IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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UV cross-linking with riboflavin in keratoconus[1]

Extract

[1] Translation of Chapters 1 to 6 of the final report *UV-Vernetzung mit Riboflavin bei Keratokonus* (Version 1.0; Status: 7 October 2016). Please note: This translation is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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The responsibility for the contents of the report lies solely with IQWiG.

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[2] Due to legal data protection regulations, employees have the right not to be named.

Key statement

Research question

The aims of the present investigation are the benefit assessments of corneal collagen cross-linking (CXL) with riboflavin and UVA radiation

- compared with purely symptomatic treatment (research question 1) as well as
- compared with a (different) CXL variant (research question 2)

in each case in patients with progressive keratoconus with regard to patient-relevant outcomes.

Conclusion

For the present benefit assessment, only the results from 3 out of the 7 studies for research question 1 and from 9 of the 12 studies for research question 2 could be used. Three studies per research question did not adequately consider data dependency (analysis unit: eye instead of patient). In a further study the underlying analysis and the results reported were incomprehensible. As in addition enquiries to authors were not answered, a total of 7 studies could not be used.

For the outcome of uncorrected visual acuity, a hint of a benefit was shown for conventional CXL compared with purely symptomatic treatment. This arose solely from the data of one study. For the outcome of best-corrected visual acuity, no hint of a benefit or harm was shown for conventional CXL. With regard to adverse effects of treatment, a hint of harm was shown.

No relevant randomized controlled trials (RCTs) and thus no results were available on the comparison of CXL variants with purely symptomatic treatment.

For the outcomes analysed, the comparison of different variants of conventional CXL showed:

- in favour of the transepithelial variant:
  - an indication of a greater benefit for best-corrected visual acuity
  - a hint of lesser harm for post-procedural pain
  - no hint in favour of or to the disadvantage of this variant for uncorrected visual acuity
- no hint in favour of or to the disadvantage of the accelerated variant for uncorrected visual acuity, best-corrected visual acuity, and adverse effects of treatment
- no hint in favour of or to the disadvantage of a variant with mechanical compression of the cornea for best-corrected visual acuity and adverse effects of treatment

In the comparison of accelerated corneal CXL with 20-minute versus 30-minute pre-procedural administration of riboflavin, the data provided no hint in favour of or to the disadvantage of one of these variants with regard to adverse effects of treatment.

No (usable) data on other patient-relevant outcomes are currently available beyond those named. Across research questions, the currently available (usable) data are to be classified as highly biased and incomplete. However, for both research questions the numerous ongoing or already completed (but so far unpublished) studies indicate that further results can be expected in the near future, especially on the outcome of vision. In summary, it seems advisable to wait for pending study results for a conclusive benefit assessment of CXL.

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List of abbreviations

Abbreviation	Meaning
ANOVA	analysis of variance
CI	confidence interval
CXL	corneal collagen cross-linking
G-BA	Federal Joint Committee (Gemeinsamer Bundesausschuss)
IPD	individual patient data
IQWiG	Institute for Quality and Efficiency in Health Care (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen)
logMAR	logarithm of the minimum angle of resolution
MD	mean difference
mW	milliwatt
RCT	randomized controlled trial
RD	risk difference
UV	ultraviolet radiation
UVA	ultraviolet radiation A

1 Background

With its letter of 26 May 2015, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess ultraviolet (UV) cross-linking with riboflavin in patients with keratoconus.

Keratoconus is a non-inflammatory degenerative disorder of the cornea of the eye, typically occurring in adolescents or young adults as a conical, mostly bilateral deformation of the centre of the cornea with parenchymal opacification and corneal thinning [1,2]. Through a pathological change in tissue structure (corneal collagen), corneal stability decreases, which leads to thinning and conical protrusion [3]. This corneal deformation leads to irregular myopic astigmatism, which, if the disease progresses, cannot be corrected with glasses and represents the main symptom of the disease [3]. Acute symptoms comprise sudden worsening of vision (short-sightedness, distorted vision and multiple images), severe pain, lacrimation, and photophobia [2-4].

Keratoconus is regarded as a rare disease, but is one of the most common corneal diseases [2]. The incidence of keratoconus is estimated to be about 1 in 2000 people of the normal population [5]. In their cohort study, Pearson et al. report that the incidence depends on age and ethnicity [6].

Keratoconus negatively affects vision-related quality of life of the patients affected and leads to increased dependency on outside help [7,8]. The consequences of disease are all the more relevant as typically the disease starts in adolescence or early adulthood and can thus considerably affect the capacity to work and personal development.

The causes of disease are largely unclear. Besides a familial and genetic disposition, among other things the following factors are associated with an increased risk of keratoconus [9,10]:

- atopic disorders, atopic dermatitis, hay fever, allergies, asthma [10-12]
- systemic disorders such as Down syndrome (trisomy 21), Ehler-Danlos syndrome, Marfan syndrome [5,11]
- frequent rubbing of the eyes [9-12]
- contact lenses [11]

In the early stages the course of keratoconus is often subclinical, whereas in later stages, besides the symptoms named above, typical characteristics are evident and, for example, irreversible stromal scars increasingly limit vision [4,10]. The natural course of disease is regarded to be progressive and irreversible, with episodes of increasing corneal thinning and protrusion accompanied by increasing irregular astigmatism and loss of vision [1,3]. In some patients the disease comes to a spontaneous halt in earlier stages. In the event of bilateral disease, the course of disease can differ considerably between the right and left eye [13].

Different classification systems exist for classifying disease severity; the (modified) division into 4 stages according to Amsler/Krumeich is commonly applied [14]. Progression is not uniformly defined either; a common criterion is however the increase of the curvature value by 1 or more dioptres (dpt) within a year [15]. Advanced keratoconus can be diagnosed in a clinical examination with a slit lamp microscope by the following 5 characteristics: Munson sign (conical indentation of the lower eyelid on downgaze), Vogt striae (vertical, parallel lines in the conus area), Fleischer ring (iron deposits below the cone), stromal thinning and corneal scars as the consequence of spontaneous corneal hydrops [4,13]. Furthermore, distorted reflex images of a placido disc or a keratometer lead to a diagnosis. Corneal computer topography can also be used for specific diagnosis; in this procedure, computer-monitored measurement of the corneal surface and structure is performed and the protrusion is displayed as a 3-dimensional coloured image [1,3,4].

So far there is no causally targeted treatment for keratoconus. The limited vision is corrected by glasses in early stages and, in the event of advanced astigmatism, by special soft or rigid contact lenses [4]. However, with increasing corneal protrusion, the fitting of contact lenses is made difficult by the different individual curvature radii and this can lead to an unstable fit as well as a suboptimal correction of vision [2,4]. Under certain preconditions, visual acuity can also be corrected by the implantation of corneal ring segments [4]. In the final stage a corneal transplantation (keratoplasty) is indicated [1-4]. Through UV cross-linking with riboflavin (synonym: corneal collagen cross-linking, CXL), for the first time a potential treatment option is available that aims to prevent or slow down disease progression [16,17].

The original CXL procedure according to the so-called Dresden protocol is performed on an outpatient basis under local anaesthetics and includes mechanical removal of the corneal epithelium [17]. The exposed cornea is initially instilled with riboflavin (vitamin B2). Subsequently the combined application of riboflavin and UVA radiation causes a cross-linking of collagen fibrils via the production of oxygen radicals, which aims to achieve greater corneal stability and stop the deformation [17]. Thus on the one hand riboflavin acts as a photosensitizer and on the other, it has a protective function for deeper lying structures of the eye, as it absorbs UV rays [1,17]. The potential perspective of slower disease progression could be opposed by complications such as post-operative infections, oedema, haze, scarring, and inflammations of the cornea which, except for scarring are reversible [15,16,18,19]. Meanwhile, different variants of the procedure are being investigated, for example transepithelial CXL or accelerated radiation; however, so far the evidence on the benefit and harm of these variants is limited [16,20,21].

2 Research question

The aims of the present investigation are the benefit assessments of CXL with riboflavin and UVA radiation

- compared with purely symptomatic treatment (research question 1) as well as
- compared with a (different) CXL variant (research question 2)

in each case in patients with progressive keratoconus with regard to patient-relevant outcomes.

3 Methods

The target population of the benefit assessment comprised patients with progressive keratoconus. The test intervention was CXL following the conventional procedure with mechanical removal of the corneal epithelium or a variant of the original procedure. The control interventions examined were a purely symptomatic or sham treatment (research question 1) or CXL variants (research question 2). Combinations of CXL with other types of surgery were not the subject of this assessment.

The following patient-relevant outcomes were used for the assessment:

- Morbidity:
  - vision (e.g. uncorrected and best-corrected visual acuity, light und glare sensitivity, contrast vision, distortions [metamorphopsia], multiple and double images),
  - pain (e.g. in the eye, head and neck)
  - foreign body sensation
  - increased lacrimation
  - tolerability for contact lenses
  - Indication for, as well as performance of, a corneal transplantation
- Health-related quality of life (including activities of daily living, dependency on outside help, effects on course of education and occupation)
- Adverse effects of treatment

Subjective outcomes (e.g. health-related quality of life) were only considered if they had been recorded with valid measurement instruments (e.g. validated scales).

Only randomized controlled trials (RCTs) were included in the benefit assessment. No limitation applied for study duration.

A systematic search for primary literature was conducted in the following databases: MEDLINE, Embase, and the Cochrane Central Register of Controlled Trials. In addition, a search for relevant systematic reviews was conducted in MEDLINE and Embase parallel to the search for relevant primary studies as well as by means of a search in the Cochrane Database of Systematic Reviews, the Database of Abstracts of Reviews of Effects, and the Health Technology Assessment Database. The search was conducted on 28 January 2016. Publicly accessible trial registries were also searched for further studies, and systematic reviews, publicly accessible documents from regulatory authorities, documents transferred by the G-BA, and documents provided in the hearing procedure on the preliminary report plan (protocol) were screened. In addition, the authors of relevant study publications were contacted in order to clarify important questions.

The selection of relevant studies was performed by 2 reviewers independently of one another for the results of the searches in bibliographic databases and publicly accessible trial registries as well as for the results of the screening of potentially relevant studies from systematic reviews, of publicly accessible documents of regulatory authorities, and of documents transferred by the G-BA.

Data were extracted into standardized tables. To evaluate the qualitative certainty of results, the risk of bias at study and outcome level was assessed and rated as low or high. The results of the individual studies were described, organized by outcomes.

If the studies were comparable regarding the research question and relevant characteristics, the individual results were pooled quantitatively by means of meta-analyses.

The data of the left and right eye of a patient are usually correlated and thus to be regarded as dependent data. A correlation between the observations has an impact on the analysis of the estimate of the variance of the group difference and thus on the limits of the confidence interval (CI) as well as on statistical significance. Non-consideration of this dependency can lead to marked deviations in results. For all studies included that did not consider the dependency of the eyes in the analysis of patient-relevant outcomes, enquiries were therefore sent to study authors, requesting additional information on the distribution of eyes and patients in the groups as well as either an adequate analysis or alternatively the submission of individual patient data (IPD). If IPD were available, IQWiG performed its own calculations. For the present benefit assessment, correspondingly only results from studies were used in which the dependency of eyes could be considered in the statistical analysis. However, for reasons of transparency and completeness, for the first research question all available results are presented in the details of the report and designated as “Results from studies in which the dependency of eyes was considered” and “Results from studies in which the dependency of eyes was not considered (unusable)”. In contrast, for the second research question only the usable results are presented, as this question does not refer to the basic assessment of the benefit or harm of CXL. The additional information gained from a comprehensive presentation of unusable results was regarded as dispensable here.

4 Results

4.1 Results of information retrieval

After exclusion of duplicates, the systematic literature search in bibliographic databases yielded a total of 543 of hits to be screened. Of these, 266 were not relevant to the topic (minimum inclusion criteria violated) and excluded. A total of 277 documents on the topic remained. Of these, 247 documents violated the detailed criteria for study inclusion and were thus not relevant for the assessment. A further 8 documents on the topic were relevant systematic reviews, which were screened for additional relevant studies. A total of 22 relevant publications were thus identified. These were 6 relevant studies (8 publications) for the first research question and 12 relevant studies (14 publications) for the second research question.

One additional relevant study on the first research question was identified by the search in further information sources (systematic reviews, publicly accessible trial registries, publicly accessible documents of regulatory authorities, documents transferred by the G-BA). Information from enquiries to authors was considered in the assessment. For the first research question, the search in trial registries identified 5 ongoing, 2 discontinued, 1 completed, and 2 studies with unknown status; for the second research question this search identified 10 ongoing, 4 completed, 1 discontinued und 1 study with unknown status, whose relevance could not be conclusively clarified.

4.2 Results on research question 1

4.2.1 Characteristics of the studies included in the assessment

Overall, 7 studies from 6 different countries (Australia, Germany, the United Kingdom, India, Iran, and the United States) were identified as relevant for the first research question of the present benefit assessment (conventional CXL compared with purely symptomatic treatment). These studies were Hersh 2011 [22-24], Lang 2015 [25,26], O'Brart 2011 [27,28], Reidy 2012 [29-32], Seyedian 2014 [33], Sharma 2015 [34], and Wittig-Silva 2014 [35-37]. No RCTs on the assessment of newer CXL variants compared with purely symptomatic treatment were available.

All 7 studies were conducted in a parallel group design, but a switch from the control group to the group treated with CXL was possible in 2 studies. From a methodological point of view, crucial differences in the type of randomization and the statistical analysis existed. In particular, only 4 of the 7 studies (Lang 2015, Reidy 2012, Sharma 2015, Wittig-Silva 2014) provided data for which the dependency of the eyes was considered or could be considered in the analysis. However, these included the study by Sharma 2015, in which the results reported and the underlying methods were incomprehensible and could thus not be used. In a total of 4 studies, a partly or completely bilateral randomization of the patients' eyes was performed, without subsequently considering the dependency of the eyes in the analysis of results. Enquiries to authors were made for these studies. No responses to these enquiries were received for 3 out of 4 studies. Wittig-Silva 2014 was an exception: the authors provided the

requested IPD, so that the study could be considered as usable in the final report. The results available for the other 3 studies remained unusable and are thus only presented in the details of the report for reasons of transparency and completeness.

As the test intervention, all 7 studies performed CXL as the original procedure according to the Dresden protocol (in the following text: conventional CXL), sometimes slightly modified, with the following components:

- use of local anaesthetics
- mechanical removal of the corneal epithelium (radius: 8 to 9 mm)
- instillation of 0.1% isotonic riboflavin solution in 20% dextran, pre- and peri-procedurally, on the exposed cornea (usually at an interval of 2 to 5 minutes for 30 minutes each)
- UVA radiation for 30 minutes: wavelength of 365 to 370 nm, irradiance of 3 mW/cm^2, radiation radius of 8 to 9 mm at a distance of 1.5 to 5.4 cm
- post-procedural care usually with antibiotic eye drops and a dressing lens up to epithelial closure, as well as pro re nata (PRN) medication with painkillers and artificial tears

In the following text, the 7 studies are characterized separately.

Studies in which the dependency of the eyes was considered

The multicentre German study **Lang 2015** included patients with early-stage, progressive keratoconus (refraction correctable with glasses or contact lenses) from the age of 12 years. Computerized randomization was performed per fax, stratified according to centres and on the basis of patients, whereby in each case only the worse eye was allocated either to CXL or sham treatment with fluorescein drops and blue light without prior epithelial removal. Recruitment was discontinued prematurely due to the poor availability of suitable study participants and the limited willingness of suitable participants to be randomized. Only 30 of the 130 patients planned could be recruited for the study and of these, 29 were randomized and analysed, of which 6 (21%) were female; 3 patients discontinued the study (no reasons reported), of which 2 were in the control arm. The median observation period was 36 months.

The unpublished, multicentre US study **Reidy 2012** included patients aged 16 to 35 years with progressive keratoconus with a corneal thickness of ≥ 400 µm, an uncorrected visual acuity of < 20/20 (corresponds to < 1.0) and a maximum corneal refractive power of 47 to 60 dpt. Computerized randomization was performed on the basis of patients, whereby in each case only the worse eye was allocated either to CXL or sham treatment with fluorescein drops and LED fixation light without prior epithelial removal. Due to reasons unknown, the study was stopped prematurely. Of 132 planned patients, only 69 could be recruited for the study and 54 analysed; of these, 18 (33%) were female and 40% wore contact lenses. The study was planned to last 24 months; however, the majority of patients (76%) could not be fully

followed up (median: 15 months). In each case the last available value of the patients was used for the analysis of results.

The single-centre Indian study **Sharma 2015** included patients from the age of 14 years with progressive keratoconus stage ≥ 2 according to the Krumeich classification and with a corneal thickness of ≥ 400 µm. Randomization was performed on the basis of the eyes, which were allocated either to CXL or invasive sham treatment with riboflavin and mechanical removal of the epithelium. A total of 43 eyes of 42 patients, including 35% women, were randomized and analysed. As only one patient had both eyes included in the study (without considering the dependency of the eyes in the analysis) the results of the study were initially still regarded to be usable. However, relevant study information was missing and enquiries to the authors were not answered, so that the underlying analysis for the results presented on the patient-relevant outcomes of uncorrected and best-corrected visual acuity was incomprehensible. It remained unclear which of the statistical tests reported in the publication were used for which analysis and what meaning the bars describing dispersion have in Figure 1. In addition, in the case of uncorrected visual acuity, inconsistent results in the text and in one graph are reported; due to the size of the bars, the p-value reported does not seem plausible. Furthermore, no comparative data on adverse effects were reported. Therefore no results from this study could be used for the present benefit assessment.

The single-centre Australian study **Wittig-Silva 2014** included patients aged 16 to 50 years with mono- or bilateral, progressive keratoconus and a corneal thickness of ≥ 400 µm. Randomization was performed in computer-generated blocks of 10 on the basis of eyes; patients were randomized to CXL or to the control group treated purely symptomatically. If the disease progressed continuously, a treatment switch of the control group eyes to the CXL group was allowed 6 months after study inclusion at the earliest. After 36 months of the overall 5-year study duration planned, of the total of 100 randomized eyes (of 77 patients) 68 eyes were still actively participating [35,37]. In the control group there was a high proportion of patients who discontinued the study or violated the protocol (after 36 months: 21 eyes [43.8%] of 20 patients [40.0%]); this could largely be explained by patients undergoing CXL or corneal transplantations. A total of 94 eyes of 72 patients were analysed after 3 years using the last observation carried forward (LOCF) method. However, after a study duration of 12 months, the discontinuation rates between treatment groups differed by more than 15 percentage points, so that for the present report only the data up to 12 months are considered. For the final report, the authors provided IPD on the patient-relevant outcomes of uncorrected and best-corrected visual acuity. These included data on 2 additional patients compared with the publication. At the time of the publication, one patient had not yet been followed up for 36 months and one patient was pregnant at her 36-month follow-up. These 2 patients were thus not considered in the analysis after 36 months reported in the publication. Data on a total of 73 patients were ultimately available for the present report, including 23 (32%) patients in whom both eyes had been randomized.

Studies in which the dependency of the eyes was not considered (unusable)

The multicentre US study **Hersh 2011** included patients from the age of 14 years with progressive keratoconus or iatrogenic ectasia and a corrected visual acuity of worse than 20/20 (corresponds to < 1.0) and a corneal thickness of > 300 µm. Computerized randomization was performed on the basis of the eyes either to CXL or to sham treatment with riboflavin alone without prior epithelial removal. A second control group ("fellow-eye control group") was allocated in a non-randomized manner, and was thus not considered for the present report. The study duration was 12 months; however, after 3 months patients from the sham treatment group were switched to the CXL group. None of the publications included on the study [22,23] were submitted after the study completion date according to the trial registry entry, so that the publications (presumably) present unplanned interim analyses with different numbers of eyes. As the respective approach for selecting the eyes analysed is not described, the number of overall eyes and patients randomized and analysed, patients with bilateral randomization, and patients who discontinued the study, is unclear. Hersh et al. 2011 [23] analysed 49 eyes of an unclear number of patients in the keratoconus subgroup and 28 eyes of 28 patients in the sham treatment group. In the preliminary publication, patient characteristics and adverse effects of CXL were only reported for a proportion of 63% of eyes in the CXL group and are thus to be assessed as being incomplete [22]. The results of the sham treatment group were in part reported incompletely for the keratoconus subgroup.

The single-centre British study **O'Brart 2011** included patients aged 18 to 70 years with early to intermediate stage, bilateral progressive keratoconus and a corneal thickness of ≥ 400 µm. In each case, one eye was randomly allocated to the CXL group and the second eye served as a control. Randomization was performed by means of sealed envelopes. The data of 22 of the 24 randomized patients, including 5 (21%) female patients and 13 (54%) patients who wore contact lenses, were analysed after a study duration of 18 months. No reason for discontinuation was reported for the 2 non-analysed patients.

The single-centre Iranian study **Seyedian 2014** included patients aged 15 to 40 years with bilateral progressive keratoconus and a corneal thickness of ≥ 400 µm. In each case one eye was allocated to the CXL group by means of a computerized random number table and the second eye served as a control. Of 35 patients included, 26 (74.3%) were followed up for 12 months and analysed.

4.2.2 Overview of extraction of data relevant to the report

For the first research question, comparative data on the patient-relevant outcomes of morbidity (vision) and adverse effects of treatment could be used from 3 of the 4 studies in which the dependency of the eyes had been considered. The results of the remaining 3 studies were unusable and are presented in the details of the report (see full final report in German) solely for reasons of completeness and transparency. The availability and usability of data from the studies identified are presented in Table 1.

Table 1: Overview of the extraction of patient-relevant outcomes, data availability (research question 1)

Outcome	**Morbidity**													
	Vision												**Health-related quality of life**[a]	**Adverse effects**
	Uncorrected visual acuity	(Best-) corrected visual acuity	Light and glare sensitivity	Contrast vision	Distortions (metamorphopsia)	Multiple and double images	Pain	Foreign body sensation	Increased lacrimation	Tolerability for contact lenses	Indication for or performance of corneal transplantation			
Results from studies in which the dependency of the eyes was considered														
Comparison of conventional CXL vs. purely symptomatic treatment														
Wittig-Silva 2014	⭘[b]	●[b]	–	–	–	–	–	–	–	–	(–)[b]		–	⭘[b]
Comparison of conventional CXL vs. sham treatment														
Lang 2015	–	●[b]	–	–	–	–	–	–	–	–	–		–	⭘
Reidy 2012	–	●[b]	–	–	–	–	–	–	–	–	–		–	–
Sharma 2015	(–)[c]	(–)[c]	–	–	–	–	–	–	–	–	–		–	(–)[d]
Results from studies in which the dependency of the eyes was not considered (unusable)														
Comparison of conventional CXL vs. purely symptomatic treatment														
O'Brart 2011	(–)	(–)	–	–	–	–	–	–	–	(–)[e]	–		–	(–)[d]
Seyedian 2015	–[f]	(–)	–	–	–	–	–	–	–	–	–		–	(–)[d]
Comparison of conventional CXL vs. sham treatment														
Hersh 2011	(–)	(–)	–	–	–	–	–	–	–	–	–		–	(–)[g]

–: no data available, (–): data available, but unusable; ⭘: data available and usable; ●: data considered in a meta-analysis
a: Including activities of daily living, dependency on outside help, effects on course of education and occupation.
b: Results from enquiry to authors.
c: Incomprehensible and partly contradictory information on results in text and graph.
d: Only data for the intervention group reported, not for the control group.
e: The control group cannot be clearly inferred from the information reported on the eyes treated with CXL.
f: Only the results recorded at baseline reported.
g: Data reported only for 63% of eyes in the CXL group.
Study names in italics: unpublished study. CXL: corneal collagen cross-linking.

4.2.3 Assessment of risk of bias at the study and outcome level

All 7 studies were assessed as having a high risk of bias at the study level, which directly resulted in a high risk of bias at the outcome level.

Studies in which the dependency of the eyes was considered

In Wittig-Silva 2014 the high risk of bias primarily arose from the lack of blinding of patients and treating staff, which, in combination with the untreated control group and the assessment of subjective outcomes (visual acuity) carried a considerable risk of bias. The dependency of the eyes was not considered in the publication; however, the authors provided the IPD on patient-relevant outcomes and agreed to the analysis published in the report. No data were available on 4 of the 100 randomized eyes, as the patients withdrew their consent before any data were collected. In addition, no baseline value was available for 9 eyes (5 patients) and 1 eye for the outcomes of uncorrected and best-corrected visual acuity, respectively.

Even though randomization was generated adequately in Lang 2015, it was unclear whether allocation was also performed in a concealed manner. Furthermore, it was unclear whether a pause for wearing contact lenses before surgery and before the follow-up visits were implemented, and if not, whether the proportion of contact lenses wearers was comparable between groups. Moreover, the outcomes reported in the publication were not predefined in the trial registry entry. Recruitment was terminated prematurely and only 30 of 130 of the study participants planned could be included.

Double-blinding was described both in Lang 2015 and Reidy 2012; however, despite all blinding measures for patients it must be assumed that due to the pain caused by the epithelial removal in CXL, patients were aware of their group allocation. In both cases the surgeons were not blinded. In addition, Reidy 2015 was assessed as having a high risk of bias due to premature study discontinuation (only 69 of the 132 patients planned were randomized), as well as the analysis of only 54 of the 69 (78%) patients included.

The risk of bias for Sharma 2015 is not presented in detail in this report, as due to the non-transparent methods and partly inconsistent presentation of results, no usable results were available.

Studies in which the dependency of the eyes was not considered (results unusable)

For Hersh 2011, O'Brart 2011 and Seyedian 2015, a high risk of bias arose solely from the fact that the dependency of the eyes was not considered in the study analysis. The entire results could not be used to derive conclusions on benefit. Therefore a detailed assessment of the risk of bias is superfluous.

4.2.4 Results on patient-relevant outcomes

4.2.4.1 Outcomes on morbidity

4.2.4.1.1 Vision: uncorrected visual acuity (uncorrected distance visual acuity)

Usable data from one study (Wittig-Silva 2014) with moderate qualitative certainty of results were available. On the basis of the IPD provided by the authors the results for 68 patients (87 eyes) were analysed and the dependency of the eyes of 19 patients with bilateral randomization could be considered. In the repeated measures analysis of variance adjusted for the baseline values, a statistically significant difference in favour of CXL was shown with regard to the change in uncorrected visual acuity (mean difference [MD] −0.12 logarithm of the minimum angle of resolution [logMAR]; 95% CI [−0.23; −0.01]; p = 0.033). Subgroup analyses of age, sex, and the baseline value of this outcome yielded no indication of effect modification through these characteristics

The potentially usable data from Sharma 2015 could not be used, as neither the underlying analysis nor the values presented were clearly comprehensible. In addition, the results reported in the text and graph results were inconsistent with regard to the significance of the group difference.

Hence, for the outcome of uncorrected visual acuity, the data provide a hint of a benefit of conventional CXL in comparison with purely symptomatic treatment.

4.2.4.1.2 Vision – best-corrected visual acuity

Usable data were available from 3 studies with moderate qualitative certainty of results (Lang 2015, Reidy 2012, Wittig-Silva 2014). CXL was compared with sham treatment in Lang 2015 and Reidy 2012 and with an untreated control group in Wittig-Silva 2014. The median follow-up period was 36 months in Lang 2015, 15 months in Reidy 2012 and 12 months in Wittig-Silva 2014. None of the 3 studies showed statistically significant differences between treatment groups with regard to changes in the best-corrected visual acuity during the course of the study. For Wittig-Silva 2014, the group difference was calculated from the IPD by means of repeated measures analysis of variance adjusted for the baseline values (MD −0.04 logMAR; 95% CI [−0.10; 0.03]; p = 0.247). Substantial heterogeneity (I^2 = 61.5%; p = 0.074) was recognizable in the meta-analytic summary of results of the 3 studies. For this reason, no overall estimate was calculated. A sensitivity analysis excluding Wittig-Silva 2014, in which relevant heterogeneity no longer existed, showed a statistically non-significant difference to the disadvantage of CXL (MD 0.08 logMAR; 95% CI [−0.01; 0.17]; p = 0.097). Subgroup analyses of age, sex and the baseline value of this outcome based on the IPD of Wittig-Silva 2014 showed no indication of effect modification through these characteristics.

Hence, the data provide no hint of a benefit or harm of conventional CXL for the outcome of best-corrected visual acuity.

4.2.4.2 Outcome "adverse effects of treatment"

Comparative data from one study (Lang 2015) with moderate qualitative certainty of results were available which, as a control intervention, conducted sham treatment with fluorescein drops in combination with blue light. This study showed significant differences in the occurrence of temporary corneal haze (risk difference [RD] 0.71; 95% CI [0.48; 0.95]; $p < 0.001$) and corneal erosions (RD 0.72; 95% CI [0.47; 0.97]; $p < 0.001$) to the disadvantage of CXL. A total of 3 (20%) patients from the CXL group, compared with 0 patients from the sham treatment group, had persistent corneal haze up to the end of study; however, this difference was not statistically significant ($p = 0.091$) and according to the authors did not lead to an impairment in best-corrected visual acuity. Furthermore, Wittig-Silva 2014 reported a mild, temporary corneal haze for all eyes treated with conventional CXL. A patient-based analysis of this outcome is not possible, as the 2 eyes of some patients were in different treatment groups. It can be assumed that the difference between groups is statistically significant. In addition, up to the usable follow-up time point of 12 months, 1 patient had a mild, diffuse corneal oedema and a paracentral infiltrate 1 week after the procedure, which was associated with the premature re-use of contact lenses and had no effect on the best-corrected visual acuity with glasses. Furthermore, 2 days after the procedure, 1 patient had a subepithelial infiltrate and an anterior chamber infection. The (clinical) symptoms had subsided 3 months after antibacterial treatment. No cases were observed in the control group. For the latter 2 outcomes, due to low frequencies of events the data are insufficient to allow a conclusion on the treatment effect.

In summary, for the adverse event of temporary (stromal) corneal haze, the data provide an indication of an effect to the disadvantage of the intervention compared with purely symptomatic or sham treatment. For corneal erosion the data provide a hint of an effect to the disadvantage of the intervention. The data are insufficient for all other reported adverse effects, so that overall, a hint of harm from CXL can be inferred compared with purely symptomatic treatment or sham treatment.

4.2.4.3 Results on other patient-relevant outcomes

No usable results were identified on any of the other patient-relevant outcomes in the studies included.

4.2.4.4 Subgroup characteristics and other effect modifiers

Subgroup analyses according to age, sex, and baseline value were possible for the outcomes of uncorrected and best-corrected visual acuity (see sections 4.2.4.1.1 and 4.2.4.1.2). Due to a lack of corresponding data, no subgroup analyses were possible for the characteristics of ethnicity, disease stage, and concomitant diseases and were thus not performed.

4.2.5 Studies of unclear relevance

For the first research question, the trial registry search identified 10 studies of unclear relevance, including 5 ongoing, 2 discontinued, 1 completed, and 2 studies with unknown status. Results relevant to the first research question of the present benefit assessment can potentially be expected from all studies identified, but especially from the following ongoing ones:

A Swedish study (DNR-949-11 [38]) is investigating CXL with a modified UV radiation mode compared with purely symptomatic treatment. For this study it is reported that randomization is patient-based. According to the trial registry entry, the study is to be completed in May 2019.

Three US studies (KLX-001 [39], KXL-002 [40] and KXL-005 [41]) are also investigating CXL with modified UV radiation modes and riboflavin, but in comparison with a sham treatment comprised of corresponding UVA radiation modes and placebo eye drops. No specific information is available on how patients or eyes were randomized. The planned end of study dates are December 2016 (KXL-005) and March 2017 (KLX-001 and KLX-002).

The fifth ongoing study, a British study (UVA/B2 [42]), is investigating conventional CXL compared with purely symptomatic treatment. One eye of each patient is randomized to CXL and the other eye serves as a control. The planned end-of-study date is unknown.

4.2.6 Evidence map

Table 2 shows the evidence map for the first research question with regard to patient-relevant outcomes at the individual study level and in summary.

Table 2: Evidence map for patient-relevant outcomes (research question 1)

	Morbidity		**Adverse effects of treatment**
	Uncorrected visual acuity	Best-corrected visual acuity	
Results from studies in which the dependency of the eyes was considered			
Lang 2015	–	↔	↓
Reidy 2012	–	↔	-
Sharma 2015	–[a]	–[a]	–[b]
Wittig-Silva 2014	↑	↔	↓
Summary	⇗	⇑⇓	⇘[c]

a: Incomprehensible, partly contradictory information in the text and graph on all patient-relevant results; data are unusable.

b: Only data for the intervention group reported, not for the control group.

c: The data provide an indication of an effect to the disadvantage of the intervention for the adverse event "temporary (stromal) corneal haze". The data provide a hint of an effect to the disadvantage of the intervention for corneal erosion. The data are insufficient for all other reported adverse effects, so that overall a hint of harm from the intervention was inferred.

-: no data reported

↔: no statistically significant difference

↑: statistically significant effect in favour of the intervention

↓: statistically significant effect in favour of the control

⇗: hint of a benefit

⇘: hint of harm

⇑⇓: no hint, indication or proof, heterogeneous result

4.3 Results on research question 2

4.3.1 Characteristics of the studies included in the assessment

Overall, 12 studies from 9 different countries (Egypt, Greece, Iran, Italy, The Netherlands, Norway, Saudi-Arabia, Sweden, and Turkey) were identified as relevant for the second research question (comparison of CXL variants). All studies were conducted in a parallel group design without a cross-over option. As with the studies on the first research question, the studies on this research question also showed methodological differences concerning the type of randomization and the statistical analyses. As a result, only data from 9 of the 12 studies could be used for the benefit assessment (Acar 2014 [43], Al-Fayez 2015 [44], Beckman Rehnman 2014 [45-47], Hashemi 2015 [48-50], Hashemian 2014 [51], Ozgurhan 2014 [52], Rossi 2015 [53], Soeters 2015 [54,55], Stojanovic 2014 [56,57]); this was because in the other 3 studies (Kanellopoulos 2012 [58], Razmjoo 2014 [59,60], Sherif 2014 [61]), neither the dependency of the eyes was considered in the analysis nor were enquiries to authors answered.

The 12 studies are described in the following text.

Studies in which the dependency of the eyes was considered

Five single-centre studies investigated conventional CXL compared with a transepithelial variant (Acar 2014, Al-Fayez 2015, Rossi 2015, Soeters 2015, Stojanovic 2014). The study size varied from 13 randomized patients in Acar 2014 to 70 patients in Al-Fayez 2015. With one exception, randomization was patient-based. Stojanovic 2014 used an intra-individually controlled design; however, the dependency of the eyes was considered in the statistical test for the group comparison (paired t-test). The planned follow-up period was at least 6 months (Acar 2014) and at most 36 months (Al-Fayez 2015). For transepithelial CXL, 3 of the 5 studies used a special riboflavin solution enriched with enhancers (Acar 2014, Rossi 2015, Soeters 2015). UVA radiation was always performed for 30 minutes with an irradiance of 3 mW/cm^2.

Two single-centre studies investigated conventional CXL compared with an accelerated variant. The study size was 31 randomized patients in Hashemi 2015 and 153 patients in Hashemian 2014. While Hashemian 2014 randomized and treated only one eye per patient, Hashemi 2015 used an intra-individually controlled design, whereby the dependency of the eyes was considered in the statistical analysis of the group difference. In Hashemi 2015 the follow-up period was 18 months and in Hashemian 2014 it was 15 months. As with conventional CXL, in the accelerated control groups the epithelium was also removed before the procedure. In Hashemi 2015 accelerated UVA radiation was conducted over 5 minutes with an irradiance of 18 mW/cm^2; the corresponding values in Hashemian 2014 were 3 minutes with 30 mW/cm^2.

The single-centre study by Beckman Rehnman 2014 investigated conventional CXL compared with a variant of mechanical compression of the cornea. Randomization was eye-based. A total of 120 eyes were included in the study, including 60 eyes of 43 patients with keratoconus and 60 eyes of healthy participants, which were not considered in the present report. The authors provided IPD for the keratoconus group, so that the dependency of eyes was able to be considered in the analysis. The present results refer to an interim analysis of the study after 6 months of a total study duration of 60 months. As with conventional CXL, in this variant the epithelium is also removed before the procedure. Mechanical compression was performed by means of a flat, rigid contact lens, which was sutured to the cornea after the preprocedural administration of riboflavin and removed again 1 hour after the UVA radiation, which lasted slightly longer than 30 minutes.

The single-centre study by Ozgurhan 2014 investigated 2 variants of accelerated CXL. One eye each of the overall 34 patients was randomized. The follow-up period was 1 month. In this context, before the procedure riboflavin was administered over 20 minutes in the one treatment group and over 30 minutes in the other, in each case with an interval of 2 minutes. UVA radiation was conducted over 5 minutes with an irradiance of 18 mW/cm^2.

Studies in which the dependency of the eyes was not considered (unusable)

In 3 single-centre studies conventional CXL was compared with accelerated UVA radiation (Kanellopoulos 2012, Sherif 2014) or a variant with partial epithelial removal (Razmjoo 2014). In Razmjoo 2014, randomization was patient-based; however, both eyes of each patient were treated in the allocated group. In Kanellopoulos 2012, an intra-individually controlled design was used and in Sherif 2014, randomization could be both bi- and unilateral with the corresponding treatment. The study size varied from 18 patients (25 eyes) in Sherif 2014 to 22 patients (44 eyes) in Razmjoo 2014. As in these 3 studies the dependency of the eyes was not considered in the analysis and the enquiries to the authors were not answered, the available results could not be used. These studies are therefore not described further in the present report.

4.3.2 Overview of the extraction of data relevant to the report

For the second research question, from 9 of the 12 studies, comparative data on the patient-relevant outcomes morbidity (vision) and/or adverse effects of treatment (including post-procedural pain) could be used. Table 3 shows the availability and usability of data from the studies identified.

Table 3: Overview of the extraction of patient-relevant outcomes; data availability (research question 2)

Outcome	**Morbidity**											**Health-related quality of life**[a]	**Adverse effects of treatment**
	Vision												
	Uncorrected visual acuity	Best-corrected visual acuity	Light und glare sensitivity	Contrast vision	Distortions (metamorphopsia)	Multiple and double images	Pain	Foreign body sensation	Increased lacrimation	Tolerability for contact lenses	Indication for or performance of corneal transplantation		
Results from studies in which the dependency of the eyes was considered													
Comparison of conventional vs. transepithelial CXL													
Acar 2014	–	–	–	–	–	–	–	–	–	–	–	–	○
Al-Fayez 2015	○	(–)[b]	–	–	–	–	–	–	–	–	–	–	○
Rossi 2015	●	●	–	–	–	–	–	–	–	–	–	–	○
Soeters 2015	●	●	–	–	–	–	–	–	–	–	–	–	○
Stojanovic 2014	○[c]	○[c]	–	–	–	–	–[d]	–	–	–	–	–	○
Comparison of conventional vs. accelerated CXL													
Hashemi 2015	○	○	–	–	–	–	–	–	–	–	–	–	○
Hashemian 2014	○	○	–	–	–	–	–	–	–	–	–	–	(–)[e]
Comparison of conventional vs. CXL with mechanical compression of the cornea													
Beckman Rehnman 2014	–	○[c]	–	–	–	–	–	–	–	–	–	–	○[c]
Comparison of variants of accelerated CXL													
Ozgurhan 2014	–	–	–	–	–	–	–	–	–	–	–	–	○

(continued)

Table 3: Overview of the extraction of patient-relevant outcomes; data availability (research question 2) (continued)

Outcome	**Morbidity**											**Health-related quality of life**[a]	**Adverse effects of treatment**
	Vision												
	Uncorrected visual acuity	Best-corrected visual acuity	Light und glare sensitivity	Contrast vision	Distortions (metamorphopsia)	Multiple and double images	Pain	Foreign body sensation	Increased lacrimation	Tolerability for contact lenses	Indication for or performance of corneal transplantation		
Results from studies in which the dependency of the eyes was not considered (data unusable)													
Comparison of conventional vs. accelerated CXL													
Kanellopoulos 2012	(–)	(–)	–	–	–	–	–	–	–	–	–	–	(–)
Sherif 2014	(–)	(–)	–	–	–	–	–	–	–	–	–	–	(–)
Comparison of conventional vs. CXL with partial removal of epithelium													
Razmjoo 2014	–	(–)	–	–	–	–	–	–	–	–	–	–	(–)

–: no data available, (–): data available, but unusable; ⭘: data available and usable; ●: data considered in a meta-analysis
a: Including activities of daily living, dependency on outside help, effects on educational and occupational development.
b: The purely graphically presented results are incomprehensible and the graph is in itself inconsistent.
c: Results from enquiry to authors.
d: The reported post-procedural pain was allocated to the outcome “adverse effects of treatment”.
e: The operationalization of the outcome (corneal haze) is incomprehensible.
CXL: corneal collagen cross-linking.

4.3.3 Assessment of the risk of bias at the study and outcome level

All studies were assessed as having a high risk of bias at the study level, which directly resulted in a high risk of bias at the outcome level.

Studies in which the dependency of the eyes was considered

Only 2 of the 9 studies provided specific information on the generation of the randomization sequence: the corresponding information was missing for all of the other studies. In addition, with the exception of Strojanovic 2014, in all studies it was unclear whether allocation concealment was ensured. In Al-Fayez 2015, Soeters 2015, Strojanovic 2014, and Beckman Rehnman 2014, the treating surgeons and the patients were explicitly not blinded; they were not explicitly blinded in any of the other studies – due to the different treatment protocols this would be difficult to achieve anyhow. Because of the lack of patient blinding, the risk of a biased assessment of outcomes increases, especially in the event of subjective outcomes such as visual acuity (detection bias). It could only be assumed for 3 studies (Beckman Rehnman 2014, Hashemi 2015, Soeters 2015) that there was no selective reporting. Further aspects were incomplete information on patient flow, unclarity about possibly missing data on the single follow-up time points, as well as deviations between the trial registry entry and the publication regarding the information on the inclusion and exclusion criteria.

Finally it should be noted that, despite enquiries to authors, missing information could only be partially clarified or not clarified at all.

Studies in which the dependency of the eyes was not considered (results unusable)

For Kanellopoulos 2012, Razmjoo 2014 and Sherif 2014, a high risk of bias arose solely from the fact that the dependency of the eyes was not considered in the study analysis. The entire results could not be used to derive conclusions on benefit. Therefore a detailed assessment of the risk of bias is superfluous.

4.3.4 Results on patient-relevant outcomes

4.3.4.1 Comparison of conventional versus transepithelial CXL

4.3.4.1.1 Outcome “morbidity” – vision – uncorrected visual acuity (uncorrected distance visual acuity)

Usable results were available from 4 studies with moderate qualitative certainty of results. Only one study (Al-Fayez 2015) showed statistically significant effects with regard to the change in values for uncorrected visual acuity during the course of the study (in favour of conventional CXL). Meta-analytical pooling of Al-Fayez 2015, Rossi 2015 and Soeters 2015 showed relevant heterogeneity of study results ($I^2 = 77.8\%$, $p = 0.011$), so that no overall estimate was calculated. For Al-Fayez 2015, missing information on the standard deviation was replaced in the meta-analysis. The study duration of 36 months also differed from that in Rossi 2015 and Soeters 2015, which each lasted 12 months. A sensitivity analysis excluding Al-Fayez 2015 was thus performed. The study results were now largely homogeneous

(I^2 = 0%; p = 0.582). The overall estimate showed no statistically significant effect (MD −0.03 logMAR 95% CI [−0.09; 0.02]; p = 0.222).

The fourth study (Strojanovic 2014) could not be considered in the meta-analysis, as bilateral treatment was performed and the dependency of the eyes could not be considered adequately for the changes in the group values. The only usable result for this study was the p-value of the paired t-test for the group difference after 12 months (p = 0.289).

In summary, for the outcome of uncorrected visual acuity the data provide no hint of a greater or lesser benefit of either treatment option.

4.3.4.1.2 Outcome "morbidity" – vision – best-corrected visual acuity

Usable results were available from 3 studies with moderate qualitative certainty of results (Rossi 2015, Soeters 2015, Stojanovic 2014). Rossi 2015 and Soeters 2015 could be pooled in a meta-analysis and the study results were largely homogeneous (I^2 = 0%, p = 1.000). A statistically significant effect was shown in favour of the transepithelial variant with regard to the change in best-corrected visual acuity during the course of the study (MD 0.07 logMAR 95% CI [0.04; 0.10]; p < 0.001). Strojanovic 2014 was not considered in the meta-analysis, as bilateral treatment was performed and the dependency of the eyes could not be considered adequately for the changes in the group values. The only usable result for this study was the p-value of the paired t-test for the group difference (p = 0.239) and hence a statistically non-significant difference in favour of the transepithelial variant.

In summary, for the outcome of best-corrected visual acuity, the data provide an indication of a benefit of transepithelial CXL compared with conventional CXL.

4.3.4.1.3 Outcome "adverse effects of treatment"

Overall, usable results were available from 5 studies with moderate qualitative certainty of results.

One study (Strojanovic 2014) reported results on post-procedural pain. The duration of pain was statistically significantly different between the treatment groups; in each group the degree of intensity was moderate and lasted about 3 times longer after conventional CXL than after transepithelial CXL (mean [standard deviation, SD] conventional: 33.90 (23.76) hours, transepithelial: 11.63 (5.89) hours; p<0.001). No further adverse effects of treatment were observed in this study.

Further adverse effects were observed in 2 studies (Soeters 2015, Acar 2014) after conventional CXL; Soeters 2015 reported that a total of 4 (15%) of 26 patients had experienced adverse effects. These included 2 patients with delayed epithelial healing with accompanying (stromal) corneal haze; in one of these patients this was potentially associated with periocular eczema and the second patient developed a deeper-lying (stromal) corneal haze after 6 months. One patient had a sterile infiltrate and one had herpes keratitis, which

were reversible after treatment. Acar 2014 reported on a patient with (stromal) corneal haze, but provided no information on whether this was temporary or persistent.

No adverse effects were reported in Rossi 2015, which included a total of 20 patients. Al-Fayez 2015 reported no complications during re-epithelialization (within the first 7 days) and no cases of persisting corneal haze after conventional CXL. No information was provided on complications in the transepithelial group.

In summary, the data provide a hint of lesser harm from transepithelial compared with conventional CXL with regard to post-procedural pain. For all other adverse effects, due to the low frequency of events the data are insufficient to allow a conclusion on the effect of treatment.

4.3.4.2 Comparison of conventional versus accelerated CXL

4.3.4.2.1 Outcome "morbidity" – vision – uncorrected visual acuity (uncorrected distant visual acuity)

Usable results were available from 2 studies with moderate qualitative certainty of results (Hashemi 2015, Hashemian 2014). Both studies reported that there were no statistically significant differences between groups with regard to uncorrected visual acuity during the course of the study. The studies were not pooled in a meta-analysis, as bilateral treatment was performed in Hashemi 2015 and the dependency of the eyes could not be considered for the changes in values in the groups. As a usable result for this study only the p-value ($p = 0.745$) of the repeated-measures analysis of variance was available, with consideration of the dependency of the eyes for the group difference, which confirmed the result of Hashemian 2014 ($p = 0.64$).

Hence, for the outcome of uncorrected visual acuity, the data provide no hint of a greater or lesser benefit of either treatment option.

4.3.4.2.2 Outcome "morbidity" – vision – best-corrected visual acuity

Usable results from 2 studies with moderate certainty of results were available (Hashemi 2015, Hashemian 2014). The results of the studies were not pooled in a meta-analysis as bilateral treatment was performed in Hashemi 2015 and the dependency of the eyes could not be considered for the changes in group values. For Hashemi 2015, only the p-value ($p = 0.551$) of the repeated measures analysis of variance on the group difference was available as a usable result; this study also reported that there was no statistically significant effect (MD: not provided; $p = 0.58$).

Hence, for the outcome of best-corrected visual acuity, the data provide no hint of a greater or lesser benefit of either treatment option.

4.3.4.2.3 Outcome "adverse effects of treatment"

Usable results were available from Hashemi 2015, in which no intra- or post-procedural complications were observed.

The data were insufficient to allow a conclusion on the treatment effect. Hence, the data provide no hint of greater or lesser harm from either treatment option.

4.3.4.3 Comparison of conventional CXL versus CXL with mechanical compression of the cornea

4.3.4.3.1 Outcome "morbidity" – vision – best-corrected visual acuity

Usable results were available from one study (Beckman Rehnman 2014) with moderate certainty of results. The analysis of the IPD provided by the authors (a repeated-measures analysis of variance) yielded no statistically significant effect with regard to the change in best-corrected visual acuity during the course of the study (MD 0.02 95% CI [−0.07; 0.10]; p = 0.703). Subgroup analyses of age and sex did not provide an indication for an effect modification through these characteristics.

Hence, for the outcome of best-corrected visual acuity, the data provide no hint of a greater or lesser benefit of either treatment option.

4.3.4.3.2 Outcome "adverse effects of treatment"

Usable results were available from Beckman Rehnman 2014 with moderate qualitative certainty of results. For the currently available interim analysis after 6 months, the authors reported one case of keratitis after conventional CXL, which was reversible after treatment.

Due to the low frequencies of events, the data were insufficient to allow a conclusion on the effect of treatment. The data provide no hint of greater or lesser harm from either treatment option with regard to adverse effects of treatment.

4.3.4.4 Comparison of different variants of accelerated CXL

4.3.4.4.1 Outcome "adverse effects of treatment"

Usable results with moderate qualitative certainty of results were available from Ozgurhan 2014 for the comparison of accelerated CXL with preprocedural administration of riboflavin over a period of 20 minutes versus 30 minutes. No intra- or post-procedural complications were observed in this study.

Due to the low number of events the data were insufficient to allow a conclusion on the effect of treatment. The data provide no hint of greater or lesser harm from either accelerated variant with regard to adverse effects of treatment.

4.3.5 Results on other patient-relevant outcomes

No usable results on any of the other patient-relevant outcomes were identified in the studies included.

4.3.6 Subgroup characteristics and other effect modifiers

Subgroup analyses of age and sex were possible for the outcome of best-corrected visual acuity in the comparison of conventional CXL versus CXL with mechanical compression of the cornea (see section 4.3.4.3.1). Due to a lack of corresponding data, no subgroup analyses of age, sex, ethnicity, disease stage, and concomitant diseases were possible for any of the other outcomes and comparisons.

4.3.7 Studies of unclear relevance

For the second research question, a total of 16 studies of unclear relevance were identified by the trial registry search.

For the comparison of conventional versus transepithelial CXL, further results on the outcome of vision are to be expected from a total of 5 studies. In particular, the TCXL-ionto study (126 patients, study duration 2 years [62]), which, according to the trial registry entry, had already been completed in December 2014, as well as the ongoing IONTO-CXL study (162 patients, study duration 12 months [63]), which is planned to run until May 2017, could be relevant for the present benefit assessment because of their comparatively high number of patients.

For the comparison of conventional CXL versus accelerated CXL, further results on the outcome of vision are to be expected from 3 studies in the near future [64-66].

For the comparison of conventional CXL versus CXL with mechanical compression of the cornea, one completed study [67] was identified.

Furthermore, results on novel variants and comparisons are to be expected from 7 studies, for example, comparison of different riboflavin schemes in conventional CXL [68,69], continuous versus pulsating UVA radiation modes, and comparison of different variants of accelerated CXL [70-74]. The multi-centre ACOS-KXL-001 study [70] was discontinued for unknown reasons, but should be emphasized due to its large planned sample size (1719 patients) compared with the other studies.

4.3.8 Evidence map

Table 4 shows the evidence map for the second research question with regard to patient-relevant outcomes at the individual study level and in summary.

Table 4: Evidence map (research question 2)

Study	Morbidity		Adverse effects of treatment
	Uncorrected visual acuity	Best-corrected visual acuity	
Comparison of conventional versus transepithelial CXL			
Acar 2014	–	–	(↔)
Al-Fayez 2015	↑	–[a]	-[b]
Rossi 2015	↔	↑	(↔)
Soeters 2015	↔	↑	(↔)
Stojanovic 2014	↔	↔	↑[c]
Summary	**⇑⇓**	**⇑**	**⇗**
Comparison of conventional versus accelerated CXL			
Hashemi 2015	↔	↔	(↔)
Hashemian 2014	↔	↔	–[d]
Summary	**⇔**	**⇔**	**(⇔)**
Comparison of conventional versus CXL with mechanical compression of the cornea			
Beckman Rehnman 2014	–	↔	(↔)
Summary	–	**⇔**	**(⇔)**
Comparison of accelerated CXL with pre-procedural riboflavin over 20 minutes versus 30 minutes			
Ozgurhan 2014	–	–	(↔)
Summary	–	–	**(⇔)**

a: Incomprehensible, contradictory information in the graph on the results for this outcome; data therefore unusable.
b: No information on adverse effects in the transepithelial CXL group.
c: On the basis of post-procedural pain.
d: The operationalization of the outcome (corneal haze) is incomprehensible.

-: no data reported

↔: no statistically significant difference

(↔): insufficient data due to low frequencies of events (insufficient to allow a conclusion on the effect of treatment)

↑: statistically significant effect in favour of the variant

⇗ : hint of lesser harm in favour of the variant

⇑: indication of a (greater) benefit in favour of the variant

⇑⇓: no hint, indication or proof; heterogeneous result

⇔: no hint of a benefit or harm of either treatment option

(⇔): no hint in favour or to the disadvantage of a treatment option; data insufficient

CXL: corneal collagen cross-linking.

5 Classification of the assessment result

Usability of study results

In the present benefit assessment, comparative data on patient-relevant outcomes could be used from only 12 (63%) of the total of 19 RCTs considered, including 3 of 7 RCTs on the first research question. The results of a total of 6 (32%) studies could not be used, as the dependency of the eyes was not considered in the study analysis and enquiries to authors regarding an analysis considering this dependency or the provision of IPD were not answered. In addition, in one study on the first research question, the data reported were methodologically and numerically incomprehensible due to the non-transparent presentation of methods and partly inconsistent presentation of results.

Hint of a benefit of conventional CXL (research question 1)

For the first research question, only the IPD provided by the authors of Wittig-Silva 2014 led to the derivation of a hint of a benefit of standard CXL compared with purely symptomatic treatment. The estimated group difference of the average change in uncorrected visual acuity within a year of −0.12 logMAR means an improvement of 5 to 6 letters and thus slightly more than an additional line on the Early Treatment Diabetic Retinopathy Study (ETDRS) eye chart that was applied [75]. However, due to the width of the CI, the group difference might be hardly perceptible or be up to 2 additional lines on the eye chart. The result of a further study, which could not however be used, was available for this outcome (O'Brart 2011); it showed no statistically significant effect, but the same direction of the effect, and thus did not contradict the results of the IPD analysis for Wittig-Silva 2014.

Comparison of variants with conventional CXL (research question 2)

The second research question was processed only on the basis of a hint of a benefit of conventional CXL.

For all available results on the comparison of variants with conventional CXL it should be noted that no conclusive conclusions can be drawn on the benefit or harm of variants compared with purely symptomatic treatment. The available results on patient-relevant outcomes showed advantages over conventional CXL only for the transepithelial variant. In particular, the indication of a greater benefit of the transepithelial variant regarding best-corrected visual acuity is however difficult to classify, as no hint of a benefit of conventional CXL was shown beforehand for this outcome.

For the accelerated variant and the variant with mechanical compression of the cornea, no differences were shown with regard to the available results on patient-relevant outcomes. However, independent of this the accelerated variant offers the advantage of shorter treatment duration.

Insufficient data

Across all research questions it should be noted that the currently available and usable data should be classified as highly biased, as well as incomplete, with regard to the availability and usability of data on patient-relevant outcomes. In addition, the available results were based on low sample sizes. For the present benefit assessment, across studies data were available only for the patient-relevant outcomes of vision (uncorrected and best-corrected visual acuity) as well as adverse effects. In particular, the results on adverse effects of treatment were poorly reported. In this context it is also unclear why immanent post-procedural pain was systematically recorded and reported only in one study. For all other patient-relevant outcomes, especially on the medical indication for or performance of a corneal transplantation and on health-related quality of life, no (comparative) data were available.

Moreover, the data available refer to a maximum study duration of 36 months and due to the progressive course of disease can only provide limited information on the long-term benefit or harm of conventional CXL and its variants.

Finally, due to a lack of data, only few of the subgroup analyses planned a priori could be conducted. For example, on the basis of the available information, no differentiated statements can be provided for the different disease stages to infer specific medical indications for CXL in patients with keratoconus.

Studies of unclear relevance

For the present benefit assessment it seems recommendable to wait for the numerous pending results on both research questions from the studies identified in the trial registries. The diversity of the comparisons investigated in these studies highlights the up-to-dateness of the topic and may in the near future change and extend the current evidence of this benefit assessment. New data are to be expected in the near future, especially on the outcome of vision. Most of the studies identified are planned to end in mid-2017 at the latest, one only in May 2019. As some of the studies already completed have so far not been published, besides the fact that 2 discontinued studies on the first research question are explicitly not to be published, publication bias cannot be excluded.

6 Conclusion

For the present benefit assessment, only the results from 3 out of the 7 studies for research question 1 and from 9 of the 12 studies for research question 2 could be used. Three studies per research question did not adequately consider data dependency (analysis unit: eye instead of patient). In a further study the underlying analysis and the results reported were incomprehensible. As in addition enquiries to authors were not answered, a total of 7 studies could not be used.

For the outcome of uncorrected visual acuity, a hint of a benefit was shown for conventional CXL compared with purely symptomatic treatment. This arose solely from the data of one study. For the outcome of best-corrected visual acuity, no hint of a benefit or harm was shown for conventional CXL. With regard to adverse effects of treatment, a hint of harm was shown.

No relevant RCTs and thus no results were available on the comparison of CXL variants with purely symptomatic treatment.

For the outcomes analysed, the comparison of different variants of conventional CXL showed:

- in favour of the transepithelial variant:
  - an indication of a greater benefit for best-corrected visual acuity
  - a hint of lesser harm for post-procedural pain
  - no hint in favour of or to the disadvantage of this variant for uncorrected visual acuity
- no hint in favour of or to the disadvantage of the accelerated variant for uncorrected visual acuity, best-corrected visual acuity, and adverse effects of treatment
- no hint in favour of or to the disadvantage of a variant with mechanical compression of the cornea for best-corrected visual acuity and adverse effects of treatment

In the comparison of accelerated corneal CXL with 20-minute versus 30-minute pre-procedural administration of riboflavin, the data provided no hint in favour of or to the disadvantage of one of these variants with regard to adverse effects of treatment.

No (usable) data on other patient-relevant outcomes are currently available beyond those named. Across research questions, the currently available (usable) data are to be classified as highly biased and incomplete. However, for both research questions the numerous ongoing or already completed (but so far unpublished) studies indicate that further results can be expected in the near future, especially on the outcome of vision. In summary, it seems advisable to wait for pending study results for a conclusive benefit assessment of CXL.

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Please see full final report for full reference list.

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