free will”	737	924
8	“self determination”	4,827	5,642
9	Parental consent [mh]	3,256	5,187
10	Third-party consent [mh]	5,980	45
11	Presumed consent [mh]	546	433
12	Informed consent by minors [mh]	216	13
13	Consent [tiab]	63,753	129,791
14	Privacy [tw]	20,931	27,133
15	Confidentiality [mh]	53,178	33,255
16	Confidentiality [tiab]	11,444	13,894
17	Personally identifiable information [mh]	40	398
18	Health record, personal [mh]	1,972	3
19	“personal information”	2,013	3
20	Access to information [mh]	7,608	22,055
21	Ownership [mh]	22,633	16,052
22	Jurisprudence [mh]	205,066	55,455
23	Law enforcement [mh]	3,727	13,843
24	Law [tiab]	91,596	102,977
25	Laws [tiab]	30,254	32,738

Number	Query	PubMed	Embase
26	Legislation, pharmacy [mh]	1,253	116,467
27	Legislation as topic [mh]	16,1747	79,483
28	Legislation, nursing [mh]	3,151	116,466
29	Legislation, medical [mh]	16,828	144
30	Legislation, hospital [mh]	3,437	11
31	Legislation, food [mh]	2,429	20
32	Legislation, drug [mh]	32,592	38
33	Medical device legislation [mh]	246	31
34	Legislation [mh]	161,747	79,483
35	Legislation [tiab]	37,252	42,935
36	Legal case [pt]	11,028	484
37	Legal guardians [mh]	3,655	574
38	Legal [tiab]	91,812	102,173
39	Liability, legal [mh]	15,669	16,513
40	Legal services [mh]	30	466
41	Intellectual property [mh]	11,558	4,018
42	Intellectual property [tiab]	2,237	2,993
43	Licensure [mh]	17,625	95,570
44	License [tiab]	7,749	3,071
45	Liability, legal [mh]	15,669	16,906
46	Liability [tiab]	19,318	23,906
47	Conflict of interest [tiab]	4,144	6,054
48	Conflict of interest [mh]	10,505	15,962
49	Civil rights [mh]	24,163	9,722
50	Authority [tiab]	23,043	79,483
51	Guaranty [tiab]	125	29,959
52	Regulation [tiab]	853,858	1,028,938
53	Acquisition	162,262	199,453
54	Social justice [mh]	12,184	12,899
55	Health equity [mh]	1,339	11,329
56	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 PR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 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 OR 53 OR 54 OR 55	2,070,868	2,102,693
57	Keratoconus	7,353	9,777
58	Keratocon*	13,812	18,665
59	Ectasia	17,447	7,885
60	Thin* cornea	3,686	5,152
61	Refractive instab*	276	16
62	Irregular astigmatism	990	817
64	Cornea* ectasi*	1,172	1,438
64	Ectatic cornea*	328	391

Number	Query	PubMed	Embase
65	Keratectasia	254	0
66	Conical cornea	7,398	137
67	57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63 OR 64 OR 65 OR 66	34,174	29,939
68	UV crosslink* (tw)	5,813	8,015
69	Corneal crosslink* (tw)	2,474	2,947
70	Corneal collagen crosslink* (tw)	1,771	1,898
71	Photochemical crosslink* (tw)	1,158	812
72	UV riboflavin crosslink* (tw)	243	353
73	Ultraviolet crosslink* (tw)	5,339	6,556
74	Collagen crosslink* (tw)	12,094	15,191
75	Cross link* (tw)	102,824	221,601
76	Crosslink* (tw)	146,824	117,083
77	Vitamin B2 (tw)	20,236	1,497
78	Riboflavin (tw)	19,014	22,584
79	CXL (tw)	1,307	1,674
80	CCL (tw)	8,099	17,721
81	KXL (tw)	36	68
82	C3-R (tw)	118	215
83	68 OR 69 OR 70 OR 71 OR 72 OR 73 OR 74 OR 75 OR 76 OR 77 OR 78 79 OR 80 OR 81 OR 82	199,200	277,439
84	83 AND 67 AND 56	67	58

Table 30 Search strings for social issues (17 or 28 September 2020)

Number	Query	PubMed	Embase
1	Patient experience [tiab]	6,298	10,356
2	Quality of life [mh]	196,954	608,788
3	Social aspects of [tiab]	2,363	3,007
4	Medical decision-making process [tiab]	28,348	198
5	Patient education [mh]	85,690	125,849
6	Patient education[tiab]	19,388	26,960
7	Patient attitude [tiab]	163	201
8	Patient preference [tiab]	4,582	6,851
9	Patient decision [tiab]	1,701	2,608
10	Patient acceptance [tiab]	2,944	3,850
11	Patient satisfaction [tiab]	37,158	52,033
12	Patient-focused [tiab]	1,637	2,291
13	Patient-centred [tiab]	6,314	8,058
14	Patient advocacy [tiab]	1,414	2,013
15	Consumer satisfaction [tiab]	770	881
16	Consumer participation [tiab]	397	380
17	Consumer preference [tiab]	420	392

Number	Query	PubMed	Embase
18	Consumer attitude [tiab]	47	49
19	Self-perception	151,749	205,413
20	Self-care	196,219	66,927
21	Self-efficacy	64,320	34,844
22	Attitude to health	545,899	115,387
23	Health education	720,045	147,607
24	Health knowledge	329,481	4,568
25	Informed choice	50,434	2,037
26	Shared decision making	12,561	14,656
27	Empowerment	13,195	19,867
28	Quality of Life	407,104	589,291
29	Adaptation, psychological	135,463	169
30	Coping	165,897	95,953
31	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28 OR 29 OR 30	1,996,327	1,328,603
32	Focus group	119,359	31,865
33	verbal communication	30,171	16,622
34	qualitative	296,582	333,720
35	survey	1,484,676	1,400,073
36	32 OR 33 OR 34 OR 35	1,834,246	1,735,156
37	31 AND 36	60,300	217,316
38	Keratoconus	7,353	9,777
39	Keratocon*	13,812	18,665
40	Ectasia	17,447	7,885
41	Thin* cornea	3,686	5,152
42	Refractive instab*	276	16
43	Irregular astigmatism	990	817
44	Cornea* ectasi*	1,172	1,438
45	Ectatic cornea*	328	391
46	Keratectasia	254	0
47	Conical cornea	7,398	137
48	38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44 OR 45 OR 46 OR 47	34,174	29,939
49	UV crosslink* (tw)	5,813	8,015
50	Corneal crosslink* (tw)	2,474	2,947
51	Corneal collagen crosslink* (tw)	1,771	1,898
52	Photochemical crosslink* (tw)	1,158	812
53	UV riboflavin crosslink* (tw)	243	353
54	Ultraviolet crosslink* (tw)	5,339	6,556
55	Collagen crosslink* (tw)	12,094	15,191
56	Cross link* (tw)	102,824	221,601
57	Crosslink* (tw)	146,824	117,083
58	Vitamin B2 (tw)	20,236	1,497
59	Riboflavin (tw)	19,014	22,584

Number	Query	PubMed	Embase
60	CXL (tw)	1,307	1,674
61	CCL (tw)	8,099	17,721
62	KXL (tw)	36	68
63	C3-R (tw)	118	215
64	51 OR 52 OR 53 OR 54 OR 55 OR 56 OR 57 OR 58 OR 59 OR 60 OR 61 OR 62 OR 63	199,200	277,439
65	48 AND 64 AND 37	12	9

Table 31 Search string for ethical issues (17 or 28 September 2020)

Number	Query	PubMed	Embase
1	Ethics [mh]	146,794	248,862
2	Medical ethics [tiab]	6,334	6,693
3	Ethical theory [mh]	3,380	3,174
4	Bioethics [mh]	10,936	39,845
5	Bioethics [tiab]	14,706	7,752
6	Morals [mh]	169,765	37,941
7	Morality [tiab]	4,464	4,964
8	Ethical theory [tiab]	301	302
9	Principle-based ethics [mh]	29,717	303,676
10	Patient rights [mh]	78,146	1,021
11	Patient autonomy [tiab]	2,347	2,810
12	Personal autonomy [mh]	17,089	14,136
13	Autonomy [tiab]	29,741	36,313
14	Social justice [mh]	12,184	12,899
16	Ethical issues [tiab]	12,058	14,227
17	Normative [tiab]	29,654	37,736
18	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17	285,704	459,758
19	Keratoconus	7,353	9,777
20	Keratocon*	13,812	18,665
21	Ectasia	17,447	7,885
22	Thin* cornea	3,686	5,152
23	Refractive instab*	276	16
24	Irregular astigmatism	990	817
25	Cornea* ectasi*	1,172	1,438
26	Ectatic cornea*	328	391
27	Keratectasia	254	0
28	Conical cornea	7,398	137
29	19 OR 20 OR 21 OR 22 OR 23 OR 24 OR 25 OR 26 OR 27 OR 28	34,174	29,939
30	UV crosslink* (tw)	5,813	8,015
31	Corneal crosslink* (tw)	2,474	2,947
32	Corneal collagen crosslink* (tw)	1,771	1,898

Number	Query	PubMed	Embase
33	Photochemical crosslink* (tw)	1,158	812
34	UV riboflavin crosslink* (tw)	243	353
35	Ultraviolet crosslink* (tw)	5,339	6,556
36	Collagen crosslink* (tw)	12,094	15,191
37	Cross link* (tw)	102,824	221,601
38	Crosslink* (tw)	146,824	117,083
39	Vitamin B2 (tw)	20,236	1,497
40	Riboflavin (tw)	19,014	22,584
41	CXL (tw)	1,307	1,674
42	CCL (tw)	8,099	17,721
43	KXL (tw)	36	68
44	C3-R (tw)	118	215
45	30 OR 31 OR 32 OR 33 OR 34 OR 35 OR 36 OR 37 OR 38 OR 39 OR 40 OR 41 OR 42 OR 43 OR 44	199,200	277,439
46	18 AND 29 AND 45	3	25

Table 32 Search string for organisational issues (17 or 28 September 2020)

Number	Query	PubMed	Embase
1	Information storage and retrieval [mh]	184,317	558
2	(information management)	361,223	15,806
3	Health information systems [mh]	1,310	2,708
4	Health information management [mh]	1,697	6,543
5	Health information exchange [mh]	889	1,122
6	Information literacy [mh]	6,113	839
7	Health equity [mh]	1,339	11,329
8	(work process)	205,910	1,116
9	(work flow)	63,794	2,607
10	Medical Education [mh]	166,094	323,456
11	Education, professional, retraining [mh]	1,242	7
12	Education, public health professional [mh]	787	8
13	Health information interoperability [mh]	162	50
14	Communication [mh]	310,737	609,002
15	Health communication [mh]	2,425	8,028
16	Quality assurance, health care [mh]	330,569	173
18	Implementation science [mh]	491	5,583
19	Organization culture [mh]	39,584	83
20	(human skills)	195,761	93
21	Sustainability [tiab]	24,742	28,829
22	(system structure)	455,292	866
23	Acceptance [tiab]	70,246	93,379
24	1 OR 2 OR 3 OR 4 OR 5 OR 6 OR 7 OR 8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22 OR 23	2,126,874	1,060,899

Number	Query	PubMed	Embase
	OR 24		
25	Keratoconus	7,353	9,777
26	Keratocon*	13,812	18,665
27	Ectasia	17,447	7,885
28	Thin* cornea	3,686	5,152
29	Refractive instab*	276	16
30	Irregular astigmatism	990	817
31	Cornea* ectasi*	1,172	1,438
32	Ectatic cornea*	328	391
33	Keratectasia	254	0
34	Conical cornea	7,398	137
35	25 OR 26 OR 27 OR 28 OR 29 OR 30 OR 31 OR 32 OR 33 OR 34	34,174	29,939
36	UV crosslink* (tw)	5,813	8,015
37	Corneal crosslink* (tw)	2,474	2,947
38	Corneal collagen crosslink* (tw)	1,771	1,898
39	Photochemical crosslink* (tw)	1,158	812
40	UV riboflavin crosslink* (tw)	243	353
41	Ultraviolet crosslink* (tw)	5,339	6,556
42	Collagen crosslink* (tw)	12,094	15,191
43	Cross link* (tw)	102,824	221,601
44	Crosslink* (tw)	146,824	117,083
45	Vitamin B2 (tw)	20,236	1,497
46	Riboflavin (tw)	19,014	22,584
47	CXL (tw)	1,307	1,674
48	CCL (tw)	8,099	17,721
49	KXL (tw)	36	68
50	C3-R (tw)	118	215
51	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 59 OR 50	199,200	277,439
52	24 AND 35 AND 51	33	16

14.2 Appendix B: List of excluded studies

14.2.1 Systematic reviews/HTAs

Incorrect study design (SR/HTA) for research question 1a (k = 81)

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81. Ziaei M, Barsam A, Shamie N, et al. Reshaping procedures for the surgical management of corneal ectasia. *Journal of Cataract and Refractive Surgery* 2015;41(4):842-72.

Higher-quality SR included for research question 1a (k = 10)

1. Institut für Qualität und Wirtschaftlichkeit im G. UV crosslinking with riboflavin in keratoconus. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) 2016.

2. Jiang Y, Yang S, Li Y, et al. Accelerated versus conventional corneal collagen cross-linking in the treatment of keratoconus: a meta-analysis and review of the literature. *Interdiscip Sci* 2019;11(2):282-86.

3. Kobashi H, Rong SS, Ciolino JB. Transepithelial versus epithelium-off corneal crosslinking for corneal ectasia. *Journal of Cataract and Refractive Surgery* 2018;44(12):1507-16.

4. Li W, Wang B. Efficacy and safety of transepithelial corneal collagen crosslinking surgery versus standard corneal collagen crosslinking surgery for keratoconus: a meta-analysis of randomized controlled trials. *BMC ophthalmology* 2017;17(1):262.

5. Liu Y, Liu Y, Zhang YN, et al. Systematic review and meta-analysis comparing modified cross-linking and standard cross-linking for progressive keratoconus. *Int J Ophthalmol* 2017;10(9):1419-29.

6. Miraftab M, Hashemi H, Abdollahi M, et al. The efficacy of standard versus accelerated epi-off corneal cross-linking protocols: a systematic review and sub-group analysis. *International Ophthalmology* 2019;39(11):2675-83.

7. Shajari M, Kolb CM, Agha B, et al. Comparison of standard and accelerated corneal cross-linking for the treatment of keratoconus: a meta-analysis. *Acta Ophthalmologica* 2019;97(1):e22-e35.

8. Valera-Cornejo DA, Vega-Estrada A, Alio JL. Invasive Pharmacology Outcomes with Different Corneal Cross-Linking Protocols: A Review. *Journal of Ocular Pharmacology & Therapeutics* 2019;35(9):475-90.

9. Wen D, Li Q, Song B, et al. Comparison of standard versus accelerated corneal collagen cross-linking for Keratoconus: A meta-analysis. *Investigative Ophthalmology and Visual Science* 2018;59(10):3920-31.

10. Wen D, Song B, Li Q, et al. Comparison of epithelium-off versus transepithelial corneal collagen cross-linking for keratoconus: A systematic review and meta-analysis. Cornea 2018;37(8):1018-24.

14.2.2 RCTs (research question 1a)

Unusable clinical efficacy and safety data (k = 7)

1. Greenstein S, Shah V, Fry K, et al. Corneal thickness changes after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *Journal of cataract and refractive surgery* 2011;37(4):691–700.

2. Greenstein SA, Fry KL, Bhatt J, et al. Natural history of corneal haze after collagen crosslinking for keratoconus and corneal ectasia: scheimpflug and biomicroscopic analysis. *Journal of cataract and refractive surgery* 2010;36(12):2105- 14.

3. Greenstein SA, Fry KL, Hersh MJ, et al. Higher-order aberrations after corneal collagen crosslinking for keratoconus and corneal ectasia. *Journal of cataract and refractive surgery* 2012;38(2):292- 302.

4. Greenstein SA, Fry KL, Hersh PS. Corneal topography indices after corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *Journal of cataract and refractive surgery* 2011;37(7):1282- 90

5. Greenstein SA, Fry KL, Hersh PS. In vivo biomechanical changes after corneal collagen cross-linking for keratoconus and corneal ectasia: 1-year analysis of a randomized, controlled, clinical trial. *Cornea* 2012;31(1):21-5

6. Hersh PS, Greenstein SA, Fry KL. Corneal collagen crosslinking for keratoconus and corneal ectasia: one-year results. *Journal of cataract and refractive surgery* 2011;37(1):149- 60. Doi: 10.1016/j.jcrs.2010.07.030

7. Kim BZ, Jordan CA, McGhee CNJ, et al. Natural history of corneal haze after corneal collagen crosslinking in keratoconus using Scheimpflug analysis. *Journal of Cataract and Refractive Surgery* 2016;42(7):1053-59.

Incorrect comparator (k = 2)

1. Brooks NO, Greenstein S, Fry K, et al. Patient subjective visual function after corneal collagen crosslinking for keratoconus and corneal ectasia. *Journal of cataract and refractive surgery* 2012;38(4):615- 19.

2. Greenstein SA, Fry KL, Hersh PS. Effect of topographic cone location on outcomes of corneal collagen cross-linking for keratoconus and corneal ectasia. *Journal of refractive surgery (Thorofare, NJ : 1995)* 2012;28(6):397- 405.

Mixed intervention (k = 2)

1. Elsaftawy HS, Ahmed MH, Saif MY, et al. Sequential intracorneal ring segment implantation and corneal transepithelial collagen cross-linking in keratoconus. *Cornea* 2015;34(11):1420- 26.
2. Sharma IP, Bakshi R, Chaudhry M. Corneal collagen cross-linking with and without simultaneous intrastromal corneal ring segment implantation: one-year pilot study. *European journal of ophthalmology* 2019;ePub ahead of print

Incorrect study design (non-randomised comparative) (k = 1)

1. Henriquez MA, Izquierdo L, Jr., Bernilla C, et al. Corneal collagen cross-linking before Ferrara intrastromal corneal ring implantation for the treatment of progressive keratoconus. *Cornea* 2012;31(7):740-5.

Unable to obtain full text (k = 1)

1. Russo V, Stella A, Monaco S, et al. Effects of Corneal Crosslinking on IOP in Patients With Keratoconus Stage I. *American academy of ophthalmology* 2008:200.

14.2.3 RCTs (research question 1b)

Included in systematic review (k = 13)

1. Bikbova G, Bikbov M. Standard corneal collagen crosslinking versus transepithelial iontophoresis-assisted corneal crosslinking, 24 months follow-up: randomized control trial. *Acta ophthalmologica* 2016;94(7):e600- e06.
2. Hagem AM, Thorsrud A, Sandvik GF, et al. Collagen crosslinking with conventional and accelerated ultraviolet-A irradiation using riboflavin with hydroxypropyl methylcellulose. *Journal of cataract and refractive surgery* 2017;43(4):511- 17.
3. Hashemi H, Fotouhi A, Miraftab M, et al. Short-term comparison of accelerated and standard methods of corneal collagen crosslinking. *Journal of cataract and refractive surgery* 2015;41(3):533- 40.
4. Hashemi H, Miraftab M, Seyedian MA, et al. Long-term results of an accelerated corneal cross-linking protocol (18 mW/cm2) for the treatment of progressive keratoconus. *American journal of ophthalmology* 2015;160(6):1164- 70.e1.
5. Hashemian H, Jabbarvand M, Khodaparast M, et al. Evaluation of corneal changes after conventional versus accelerated corneal cross-linking: a randomized controlled trial. *Journal of refractive surgery (thorofare, NJ : 1995)* 2014;30(12):837- 42.
6. Lombardo M, Giannini D, Lombardo G, et al. Randomized controlled trial comparing transepithelial corneal cross-linking using iontophoresis with the Dresden protocol in progressive keratoconus. *Ophthalmology* 2017;124(6):804- 12.
7. Lombardo M, Serrao S, Raffa P, et al. Novel technique of transepithelial corneal cross-linking using iontophoresis in progressive keratoconus. *Journal of Ophthalmology* 2016:1-11.
8. Mastropasqua L, Nubile M, Lanzini M, et al. Morphological modification of the cornea after standard and transepithelial corneal cross-linking as imaged by anterior segment optical coherence tomography and laser scanning in vivo confocal microscopy. *Cornea* 2013;32(6):855-61.
9. Nawaz S, Gupta S, Gogia V, et al. Trans-epithelial versus conventional corneal collagen crosslinking: A randomized trial in keratoconus. *Oman J Ophthalmol* 2015;8(1):9-13.
10. Sadoughi MM, Einollahi B, Baradaran-Rafii A, et al. Accelerated versus conventional corneal collagen cross-linking in patients with keratoconus: an intrapatient comparative study. *International ophthalmology* 2018;38(1):67- 74.

11. Sherif AM. Accelerated versus conventional corneal collagen cross-linking in the treatment of mild keratoconus: a comparative study. *Clinical ophthalmology (auckland, NZ)* 2014;8:1435- 40.

12. Shetty R, Pahuja NK, Nuijts RM, et al. Current Protocols of Corneal Collagen Cross-Linking: visual, Refractive, and Tomographic Outcomes. *American journal of ophthalmology* 2015;160(2):243- 49.

13. Soeters N, Wisse RP, Godefrooij DA, et al. Transepithelial versus epithelium-off corneal cross-linking for the treatment of progressive keratoconus: a randomized controlled trial. *American journal of ophthalmology* 2015;159(5):821- 8.e3.

Mixed population (k = 3)

1. Hallahan KM, Rocha K, Roy AS, et al. Effects of corneal collagen crosslinking on Ocular Response Analyzer Waveform derived variables in keratoconus and post-LASIK ectasia. *Investigative Ophthalmology and Visual Science* 2014;55 (13):3722.

2. Khairy HA, Elsawy MF, Said-Ahmed K, et al. Accelerated versus standard corneal cross linking in the treatment of ectasia post refractive surgery and penetrating keratoplasty: a medium term randomized trial. *Int J Ophthalmol* 2019;12(11):1714-19.

3. Rush SW, Rush RB. Epithelium-off versus transepithelial corneal collagen crosslinking for progressive corneal ectasia: a randomised and controlled trial. *British journal of ophthalmology* 2017;101(4):503- 08.

Incorrect outcome (k = 2)

1. Godefrooij DA, El Kandoussi M, Soeters N, et al. Higher order optical aberrations and visual acuity in a randomized controlled trial comparing transepithelial versus epithelium-off corneal crosslinking for progressive keratoconus. *Clinical ophthalmology (auckland, NZ)* 2017;11:1931- 36.

2. Mahdavi Fard A, Daei Sorkhabi R, Khazaei M, et al. The effects of collagen cross-linking on corneal density: a comparison between accelerated and conventional methods. *International ophthalmology* 2019;39(7):1559- 66.

Incorrect study design (conference abstract) (k =1)

1. Serrao S, Lombardo G, Rosati M, et al. Preliminary results of a randomized controlled trial comparing transepithelial corneal cross-linking with iontophoresis and standard cross-linking in patients with progressive keratoconus. *Investigative ophthalmology & visual science* 2016;57(12):2892.

Unusable efficacy outcomes (k = 1)

1. Kanellopoulos AJ. Long-term safety and efficacy follow-up of prophylactic higher fluence collagen cross-linking in high myopic laser-assisted in situ keratomileusis. *Clinical Ophthalmology* 2012;6(1):1125-30.

14.3 Appendix C: Ongoing and recently completed clinical trials

Searches for ongoing and recently completed clinical trials meeting our PICO criteria were undertaken in September 2020. This included trials of patients with keratoconus and corneal ectasia (for safety only). A total of 19 trials were identified as recruiting (or not yet recruiting), active or recently completed (2019 or 2020) (***Table 33***). There are four RCTs comparing CXL to sham or no treatment, including one on paediatric patients (10–16 years of age).

Table 33 Recruiting, active and recently completed clinical trials

Trial registry ID	Indication; Target sample size	Design	Intervention; Comparator(s)	Primary outcomes	Expected completion date; Status
ClinicalTrials.gov *(total hits = 120; search date = 02.09.2020)*					
NCT03879421	Keratoconus; 44 participants	Non-RCT	Epithelium-off accelerated CXL; Epithelium-on accelerated CXL	K_{max} (dioptres); CCT (µm)	April 2019; Recruiting
NCT03442751	Progressive keratoconus; 279 participants	RCT	CXL treatments; sham procedure	K_{max}	November 2019; Active
NCT03990506	Keratoconus; 30 participants	RCT	Transepithelial PiXL, standard PiXL	UCVA; K_{mean}, K_1, K_2, K_{max}; ocular discomfort scores	June 2021; Recruiting
NCT03918408	Keratoconus; 300 participants	RCT	Pulsed accelerated (30mW, 5 sec on 5 sec off, 10 min illumination); conventional (9mW, continuous 10 min illumination)	K_{mean}	June 2029; Recruiting
NCT04439552	Keratoconus; 60 participants	Non-RCT	CXL surgery to treat keratoconus; control (age- and sex-matched healthy volunteers)	Neural activity related to pain	August 2023; Not yet Recruiting
NCT04213885	Keratoconus, Unstable Ectasia Corneal; 300 participants	RCT	Pulse accelerated (30mW 5 sec on 5 sec of 10 min illumination – PXL-330 platinum device); conventional (9mW continuous, 10 min illumination – PXL-330 platinum device)	K_{mean}	September 2029; Recruiting
WHO International Clinical Trials Registry Platform *(total hits = 74, search date = 07.09.2020)*					
IRCT20190508043529N1	Progressive keratoconus; 124 participants	RCT	Continuous-light accelerated CXL (9mW/cm^2,10 mins); Pulsed-light accelerated (9mW/cm^2, 20 mins)	BCVA	NR; Recruitment complete
ChiCTR190	Progressive	Non-	Accelerated CXL; non-	Corneal topographic map parameters; thinnest	October 2023; Not

0027216	keratoconus; 100 participants	RCT	surgical treatment	point thickness of cornea	yet recruiting
NCT04532788	Keratoconus; 124 participants	RCT	Customized CXL (i.e. Dresden protocol); standard crosslinking	K_{max}	November 2022; Not yet recruiting
ChiCTR2000032444	Keratoconus; 150 participants	Non-RCT	Epithelium-off CXL; transepithelial CXL; control group (no intervention)	K_{max}; K_1; K_2; anterior astigmatism; thickness of thinnest point of cornea; CCT	May 2025; Recruiting
NCT04427956	Progressive keratoconus; 90 participants	RCT	Isotonic riboflavin CXL; Hypotonic riboflavin CXL; iontophoresis CXL	UCVA; K_{max}; K_1	December 2021; Recruiting
Cochrane Library Trials *(total hits = 182, search date =07.09.2020)*					
CINAHL 141887076	Bilateral keratoconus; 34 participants	RCT	Standard CXL; epi-disruption CXL	UCVA, BCVA, keratometry, pachymetry	July 2020; Completed
ACTRN12613000143729	Keratoconus; 100 participants	RCT	CXL; no treatment	K_{max}	NR; Active
CTRI/2015/06/005926	Keratoconus; 100 participants	RCT	Continuous accelerated CXL-UVA; Pulse mode CXL-UVA	Clinical efficacy and safety (undefined)	NR; Recruiting
EUCTR2016-001460-11-GB	Keratoconus; 30 adults, 30 adolescent participants	RCT	CXL; placebo	K_{max}	NR; Active
CN-01944383	Paediatric (9-16 years old) keratoconus; 34 participants	RCT	Standard CXL 3 mW/cm^2; accelerated CXL 18 mW/cm^2.	UCVA, corrected distance visual acuity, K_{max}, corneal astigmatism, CCT, manifest refraction spherical equivalent	June 2019; Completed
IRCT20161231028N1	Keratoconus; 50 participants	RCT	Standard CXL; trans-epi CXL	K_{max}; time required for re-epithelialisation; UCVA; BCVA	NR; Recruiting
IRCT20100706004333N3	Bilateral keratoconus patients with Down Syndrome; 30 participants	RCT	Accelerated CXL; standard CXL	Corneal biomechanics, corneal keratometry	Recruiting
ISRCTN17303768	Children with keratoconus (10–16 years old); 60 participants	RCT	CXL; normal care (glasses or contact lenses)	K2	February 2020; Active

Abbreviations

BCVA = best corrected visual acuity, **CCT** = central corneal thickness, **CXL** = corneal collagen crosslinking, **epi** = epithelial, **K_1** = flattest meridian keratometry , **K_2** = steepest meridian keratometry, **K_{max}** = maximal keratometry, **K_{mean}** = mean keratometry, **NR** = not reported, **RCT** = randomised controlled trial, **UCVA** = uncorrected visual acuity, **UVA** = ultra violet light A.

14.4 Appendix D: Other CXL variations

Studies (systematic reviews and RCTs only) identified by our database search for CXL variations are listed. These variations were not included in question 1b (which compared accelerated and transepithelial CXL with standard CXL) as they are less commonly used in Swiss practice.

Systematic reviews

Corneal compression during CXL

1. Institut für Qualität und Wirtschaftlichkeit im G. UV crosslinking with riboflavin in keratoconus. Cologne: Institut fuer Qualitaet und Wirtschaftlichkeit im Gesundheitswesen (IQWiG) 2016.

RCTs

Corneal compression during CXL

2. Beckman KA, Gupta PK, Farid M, et al. Corneal crosslinking: Current protocols and clinical approach. *Journal of Cataract and Refractive Surgery* 2019;45(11):1670-79.

3. Rehnman JB, Behndig A, Hallberg P, et al. Initial results from mechanical compression of the cornea during crosslinking for keratoconus. *Acta ophthalmologica* 2014;92(7):644- 49.

4. Rehnman JB, Lindén C, Hallberg P, et al. Treatment effect and corneal light scattering with 2 corneal cross-linking protocols: A randomized clinical trial. *JAMA Ophthalmology* 2015;133(11):1254-60.

Use of corneal healing agents

5. Bata AM, Witkowska KJ, Wozniak PA, et al. Effect of a matrix therapy agent on corneal epithelial healing after standard collagen cross-linking in patients with keratoconus: A randomized clinical trial. *JAMA Ophthalmology* 2016;134(10):1169- 76.

6. Gumus K, Guerra MG, de Melo Marques SH, et al. A new matrix therapy agent for faster corneal healing and less ocular discomfort following epi-off accelerated corneal cross-linking in progressive keratoconus. *Journal of refractive surgery* 2017;33(3):163- 70.

7. Kirgiz A, Akdemir MO, Yilmaz A, et al. The use of autologous serum eye drops after epithelium-off corneal collagen crosslinking. *Optom Vis Sci* 2020;97(4):300-04.

8. Kymionis GD, Liakopoulos DA, Grentzelos MA, et al. Effect of the regenerative agent poly(carboxymethylglucose sulfate) on corneal wound healing after corneal cross-linking for keratoconus. *Cornea* 2015;34(8):928- 31.

9. Cagini C, Messina M, Torroni G, et al. Efficacy of topical microemulsion of fatty acids of the omega-3 series on the sub-epithelial corneal nerves regeneration after epithelium-off corneal collagen cross-linking for keratoconus. *International Ophthalmology* 2020;40(1):205-12.

Varied riboflavin concentrations, application times or solutions

10. Franch A, Birattari F, Dal Mas G, et al. Evaluation of intrastromal riboflavin concentration in human corneas after three corneal cross-linking imbibition procedures: A pilot study. *Journal of Ophthalmology* 2015:1-5.

11. M JL, Greenstein SA, Gelles JD, et al. Corneal haze after transepithelial collagen cross-linking for keratoconus: A Scheimpflug densitometry analysis. *Cornea* 2020

12. Lesniak SP, Hersh PS. Transepithelial corneal collagen crosslinking for keratoconus: six-month results. *Journal of cataract and refractive surgery* 2014;40(12):1971- 79.

13. Price MO, Fairchild K, Feng MT, et al. Prospective randomized trial of corneal cross-linking riboflavin dosing frequencies for treatment of keratoconus and corneal ectasia. *Ophthalmology* 2018;125(4):505- 11.

14. Rosenblat E, Hersh PS. Intraoperative corneal thickness change and clinical outcomes after corneal collagen crosslinking: standard crosslinking versus hypotonic riboflavin. *Journal of cataract and refractive surgery* 2016;42(4):596- 605.

Pulsed versus continuous UV light

15. Peyman A, Nouralishahi A, Hafezi F, et al. Stromal demarcation line in pulsed versus continuous light accelerated corneal cross-linking for keratoconus. *Journal of refractive surgery* 2016;32(3):206- 08.

Postoperative pain relief

16. Pang X, Fan ZJ, Peng XJ, et al. Clinical evaluation of pranoprofen combined with fluorometholone eye drops on postoperative reaction of corneal cross-linking. *Eye science* 2012;27(4):173- 77.

17. Sameen M, Khan MS, Habib A, et al. Comparison of analgesic effect of preoperative topical Diclofenac versus Ketorolac on postoperative pain after corneal collagen cross linkage. *Pak J Med Sci* 2017;33(5):1101-05.

Topography-guided CXL versus standard CXL

18. Nordström M, Schiller M, Fredriksson A, et al. Refractive improvements and safety with topography-guided corneal crosslinking for keratoconus: 1-year results. *British journal of ophthalmology* 2017;101(7):920- 25.

14.5 Appendix E: Tables from Chapter 7 (efficacy and safety)

Research question 1a

Characteristics of included studies

Table 34 Study profile of included systematic review for research question 1a (safety)

Author (year)	Databases searched Search date Methodological limits	Inclusion/exclusion criteria	Number/type of included studies Number of eyes	Duration of follow-up
Shalchi (2015)[26]	Medline 26 January 2014 No date or language limits	Inclusion criteria RCTs (comparing either standard or transepithelial CXL with no treatment, no minimum number of included eyes or follow-up) or case series (with minimum 20 included eyes and 12-month follow-up) in humans, published in any language. Exclusion criteria Animal and ex-vivo studies, studies of patients with non-keratoconus corneal ectatic pathologies (including pellucid marginal degeneration and post-refractive-surgery ectasia), studies where CXL was performed in combination with other surgical procedures (including intracorneal segment insertion, excimer laser procedures or iontophoresis techniques).	45 studies: 40 case series, 3 RCTs, 2 non-randomised comparative studies Approximately 2,033 eyes	12–72 months

Abbreviations
CXL = corneal collagen crosslinking, **RCTs** = randomised controlled trials.

Table 35 Study profiles of included RCTs for research question 1a (safety and efficacy)

Author (year); location	Inclusion criteria; sample size (eyes)	Design; Eye allocation*; follow-up	Intervention and comparator	Outcomes
Hersh (2017a)[66] United States	Age ≥14 years, axial topography pattern consistent with keratoconus, K_{max} ≥47D on corneal topography, inferior to superior ratio >1.5 on topography mapping, CDVA <20/20, corneal thickness ≥300µm (measured by Pentacam) and diagnosis of progressive keratoconus. Total = 205; intervention = 102; control = 103	RCT, open label, crossover at 3 months B 12 months	***Intervention*** Standard CXL† ***Comparator*** Riboflavin 0.1% plus dextran drops only. No epithelial removal.	K_{max} CDVA UDVA SE Safety
Hersh (2017b)[85] United States	Age ≥14 years, axial topography pattern consistent with corneal ectasia including relative inferior steepening with inferior:superior ratio >1.5D, CDVA <20/20, corneal thickness ≥300µm at the thinnest area (measured by Pentacam). Total = 179; intervention = 91; control = 88	RCT, open label, crossover at 3 months B 3 months‡	***Intervention*** Standard CXL† ***Comparator*** Riboflavin 0.1% plus dextran drops only. No epithelial removal.	Safety
Malik (2017)[86] Pakistan	Diagnosis of bilateral progressive keratoconus Total = 60; intervention = 30; control = 30	RCT, open label, crossover at 3 months A 3 months	***Intervention*** Standard CXL† ***Comparator*** No treatment	K_{mean}
Lang (2015)[87] Germany	Keratoconus at early stage (defined as correction of refractive error possible with spectacles or contact lenses) and proven progression Total = 29; intervention = 15; control = 14	RCT, double-blind (after 5th follow-up) §, no crossover B 36 months	***Intervention*** Standard CXL† ***Comparator*** Application of fluorescein eye drops every 2 mins for 30 mins, radiation with visible blue light for 30 mins and no epithelial removal.	K_{max} K_{min} BCVA UCVA CCT Safety

Author (year); location	Inclusion criteria; sample size (eyes)	Design; Eye allocation*; follow-up	Intervention and comparator	Outcomes
Sharma (2015)[84] India	Patient age >14 years with keratoconus stage II or more according to Amsler Krumeich classification and documented progression and decrease in CDVA. Total = 23; intervention = 23; control = 20	RCT, double-blind, no crossover A/B 6 months	***Intervention*** Standard CXL† ***Comparator*** Sham treatment involved epithelial debridement, riboflavin administration but no UVA light.	K_{max} K_{min} Cylinder
Seyedian (2015)[71] Iran	Age 15–40 years, confirmed bilateral keratoconus based on clinical and topography findings, bilateral minimum corneal thickness of 400µm as measured with Pentacam, maximum keratometry of 60D in each eye based on Pentacam readings and evidence keratoconus is progressing. Both eyes of each patient must meet criteria indicative of keratoconus over previous 12 months Total = 52; intervention = 26; control = 26	RCT, open label, no crossover A 12 months	***Intervention*** Standard CXL† ***Comparator*** No treatment	K_{max} K_{mean} BSCVA Cylinder SE CCT
Wittig-Silva (2014)[72] Australia	Age 16–50 years, unequivocal clinical or video-keratographic diagnosis of keratoconus, clinically significant progression of keratoconus 6–12 months following diagnosis. Total = 94; intervention = 46; control = 48	RCT, open label, no crossover A/B 36 months	***Intervention*** Standard CXL† ***Comparator*** No treatment	K_{max} K_{min} BSCVA UCVA Cylinder SE Sphere TCT CCT Safety

Author (year); location	Inclusion criteria; sample size (eyes)	Design; Eye allocation*; follow-up	Intervention and comparator	Outcomes
Wittig-Silva (2008)‖ [88] Australia	Age 16–50 years, unequivocal clinical or video-keratographic diagnosis of keratoconus, clinically significant progression of keratoconus 6–12 months following diagnosis. Total = 66; intervention = 33; control = 33	RCT, open label, no crossover A/B 12 months	***Intervention*** Standard CXL† ***Comparator*** No treatment	K_{max} Safety
Da Candelaria Renesto (2012)[68] Brazil	Compliant patients age 15–60 years with documented keratoconus with BCVA≤0.48 logMAR, increased or proven intolerance to contact lenses, penetrating keratoplasty referred by a doctor, corneal thickness ≥400µm at thinnest point and good health. Total = 39; intervention = 19; control = 20	RCT, open label, no crossover A/B 3 months	***Intervention*** Standard CXL† ***Comparator*** Riboflavin 0.1% (w/v) eyedrops (10 mg riboflavin-5-phosphate in 20% [w/v] dextran-T-500) 4 times per day for 1 month.	K_{mean} UCVA BSCVA Cylinder SE
O'Brart (2011)[70] United Kingdom	Patients with keratoconus grade I (early) to III (moderate) according to Amsler Krumeich classification with documented or reported progression, reduced UCVA or BCVA by >1 line and/or worsening of refractive or corneal astigmatism, keratometry or cone apex power by 0.75D over previous 18 months. Total = 48; intervention = 24; control = 24	RCT, single-blind (assessor for subjective outcomes), no crossover A 18 months	***Intervention*** Standard CXL† ***Comparator*** No treatment	BSCVA UCVA Cylinder SE CCT

Abbreviations

BCVA = best corrected visual acuity, **BSCVA** = best spectacle corrected visual acuity, **CDVA** = corrected distance visual acuity, **CXL** = corneal collagen crosslinking, **D** = dioptre; **RCT** = randomised controlled trial, **UCVA** = uncorrected visual acuity, **UDVA** = uncorrected distance visual acuity, **UV** = ultraviolet.

Notes

*Eye allocation **A** = both eyes of patients included in trial, **B** = one eye included in trial, **A/B** = some patients had both eyes included in the trials, some patients had one eye included.

†Standard CXL describes the Dresden protocol (epithelium removed, UVA 3mW/cm^2 for 30 minutes)

‡Total duration of follow-up is 12 months; however, comparative safety data only reported until 3 months.

§The authors state that "patients were informed about possible symptoms of dry eye and pain due to epithelial removal. However, patients were not informed about the connection of these symptoms with the placebo or CXL treatment. The patients therefore were not fully aware of their assignment to the placebo or CXL group."

‖ This study reports the preliminary findings of a subset of patients from the same RCT as Wittig-Silva (2014).

Risk of bias

Table 36 Summary of AMSTAR results

Question	Yes/No
Did the study include a PICO?	**Yes**
Were the methods established a priori and deviations reported?	**No**
Study design selection criteria explained appropriately?	**Yes**
Was a comprehensive literature search strategy used?	**No**
Was study selection performed in duplicate?	**No**
Was data extraction performed in duplicate?	**No**
Were excluded studies listed with justification for exclusion?	**Yes**
Were included studies described in adequate detail?	**No**
Was risk of bias assessed appropriately for RCTs?	**No**
Was risk of bias assessed appropriately for NRSIs?	**No**
Were sources of funding reported for included studies?	**No**
If MA was performed, was the method appropriate?	**No MA**
If MA was performed, was the impact of bias assessed?	**No MA**
Was bias accounted for when interpreting/discussing the results?	**Yes**
Were sources of heterogeneity discussed?	**Yes**
Was publication bias assessed?	**No MA**
Were sources of conflicts of interest declared by the authors?	**Yes**
Overall	**Critically low**

Abbreviations
MA = meta-analysis, **NRSI** = non-randomised studies of intervention, **PICO** = population intervention comparator outcome; **RCT** = randomised controlled trial.
Source
Shalchi (2015) [26]

Findings: clinical efficacy

Table 37 Summary of results from meta-analyses comparing mean or standardised mean difference of CXL with sham or no treatment

Outcome	Follow-up time Mean difference between CXL and no treatment (95% CI); p value					
	1 month	*3 months*	*6 months*	*12 months*	*24 months*	*36 months*
K_{max} (D)	2.50 (0.49, 4.51) p = 0.01	-1.15 (-2.93, 0.63) p = 0.21	-1.80 (-3.51, -0.08) p = 0.04	-1.71 (-2.89, -0.54) p = 0.004	-2.66 (-4.78, -0.54) p = 0.01	-1.85 (-3.44, -0.25) p = 0.02
K_{mean} (D)	0.17 (-3.40, 3.74) p = 0.93	-2.14 (-4.67, -3.41) p = 0.09	NR	-0.50 (-3.93, 2.93) p = 0.77	NR	NR
K_{min} (D)	NR	NR	0.00 (-2.77, 2.77) p = 1.00	-1.08 (-3.83, 1.67) p = 0.44	-1.83 (-4.62, 0.96) p = 0.20	-1.11 (-3.12, 0.89) p = 0.28
Cylinder (D)	-0.23 (-1.08, 0.62) p = 0.39	-0.13 (-0.98, 0.72) p = 0.76	NR	0.10 (-0.76, 0.96) p = 0.83	-0.10 (-1.68, 1.48) p = 0.90	0.27 (-1.32, 1.86) p = 0.74
Spherical equivalent (D)	-0.27 (-0.87, 0.32) p = 0.37	-0.07 (-0.66, 0.52) p = 0.81	-0.10 (-0.83, 0.63) p = 0.79	0.30 (-0.24, 0.85) p = 0.28	0.52 (-0.77, 1.81) p = 0.43	0.18 (-1.17, 1.53) p = 0.79
Outcome	**Follow-up time Standardised mean difference between CXL and no treatment (95% CI); p value**					
	1 month	*3 months*	*6 months*	*12 months*	*24 months*	*36 months*
BCVA*	0.97 (-0.02, 1.95) p = 0.06	-0.35 (-1.34, 0.64) p = 0.49	-1.45 (-2.80, -0.11) p = 0.03	-0.96 (-1.76, -0.16) p = 0.02	-0.24 (-1.61, 1.13) p = 0.73	0.51 (-0.52, 1.53) p = 0.33
UCVA*	0.49 (0.08, 0.89) p = 0.02	-0.41 (-0.81, 0.00) p = 0.05	-0.57 (-1.05, -0.09) p = 0.02	-0.88 (-1.25, -0.51) p = <0.01	-0.64 (-1.21, -0.07) p = 0.03	-0.71 (-1.28, -0.14) p = 0.02

Abbreviations
BCVA = best corrected visual acuity, **CI** = confidence interval, **D** = dioptres, **NR** = not reported, **UCVA** = uncorrected visual acuity.
Notes
*Both BCVA and UCVA have no units. Means had to be standardised due to differences between studies in the units of measurement used.
A negative value for mean difference or standardised mean difference favours CXL; a positive value for mean difference or standardised mean difference favours no treatment.
Cells highlighted in green indicate a statistically significant difference between CXL and sham or no treatment in favour of CXL.
Cells highlighted in orange indicate a statistically significant difference between CXL and sham or no treatment in favour of no treatment.

Table 38 Weighted absolute mean differences of outcomes from baseline at different time points for CXL and sham or no treatment arms

Outcome	Length of follow-up Weighted absolute mean change from baseline for CXL and no treatment Mean ± standard deviation											
	1 month		*3 months*		*6 months*		*12 months*		*24 months*		*36 months*	
	CXL	NT	CXL	NT	CXL	NT	CXL	NT	CXL	NT	CXL	NT
K_{max}	NR	NR	-0.55 ± 1.78	0.6 ± 0.38	-0.99 ± 2.49	0.86 ± 0.38	-1.16 ± 1.97	0.96 ± 0.58	NR	NR	-0.88 ± 2.15	1.42 ±1.14
K_{mean}	NR	NR	-1.59 ± 2.99	0.93 ± 0.60	NR	NR	NR	NR	NR	NR	NR	NR
K_{min}	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	-0.67 ±1.87	0.95 ± 0.54
Cylinder	NR	NR	NR	NR	NR	NR	-0.43 ±1.38	-0.23 ± 1.11	NR	NR	NR	NR
Spherical equivalent	-0.19 ± 1.36	0.14 ± 0.90	0.10 ± 0.97	0.18 ± 0.85	NR	NR	0.17 ± 0.40	-0.09 ± 0.58	NR	NR	NR	NR

Abbreviations
CXL = corneal collagen crosslinking, **NR** = not reported (only one study available at this time point), **NT** = no treatment.

Table 39 Mean change from baseline to 18 months and comparison between CXL and untreated eyes for UCVA

Treatment	Baseline UCVA (Snellen decimal equivalent)	Mean change ± SD at 18 months follow-up (Snellen decimal equivalent)
CXL	0.27	0.06
No treatment	0.22	-0.01
p value	NR	0.2

Abbreviations
UCVA = uncorrected visual acuity, **CXL** = corneal collagen crosslinking, **NR** = not reported, **SD** = standard deviation.
Notes
Measure of variance not provided.
Source
O'Brart (2011)[70]

Table 40 Mean change from baseline to 18 months and comparison between CXL no treatment for BCVA

Treatment	Mean BCVA at baseline (Snellen decimal equivalent)	Mean change in BCVA at 18 months (Snellen decimal equivalent)
CXL	0.82	0.12
No treatment	0.78	0.13
p value	NR	0.98

Abbreviations
BCVA = best corrected visual acuity, **CXL** = corneal collagen crosslinking, **NR** = not reported, **SD** = standard deviation.
Notes
Measure of variance not provided.
Source
O'Brart [70]

Table 41 Mean change in TCT for CXL and untreated eyes measured at 12, 24 and 36 months follow-up

Pachymetry device	Baseline TCT Mean ± SD		12 months Mean change in TCT ± SD		24 months Mean change in TCT ± SD		36 months Mean change in TCT ± SD	
	CXL	NT	CXL	NT	CXL	NT	CXL	NT
Ultrasound	444 ± 34 µm	454 ± 30 µm	3.53 ± 3.50 µm	-5.40 ± 3.38 µm	4.14 ± 4.63 µm	-4.30 ± 4.19 µm	5.86 ± 4.30 µm	-9.60 ± 4.25 µm
p value	0.153		0.07		0.18		0.013	
Orbscan	429 ± 43 µm	424 ± 47 µm	-33.69 ± 4.18 µm	-10.08 ± 3.42 µm	-23.16 ± 5.16 µm	-12.84 ± 3.58 µm	-19.52 ± 5.06 µm	-17.01 ± 3.63 µm
p value	0.652		<0.001		0.101		0.686	

Abbreviations
CXL = corneal collagen crosslinking, **NT** = no treatment, **SD** = standard deviation, **TCT** = thinnest corneal thickness.
Source
Wittig-Silva (2014)[72]

Table 42 Mean change in CCT between CXL and untreated eyes at 12 months follow-up

Device	No treatment mean change ± SD	CXL Mean change ± SD	p value
Ultrasound	-21.75 ± 13.67 µm	-19.33 ± 16.45 µm	0.825
Pentacam	-3.52 ± 6.03 µm	-3.61 ± 11.52 µm	0.852

Abbreviations
CCT = central corneal thickness, **CXL** = corneal collagen crosslinking, **SD** = standard deviation.
Source
Seyedian (2015)[71]

Table 43 Mean change from baseline to 18 months and comparison between CXL and no treatment for CCT

Treatment	Baseline Mean	18 months Mean
CXL	483 µm	+ 4.0 µm
No treatment	482 µm	+ 6.0 µm
p value	NR	0.9

Abbreviations
CCT = central corneal thickness, **CXL** = corneal collagen crosslinking, **NR** = not reported, **SD** = standard deviation, **µm** = micrometres.
Notes
Measure of variance not provided.
Source
O'Brart (2011)[70]

Table 44 Comparison of CCT between CXL and sham treated eyes at 36 months follow-up

Baseline CCT Mean ± SD µm		CCT at 36 months Mean ± SD µm	
CXL	Sham	CXL	Sham
468.8 ± 27.8	466.8 ± 25.4	449.2 ± 72	467.3 ± 24
p = 0.91		p = 0.96	

Abbreviations
CCT = central corneal thickness, **CXL** = corneal collagen crosslinking, **SD** = standard deviation, **µm** = micrometres.
Source
Lang (2015)[87]

Table 45 Cylinder at 1 week, 1 month, 3 months and 6 months follow-up and comparison between CXL and sham

Intervention	Mean cylinder ± SD at various follow-up times (Dioptres)				
	Baseline	1 week	1 month	3 months	6 months
CXL	2.62 ± 2.60	2.5 ± 2.24	2.5 ± 1.64	2.0 ±2.03	2.0 ± 1.79*
Sham	2.89 ± 2.11	NR	NR	NR	NR
p value†	p = 0.71	NR	NR	NR	p = 0.01

Abbreviations
CXL = corneal collagen crosslinking, **NR** = not reported, **SD** = standard deviation.
Notes
* Significantly different from baseline (p = 0.01)
† Comparison between sham and CXL group.
Source
Sharma (2015)[84]

Table 46 Mean change from baseline to 18 months and comparison between CXL and no treatment for cylinder

Intervention	Mean cylinder at baseline (Dioptres)	Mean change in cylinder at 18 months (Dioptres)
CXL	-3.8	-0.5
No treatment	-3.92	-0.64
p value	NR	0.9

Abbreviations
CXL = corneal collagen crosslinking, **NR** = not reported, **SD** = standard deviation.
Source
O'Brart (2011)[70]

Table 47 Mean change from baseline to 18 months and comparison between CXL and no treatment for spherical equivalent

Intervention	Mean spherical equivalent at baseline (Dioptres)	Mean change in spherical equivalent at 18 months follow-up (Dioptres)
CXL	-2.34	0.82
No treatment	-2.66	0.11
p value	NR	0.20

Abbreviations
CXL = corneal collagen crosslinking, **SD** = standard deviation.
Notes
Measure of variance not provided.
Source
O'Brart (2011)[70]

Table 48 Comparison of mean change in sphere between CXL and no treatment at 12, 24 and 36 months follow-up

	Baseline Mean ± SD	12 months Mean change ± SD	24 months Mean change ± SD	36 months Mean change ± SD
CXL	-1.40 ± 4.35 µm	0.52 ± 0.45 µm	0.50 ± 0.49 µm	-0.16 ± 0.45 µm
NT	-0.84 ± 4.06 µm	-0.41 ± 0.45 µm	-0.06 ± 0.46 µm	-0.20 ± 0.53 µm
p value	0.520	0.147	0.404	0.948

Abbreviations
CXL = corneal collagen crosslinking, **NT** = no treatment, **SD** = standard deviation.
Source
Wittig-Silva (2014)[72]

Findings: safety

Table 49 Summary of safety outcomes in the systematic review

Outcome	RCT % (n/N)	Case series Median % (range)
Failure to re-epithelise (1 week–26 months)	NR	k = 9 median, 0.0% (range NA)
Stromal oedema (6 weeks–36 months)	k = 1 median, 1.68% (range, NA)	k = 6 median, 17.5% (range, 0.0–70.0%)
Sterile infiltrates (12–36 months)	NR	k = 6 median, 2.5% (range, 0.0–4.0%)
Golden striae (12–24 months)	NR	k = 2 median = NA (range, 43.5–62%)
Stromal haze (3–24 months)	NR	k = 12 median, 9.8% (range, 0.0–100.0%)
Corneal scar formation (1–24 months)	NR	k = 5 median, 0.0% (range, 0.0–6.0%)
Microbial keratitis (12–36 months)	NR	k = 7 median, 0.0% (range: 0.0–3.0%)

Abbreviations
k = number of studies, **NA** = not applicable, **NR** = not reported, **RCT** = randomised controlled trials.
Source
Shalchi (2015)[26]

Table 50 Comparative safety reported in RCTs

	Study ID				
	Hersh (2017a) [66]	**Hersh (2017b) [85]**	**Lang (2015)[87]**	**Wittig-Silva (2014) [72]**	**Wittig-Silva (2008)* [88]**
Study details					
Duration of follow-up (maximum)	12 months	12 months	36 months	36 months	12 months
Keratoconus or ectasia patients	Keratoconus only	Ectasia only (post refractive surgery)	Keratoconus only	Keratoconus only	Keratoconus only
Comparator details	Sham	Sham	Sham	Untreated	Untreated
Safety outcomes					
Keratitis	Punctate keratitis occurring in >5% of patients after CXL <u>3-month follow-up</u> I = 25/102 eyes (25%); C = 8/103 eyes (8%) Ulcerative keratitis One patient, originally assigned to the control group, developed ulcerative keratitis 3 days after crossing over to receive CXL.	Punctate keratitis occurring in >5% of patients after CXL <u>3-month follow-up</u> I = 18/91 eyes (20%); C = 3/88 eyes (3%)	I = 0/15 eyes (0%); C = 0/14 eyes (0%)	NR	NR
Corneal vascularisation	NR	NR	NR	<u>3-year follow-up</u> I = 1/41 eyes (2.4%); C = 1/27 eyes (3.7%)	NR
Sub-epithelial infiltrates	NR	NR	I = 0/15 eyes (0%); C = 0/14 eyes (0%)	NR	NR

	Study ID				
	Hersh (2017a) [66]	**Hersh (2017b) [85]**	**Lang (2015)[87]**	**Wittig-Silva (2014) [72]**	**Wittig-Silva (2008)* [88]**
Epithelial defects or opacities	Reported as adverse event occurring in >5% of patients after CXL 1-week follow-up I = 23/102 eyes (23%); C = 1/103 eyes (1%)	Reported as adverse event occurring in >5% of patients after CXL 1-week follow-up I = 24/91 eyes (26%); C = 3/88 eyes (3%)	Defects post treatment† I = 15/15 eyes (100%); C = 3/14 eyes (21%)	NR	NR
Haze	Reported as adverse event occurring in >5% of patients after CXL 3-month follow-up I = 58/102 eyes (57%); C= 4/103 eyes (4%)‡	Reported as adverse event occurring in >5% of patients after CXL 3-month follow-up I = 62/91 eyes (68%); C = 7/88 eyes (8%)§	Overall I =15/15 eyes (100%); C = 4/14 eyes (29%) p <0.01 (less haze in comparator group) Number of eyes with haze per grade‖ *Grade 0* I = 0/15 (0%); C = 10/14 (71%) *Grade 1* I = 3/15 (20%); C = 1/14 (7%) *Grade 2* I = 11/15 (73%); C = 3/14 (21%) *Grade 3* I = 1/15 (7%); C = 0/14 (0%)	NR	NR

	Study ID				
	Hersh (2017a) [66]	**Hersh (2017b) [85]**	**Lang (2015)[87]**	**Wittig-Silva (2014) [72]**	**Wittig-Silva (2008)* [88]**
Corneal erosions	NR	NR	Overall I = 14/15 eyes (93%); C = 3/14 eyes (21%) p <0.01 (less erosions in comparator group) <u>Number of eyes with erosions per grade‖</u> *Grade 0* I = 1/15 (7%); C = 11/14 (79%) *Grade 1* I = 1/15 (7%); C = 0/14 (0%) *Grade 2* I = 2/15 (13%); C = 1/14 (7%) *Grade 3* I = 9/15 (60%); C = 1/14 (7%) *Grade 4* I = 2/15 (13%); C = 1/14 (7%)	NR	NR
Ocular pain	Reported as adverse event occurring in >5% of patients after CXL <u>3-month follow-up</u> I = 17/102 eyes (17%); C = 3/103 eyes (3%)	Reported as adverse event occurring in >5% of patients after CXL <u>3-month follow-up</u> I = 24/91 eyes (26%); C = 0/88 eyes (0%)	NR	NR	NR
Need for subsequent surgery	NR	NR	I = 0/15 eyes (0%); C = 0/14 eyes (0%)	NR	NR

	Study ID				
	Hersh (2017a) [66]	**Hersh (2017b) [85]**	**Lang (2015)[87]**	**Wittig-Silva (2014) [72]**	**Wittig-Silva (2008)* [88]**
Corneal striae	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 24/102 eyes (24%); C = 12/103 eyes (12%)	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 8/91 eyes (9%); C = 6/88 eyes (7%)	NR	NR	In the intervention group, confocal microscopy revealed some highly reflective striae in the mid-posterior stroma. These were not observed in the control group and were not observed prior to treatment. Striae were most prominent 1–3 months after treatment and became less obvious at subsequent follow-ups.
Blurred vision	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 16/102 eyes (16%); C = 2/103 eyes (2%)	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 15/91 eyes (17%); C = 4/88 eyes (5%)	NR	NR	NR
Photophobia	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I =11/102 eyes (11%); C = 0/103 eyes (0%)	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 17/91 eyes (19%); C = 0/88 eyes (0%)	NR	NR	NR
Conjunctival hyperaemia	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 10/102 eyes (10%); C = 1/103 eyes (1%)	NR	NR	NR	NR

	Study ID				
	Hersh (2017a) [66]	**Hersh (2017b) [85]**	**Lang (2015)[87]**	**Wittig-Silva (2014) [72]**	**Wittig-Silva (2008)* [88]**
Ocular irritation	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 10/102 eyes (10%); C = 1/103 eyes (1%)	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 8/91 eyes (9%); C =1/88 eyes (1%)	NR	NR	NR
Dry eye	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 6/102 eyes (6%); C = 2/103 eyes (2%)	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 13/91 eyes (14%); C = 4/88 eyes (5%)	NR	NR	NR
Increased lacrimation	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 5/102 eyes (5%); C = 0/103 eyes (0%)	Reported as adverse event occurring in >5% of participants after CXL 3-month follow-up I = 9/91 eyes (10%); C = 1/88 eyes (1%)	NR	NR	NR

Abbreviations

AE = adverse event, **C** = comparator, **CXL** = corneal collagen crosslinking, **I** = intervention, **ID** = identification, **NR** = not reported, **SD** = standard deviation.

Notes

*This study reports preliminary findings for a subset of patients from the same RCT as Wittig-Silva (2014).

† Authors note that epithelial defects in the intervention group were due to removal of epithelium whilst those in the control group were probably due to drying of the ocular surface (despite intensive eye drop application during the CXL process).

‡ Authors note that after 12 months all but 2 eyes showed a complete resolution of haze (unclear which treatment group these eyes belong to).

§ Authors note that after 12 months all but 5 eyes showed a complete resolution of haze (unclear which treatment group these eyes belong to).

‖ Both haze and corneal erosions appear to have been categorised into grades but the grading system was not reported in the study.

Research question 1b

Characteristics of included studies

Table 51 Characteristics of included studies assessing clinical efficacy and safety of accelerated CXL

Author; Year; Country	Inclusion criteria; Sample size	Design; Eye allocation type*; Setting; Follow-up	Intervention; Comparator	Relevant outcomes
Systematic review				
Kobashi (2020)[69] Japan (countries of included studies: Norway, Iran, Egypt, India)	Studies discussing progressive keratoconus included. Progressive keratoconus defined as increase ≥1D in steepest K, degradation of VA and an increase ≥1D in manifest cylinder over proceeding 12 months. Human studies, published in English, comparing standard CXL with accelerated CXL, with at least 12 months follow-up were eligible for inclusion. n = 6 RCTs (379 eyes)	Systematic review, Level I NR NR 12 months	***Accelerated CXL*** Epithelium off, UVA ≥9mW/cm^2 for ≤10 minutes ***Standard CXL***†	***Clinical efficacy*** BSCVA, UCVA, CCT, K_{max}, Cylinder, SE ***Safety*** Complications
RCTs				
Hashemi (2020)[77]‡ Iran	Patients aged 15–35 years with detected progression of keratoconus, keratometry <55D and MCT >400µm. n = 62 eyes	RCT, open-label A Single centre Recruited from Noor Eye Hospital, Tehran, Iran 48 months	***Accelerated CXL*** Epithelium off, UVA 18mW/cm^2 for 5 minutes ***Standard CXL***†	***Clinical efficacy*** UDVA, CDVA, CCT, TCT, K_{max}, K_{min}, Cylinder, SE ***Safety*** Complications

Iqbal (2020)[78] Egypt	Patients aged <18 years with documented progression of keratoconus (Amsler-Krumeich Grade I-III), TCT >400µm. n = 271 eyes	RCT, open-label A Multicentre Treated at three major private Egyptian eye centres in Sohag, Zagazig and Cairo. 24 months	***Accelerated CXL 1§*** Epithelium off, UVA 30mW/cm^2 for 4 minutes ***Accelerated CXL 2*** Transepithelial using riboflavin 0.25%, benzalkonium chloride and hydroxypropyl methylcellulose and UVA 45mW/cm^2 for 2 minutes and 40 seconds ***Standard CXL***†	***Clinical efficacy*** UDVA, CDVA, Pachymetry, K_{max}, Sphere, Cylinder, SE ***Safety*** Complications
Eissa (2019)[75] Egypt	Patients aged <16 years, TCT ≥400µm, clear cornea with documented diagnosis of bilateral keratoconus. N = 68 eyes	RCT, double-blind A Single centre Treated at Magrabi Aseer Specialized Eye Hospital in the Kingdom of Saudi Arabia 36 months	***Accelerated CXL*** Transepithelial CXL, UVA 18mW/cm^2 for 5 minutes ***Standard CXL***†	***Clinical efficacy*** UCVA, CDVA, CCT, K_{max}, MRSE ***Safety*** Complications
Hagem (2019)[76]‖ Norway	Patients with progressive keratoconus over preceeding 3–12 months. Progression defined by at least one of the following: increase ≥1D in K_{max}, increase ≥1D in corneal cylinder, or minimum decrease in SE of 0.5D. Corneal thickness >360µm. n = 40 eyes	RCT, open-label B Single centre Treated at Department of Ophthalmology, Oslo University Hospital, Oslo, Norway 24 months	***Accelerated CXL*** Epithelium off, UVA 9mW/cm^2 for 10 minutes ***Standard CXL***†	***Clinical efficacy*** UDVA, CDVA, K_{max}, K_{mean}, K_1, K_2 ***Safety*** Complications

Choi (2017)[90] South Korea	Patients with progressive keratoconus (documented by serial topography). Progression defined as: increase >1.5D in K_{max} and decrease >5% in TCT. n = 28 eyes	RCT, open-label A/B Single centre Treated at Severance Hospital, Seoul, South Korea 6 months	***Accelerated CXL*** Epithelium off, UVA 30mW/cm^2 for 3 minutes ***Standard CXL***†	***Clinical efficacy*** BCDVA, $K_{max,}$, K_{mean}, K_{min}, Sphere, Cylinder, SE ***Safety*** None
Ramjzoo (2017)[91] Iran	Patients with documented keratoconus (progression observed in preceding 3 months) and refractive error >2D. Corneal thickness >400µm. n = 40	RCT, open-label A NR 6 months	***Accelerated CXL*** Epithelium off, UVA 18mW/cm^2 for 5 minutes ***Standard CXL***†	***Clinical efficacy*** BCVA, TCT, $K_{max,}$ K_1, K2, Sphere, Cylinder, SE ***Safety*** None

Abbreviations

BCDVA = best corrected distance visual acuity, **BCVA** = best corrected visual acuity, **BSCVA** = best spectacle corrected visual acuity, **CCT** = central corneal thickness, **CDVA** = corrected distance visual acuity, **CXL** = corneal collagen crosslinking, **D** = dioptres, $\mathbf{K_{max}}$ = maximum keratometry score, $\mathbf{K_{mean}}$ = mean keratometry score, $\mathbf{K_{min}}$ = minimum keratometry score, $\mathbf{K_1}$ = flattest meridian keratometry, $\mathbf{K_2}$ = steepest meridian keratometry, **MCT** = minimum corneal thickness, **MRSE** = manifest refraction spherical equivalent, **NR** = not reported, **RCT** = randomised controlled trial, **SE** = spherical equivalent, **TCT** = thinnest corneal thickness, **UCVA** = uncorrected visual acuity, **US** = ultrasound, **UVA** = ultraviolet light A, **VA** = visual acuity.

Notes

***** Eye allocation type either: A – both eyes of same patient included, or B – one eye from each patient included, or mixture of both.

† Standard CXL describes the Dresden protocol (epithelium removed, UVA 3mW/cm^2 for 30 minutes)**.**

‡ This study reports longer term outcomes (48 months) for the same RCT (Hashemi 2015) included in the systematic review by Kobashi (2020).

§ Results for epithelium off accelerated variant reported only.

‖ This study reported longer-term outcomes (24 months) for the same RCT (Hagem 2017) included in the systematic review by Kobashi (2020).

Table 52 Characteristics of included studies assessing clinical efficacy and safety of transepithelial CXL

Author; Year; Country	Inclusion criteria; Sample size	Design; Eye allocation type*; Setting; Follow-up	Intervention; Comparator	Relevant outcomes
Systematic reviews				
Zhang (2018)[81] China (countries of included studies: Italy, the Netherlands,India and Russia)	RCTs of patients diagnosed with progressive keratoconus, mean age >18 years, comparing standard CXL with transepithelial CXL (including iontophoresis-assisted techniques). n = 6 RCTs (344 eyes)	Systematic review, Level I NR NR 24 months	***Transepithelial CXL*** Epithelium kept on and UVA 3mW/cm^2 for 30 minutes ***Standard CXL†*** Two studies used iontophoresis to assist ribiflavin saturation	***Clinical efficacy*** UDVA, CDVA, CCT, K_{mean}, K_1, K_2, SE ***Safety*** Complications
RCTs				
Bamdad (2020)[67] Iran	Patients with bilateral keratoconus (according to Rabinowitz criteria for patients aged 18–25 years). Progression defined as increase ⩾ 1D in K_{mean} or reduction ⩾one line in BCVA within preceeding 12 months. n = 60 eyes	RCT, double-blind A Single centre Treated at Khalili Hospital 6 months	***Transepithelial CXL*** Epithelium kept on but disrupted using epithelium disrupter. UVA irradiation at 9mW/cm^2 for 10 minutes ***Standard CXL*** Epithelium removed. UVA delivery consistent with transepithelial group	***Clinical efficacy*** BSCVA, UCVA, TCT, K_{mean}, SE ***Safety*** None
Al Zubi (2019)[74] Jordan	Patients with keratoconus aged ⩾18 years with documented progression defined as increase >0.5D (over preceeding 6 months) or increase >1D (over preceeding 12 months) in steepest K, plus keratometry 46–56D and TCT ⩾400µm. n = 80 eyes	RCT, open-label B Single centre Tertiary care setting 12 months	***Transepithelial CXL*** Epithelium kept on. Riboflavin drops administered every 3–5 minutes for 30 minutes. UVA radiation applied at 3mW/cm^2 for 30 minutes ***Standard CXL†***	***Clinical efficacy*** CDVA, CCT, K_{mean}, SE ***Safety*** Complications

Lombardo (2019)[79]§ Italy	Patients with confirmed progressive keratoconus defined by increase ⩾1D in K_{max} (derived from Placido disk topography) over preceeding 12 months. n = 34 eyes	RCT, open-label A/B Single centre Conducted at clinical trials centre of Istituto di Ricovero e Cura a Carattere Scientifico Fondazione G.B. Bietti, Rome, Italy 24 months	***Transepithelial CXL*** Epithelium kept on. Sterile Biopore membrane attached to plastic cylinder pressed against central cornea to remove precorneal mucin layer. Corneal soaking with riboflavin solution performed using commercial iontophoresis device, after which, UVA applied at 10mW/cm^2 for 9 minutes ***Standard CXL†***	***Clinical efficacy*** UDVA, CDVA, CCT, K_{max}, SE ***Safety*** Complications
Cifariello (2018)[92] Italy	Patients aged 18–40 years with progressive keratoconus documented through clinical and instrumental (topographic, pachymetric, aberrometric) worsening in preceeding 6 months. No corneal scarring. n = 40 eyes	RCT, open-label A/B Single centre Conducted at University of Molise, Italy 24 months	***Transepithelial CXL*** Epithelium kept on. Corneal imbibition obtained with 0.1% riboflavin-15% dextran solution with tris-hydroxymethylamiuno-methane and ethylenediam inetetraacectic acid solution. UVA radiation applied at 3mW/cm^2 for 30 minutes ***Standard CXL†***	***Clinical efficacy*** BCVA, MCT, K_{mean}, K_1, K_2 ***Safety*** Complications
Al Fayez (2015)[73] Saudi Arabia	Patients with documented progressive keratoconus (Amsler-Krumeich stage I–II) with corneal thickness ⩾400μm, K_{mean} ⩽53D and clear cornea with no Vogt striae. Progression defined as increase ⩾1D in K_{max} or manifest astigmatism within preceeding 12 months based on corneal topography. n = 70 eyes	RCT, open-label B Multicentre Conducted at The Eye and Laser Centre and King Abdulaziz University Hospital 36 months	***Transepithelial CXL*** Epithelium kept on. Corneal light shield used to prolong riboflavin availability. UVA irradiation begun after confirming stromal saturation. CXL performed using UVA 3mW/cm^2 for 30 minutes ***Standard CXL†***	***Clinical efficacy*** UCVA, CDVA, Corneal thickness, K_{max}, Refraction ***Safety*** Complications

Stojanovic (2014)[80] Norway	Patients with documented progression of keratoconus (Amsler-Krumeich stage II–III) during preceeding 12 months. Progression defined as increase of 1D of astigmatism or myopia or increase of 1.5D in K_{mean}. TCT ≥400µm. n = 40 eyes	RCT, open-label A Single centre Conducted at the Eye Department of University Hospital North Norway, Tromsø, Norway 12 months	***Transepithelial CXL*** Epithelium kept on. Riboflavin solution without dextran applied until riboflavin saturation verified by slit-lamp inspection. CXL performed using UVA 3mW/cm^2 for 30 minutes ***Standard CXL†***	***Clinical efficacy*** UDVA, CDVA, Pachymetry, K_{max}, K_1, K_2, Cylinder, SE ***Safety*** Pain

Abbreviations

BCVA = best corrected visual acuity, **BSCVA** = best spectacle corrected visual acuity, **CCT** = central corneal thickness, **CDVA** = corrected distance visual acuity, **CXL** = corneal collagen crosslinking, **D** = dioptres, **K_{max}** = maximum keratometry score, **K_{mean}** = mean keratometry score, **K_{min}** = minimum keratometry score, **K_1** = flattest meridian keratometry, **K_2** = steepest meridian keratometry, **MCT** = minimum corneal thickness, **MRSE** = manifest refraction spherical equivalent, **NR** = not reported, **RCT** = randomised controlled trial, **SE** = spherical equivalent, **TCT** = thinnest corneal thickness, **UCVA** = uncorrected visual acuity, **UDVA** = uncorrected distance visual acuity, **US** = ultrasound, **UVA** = ultraviolet light A, **VA** = visual acuity.

Notes

***** Eye allocation type either: A – both eyes of same patient, or B – one eye from each patient, or mixture of both.

† Standard CXL describes the Dresden protocol (epithelium removed, UVA 3mW/cm^2 for 30 minutes).

‡An accelerated protocol was used in this study in both the transepithelial and control group. For the purposes of reporting the control group will still be referred to as 'standard CXL'.

§ This study reports longer term outcomes (24 months) for the same RCT (Lombardo 2017) included in the systematic review by Zhang (2018).

Table 53 Summary table for AMSTAR appraisal

Question	Kobashi (2020) [69] Accelerated vs standard CXL	Zhang (2018)[81] Transepithelial vs standard CXL
Did the study include a PICO?	**Yes**	**Yes**
Were the methods established a priori and deviations reported?	**No**	**No**
Study design selection criteria explained appropriately?	**No**	**No**
Was a comprehensive literature search strategy used?	**Partial yes**	**Partial yes**
Was study selection performed in duplicate?	**No**	**Yes**
Was data extraction performed in duplicate?	**Yes**	**Yes**
Were excluded studies listed with justification for exclusion?	**No**	**Yes**
Were included studies described in adequate detail?	**Yes**	**Partial yes**
Was risk of bias assessed appropriately for RCTs?	**Yes**	**Partial yes**
Was risk of bias assessed appropriately for NRSIs?	**NA**	**NA**
Were sources of funding reported for included studies?	**No**	**No**
If MA was performed, was the method appropriate?	**Yes**	**Yes**
If MA was performed, was the impact of bias assessed?	**No**	**No**
Was bias accounted for when interpreting/discussing the results?	**No**	**No**
Were sources of heterogeneity discussed?	**Yes**	**Yes**
Was publication bias assessed?	**No**	**Yes**
Were sources of conflicts of interest declared by the authors?	**Yes**	**Yes**
Overall	**Low**	**Low**

Abbreviations
CXL = corneal collage crosslinking.

Findings: efficacy

Table 54 Evidence for standard* versus accelerated CXL

Author (year)	UCVA	BCVA	CCT	TCT	K_{max}	K_{mean}	K_{min}	K_1	K_2	Sphere	Cylinder	SE
Systematic review†												
Kobashi (2020) [69]	↔12mo	↓12mo	↔12mo	NR	↔12mo	NR	NR	NR	NR	NR	↑12mo	↔12mo
RCTs not included in systematic review‡												
Hashemi (2020)§ [77]	↔48mo	↔48mo	↔48mo	↔48mo	Anterior 3mm ↓48mo‖ Anterior 8mm ↓48mo‖ Posterior ↔48mo	NR	Anterior 3mm ↔48mo Posterior ↔48mo	NR	NR	NR	↔48mo	↔48mo
Iqbal (2020) [78]	↓6mo ↔12mo ↓24mo	↔6mo ↓12mo ↓24mo	NR	↑6mo ↑12mo ↑24mo	↔6mo ↔12mo ↓24mo	NR	NR	NR	NR	↓6mo ↔12mo ↓24mo	↔6mo ↔12mo ↓24mo	↔6mo ↔12mo ↓24mo
Eissa (2019) [75]	↑12mo ↑24mo ↑36mo	↑12mo ↑24mo ↑36mo	↔12mo ↔24mo ↔36mo	NR	↑12mo ↑24mo ↑36mo	NR	NR	NR	NR	NR	NR	NR
Hagem (2019) §[76]	↔24mo	↔24mo	NR	NR	↔24mo	↔24mo	NR	↔24mo	↔24mo	NR	NR	NR
Choi (2017) [90]	NR	↔6mo	NR	NR	↓6mo PC ↔6mo AKR	↓6mo PC ↔6mo AKR	↔6mo PC ↔6mo AKR	NR	NR	↔6mo	↔6mo	↔6mo
Ramjzoo (2017) [91]	NR	↔6mo	NR	↔6mo	↔6m	NR	NR	↔6mo	↔6mo	↔6mo	↔6mo	↔6mo
Summary	Varied 6–48mo	Varied 6–48mo	↔12–48mo	↔6–48mo	↔6mo ↑12–48mo	↔6–24mo	↔6–48mo	↔6–24mo	↔6–24mo	↔/↓6–12mo ↓24mo	↔6–48mo	↔6–12mo Varied 12–48mo

Abbreviations

AKR = auto kerato-refractometer, **BCVA** = best corrected visual acuity, **CCT** = central corneal thickness, $\mathbf{K_{max}}$ = maximum keratometry score, $\mathbf{K_{mean}}$ = mean keratometry score, $\mathbf{K_{min}}$ = minimum keratometry score, $\mathbf{K_1}$ = flattest meridian keratometry, $\mathbf{K_2}$ = steepest meridian keratometry, **mo** = months, **NR** = not reported, **PC** = pentacam, **RCT** = randomised controlled trial, **SE** = spherical equivalent, **TCT** = thinnest corneal thickness, **UCVA** = uncorrected visual acuity.

Notes

* Standard CXL describes the Dresden protocol (epithelium removed, UVA 3mW/cm^2 for 30 minutes).

† The most recent and up-to-date systematic review of randomised controlled trial evidence identified on this variation.

‡ RCTs either published after the systematic review search date or within the systematic review search data but not included in the review.

§This study provides longer term follow-up for the same RCT included in the systematic review by Kobashi (2020).

‖ Subgroup analyses indicated the significant improvement in K_{max} was only apparent for peripheral keratoconus (not central keratoconus).

Key

Outcomes indicate direction of effects at various follow-up times: ↑ = statistically significant effect in favour of variant (accelerated CXL). ↓= statistically significant effect in favour of standard CXL technique. ↔ = not statistically different. (↑) = statistical analysis not carried out, but results favour variant. (↓) = statistical analysis not carried out, but results favour standard CXL technique. (↔) = statistical analysis not carried out, but results indicate no difference.

Table 55 Mean change in UCVA and BCVA between standard and accelerated CXL over time

Follow-up	Change in UCVA* (logMAR) Mean ± SD	Change in BCVA* (logMAR) Mean ± SD
6 months	CXL = - 0.14 ± 0.07 ACXL = - 0.09 ± 0.05 p = 0.0007	CXL = - 0.07 ± 0.07 ACXL = - 0.06 ± 0.04 p = 0.08
12 months	CXL = - 0.18 ± 0.11 ACXL = - 0.16 ± 0.05 p = 0.09	CXL = - 0.20 ± 0.16 ACXL = - 0.11 ± 0.07 p = 0.004
24 months	CXL = - 0.26 ± 0.12 ACXL = - 0.04 ± 0.22 p = 0.0001	CXL = - 0.24 ± 0.18 ACXL = - 0.03 ± 0.21 p = 0.0001

Abbreviations
ACXL = accelerated corneal collagen crosslinking, **BCVA** = best corrected visual acuity, **CXL** = corneal collagen crosslinking, **SD** = standard deviation, **UCVA** = uncorrected visual acuity.
Notes
*Changes are postoperative minus preoperative values
Source
Iqbal (2020)[78]

Table 56 Comparison of UCVA and BCVA between standard and accelerated CXL at 12, 24 and 36 months follow-up

Visual acuity	Baseline	12 months	24 months	36 months
UCVA (logMAR) mean ± SD	CXL = 0.21 ± 1.10 ACXL = 0.18 ± 1.40 p = 0.12	CXL = 0.20 ± 1.00 ACXL = 0.11 ± 1.60 p <0.05	CXL = 0.20 ± 0.92 ACXL = 0.11 ± 1.52 p <0.05	CXL = 0.20 ± 1.0 ACXL = 0.11 ± 1.60 p <0.05
BCVA (logMAR) mean ± SD	CXL = 0.10 ± 1.22 ACXL = 0.08 ± 1.22 p = 0.321	CXL = 0.06 ± 1.22 ACXL = 0.03 ± 1.60 p <0.05	CXL = 0.06 ± 1.40 ACXL = 0.03 ± 1.40 p <0.05	CXL = 0.06 ± 1.3 ACXL = 0.03 ± 1.52 p <0.05

Abbreviations
ACXL = accelerated corneal collagen crosslinking, **BCVA** = best corrected visual acuity, **CXL** = corneal collagen crosslinking, **SD** = standard deviation, **UCVA** = uncorrected visual acuity.
Source
Eissa (2019)[75]

Table 57 Mean change in TCT between standard and accelerated CXL over time

Follow-up	Change in TCT (µm)* Mean ± SD
6 months	CXL = - 3.54 ± 2.54 ACXL = - 1.14 ± 3.34 p = 0.02
12 months	CXL = - 4.6 ± 8.83 ACXL = - 3.5 ± 7.85 p = 0.04
24 months	CXL = - 8.9 ± 14.95 ACXL = - 3.71 ± 7.76 p = 0.01

Abbreviations
ACXL = accelerated corneal collagen crosslinking, **CXL** = standard corneal collagen crosslinking, **SD** = standard deviation, **TCT** = thinnest corneal thickness.
Notes
*Changes are postoperative minus preoperative values
Source
Iqbal (2020)[78]

Table 58 Change in K_{max} / comparison of K_{max} between standard and accelerated CXL over time

Timepoint	Iqbal (2020) Change in K_{max} (D)* Mean ± SD	Eissa (2019) Mean ± SD K_{max} (D)	Choi (2017) Change in K_{max} (D)* Mean ± SD
Baseline	NA	CXL = 47.19 ± 1.62 ACXL = 46.87 ± 0.77 p = 0.308	NA
6 months	CXL = - 0.43 ± 0.65 ACXL = - 0.32 ± 0.53 p = 0.38	NR	CXL = - 0.55 ± 0.89 ACXL = - 0.32 ± 0.86 p = 0.015
12 months	CXL = - 0.60 ± 0.85 ACXL = - 0.58 ± 0.93 p = 1.00	CXL = 46.41 ± 1.59 ACXL = 45.47 ± 0.44 p <0.05	NR
24 months	CXL = - 1.17 ± 1.01 ACXL = - 0.23 ± 1.17 p = 0.0001	CXL = 46.43 ± 1.43 ACXL = 45.48 ± 0.44 p <0.05	NR
36 months	NR	CXL = 46.45 ± 1.43 ACXL = 45.47 ± 0.54 p <0.05	NR

Abbreviations
ACXL = accelerated corneal collagen crosslinking, **CXL** = standard corneal collagen crosslinking, **D** = dioptres, **NR** = not reported, **SD** = standard deviation.
Notes
*Changes are postoperative minus preoperative values
Source
Iqbal (2020)[78], Choi (2017)[90] and Eissa (2019)[75]

Table 59 Change in K_{max} measurements at 48 months follow-up

Location of K_{max} measurement	Change in K_{max} (D) at 48 months* Mean ± SD
Anterior 3 mm	CXL = -1.35 ± 1.39 ACXL = - 0.36 ± 1.10 p = 0.011
Anterior 8 mm	CXL = - 1.50 ± 1.82 ACXL = - 0.37 ± 1.58 p = 0.029
Posterior	CXL = 0.02 ± 0.26 ACXL = 0.06 ± 0.14 p = 0.575

Abbreviations
ACXL = accelerated corneal collagen crosslinking, **CXL** = standard corneal collagen crosslinking, **D** = dioptres, **SD** = standard deviation.
Notes
*Changes are postoperative minus preoperative values
Source
Hashemi (2020)[77]

Table 60 Mean change in sphere, cylinder and spherical equivalent between standard and accelerated CXL over time

Follow-up	Change in sphere (D)* Mean ± SD	Change in cylinder (D)* Mean ± SD	Change in SE (D)* Mean ± SD
6 months	CXL = 0.37 ± 0.28 ACXL = 0.25 ± 0.12 p = 0.02	CXL = 0.07 ± 0.20 ACXL = 0.09 ± 0.18 p = 0.87	CXL = 0.40 ± 0.28 ACXL = 0.30 ± 0.16 p = 0.08
12 months	CXL = 0.60 ± 0.35 ACXL = 0.49 ± 0.24 p = 0.06	CXL = 0.21 ± 0.016 ACXL = 0.21± 0.23 p = 0.94	CXL = 0.69 ± 0.35 ACXL = 0.65 ± 0.27 p = 0.71
24 months	CXL = 1.09 ± 1.11 ACXL = 0.20 ± 0.74 p = 0.0001	CXL = 0.31 ± 0.19 ACXL = 0.01 ± 0.45 p = 0.001	CXL = 1.23 ± 0.12 ACXL = 0.20 ± 0.92 p = 0.0001

Abbreviations
ACXL = accelerated corneal collagen crosslinking, **CXL** = standard corneal collagen crosslinking, **D** = dioptres, **SD** = standard deviation, **SE** = spherical equivalent.
Notes
*Changes are postoperative minus preoperative values
Source
Iqbal (2020)[78]

Table 61 Evidence for transepithelial versus standard* CXL

Author (year)	UCVA	BCVA	MCT	CCT	TCT	K_{max}	K_{mean}	K_1	K_2	Sphere	Cylinder	SE
Systematic review †												
Zhang (2018)[81]‡	↔6–24mo	↔6–24mo	NR	↓6–24mo	NR	NR	↓6–24mo	↔6–24mo	↔6–24mo	NR	NR	↔6–24mo
RCTs not included in systematic review §												
Bamdad (2020)[67]	↔6mo	↔6mo	NR	NR	↑6mo	NR	↔6mo	NR	NR	NR	NR	↔6mo
Al Zubi (2019)[74]	NR	↔3mo ↔6mo ↔12mo	NR	↔6mo ↔12mo	NR	NR	↔3mo ↔6mo ↔12mo	NR	NR	NR	↔3mo ↔6mo ↔12mo	↔3mo ↔6mo ↔12mo
Lombardo (2019)[79] ‖	↔24mo	↔24mo	NR	↔24mo	NR	↔24mo	NR	NR	NR	NR	NR	↔24mo
Cifariello (2018)[92]	NR	↓24mo	↔24mo	NR	NR	NR	↔24mo	↓24mo	↓24mo	NR	NR	NR
Al Fayez (2015)[73]	↔3mo ↔6mo ↓12mo ↓24mo ↓36mo	↔6mo ↔12mo ↔24mo ↔36mo	‘corneal thickness’ ↔36mo			↔ 3mo ↔ 6mo ↓12mo ↓24mo ↓36mo	NR	NR	NR	‘refraction’ ↔36mo		
Stojanovic (2014)[80]	↔1mo ↔6mo ↔12mo	↔1mo ↔6mo ↔12mo	‘pachymetry’ ↔1mo ↔6mo ↔12mo			↔1mo ↔6mo ↔12mo	NR	↔1mo ↔6mo ↔12mo	↔1mo ↔6mo ↔12mo	NR	↔1mo ↔6mo ↔12mo	↔1mo ↔6mo ↔12mo
Summary	↔3-6mo ↓ 12–36mo	↔6–36mo	↔6–36mo			↔1–12mo ↓ 12–36mo	↔3–24mo	↔1–12mo ↓ 24mo	↔1–12mo ↓ 24mo	↔1–36mo		

Abbreviations

BCVA = best corrected visual acuity, **CCT** = central corneal thickness, K_{max} = maximum keratometry score, K_{mean} = mean keratometry score, K_{min} = minimum keratometry score, K_1 = flattest meridian keratometry, K_2 = steepest meridian keratometry, **MCT** = mean corneal thickness, **mo** = months, **NR** = not reported, **RCT** = randomised controlled trial, **SE** = spherical equivalent, **TCT** = thinnest

corneal thickness, **UCVA** = uncorrected visual acuity.

Notes

***** Standard CXL describes the Dresden protocol (epithelium removed, UVA 3mW/cm^2 for 30 minutes).

†The most recent and up-to-date systematic review of randomised controlled trial evidence identified on this variation.

‡The time point at which the data was meta-analysed was not reported. It is possible data was pooled across various time points.

§ RCTs either published after the systematic review search date or within the systematic review search data but not included.

‖ This study provides longer term follow-up for the same RCT included in the systematic review by Zhang (2018).

Key

Outcomes indicate direction of effects at various follow-up times ↑ = statistically significant effect in favour of variant (transepithelial CXL). ↓ = statistically significant effect in favour of standard CXL technique. ↔ = not statistically different. (↑) = statistical analysis not carried out, but results favour variant. (↓) = statistical analysis not carried out, but results favour standard CXL technique. (↔) = statistical analysis not carried out, but results indicate no difference.

Table 62 UCVA at 12, 24 and 36 months follow-up

	UCVA (mean ± logMAR)			
	Baseline	**12 months**	**24 months**	**36 months**
Transepithelial CXL	0.9 ± 0.2	-0.1	0.06	0.1
Standard CXL	0.8 ± 0.3	-0.14	-0.18	-0.2
p value	0.45	0.007	<0.0001	<0.0001

Abbreviations
CXL = corneal collagen crosslinking, **D** = dioptres, **SD** = standard deviation, **UCVA** = uncorrected visual acuity.
Notes
Values estimated from Figure 2 provided by Al Fayez (2015) using WebPlotDigitizer.[83]
Source
Al Fayez (2015)[73]

Table 63 TCT at 6 months follow-up

	TCT (mean ± SD µm)	
	Baseline	**6 months**
Transepithelial CXL	455.80 ± 32.70	451.90 ± 39.70
Standard CXL	459.20 ± 37.4	433.50 ± 33.50
p value	0.70	0.0001

Abbreviations
CXL = corneal collagen crosslinking, **SD** = standard deviation, **TCT** = thinnest corneal thickness.
Source
Bamdad (2020)[67]

Table 64 K_1 and K_2 at 24 months follow-up

	K_1 (mean ± SD D)		K_2 (mean ± SD D)	
	Baseline	**24 months**	**Baseline**	**24 months**
Transepithelial CXL	45.84 ± 2.53	46.44 ± 3.67	48.86 ± 3.27	49.75 ± 3.47
Standard CXL	44.62 ± 2.63	44.71 ± 3.03	47.75 ± 3.20	47.76 ± 3.47
p value	NR	0.01	NR	0.01

Abbreviations
CXL = corneal collagen crosslinking, **D** = dioptres, **K_1** = flattest meridian keratometry, **K_2** = steepest meridian keratometry, **SD** = standard deviation.
Source
Cifariello (2018)[92]

Table 65 K_{max} at 12, 24 and 36 months follow-up

	K_{max} (mean ± SD D)			
	Baseline	**12 months**	**24 months**	**36 months**
Transepithelial CXL	NR	-0.75	0.75	1.1
Standard CXL	NR	-1.62	-2.19	-2.44
p value	NR	0.0007	<0.0001	<0.0001

Abbreviations
CXL = corneal collagen crosslinking, **D** = dioptres, **K_{max}** = maximum keratometry, **SD** = standard deviation.
Notes
Values estimated from Figure 1 provided by Al Fayez (2015) using WebPlotDigitizer,[83]
Source
Al Fayez (2015)[73]

Findings: safety

Table 66 Evidence for safety for accelerated versus standard* CXL

Author (year)	Result
Systematic review†	
Kobashi (2020)[69]	(↔12mo)
RCTs not included in systematic review‡	
Hashemi (2020)[77]§	(↔48mo)
Iqbal (2020)[78]	(↑24mo)
Eissa (2019)[75]	(↔36mo)
Hagem (2019)[76]§	(↔24mo)
Choi (2017)[90]	NR
Ramjzoo (2017)[91]	NR
Summary	↔0–36mo

Abbreviations
CXL = corneal collagen crosslinking, **mo** = months, **NR** = not reported.
Notes
***** Standard CXL describes the Dresden protocol (epithelium removed, UVA 3mW/cm^2 for 30 minutes)**.**
† The most recent and up-to-date systematic review of randomised controlled trial evidence identified on this variation.
‡ RCTs either published after the systematic review search date or within the systematic review search data but not included.
§ This study provides longer-term follow-up for the same RCT included in the systematic review by Kobashi (2020).
Key
↑ = statistically significant effect in favour of variant. ↓ = statistically significant effect in favour of standard CXL technique. ↔ = not statistically different. (↑) = statistical analysis not carried out, but results favour variant. (↓) = statistical analysis not carried out, but results favour standard CXL technique. (↔) = statistical analysis not carried out, but results indicate no difference.

Table 67 Evidence for safety for transepithelial versus standard* CXL

Author (year)	Result
Systematic review†	
Zhang (2018)[81]‡	(↑6–24mo)

RCTs not included in systematic review§	
Bamdad (2020)[67]	NR
Al Zubi (2019)[74]	(↑3–4mo)
Lombardo (2019)[79]‖	NR
Cifariello (2018)[92]	(↔24mo)
Al Fayez (2015)[73]	↑intraoperative(comfort) (↔6mo)
Stojanovic (2014)[80]	↔average pain score ↑pain length
Summary	↔/ ↑ 0–4mo

Abbreviations

CXL = corneal collagen crosslinking, **mo** = months, **NR** = not reported.

Notes

***** Standard CXL describes the Dresden protocol (epithelium removed, UVA 3mW/cm^2 for 30 minutes).

† The most recent and up-to-date systematic review of randomised controlled trial evidence identified on this variation.

‡The time point at which the data was meta-analysed was not reported. It is possible data was pooled across various time points.

§ RCTs either published after the systematic review search date or within the systematic review search data but not included.

‖ This study provides longer-term follow-up for the same RCT included in the systematic review by Zhang (2018).

Key

↑ = statistically significant effect in favour of variant. ↓ = statistically significant effect in favour of standard CXL technique. ↔ = not statistically different. (↑) = statistical analysis not carried out, but results favour variant. (↓) = statistical analysis not carried out, but results favour standard CXL technique. (↔) = statistical analysis not carried out, but results indicate no difference.

14.6 Appendix F: Other HTAs

Five Health Technology Assessment Reports were identified that evaluated the clinical efficacy and/or safety of CXL compared with sham or no treatment (***Table 68***) and one Health Technology Assessment Report was identified that evaluated the clinical efficacy and/or safety of standard CXL compared with standard and accelerated CXL (***Table 69***).

Table 68 List of HTAs evaluating the efficacy and/or safety of CXL compared with sham or no treatment

Author year	Title	Databases searched and search date	Inclusion criteria	Exclusion criteria	Studies included and conclusions on clinical efficacy of CXL	Studies included and conclusions on safety of CXL	Cost-effectiveness of CXL
Health Technology Wales 2018[155]	Clinical and cost efficacy of epithelium-off corneal cross-linking (CXL) to treat adults with keratoconus	*Databases searched* Medline, Embase and the Cochrane database of systematic reviews, plus guideline and technology appraisal databases and websites relevant to healthcare and government in Wales. *Search date* 23–25 August 2017	SRs of RCTs and economic studies published after 2000 or RCTs published after 2013 reporting outcomes in adults with keratoconus undergoing epithelium-off CXL compared with accelerated CXL, contact lenses, glasses or no treatment. Outcomes of interest included: changes in maximal keratometry, corneal power/thickness,	After the most relevant SR was determined, RCTs published before its end-search date (January 2016) were excluded, and any RCT with less than 1-year follow-up (in line with the included SR).	*Studies included* 1 SR (including 5 RCTs) *Conclusions* *Thinnest corneal thickness* NS difference between groups. Mean difference 1.46 µm (95% CI -2.77, 5.68) p = 0.50 *BCVA* Significant difference between groups in favour of CXL. Mean difference -0.09 logMAR (95% CI -0.14, -0.04) p = 0.0005 The authors note this difference is unlikely to reflect a clinically significant difference. An expert reviewer for Health Technology Wales proposed	*Studies included* Same SR as for efficacy *Conclusions* No safety outcomes reported.	Evidence for cost-effectiveness of CXL is limited. A detailed and robust economic model suggests a high likelihood that CXL is cost-effective (dependent on the clinical efficacy and effect duration of CXL).

			UCVA, health related quality of life, delay of disease progression and adverse events.		the difference in rate of deterioration had the potential to become substantial over a longer follow-up period. *Cylindrical refraction* NS difference between groups. Mean difference -0.25 D (95% CI -0.76, 0.26) p = 0.34 *K_{max}* All included RCTs reported a reduction in maximum curvature of the cornea in favour of CXL. Significant heterogeneity in treatment effect size existed for K_{max}, UCVA and SE; therefore, these outcomes were not meta-analysed.		
IQWIG 2016[156]	UV cross-linking with riboflavin in keratoconus	*Databases searched* Medline, Embase, Cochrane *Search date* 28 January 2016	RCTs reporting on morbidity (UCVA, BCVA), pain, foreign body sensation, increased lacrimation, tolerability for contact lenses, indication and performance of corneal transplantation, HRQL and adverse effects	NR	*Studies included* *UCVA* 1 RCT *BCVA* 3 RCTs *Conclusions* *UCVA* Slight benefit shown for standard CXL (epithelium off) compared with purely symptomatic treatment based on outcomes from one study.	*Studies included* 2 RCTs *Conclusions* A negative effect of CXL compared with purely symptomatic treatment was found with regard to temporary (stromal) corneal haze and corneal erosion. Insufficient data on other adverse	NR

					BCVA No hint of benefit or harm found for CXL	events to make a comparison.	
Cochrane Collaboration 2015[157]	Corneal collagen crosslinking for treating keratoconus	*Databases searched* Cochrane Central Register of Controlled Trials, Ovid Medline, EMBASE, Latin American and Caribbean Health Sciences Literature Database, CINAHL, OpenGrey, the MetaRegister of Controlled Trials (mRCT), ClinicalTrials.gov and the World Health Organisation International Clinical Trials Registry Platform. *Search date* 28 August 2014	RCTs with participants of any age diagnosed with keratoconus comparing CXL to no treatment.	Studies with participants who had CXL for conditions other than keratoconus or those who had undergone prior treatment, and trials that compared different ways of doing CXL and did not have a control (no treatment) group.	*Studies included* 3 RCTs (outcomes reported narratively) *Conclusions* *K_{max}* Increases in K_{max} less likely in the CXL group up to 36 months; however, differences not significant. *UCVA* Eyes undergoing CXL had better UCVA at 12 months *Pachymetry* Data inconsistent *SE* One RCT reported no difference at 12 months	*Studies included* 2 RCTs (outcomes reported narratively) *Conclusions* Adverse effects were not uncommon following CXL. They were mostly transient and of low clinical significance. There were no adverse effects reported in the control groups.	NR
HAS 2015[154]	Corneal collagen crosslinking and intra-corneal rings in the treatment of	*Databases searched* Medline, the Pascal database and the Cochrane Library, plus searches of	Prospective controlled trials (randomised or not), or case series of patients with corneal ectasia ('primary',	Non-English or Non-French language publications, medico-economic studies, SRs, general reviews, letters,	Due to a mixed patient population (including keratoconus, pellucid marginal degeneration and post-LASIK corneal ectasia patients) this HTA did not meet our reviews inclusion criteria for	*Studies included* 9 in total (1 RCT, 3 NRC, 5 CS) *Conclusions*	NR

	corneal ectasia	HTA websites and ophthalmology society websites. *Search date* July 2014	including keratoconus and pellucid marginal degeneration or 'secondary', including post-LASIK ectasia), pachymetry ≥400µm, transparent cornea, no history of corneal surgery. Outcomes of interest were K_{max} and adverse events with minimum follow-up of 6 months.	editorials, non-prospective studies, articles without original results, off-topic articles, duplicates, articles with <30 patients, case reports, recommendations for clinical practice or HTAs whose methodological quality was insufficient (e.g. did not include description of literature selection method).	efficacy.	Safety data was collected and reported differently among the included studies. Definitions for complications rarely explained. The main adverse events were infection, infiltrates, corneal oedema, corneal scars and corneal haze. In general, these complications occurred in <10% of patients with the exception of oedema (reported in 0–55% of patients) and haze (reported in 2–100% of patients). Corneal oedema and haze were generally transient.	
NUTH and YHEC 2013[24]	Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus: A	*Databases searched* Medline, Medline in process, Embase, Cochrane library, Cinahl, Science Citation Index, Inspec, Conference Pro-	English language, human studies, patients with keratoconus or keratectasia, studies using photochemical corneal cross-linkage using riboflavin and ultraviolet radiation	Abstracts with no clinical outcomes, non-systematic reviews and editorials, laboratory or animal studies, conference abstracts unless they reported specific adverse events not reported in	This HTA evaluated the efficacy of CXL in terms of pre- vs post-operative outcomes as well as treated vs control groups. Only conclusions from the treated vs control group comparison is discussed below *Studies included*	*Studies included* Evidence to inform safety comprised outcomes from 26 studies investigating safety of the epithelium off technique (23 case studies,	NR

	systematic review	ceedings Citation Index (Web of Science), Science Direct, ZETOC, OAIster, OpenGrey, EuroScan, WorldWideScience.org, ClinicalTrials.gov, International Clinical Trials Registry Platform, Nexis, National Institute for Health Research, Australian Safety and Efficacy Register of New Interventional Procedures (ASERNIP) *Search date* 30 and 31 October 2012 (depending on database)	alone or in combination or in sequence with other treatments, original reports, reports with standardised measurements on outcome events such as technical access, safety, efficacy durability, vision, quality of life or patient satisfaction, systematic reviews, meta-analyses, RCTs, observational studies, retrospective analyses, case series, case studies, letters, comments and conference abstracts	published literature, papers not reporting the outcomes defined in the protocol, papers using CXL on other patient groups, papers published before 2000, non-English studies with no English abstract, *For efficacy outcomes only:* Papers with fewer than 10 patients or less than 6 months follow-up were excluded	*K_{max}* 3 RCTs *Visual acuity* 4 RCTs *Astigmatism* 2 RCTs *Conclusions* *K_{max}* Statistically significant reduction in K_{max} for CXL compared with no treatment arm at 12 months *Visual acuity* No significant differences for UCVA, but a significant improvement in BCVA at 12 months in favour of CXL. However, 1 RCT reporting at 18 months found no significant difference in BCVA between CXL and control groups. *Astigmatism* No significant difference between CXL and control group.	1 RCT and 2 retrospective chart reviews) plus any safety events reported in the 49 papers included for efficacy (also all epithelium off technique). *Conclusions* CXL is generally reported as safe but serious complications do occur including the need for corneal transplants and long-term loss in visual acuity. Most events resolved over time with no major consequences for the patient.	

Abbreviations

BCVA = best corrected visual acuity, **CI** = confidence interval, **CS** = case series, **CXL** = corneal collagen crosslinking, **HAS** = Haute Autorité de Santé, **HRQL** = health-related quality of life, **HTA** = health technology assessment, **IQWIG** = Institut für Qualität und Wirtchaftlichkeit im Gesundheitswesen, **K_{max}** = maximum keratometry, **NR** = not reported, **NRC** = non-randomised comparative study, **NS** = not significant, **NUTH** = Newcastle Upon Tyne Hospitals, **RCTs** = randomised controlled trials, **SR** = systematic review, **UCVA** = uncorrected visual acuity, **YHEC** = York Health Economics Consortium.

Table 69 List of HTAs evaluating the safety and/or clinical efficacy of standard CXL with accelerated or transepithelial CXL

Author year	Title	Databases searched and search date	Inclusion criteria	Exclusion criteria	Studies included and conclusions on clinical efficacy of CXL variations	Studies included and conclusions on safety of CXL variations	Cost-effectiveness of CXL variations
IQWIG 2016[156]	UV crosslinking with riboflavin in keratoconus	*Databases searched* Medline, Embase, Cochrane *Search date* 28 January 2016	RCTs reporting on morbidity (UCVA, BCVA), pain, foreign body sensation, increased lacrimation, tolerability for contact lenses, indication and performance of corneal transplantation, HRQL and adverse effects	NR	*Studies included* *UCVA* 4 RCTs *BCVA* 3 RCTs *Conclusions* *UCVA* For standard vs transepithelial: no difference For standard vs accelerated: no difference *BCVA* For standard vs transepithelial: indication of greater benefit in favour of transepithelial CXL For standard vs accelerated: no difference	*Studies included* 5 RCTs *Conclusions* For standard vs transepithelial: hint of lesser harm for postoperative pain in favour of transepithelial CXL For standard vs accelerated: no difference	NR

Abbreviations

BCVA = best corrected visual acuity, **CXL** = collagen corneal crosslinking, **HTA** = health technology assessment, **IQWIG** = Institut für Qualität und Wirtchaftlichkeit im Gesundheitswesen, **NA** = not applicable, **RCTs** = randomised controlled trials, **UCVA** = uncorrected visual acuity, **UV** = ultraviolet.