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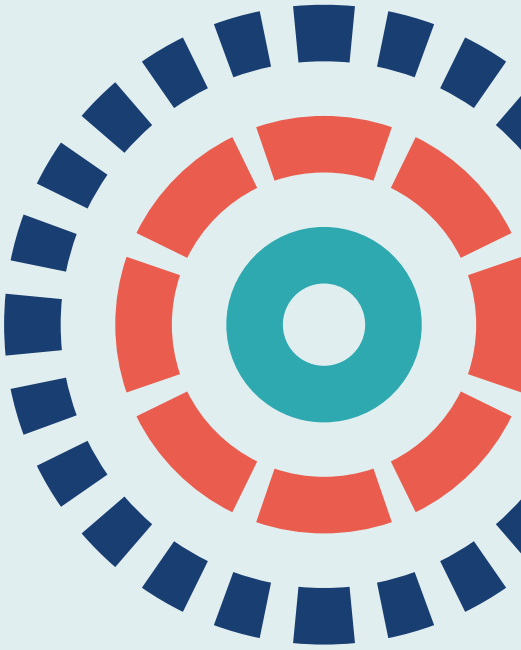

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Epithelium-off corneal cross-linking surgery compared with standard care in 10- to 16-year-olds with progressive keratoconus: the KERALINK RCT

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Abstract

Epithelium-off corneal cross-linking surgery compared with standard care in 10- to 16-year-olds with progressive keratoconus: the KERALINK RCT

Daniel FP Larkin,[1*] Kashfia Chowdhury,[2] Caroline J Doré,[2] Catey Bunce,[1] Jennifer M Burr,[3] Emilia Caverly,[2] Lisa French,[2] Dimitra Kopsini,[2] Anne Klepacz,[4] Mathew Raynor,[5] Matthew Edwards[5] and Stephen J Tuft[1]

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Background: Keratoconus is a disease of the cornea affecting vision that is usually first diagnosed in the first three decades. The abnormality of corneal shape and thickness tends to progress until the patient reaches approximately 30 years of age. Epithelium-off corneal cross-linking is a procedure that has been demonstrated to be effective in randomised trials in adults and observational studies in young patients.

Objectives: The KERALINK trial examined the efficacy and safety of epithelium-off corneal cross-linking, compared with standard care by spectacle or contact lens correction, for stabilisation of progressive keratoconus.

Design: In this observer-masked, randomised, controlled, parallel-group superiority trial, 60 participants aged 10–16 years with progressive keratoconus were randomised; 58 participants completed the study. Progression was defined as a 1.5 D increase in corneal power measured by maximum or mean power (K2) in the steepest corneal meridian in the study eye, measured by corneal tomography.

Setting: Referral clinics in four UK hospitals.

Interventions: Participants were randomised to corneal cross-linking plus standard care or standard care alone, with spectacle or contact lens correction as necessary for vision, and were monitored for 18 months.

Main outcome measures: The primary outcome was K2 in the study eye as a measure of the steepness of the cornea at 18 months post randomisation. Secondary outcomes included keratoconus progression, visual acuity, keratoconus apex corneal thickness and quality of life.

Results: Of 60 participants, 30 were randomised to the corneal cross-linking and standard-care groups. Of these, 30 patients in the corneal cross-linking group and 28 patients in the standard-care group were analysed. The mean (standard deviation) K2 in the study eye at 18 months post randomisation

was 49.7 D (3.8 D) in the corneal cross-linking group and 53.4 D (5.8 D) in the standard-care group. The adjusted mean difference in K2 in the study eye was −3.0 D (95% confidence interval −4.93 D to −1.08 D; $p = 0.002$), favouring corneal cross-linking. Uncorrected and corrected differences in logMAR vision at 18 months were better in eyes receiving corneal cross-linking: −0.31 (95% confidence interval −0.50 to −0.11; $p = 0.002$) and −0.30 (95% confidence interval −0.48 to −0.11; $p = 0.002$). Keratoconus progression in the study eye occurred in two patients (7%) randomised to corneal cross-linking compared with 12 (43%) patients randomised to standard care. The unadjusted odds ratio suggests that, on average, patients in the corneal cross-linking group had 90% (odds ratio 0.1, 95% confidence interval 0.02 to 0.48; $p = 0.004$) lower odds of experiencing progression than those receiving standard care. Quality-of-life outcomes were similar in both groups. No adverse events were attributable to corneal cross-linking.

Limitations: Measurements of K2 in those eyes with the most significant progression were in some cases indicated as suspect by corneal topography device software.

Conclusions: Corneal cross-linking arrests progression of keratoconus in the great majority of young patients. These data support a consideration of a change in practice, such that corneal cross-linking could be considered as first-line treatment in progressive disease. If the arrest of keratoconus progression induced by corneal cross-linking is sustained in longer follow-up, there may be particular benefit in avoiding the later requirement for contact lens wear or corneal transplantation. However, keratoconus does not continue to progress in all patients receiving standard care. For future work, the most important questions to be answered are whether or not (1) the arrest of keratoconus progression induced by corneal cross-linking is maintained in the long term and (2) the proportion of those receiving standard care who show significant progression increases with time.

Trial registration: Current Controlled Trials ISRCTN17303768 and EudraCT 2016-001460-11.

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Glossary

K2 Mean corneal power on meridian of maximum corneal steepness.

K_{max} Corneal power at point of maximum corneal steepness.

List of abbreviations

CF	counting fingers
CHU9D	Child Health Utility 9D
CI	confidence interval
CVAQC-25	Cardiff Visual Ability Questionnaire for Children
CXL	corneal cross-linking
ETDRS	Early Treatment of Diabetic Retinopathy Study
HM	hand motion
IDMC	Independent Data Monitoring Committee
ITT	intention to treat
logMAR	minimum angle of resolution
NIHR	National Institute for Health Research
NPL	no perception of light
PI	principal investigator
PL	perception of light
RCT	randomised controlled trial
SD	standard deviation
SER	spherical equivalent refraction
TMG	Trial Management Group
TSC	Trial Steering Committee
UV	ultraviolet
VF	Visual Function Index

Plain English summary

Keratoconus is a long-term disorder causing increasing steepening and thinning of the cornea, the clear front wall of the eye. It leads to progressive distortion of vision. In most cases keratoconus starts during the teenage years and stops progressing when people are about 30 years old. It is often more severe if it starts in childhood. It can progress quite quickly to a stage that good vision cannot be achieved by standard care (wearing glasses and contact lenses) and a transplant operation becomes necessary. Recently, a new surgical intervention involving the removal of the surface layer of the cornea ('epithelium-off'), the administration of eye drops and the application of ultraviolet light has become available. The procedure can be performed under local anaesthesia in most patients. It is called corneal cross-linking. It is believed to stop keratoconus progression by increasing the stiffness of the cornea, but previous research has been of poor quality.

KERALINK was a high-quality randomised trial to see if the new treatment really works. Young people with confirmed keratoconus progression in one or both eyes were randomly allocated to the new treatment in addition to standard care, or to standard care alone. In total, 60 young people aged 10–16 years participated (30 allocated to the new treatment and 30 allocated to standard care alone).

Participants were followed up for 18 months. The primary outcome was the degree of distortion of the cornea at 18 months. Other outcomes included vision, need for glasses and contact lenses, quality of life, and safety. We found significantly less distortion in eyes receiving the new treatment. This shows that the new treatment is effective in preventing disease progression. Participants allocated to the new treatment group also had better vision and were less likely to need to wear glasses or contact lenses, and there were no treatment-related complications.

Scientific summary

Background

Keratoconus is a disease of the cornea affecting vision that is usually diagnosed in the second and third decades. The abnormality of corneal shape and thickness tends to progress from the age at onset until around the end of the third decade and then stabilise spontaneously. The KERALINK trial was designed to compare the efficacy and safety of corneal cross-linking in stabilising the progression of keratoconus with standard care by spectacle or contact lens correction in children and young patients. Keratoconus is characterised by thinning and distortion of the cornea that results in visual loss from complex refractive error and corneal opacification. The prevalence in Europe has been reported as 1 in 1163 (Nielsen K, Hjortdal J, Aagaard Nohr E, Ehlers N. Incidence and prevalence of keratoconus in Denmark. *Acta Ophthalmol* Scand 2007;**85**:890–2) and 1 in 375 (Godefrooij DA, de Wit GA, Uiterwaal CS, Imhof SM, Wisse RP. Age-specific incidence and prevalence of keratoconus: a nationwide registration study. *Am J Ophthalmol* 2017;**175**:169–72). Initial referral to hospital clinics typically occurs during the second or third decade (the mean age at diagnosis is 28 years), with progression until the early 30s in most affected eyes.

In its early stages keratoconus causes worsening of vision on account of increasing myopia and irregular astigmatism. Spectacle correction provides good visual acuity in early disease only; later, increasing irregular astigmatism requires correction with rigid contact lenses to achieve best vision. Patients with more advanced keratoconus lose contact lens-corrected visual acuity on account of corneal opacification, and corneal transplant surgery is eventually required in > 20% of patients. Keratoconus first diagnosed in children is often more advanced than that first diagnosed in adults, with faster subsequent disease progression.

The most important parameters used in the assessment of keratoconus are the curvature of the cornea [presented as dioptre power (D)], the apical corneal thickness in μm, refraction and best corrected visual acuity. Early disease can be detected by corneal topography, which demonstrates thinning and irregularity of corneal curvature. Quantification of steepness of the corneal curvature in horizontal, vertical and multiple oblique meridians identifies the mean power in the meridian of maximum corneal steepness (K2) and the point of maximum steepness (K_{max}).

Although current routine clinical care involves treatment of the consequences of keratoconus on refraction or replacement of the diseased cornea by a transplant, the concept of stabilising keratoconus and arresting its progression at a stage when there is still good uncorrected or spectacle-corrected vision is relatively recent. Corneal cross-linking increases the stiffness of the cornea, which can arrest the progression of early keratoconus. It is currently the only intervention for this purpose. In the epithelium-off corneal cross-linking procedure, the corneal epithelium is removed, riboflavin eye drops are administered and the cornea is exposed to ultraviolet light for ≥ 8 minutes. Corneal cross-linking has been reported to be effective in arresting keratoconus progression in the majority of treated adult eyes in a number of non-randomised studies (including Henriquez *et al.* 2011 and Hersh *et al.* 2011) and randomised controlled trials [O'Brart DP, Chan E, Samaras K, Patel P, Shah SP. A randomised, prospective study to investigate the efficacy of riboflavin/ultraviolet A (370 nm) corneal collagen cross-linkage to halt the progression of keratoconus. *Br J Ophthalmol* 2011;**95**:1519–24, and Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology* 2014;**121**:812–21]. In the larger study by Wittig-Silva *et al.* in patients aged 16–50 years a significant difference in progression of corneal power in the steepest axis (termed 'K_{max}' by these authors but in later publications widely designated 'K2') between corneal cross-linking-treated and control eyes was reported: an improvement

in corneal cross-linking-treated eyes with flattening of K_{max} by −1.03 ± 0.19 D compared with an increase in the K_{max} of control eyes of +1.75 ± 0.38 D at 36 months (Wittig-Silva C, Chan E, Islam FM, Wu T, Whiting M, Snibson GR. A randomized, controlled trial of corneal collagen cross-linking in progressive keratoconus: three-year results. *Ophthalmology* 2014;**121**:812–21). Adverse effects were not uncommon but mostly transient, including corneal oedema, superficial opacification and recurrent corneal erosions. Despite increasing information in relation to the efficacy of corneal cross-linking, a Cochrane Review conducted in 2015 concluded that evidence for the use of corneal cross-linking in the management of keratoconus is limited because of the lack of properly conducted randomised controlled trials (Sykakis E, Karim R, Evans JR, Bunce C, Amissah-Arthur KN, Patwary S, *et al.* Corneal collagen cross-linking for treating keratoconus. *Cochrane Database Syst Rev* 2015;**3**:CD010621).

A number of observational studies of corneal cross-linking in keratoconus in younger subjects (aged < 19 years) have been published, each with limitations but each reporting effectiveness. Inclusion criteria included several parameters that are well recognised to be characterised by inter-test variability. Findings included improved visual acuity, reduced K_{max}, reduced myopic spherical equivalent on refraction testing and flattening on keratometry readings compared with pre-corneal cross-linking. Godefrooij *et al.* reported progression in 22% within 5 years of corneal cross-linking (Godefrooij DA, Soeters N, Imhof SM, Wisse RP. Corneal cross-linking for pediatric keratoconus: long-term results. *Cornea* 2016;**35**:954–8). Although the findings from these studies suggested that there was a beneficial effect of corneal cross-linking, more robust evidence is required to inform practice. Of note, no randomised trial has been undertaken in young patients.

The KERALINK trial was designed to investigate the efficacy and safety of the established technique of corneal cross-linking in progressive keratoconus in the paediatric age group, in which there is high potential for keratoconus progression on account of early disease onset. KERALINK was a multicentre randomised controlled trial in this patient group evaluating epithelium-off corneal cross-linking, the technique of corneal cross-linking that has been demonstrated to be effective in adults. Although we intend to follow up the trial participants for several years to ascertain the duration of keratoconus stability, it is clear that arrested progression in a paediatric patient is likely to (1) obviate the need for contact lens correction and for later corneal transplant surgery and (2) have correspondingly greater health and cost benefits than if corneal cross-linking was undertaken in adults.

Trial design

An observer-masked, randomised controlled, parallel-group superiority trial in patients aged 10–16 years with progressive keratoconus receiving corneal cross-linking and standard care or standard care only.

Methods

Participants and interventions

Patients aged 10–16 years were recruited following confirmation of progressive keratoconus in one or both eyes on the basis of increase in K_{max} or K2 of at least 1.5 D over a minimum of 3 months. Participants were randomised to receive corneal cross-linking or standard care alone. The corneal cross-linking procedure comprised the removal of the corneal epithelium, administration of riboflavin eye drops (VibeX Rapid™; Avedro, Inc., a Glaukos company, Glaukos Corporation, San Clemente, CA, USA) and application of ultraviolet light using standardised parameters. Participants in the standard-care group received spectacles or contact lenses as necessary to correct vision.

Outcome measures

The primary outcome measure was K2, measured using Pentacam (Pentacam HR, Oculus GmbH, Wetzlar, Germany) corneal topography, at 18 months post randomisation. Secondary outcomes were keratoconus

progression (defined as increase of > 1.5 D in K2), time to progression, uncorrected and corrected visual acuity, refraction, corneal thickness at the keratoconus apex and vision-related quality of life assessed by Child Health Utility 9D and Cardiff Visual Ability Questionnaire for Children. Safety was analysed in all participants. Patients in both groups were followed up at 3, 6, 9, 12, 15 and 18 months post randomisation. Quality-of-life questionnaires were completed at 6, 12 and 18 months post randomisation. At each trial visit an observer, masked to the randomised allocation, obtained triplicate K2 and K_{max} measurements, the mean value of which was used in analyses.

Sample size

Using our definition of progression as an increase in K2 of > 1.5 D, a sample size of 46 patients was estimated to be required to detect a difference between groups at the 5% significance level with 90% power, assuming a standard deviation of 1.5 D. The total sample size was increased to 60 patients (30 in each group) to allow for up to 24% loss to follow-up. These estimates were based on 12- and 24-month data reported by Wittig-Silva *et al.*, from which we estimated a pooled standard deviation of the changes of 1.476 D. Following adjustment of the sample size to take account of 10% loss to follow-up, and assuming that 20% of the standard-care group would cross over to corneal cross-linking or proceed to corneal transplantation, our planned total sample size of 60 patients would still provide at least 80% power to detect the clinically important difference.

Randomisation

Patients were randomised in a 1 : 1 ratio to receive either corneal cross-linking or standard care using an independent online randomisation service. This computer-generated system was custom designed to trial requirements and used a minimisation algorithm incorporating a random element, stratifying by treatment centre and whether progression was confirmed in one eye or both eyes at randomisation.

Statistical analysis

Analysis of the primary outcome was conducted following the intention-to-treat principle, with all randomised patients analysed in their allocated group whether or not they received their randomised treatment. A multilevel repeated measures linear regression model was used to estimate the difference between the treatment groups in K2 values at 18 months, adjusting for baseline values. A sensitivity analysis was conducted on the primary outcome to assess the robustness of results to treatment crossover or failure to receive any treatment following randomisation.

Each continuous secondary outcome measure on the study eye was analysed using a multilevel repeated-measures linear regression model: uncorrected and best corrected visual acuity [measured as logMAR (logarithm of the minimum angle of resolution) using Early Treatment of Diabetic Retinopathy Study vision testing chart], apical corneal thickness measurement (measured using ultrasound) and spherical equivalent refraction.

For categorical secondary outcomes, logistic regression models were fitted to examine the effect of treatment on keratoconus progression (yes/no), defined as increase in K2 of > 1.5 D from randomisation to 18 months or requirement for change from spectacles to rigid contact lenses for correction of vision and refractive astigmatism (absolute value of cylinder power > 0.75 D). Subgroup analysis was undertaken to investigate whether the effect of treatment differed according to ethnicity or history of atopy. We carried out exploratory analyses using both K2 and K_{max} values to establish which is a more sensitive measure of clinically/visually significant progression of keratoconus.

Results

Of the 60 recruited patients, all in the corneal cross-linking group and 28 patients in the standard-care group were analysed (intention to treat). Five patients crossed over from standard care to corneal cross-linking after 9 months and one patient in the corneal cross-linking group did not undergo the allocated procedure.

Primary outcome

The mean K2 in the study eye 18 months following randomisation was 49.7 D (standard deviation 3.8 D) in the corneal cross-linking group and 53.4 D (standard deviation 5.8 D) in the standard-care group. The adjusted difference in K2 in the study eye was −3.0 D (95% confidence interval −4.93 to −1.08 D; $p = 0.002$), meaning that K2 was 3 D lower at 18 months post randomisation in eyes receiving corneal cross-linking than in those receiving standard care.

Secondary outcomes

- Keratoconus progression in the study eye within 18 months occurred in only two patients (7%) randomised to corneal cross-linking, compared with 12 patients (43%) randomised to standard care. Cox proportional hazards regression analysis found that patients in the corneal cross-linking group had an 87% lower hazard of progression than those receiving standard care alone.
- Mean uncorrected and corrected visual acuity in the two groups diverged with time since randomisation. On average, the study eye of patients in the corneal cross-linking group had significantly better uncorrected and best corrected visual acuity at 18 months than the study eye of patients receiving standard care alone ($p = 0.002$ and $p = 0.002$, respectively).
- We found no significant differences between the corneal cross-linking group and the standard-care group in refraction, measured as spherical equivalent, or in apical corneal thickness at 18 months.
- Patients' quality of life improved from baseline in the corneal cross-linking group at 18 months as measured using Cardiff Visual Ability Questionnaire for Children and Child Health Utility 9D, but there was no significant difference between groups at 18 months ($p = 0.22$ and 0.14, respectively).
- There were no treatment-related adverse events in either group.

Conclusions

Main findings

The primary trial outcome finding was that corneal power in the steepest meridian (K2) in the study eye was 3 D lower in patients receiving corneal cross-linking than in those receiving standard care, and this difference was statistically significant. The finding of significant differences in uncorrected and best corrected visual acuity between the trial groups indicates that patients randomised to corneal cross-linking had significantly better vision at 18 months without and with spectacle correction, indicating that the difference between the groups was also clinically significant.

An important secondary outcome demonstrating efficacy of corneal cross-linking in halting keratoconus progression in this trial age group was that progression in the study eye by 18 months occurred in only 2 patients (7%) randomised to corneal cross-linking compared with 12 (43%) randomised to standard care. Time-to-event analysis indicated an 87% lower hazard of progression on the corneal cross-linking group ($p = 0.008$). These primary and secondary trial outcomes provide clear evidence of efficacy of corneal cross-linking in stabilising keratoconus progression in 10- to 16-year-olds with progressive keratoconus. There were no treatment related adverse events in either group.

Our findings in context of previously published reports

With respect to the important findings on keratoconus progression and visual acuity, our results are in agreement with those from randomised controlled trials in adult patients comparing corneal cross-linking with standard care for keratoconus. Our findings reduce the uncertainty on efficacy of corneal cross-linking and provide clear evidence in the paediatric age group.

The finding of significant progression in only 43% of patients receiving standard care, as defined by K2 change > 1.5 D after 18 months, is of particular note in the context of previously published reports. Earlier publications from uncontrolled studies reporting the effectiveness of corneal cross-linking in halting keratoconus progression in young patients could now be re-evaluated in the light of our observation.

It is possible that, in these uncontrolled studies, keratoconus that reportedly did not progress in some patients who were treated with corneal cross-linking might have spontaneously stabilised without intervention.

Strengths of the trial

Evidence is provided on progressive keratoconus up to the age of 16 years, a population in which there is currently no published randomised evidence. As the prognosis for long-term vision when keratoconus onset occurs at a young age is known to be poor, the greatest need is to identify the efficacy of corneal cross-linking in paediatric patients.

Precision in measurement of corneal power

Our trial used methods that directly address the key problem of measurement variability in corneal topography and used a definition of progression that required a greater change in K2, itself a more representative measure of corneal power than K_{max}, which has been more widely used in earlier studies.

Future work

The most important questions to be answered are whether or not (1) the arrest of keratoconus progression induced by corneal cross-linking is maintained in the long term and (2) the proportion of those receiving standard care who show significant progression increases with time.

Trial registration

This trial is registered as ISRCTN17303768 and EudraCT 2016-001460-11.

Funding

This project was funded by the Efficacy and Mechanism Evaluation (EME) programme, a Medical Research Council (MRC) and National Institute for Health Research (NIHR) partnership. This will be published in full in *Efficacy and Mechanism Evaluation*; Vol. 8, No. 15. See the NIHR Journals Library website for further project information. The trial sponsor is University College London. This research was otherwise supported in part by the NIHR Moorfields Biomedical Research Centre and the NIHR Moorfields Clinical Research Facility, London, United Kingdom.

Chapter 1 Introduction

Keratoconus is characterised by the thinning and distortion of the cornea that results in visual loss from complex refractive error and corneal opacification. The prevalence in Europe has been reported as 1 in 1163[1] and 1 in 375.[2] Higher prevalence is reported in some Asian regions: a prevalence of 1 in 43 was found in a survey[3] of adults aged ≥ 30 years in rural India, but the diagnostic criteria differed from those used in European studies. Variation in reported prevalence is likely to be accounted for by true differences associated with ethnicity but also by inconsistent case definition in surveys. Initial referral to hospital clinics is usually in patients' second or third decade (mean age at diagnosis 28 years),[2] and in most affected eyes progression continues until the patient is in their early 30s. In its earliest stage and prior to symptoms, keratoconus can be diagnosed on the basis of typical images on corneal topography. With progression it causes worsening of vision on account of increasing myopia and irregular astigmatism. Spectacle correction provides good visual acuity only in early disease; later, increasing irregular astigmatism requires correction with rigid contact lenses to achieve best vision. Patients with more advanced keratoconus lose contact lens-corrected visual acuity on account of corneal opacification, and corneal transplant surgery is eventually required in > 20% of patients.[4] Keratoconus is often more advanced if it is first diagnosed in childhood, with a subsequent disease progression faster than that in adults.[5]

The most important parameters used in the assessment of keratoconus are the curvature of the cornea [presented as *K* and measured in dioptres power (D)], the apical corneal thickness in μm, refraction and best corrected visual acuity. Early subclinical disease can be detected by corneal topography, which demonstrates irregularity of corneal curvature and thinning. Quantification of steepness of the corneal curvature in horizontal, vertical and multiple oblique meridians identifies the meridian of maximum corneal steepness (the mean corneal power on which meridian is designated K2) and the point of maximum steepness (K_{max}).

Although standard care, described above, involves treatment of the refractive consequences of keratoconus or replacement of the diseased cornea by a transplant, the concept of stabilising keratoconus and arresting its progression while there is still good uncorrected or spectacle-corrected vision is relatively recent. Corneal cross-linking (CXL) is believed to increase the stiffness of the cornea by mechanisms that are not understood, and can arrest the progression of early keratoconus.[6] It is currently the only intervention for the stabilisation of keratoconus. In the epithelium-off CXL procedure, the corneal epithelium is removed, riboflavin eye drops (Vibex Rapid, Avedro,Waltham, MA, USA) are administered and the cornea is exposed to ultraviolet (UV) light for ≥ 8 minutes depending on the procedure protocol used. CXL has been reported to be effective in arresting keratoconus progression in the majority of treated adult eyes in a number of non-randomised studies (including Henriquez *et al.*[7] and Hersh *et al.*[8]) and randomised controlled trials (RCTs) (O'Brart *et al.*[9] and Wittig-Silva *et al.*[10]). In the larger trial by Wittig-Silva *et al.*,[10] a significant difference in change in corneal power in the steepest axis (termed 'K_{max}' by these authors but in later publications widely designated 'K2') between CXL-treated and control eyes was reported at 36 months: K_{max} fell by -1.03 ± 0.19 D in CXL-treated eyes (i.e. corneal flattening), but increased by $+1.75 \pm 0.38$ D in control eyes. Adverse effects were not uncommon but were mostly transient, and included corneal oedema, superficial opacification and recurrent corneal erosions. Despite the increasing availability of information in relation to the efficacy of CXL, a Cochrane Review conducted in 2015[11] concluded that evidence for the use of CXL in the management of keratoconus is limited because of the lack of properly conducted RCTs.

In terms of younger subjects, a number of observational studies of CXL in keratoconus patients aged < 19 years have been published, each with limitations but each reporting effectiveness.[12–16] In one of the earliest publications, Caporossi *et al.*[12] reported an uncontrolled study of 152 keratoconus patients ranging in age from 10 to 18 years; however, information on follow-up post CXL was available for only 61% of patients. Inclusion criteria included several parameters that are well recognised to be

characterised by inter-test variability. In this treated patient group, a statistically significant reduction in '*K* average' of −0.4 D was found. Vinciguerra *et al.*[13] reported on 40 CXL-treated eyes in patients aged 9–18 years (mean 14.2 years) with progressive keratoconus in a non-randomised prospective study. Findings included improved visual acuity, reduced myopic spherical equivalent on refraction testing and flattening on keratometry readings compared with pre-CXL. Godefrooij *et al.*[14] reported progression in 22% within 5 years of CXL. Although the findings from these studies suggested that there was a beneficial effect of CXL, more robust evidence is required to inform practice. Of note, to our knowledge no randomised trial has been undertaken in young patients despite the fact that the potential for visually significant keratoconus progression is greatest in this age group.

The aim of the KERALINK trial was to establish whether or not epithelium-off CXL (the CXL technique that has been demonstrated to be effective in adults) is efficacious in stabilising keratoconus progression compared with standard care and is safe in children and young people between the age of 10 and 16 years. The specific objectives were to assess changes in (1) corneal shape (measured as K2, the mean power on the steepest keratometric meridian on topography), (2) visual acuity, (3) refraction and (4) corneal thickness at the corneal apex. Patient-reported effects on quality of life were also explored. Patients were followed up at 3-monthly intervals for 18 months following randomisation.

Arresting progression in a paediatric patient would be likely to (1) obviate the need for contact lens correction and later corneal transplant surgery and (2) have correspondingly greater health and cost benefits than if CXL were undertaken in adults. Trial findings will inform ophthalmologists and optometrists as well as future research and treatment policy.

Chapter 2 Methods

Trial design

The KERALINK trial was a two-arm, randomised, multicentre, parallel-group, observer-masked RCT. Patients were randomised 1 : 1 to receive either CXL in one or both eyes (depending on whether progression was confirmed in one eye or both) followed by standard management or standard care (which included the provision of glasses and/or contact lenses as required for best corrected visual acuity) alone.

Patient eligibility criteria

Inclusion criteria

- Patients were eligible to participate if they were aged 10–16 years and keratoconus progression in one or both eyes had been confirmed using Pentacam (Pentacam HR, Oculus GmbH, Wetzlar, Germany) or other topography devices. Progression, for the purposes of determining eligibility, was defined as an increase of $\geq$ 1.5 D in K2 or K_{max} on Pentacam corneal topography (or equivalent on other topography devices) between two examinations using the same scanning device at least 3 months apart.
- Patients and their parents/guardians were required to be sufficiently fluent in English to provide assent and informed consent and to complete the patient-reported outcome measures.
- Patients had to be willing to attend follow-up visits.

Exclusion criteria

- Apex corneal scarring in advanced keratoconus.
- Apex corneal thickness $<$ 400 µm.
- K2 $>$ 62 D and/or K_{max} $>$ 70 D on Pentacam topography at screening.
- Rigid contact lens wear in both eyes and unable to abstain from lens wear for 7 days pre examinations.
- Corneal comorbidity.
- Down syndrome.
- Any clinical condition that the investigator considered would make the patient unsuitable for the trial, including pregnancy.
- Participation in other clinical trials that would materially impact on the KERALINK trial.

The trial was conducted in five secondary care NHS clinics in England and Wales: Moorfields Eye Hospital NHS Foundation Trust, the Royal Liverpool & Broadgreen University Hospitals NHS Trust, Sheffield Teaching Hospital NHS Foundation Trust, Aneurin Bevan University Health Board and Manchester University NHS Foundation Trust (see *Appendix 1*).

Protocol amendments

A series of amendments, both major and minor, were made to the protocol. All relevant approvals for these amendments were obtained before implementation and the major amendments have been summarised in *Appendix 2*.

Trial interventions

Screening

Written informed consent to enter and be randomised into the trial was obtained from parents/guardians/person with legal responsibility (including legal authorities) for children, after explanation of the aims, methods, benefits and potential hazards of the trial and before any trial-specific procedures were performed. The only procedures that could be performed in advance of obtaining written informed consent were those that would be performed on all patients receiving the usual standard of care.

Group A: experimental intervention (corneal cross-linking)

Patients randomised to receive CXL underwent the procedure no later than 4 weeks following randomisation but as soon as was feasible in all cases.

Patients in whom both eyes were eligible and who were randomised to CXL could choose whether or not to have the procedure on both eyes at the same time. Those patients randomised to CXL who chose not to have the surgery were managed in the same way as patients in the standard-care group.

In patients in whom both eyes were eligible, management of the second eye was in accordance with the randomised allocation for the first eye, unless the patient specifically preferred otherwise. If only one eye was eligible at the time of randomisation, but during the course of the trial the second eye developed progressive keratoconus, then management of the second eye was in accordance with the randomised allocation.

Corneal cross-linking was carried out in one or both eyes (depending on whether progression was confirmed in one eye or both eyes), under general or local anaesthesia as applicable, followed by standard management. The surgical procedure was as follows: insertion of lid speculum, manual removal of corneal epithelium with a spatula, administration of riboflavin eye drops every 2 minutes for 10 minutes followed by application of pulsed UV light using standardised parameters of 10 mW/cm^2 for a total energy dose of 5.4 J/cm^2 administered over 8 minutes (Avedro KXL). This CXL protocol is used increasingly often and differs from the originally reported 'Dresden' protocol in that the UV light application time is reduced; the protocols have been found to be similarly effective in young patients.[15] On completion of the procedure, one drop of povidone iodine (Minims povidone iodine 5%, Bausch & Lomb UK Ltd, Kingston upon Thames, UK) and a therapeutic contact lens were applied to the treated eye. Management post CXL was (1) proxymetacaine (Minims proxymetacaine hydrochloride 0.5%, Bausch & Lomb UK Ltd, Kingston upon Thames, UK) eye drops every 2 hours as required and 250 mg of naproxen (AAH Pharmaceuticals Ltd, Coventry, UK) twice per day, both as required for analgesia; (2) 0.5% moxifloxacin (Moxivig 0.5%, Novartis Pharmaceuticals UK Ltd, London, UK) eye drops every 6 hours for 1 week as infection prophylaxis; and (3) 0.1% dexamethasone (Maxidex 0.1%, Novartis Pharmaceuticals UK Ltd) eye drops every 6 hours for 1 week, then every 12 hours for 1 week, then 0.1% fluorometholone eye drops every 12 hours for 1 week. Patients randomised to CXL attended an extra examination at 1 week post CXL for the removal of the contact lens and confirmation of corneal re-epithelialisation.[17]

Group B: control intervention (standard care)

The control group received standard management, comprising refraction testing and provision of glasses and/or contact lens fitting for one or both eyes as required for best corrected visual acuity.[17] If patients randomised to standard care developed more visually significant keratoconus, additional treatments were discussed with the patient and parents, including crossover to the CXL group. If more advanced disease and poor spectacle- and/or lens-corrected visual acuity developed during the course of the trial, corneal transplantation was offered.

Outcomes

Primary outcome measure

The primary outcome measure was the difference between the two groups in K2 in the study eye at 18 months post randomisation, measured using standard Pentacam imaging. *K* is the corneal power at a given point on Pentacam topography, measured in dioptres (D). K2 is the value of corneal power on the steepest corneal meridian and more representative than K_{max}, which is the corneal power at the steepest point in the cornea. For each patient, the eye with the more advanced keratoconus (highest value of K2 and with documented increase of > 1.5 D between examinations prior to randomisation) at the time of randomisation was defined as the study eye for the primary analysis, unless that eye had previously been treated by CXL or corneal transplantation.

Secondary outcome measures

- Keratoconus progression (yes/no) defined as > 1.5 D increase in K2 from baseline (at randomisation) to 18 months post randomisation or requirement for change from spectacle to rigid contact lens correction of vision, as the latter precluded reliable topographic measurements.
- Time from randomisation to keratoconus progression (defined as > 1.5 D increase in K2 from baseline).
- Uncorrected and best corrected visual acuity [measured as logMAR (log of the minimum angle of resolution) using the Early Treatment of Diabetic Retinopathy Study (ETDRS) testing chart].
- Refraction (measured dioptres spherical equivalent, myopia and astigmatism).
- Apical corneal thickness measurement (ultrasound).
- Quality of life as assessed using the Child Health Utility 9D (CHU9D) and the Cardiff Visual Ability Questionnaire for Children (CVAQC-25).

Details for outcome measures

Patients in the CXL and standard-care groups were followed up at 3, 6, 9, 12, 15 and 18 months post randomisation. The quality-of-life questionnaires were completed at 6, 12 and 18 months post randomisation.

K2 measurement

K2 measurements from Pentacam images were used as the indicators of disease progression. The probability is high that increases of > 1.5 D in K2 would discriminate between a true change in the steepest corneal meridian and artefact. A change of this magnitude was clinically significant, indicating a likelihood of improved visual acuity with correction of the refractive change. At each trial visit, an observer masked to the randomised allocation obtained triplicate K2 measurements, the mean value of which was used in analyses. To account for the possibility of inter-test and intra-test variation in topographic analysis, if any patient was found to have an increase in K2 of > 1.5 D, then measurements were taken again at a subsequent visit (i.e. 3 months later). Only those with progression found for the first time at 18 months needed a further 21-month examination.

Following scanning, the software performs an analysis and generates a yellow or red flag, as appropriate, to indicate unsatisfactory scan quality. Although poor inter-test repeatability of K_{max} but not K2 has been found to be a feature of Pentacam scanning,[18] and repeatability in general declines in advancing keratoconus,[18,19] if the examining optometrist reported a scan with a red flag then all measurements from that scan, including K2 and K_{max}, were considered unreliable. For the primary analysis, the mean K2 and K_{max} values were calculated on measurements from reliable scans only. If all three scans were noted to have red flags, then the K2 and K_{max} values at that visit were not included in the analysis. As a result, K2 data were missing for two patients at 18 months (see *Figure 1*).

Uncorrected and best corrected visual acuity (measured as logMAR using the Early Treatment of Diabetic Retinopathy Study chart)

Distance visual acuity was recorded as the number of correct letters read in the ETDRS chart at a distance of 4 m. The ETDRS chart comprises 14 lines with five letters per line (i.e. 70 letters in total). With the ETDRS scoring system:

- If ≥ 20 letters are read correctly at a starting distance of 4 m, the visual acuity score is equal to the number of letters read correctly + 30.
- If < 20 letters are read correctly at a starting distance of 4 m, the visual acuity score is equal to the number of letters read correctly at 4 m plus the number of letters on the first six lines read correctly at 1 m.
- If no letters are read correctly at either the 4-m distance or the 1-m distance, tests of counting fingers (CF), hand motion (HM), perception of light (PL) and no perception of light (NPL) will be performed.

The visual acuity score was converted to logMAR equivalents using the formula:

$$\text{logMAR} = 1.7 - 0.02 \times (\text{visual acuity score}). \quad (1)$$

With this conversion, a five-letter difference in visual acuity is equivalent to a difference of 0.1 logMAR.

For patients who could not read any letters correctly in the EDTRS chart at a distance of 1 m, assessments of CF, HM, PL and NPL were assigned visual acuity logMAR values of 2.10, 2.40, 2.70 and 3.00, respectively. Therefore, visual acuity logMAR ranged from –0.3 to 3.0, with lower values indicating better visual acuity. The terms uncorrected and corrected refer to measurements without and with, respectively, best spectacle or contact lens correction.

Refraction

The spherical equivalent refraction (SER) was calculated by adding half of the cylinder power (cyl) to the sphere power:

$$\text{SER} = \text{sphere} + \left(\frac{\text{cyl}}{2}\right). \quad (2)$$

The number of patients with refractive astigmatism was based on a refractive cylinder. An absolute cylinder power of ≥ 0.75 D represented significant refractive astigmatism.

Apical corneal thickness measurement

To our knowledge, biomechanical and ultrastructural studies to date have not been able to demonstrate the mechanism by which CXL stiffens the cornea. The KERALINK trial examined changes in thickness of the cornea using ultrasound. Corneal apex thickness measurements were correlated with changes in corneal shape and visual parameters. This will confirm whether or not arrest of keratoconus progression following CXL is accompanied by arrest of progressive thinning.

Child Health Utility 9D

The CHU9D is a paediatric generic preference-based measure of health-related quality of life. It consists of a descriptive system and a set of preference weights, giving utility values for each health state described by the descriptive system, allowing the calculation of quality-adjusted life-years for use in cost–utility analyses. It has been validated for self-completion in an adolescent population (11–17 years).[20–24] The questionnaire consists of nine items, each with a five-level response category. Each item relates to a particular domain – worry, sadness, pain, tiredness, annoyance, school, sleep, daily routine and activities (see *Appendix 3*). Higher scores on this questionnaire relate to better outcomes.

Cardiff Visual Ability Questionnaire for Children

The CVAQC-25 is a 25-item vision-specific questionnaire designed for children.[25] The items, each rated on a four-point scale, cover areas such as education, near and distance vision, getting around, social interaction, entertainment and sports (see *Appendix 3*). The raw CVAQC-25 scores are transformed into logarithmic scores using a Rasch calculator designed by the developers of the questionnaire. A questionnaire was considered missing if > 33% of data were missing. Lower scores on this questionnaire relate to better outcomes.

Sample size

A difference between the groups in the change in K2 of 1.5 D or more from randomisation to 18 months would be viewed as a clinically important difference (based on Wittig-Silva *et al.*'s[10] RCT of CXL in adults). A K2 increase of > 1.5 D would discriminate between a true change in the steepest corneal meridian and a measurement artefact and would be visually significant.

A sample size of 46 patients would be required to detect this difference at the 5% significance level with 90% power, assuming a standard deviation (SD) of 1.5 D. The total sample size was increased to 60 patients (30 per group) to allow for up to 24% loss to follow-up. These estimates were based on 12- and 24-month data reported by Wittig-Silva *et al.*,[10] from which we estimated a pooled SD of the changes of 1.476 D.

We expected that, on average, there would be 10% loss to follow-up in both groups. In the trial by Wittig-Silva *et al.*,[10] 19% of patients withdrew, crossed over to CXL or had a transplant by 18 months. However, 18% of patients in the control group received either CXL or a transplant. If we specifically adjust the sample size to take account of 10% loss to follow-up and 20% of the control group cross over to CXL or transplant, then our planned total sample size of 60 patients would still provide at least 80% power to detect a clinically important difference. The trial design dictated that children could not cross over to CXL before 9 months from randomisation.

Randomisation

Patients were randomised in a 1 : 1 ratio to receive either standard medical care or CXL using an independent online randomisation service (www.sealedenvelope.com). The computer-generated system was custom designed to trial requirements. It used a minimisation algorithm incorporating a random element, stratifying by treatment centre and whether progression was confirmed in one eye or both eyes at randomisation.

The responsibility for enrolling and randomising patients into the trial lay with the principal investigator (PI) and staff at the trial site. Individuals at participating centres were provided with a secure login for the sealedenvelope.com website during the site activation procedure. The randomisation result was shown directly online, with an e-mail confirmation to the user and also to the trial manager.

Blinding (masking)

Owing to the nature of the intervention, neither the patients nor the treating clinicians and site staff were masked to the treatment allocation. However, optometrists performing outcome assessments were unaware of treatment allocation. The PI and treating clinicians were not aware of the primary outcome values (K2) measured by the optometrists during the follow-up assessments.

Statistical methods

Primary outcome analysis

The primary outcome analysis was conducted following the intention-to-treat (ITT) principle, with all randomised patients analysed in their allocated group whether or not they received their randomised treatment.

A multilevel repeated measures linear regression model was used to estimate the difference in K2 values between the treatment groups at 18 months. This model used all K2 data from 3 months to 18 months. The statistical analysis plan has been published in full.[26]

The model included fixed effects for K2 at randomisation (continuous), treatment group (two categories: standard care and CXL), time (six categories: 3, 6, 9, 12, 15 and 18 months), treatment by time interaction, and the stratifying variables centre and number of eyes progressed at randomisation. A random patient effect was included to take account of clustering by patient. The model coefficients were estimated using the robust standard errors technique, to allow for unequal variances in the two randomised groups. This analysis was equivalent to modelling the change in K2 adjusting for K2 values at randomisation.

The model made assumptions about random effects distributions, correlation structure and residuals. Model assumptions were assessed using residual plots.

Secondary outcome analysis

Continuous secondary outcomes

Each of the following continuous secondary outcome measures on the study eye were analysed using a separate multilevel repeated measures linear regression model:

- uncorrected and best corrected visual acuity (measured as logMAR using the EDTRS chart)
- apical corneal thickness measurement (measured using ultrasound)
- SER.

Each model included fixed effects for treatment, time, treatment by time interaction, baseline value of the associated outcome and stratifying variables. A random patient effect was included to take account of clustering by patient.

Categorical secondary outcomes

Separate, unadjusted logistic regression models were fitted to compare the effect of treatment on the categorical variables:

- Keratoconus progression (yes/no) was defined as an increase of > 1.5 D in K2 from randomisation to 18 months or requirement for change from spectacles to rigid contact lenses for correction of vision, as the latter precluded reliable topographic measurements. Acknowledging inter-test and intra-test variation in topographic analysis, it was specified that disease progression (i.e. an increase in K2 of > 1.5 D) in any patient had to be confirmed at a subsequent visit (i.e. 3 months later).
- Refractive astigmatism (absolute value of cylinder power > 0.75 D).

Time-to-event outcome

Time to keratoconus progression was visually displayed using Kaplan–Meier survival plots, and the differences between the groups in the interval from randomisation to progression were compared using an unadjusted Cox regression model. The first date when progression was observed was the date of event used for this analysis.

Adverse events and serious adverse events

The proportions of patients experiencing at least one adverse event and patients experiencing at least one serious adverse event were summarised by treatment group. The number and percentage of adverse events and serious adverse events are presented descriptively, but no formal analysis was performed.

Sensitivity analysis of primary outcome

Sensitivity analysis was conducted on the primary outcome to assess the robustness of results to treatment crossover or failure to receive any treatment following randomisation. In the event of crossover from one randomised group to the other, we performed analyses of the primary outcome on a per-protocol basis. The per-protocol analysis excluded any information collected from a patient after crossover. This analysis also excluded data from patients who did not receive the treatment to which they were randomised.

Subgroup analysis

The regression model for the primary outcome was extended by adding interaction terms to investigate the effect of treatment on prespecified subgroups. We included interactions between treatment and family history of keratoconus, atopy and ethnicity to investigate whether or not the effect of treatment differs for each of these factors. We also planned to explore the moderating effect of number of eyes progressed at the time of randomisation and family history of keratoconus but did not carry out this subgroup analysis owing to the small numbers in each subgroup.

Exploratory outcome analysis

K_{max} was analysed as an exploratory outcome, using a similar model as for the primary outcome. We carried out exploratory analyses using both K2 and K_{max} values to establish which was a more sensitive measure of clinically/visually significant progression of keratoconus.

Chapter 3 Results

Participant flow

In total, 240 potential patients were screened for entry to the trial, of whom 180 were excluded. Reasons for losses and exclusions are presented in *Figure 1*.

Recruitment

The first patient was randomised on 28 October 2016, and the recruitment total of 60 was reached on 26 September 2018. The numbers of patients screened and randomised at each site are presented in *Table 1*.

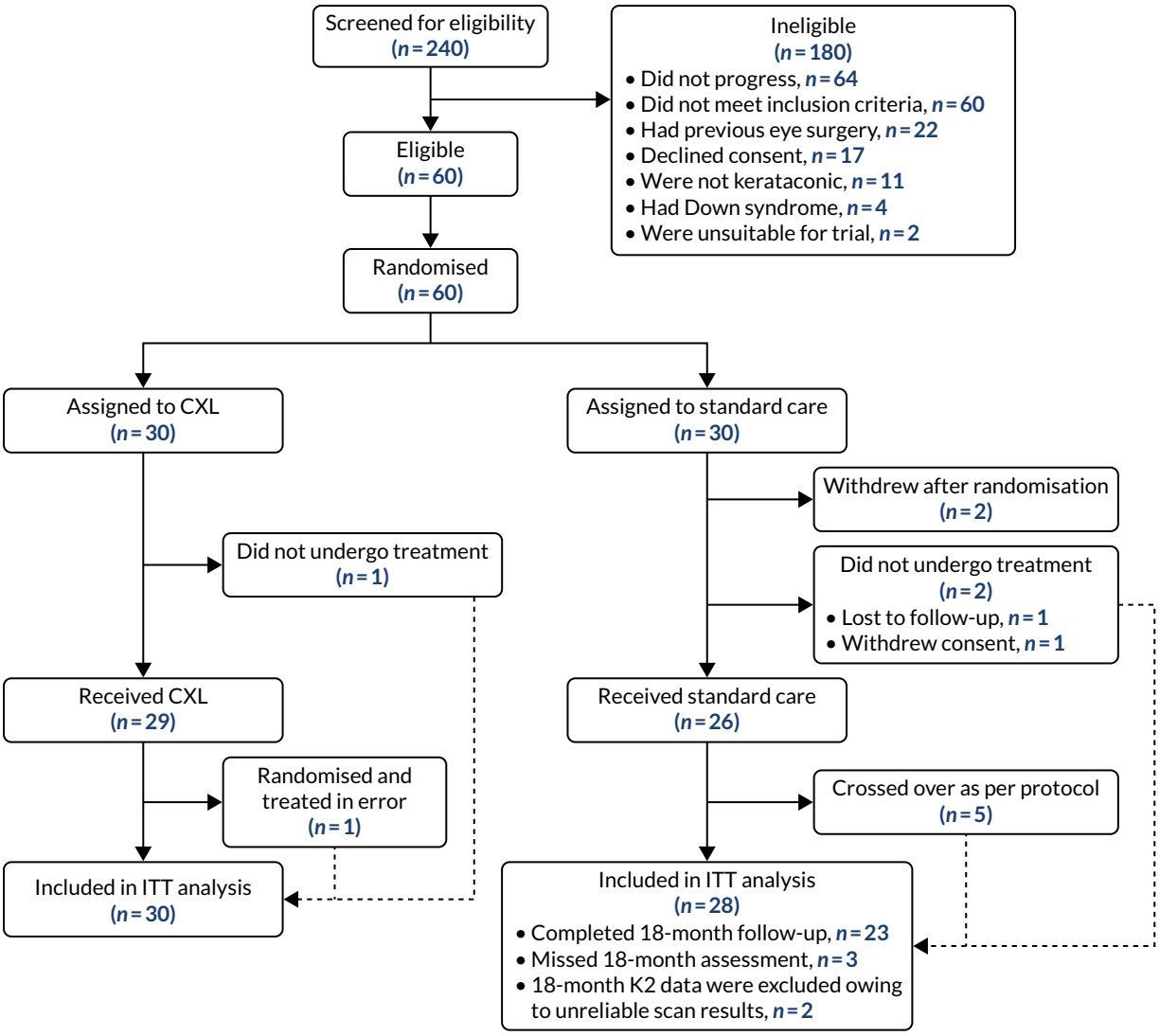

FIGURE 1 Trial CONSORT flow diagram. Reproduced with modification and permission from Larkin *et al.*[27] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to distribute this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by-nd/4.0/.

TABLE 1 Numbers screened and randomisation by site

Participating site	Site activation date	Number of potential participants		
		Screened	Not eligible	Randomised
Moorfields Eye Hospital, London	3 October 2016	175	124	51
Royal Hallamshire Hospital, Sheffield	6 December 2016	20	14	6
Royal Liverpool University Hospital	23 February 2017	13	13	0
Royal Gwent Hospital, Newport	13 March 2018	1	0	1
Manchester Royal Eye Hospital	10 May 2018	31	29	2
Total across sites		240	180	60

Of the 60 patients randomised, two patients in the standard-care group withdrew from the trial before their 3-month visit, and a further two patients withdrew before 18 months. One patient in the CXL group did not receive the allocated treatment but remained in the trial for follow-up. One further patient randomised to CXL was subsequently found to have a pre-randomisation K2 increase of only 1.2 D and, therefore, did not meet the 1.5 D increase criterion for trial eligibility. As the patient had already undergone CXL by the time that this error was discovered, we continued to follow up the patient. A major protocol deviation was recorded (see *Appendix 4*). All 58 patients who had a baseline K2 measure and at least one follow-up were included in the mixed model for the primary outcome analysis.

Baseline data

The baseline characteristics of the two randomised groups are presented in *Table 2*. The mean age of participants was similar in both treatment groups: 15 years (SD 1.1 years) in the CXL group and 15 years (SD 1.6 years) in the standard-care group. In keeping with clinicians' experience of managing keratoconus patients, the minority of participants ($n = 18$, 27%) were female. The largest ethnic group (45%) was Asian/Asian British. The two trial groups differed with respect to sex and ethnicity. However, as randomisation was carried out using an independent online service, this difference was due to chance.

TABLE 2 Baseline characteristics by treatment group

Characteristic	Treatment group		
	CXL ($N = 30$)	Standard care ($N = 30$)	Total ($N = 60$)
Minimisation factors			
Treatment centre, *n* (%)			
Moorfields	25 (83.3)	25 (83.3)	50 (83.3)
Sheffield	2 (6.7)	4 (13.3)	6 (10.0)
Liverpool	1 (3.3)	0 (0.0)	1 (1.7)
Newport	1 (3.3)	0 (0.0)	1 (1.7)
Manchester	1 (3.3)	1 (3.3)	2 (3.3)
Number of eligible eyes, *n* (%)			
One	27 (90.0)	26 (86.7)	53 (88.3)
Two	3 (10.0)	4 (13.3)	7 (11.7)

TABLE 2 Baseline characteristics by treatment group (*continued*)

Characteristic	Treatment group		Total (*N* = 60)
	CXL (*N* = 30)	Standard care (*N* = 30)	
Patient characteristics			
Age (years), mean (SD)	15.2 (1.1)	15.2 (1.6)	15.2 (1.4)
Sex, *n* (%)			
Male	25 (83.3)	19 (63.3)	44 (73.3)
Female	5 (16.7)	11 (36.7)	16 (26.7)
Ethnicity, *n* (%)			
White	12 (40.0)	5 (16.7)	17 (28.3)
Mixed	4 (13.3)	2 (6.7)	6 (10.0)
Asian or Asian British	10 (33.3)	17 (56.7)	27 (45.0)
Black or black British	3 (10.0)	4 (13.3)	7 (11.7)
Other ethnic groups	1 (3.3)	2 (6.7)	3 (5.0)
Use of refractive correction aid, *n* (%)			
No	9 (30.0)	10 (33.3)	19 (31.7)
Yes	21 (70.0)	20 (66.7)	41 (68.3)
Refractive correction aid, *n* (%)			
Glasses	18 (60.0)	17 (56.7)	35 (58.3)
Contact lenses	0 (0.0)	1 (3.3)	1 (1.7)
Both	3 (10.0)	2 (6.7)	5 (8.3)
Type of lenses, *n* (%)			
Soft lenses	3 (10.0)	0 (0.0)	3 (5.0)
Rigid gas permeable	0 (0.0)	3 (10.0)	3 (5.0)
Family history of keratoconus, *n* (%)			
No	24 (80.0)	28 (93.3)	52 (86.7)
Yes	6 (20.0)	2 (6.7)	8 (13.3)
History of atopy, *n* (%)			
No	20 (66.7)	14 (46.7)	34 (56.7)
Yes	10 (33.3)	16 (53.3)	26 (43.3)
K2 (D), mean (SD)			
Study eye	49.1 (3.5)	50.2 (3.4)	49.7 (3.5)
Fellow eye	50.5 (3.5)	49.7 (4.0)	50.0 (3.5)
K_{max} (D), mean (SD)			
Study eye	56.0 (4.8)	57.2 (5.7)	56.6 (5.3)
Fellow eye	52.7 (2.3)	56.9 (7.0)	55.1 (5.6)
Apical thickness (μm), mean (SD)			
Study eye	512 (47.9)	507 (41.2)	509 (44.5)
Fellow eye	492 (66.6)	519 (60.4)	507 (59.2)
Uncorrected visual acuity (logMAR), mean (SD)			
Study eye	0.6 (0.4)	0.7 (0.4)	0.7 (0.4)
Fellow eye	0.4 (0.1)	0.5 (0.4)	0.5 (0.3)

continued

TABLE 2 Baseline characteristics by treatment group (*continued*)

Characteristic	Treatment group		Total (*N* = 60)
	CXL (*N* = 30)	Standard care (*N* = 30)	
Best corrected visual acuity (logMAR), mean (SD)			
Study eye	0.5 (0.4)	0.5 (0.4)	0.5 (0.4)
Fellow eye	0.4 (0.2)	0.2 (0.2)	0.3 (0.2)
Refraction (spherical equivalent) (D), mean (SD)			
Study eye	2.1 (2.9)	1.3 (2.4)	1.7 (2.6)
Fellow eye	1.1 (0.9)	0.8 (2.6)	0.9 (1.9)
Refractive astigmatism, *n* (%)			
Study eye	23 (76.7)	25 (83.3)	48 (80.0)
Fellow eye	2 (6.7)	3 (10.0)	5 (8.3)
CHU9D utility score, mean (SD)	0.9 (0.1)	0.9 (0.1)	0.9 (0.1)
CVAQC-25 score, mean (SD)	−1.1 (1.0)	−1.2 (1.1)	−1.2 (1.0)

Participants were evenly distributed between treatment groups with regard to the minimisation factors – site and number of eyes progressed at baseline. In seven patients (12%), both eyes had progressed at baseline and were eligible for randomisation. Forty-one patients (68%) were using a refractive corrective aid at baseline, of whom the majority (*n* = 35, 85%) were using glasses; five patients were using both glasses and contact lenses and one reported using only contact lenses. Of those using contact lenses, three reported using rigid contact lenses.

The mean K2 in the study eye was 49 D (SD 3.5 D) in the CXL group and 50 D (SD 3.4 D) in the standard-care group. All outcome measures at baseline were observed to be similar between the two treatment groups.

Numbers analysed

The numbers of patients included in each analysis model are summarised in *Table 3*.

Owing to the nature of the model used in the analysis of primary and secondary continuous outcomes (mixed model), all patients having at least a baseline and an additional visit were included in the analysis. Therefore, the final primary outcome analysis was based on 58 patients: 30 in the CXL group and 28 in the standard-care group.

Outcomes and estimation

Primary outcome

The results of the analysis of the primary outcome are summarised in *Figure 2* and *Table 4*. The mean K2 in the study eye at 18 months post randomisation was 50 D (SD 3.8 D) in the CXL group and 53 D (SD 5.8 D) in the standard-care group. The adjusted difference in K2 in the study eye at 18 months was −3.0 D [95% confidence interval (CI) −4.93 to −1.08 D], with a *p*-value of 0.002. This suggests

TABLE 3 Numbers analysed in each outcome model

Outcome	Treatment group (*n*)	
	CXL (*n* = 30)	Standard care (*n* = 30)
Primary outcome (ITT)	30	28
Sensitivity of primary outcome (per protocol)	28	27
Secondary outcome		
Uncorrected visual acuity	30	28
Best corrected visual acuity	30	28
Apical thickness	30	27
Spherical equivalent refractive error	30	28
CVAQC-25	29	27
CHU9D	28	26
Keratoconus progression	30	28
Refractive astigmatism	30	25
Time to keratoconus progression (years)	30	30

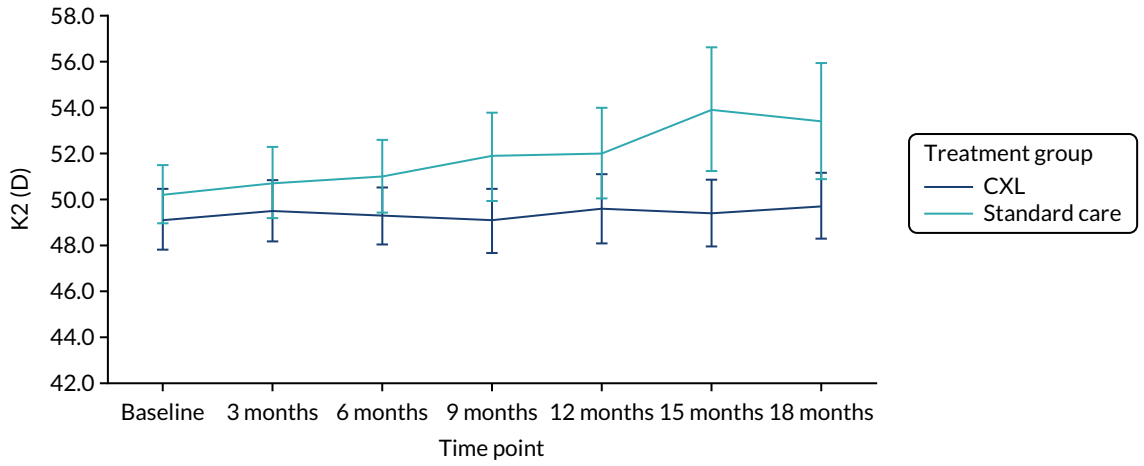

FIGURE 2 K2 in the study eye in the ITT population (primary outcome population). Reproduced with modification and permission from Larkin *et al.*[27] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to distribute this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by-nd/4.0/.

that, on average, at 18 months post randomisation, patients receiving CXL in the trial had a K2 value 3 D lower than that of patients receiving standard care. This difference is statistically and clinically significant, as the 95% CI included the clinically important difference of 1.5 D that corresponded to keratoconus progression.

Five patients crossed over from standard care to CXL after 9 months and one patient in the CXL group did not undergo their allocated procedure. A further patient randomised to CXL was subsequently found to be ineligible for the trial (increase in baseline $K_{max} < 1.5$ D). Per-protocol analysis excluding this patient at baseline and patients at the time of crossover did not change the observed ITT results.

TABLE 4 Primary outcome analyses: K2 in the study eye at 18 months post randomisation, by treatment group

K2 in study groups	Treatment group: CXL *n*	CXL Mean (SD)	Standard care *n*	Standard care Mean (SD)	Adjusted coefficient (95% CI)[a]	*p*-value
Primary outcome						
K2 (D) – ITT population	30	49.7 (3.8)	23	53.4 (5.8)	−3.00 (−4.93 to −1.08)	0.002
Sensitivity analysis of primary outcome						
K2 (D) – PP population	28	49.4 (3.4)	19	53.2 (5.8)	−3.23 (−5.21 to −1.26)	0.001
K2 (D) (including all scans with red flags)	30	49.7 (3.8)	25	54.5 (7.3)	−3.73 (−6.58 to −0.90)	0.01

PP, per protocol.
a Adjusted for baseline K2 and minimisation factors site and number of eyes progressed.

Data from patients were excluded from the average K2 calculation at some visits because some topographic measurements were categorised as unreliable by Pentacam device software (measurements from red-flagged scans). It is recognised that repeatability of topography scans diminishes in eyes with advanced keratoconus, one probable cause being difficulty in fixation of gaze during image capture.[18,19] We carried out supportive analysis on the primary outcome by including data on these patients in the primary model, to examine the impact of inclusion of these measures from patients with advanced disease on the observed treatment effect. *Figure 3* shows the mean and CIs at each follow-up visit in this population, by treatment. There is divergence in the mean K2 between treatment groups at the 18 month time point, as shown in *Figure 3* compared with that in *Figure 2*. The observed difference was greater (−3.73 D) but with a wider 95% CI of −6.58 to −0.90 D ($p = 0.01$).

Secondary outcomes

Table 5 summarises the analysis of the secondary outcomes. The mean uncorrected and best corrected visual acuity diverged with time between the groups (*Figures 4* and *5*). We found no significant differences between the CXL and standard-care groups in apical corneal thickness (*Figure 6*) and refraction measured as spherical

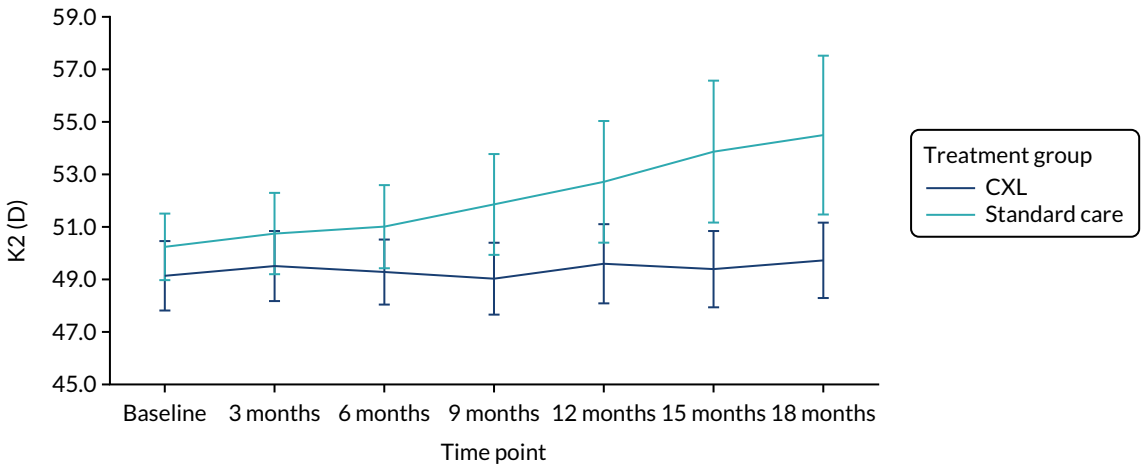

FIGURE 3 K2 in the study population including red-flagged measures from patients with advanced disease at 18 months by treatment group. Reproduced with modification and permission from Larkin *et al.*[27] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to distribute this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by-nd/4.0/.

TABLE 5 Secondary outcome analyses at 18 months post randomisation

Secondary outcomes	Treatment group: CXL *n*	CXL Mean (SD)	Standard care *n*	Standard care Mean (SD)	Adjusted coefficient (95% CI)[a]	*p*-value
Apical corneal thickness (μm)	28	501.8 (38.0)	22	479.9 (46.3)	16.37 (−2.87 to 35.61)	0.10
Uncorrected visual acuity (logMAR)[b]	29	0.5 (0.3)	25	0.8 (0.6)	−0.31 (−0.50 to −0.11)	0.002
Best corrected visual acuity (logMAR)[b]	29	0.4 (0.4)	25	0.6 (0.6)	−0.30 (−0.48 to −0.11)	0.002
Refraction [spherical equivalent (D)]	30	3.2 (2.4)	25	4.0 (2.4)	−0.75 (−1.69 to 0.18)	0.11
CHU9D utility score	28	1.0 (0.1)	25	0.9 (0.1)	0.02 (−0.017 to 0.05)	0.14
CVAQC-25 score	29	−1.2 (0.8)	25	−1.1 (0.9)	−0.26 (−0.69 to 0.14)	0.22
	n	*n* (%)	*n*	*n* (%)	Unadjusted odds ratio (95% CI)[c]	
Confirmed keratoconus progression[d]	30	2 (6.7)	28	12 (42.9)	0.10 (0.02 to 0.48)	0.004
Refractive astigmatism[e]	30	28 (93.3)	25	22 (88.0)	1.91 (0.29 to 12.44)	0.50
	n	*n*	*n*	*n*	Unadjusted hazard ratio (95% CI)[c]	
Time to confirmed keratoconus progression (years)[d]	30	See *Figure 4*	30	See *Figure 4*	0.13 (0.03 to 0.59)	0.008

a Adjusted for baseline K2 and minimisation factors, site and number of eyes progressed.
b Lower logMAR scores correspond to better visual acuity.
c Unadjusted analysis was carried out because of the small proportion of participants having a progression event.
d Two patients in the CXL group and one patient in the standard-care group had unconfirmed progression at 18 months.
e An absolute cylinder of 0.75 D or more represents significant refractive astigmatism.

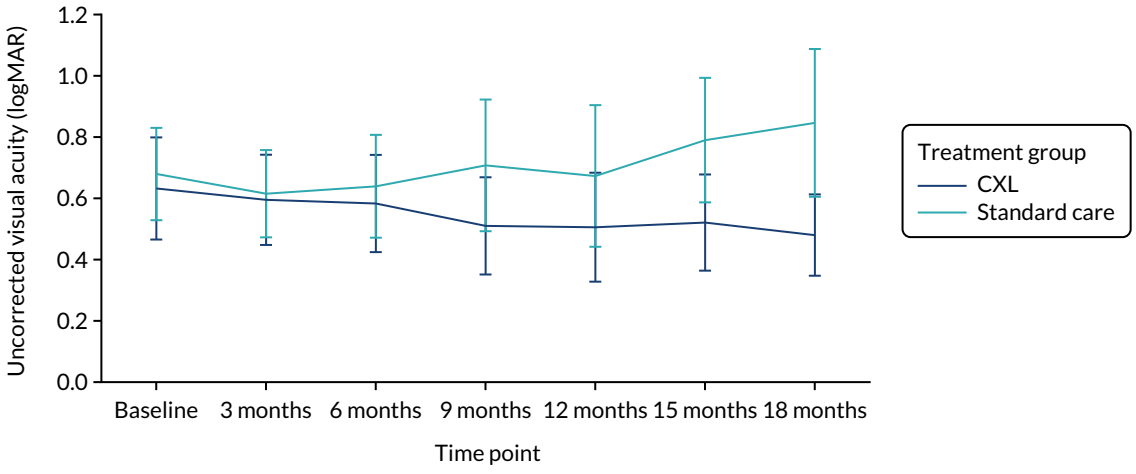

FIGURE 4 Uncorrected visual acuity by treatment group. Reproduced with modification and permission from Larkin *et al.*[27] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to distribute this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by-nd/4.0/.

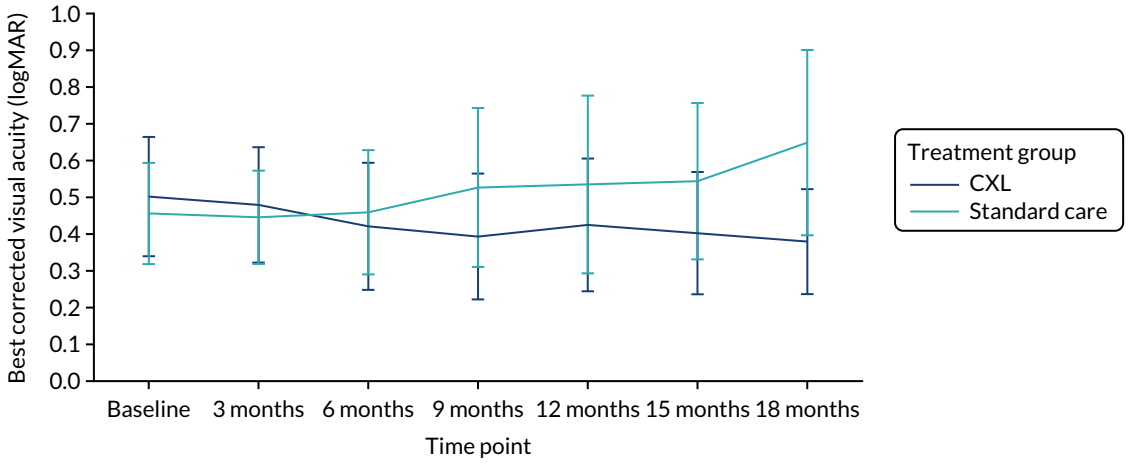

FIGURE 5 Best corrected visual acuity by treatment group. Reproduced with modification and permission from Larkin *et al.*[27] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to distribute this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by-nd/4.0/.

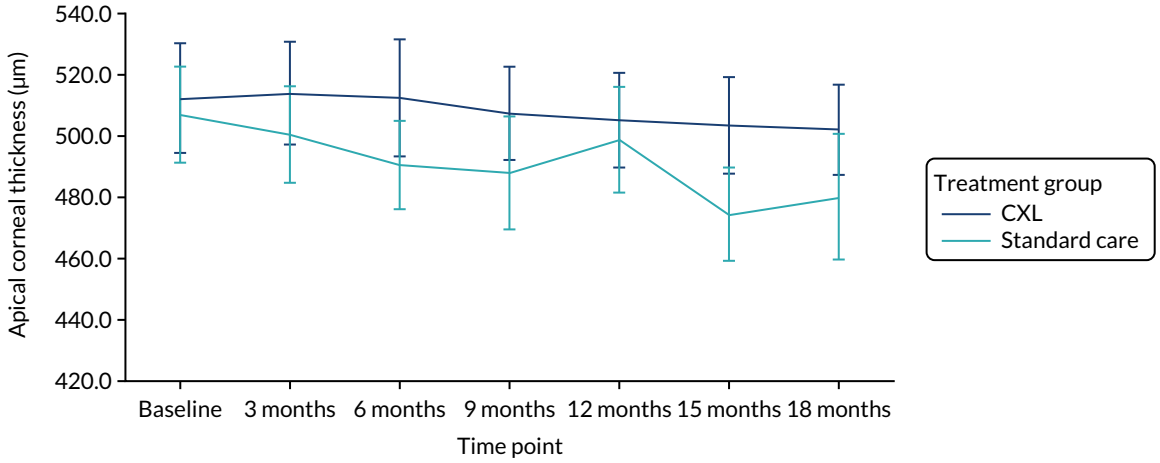

FIGURE 6 Apical corneal thickness by treatment group. Reproduced with modification and permission from Larkin *et al.*[27] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to distribute this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by-nd/4.0/.

equivalent at 18 months. On average, eyes in the CXL group had significantly better uncorrected and best corrected visual acuity (logMAR scores were lower) compared with those in standard care ($p = 0.002$ and 0.002, respectively) (see *Table 5*). This indicates that eyes in the CXL group had significantly better vision at 18 months as measured by visual acuity. Of CXL patients, 93% had refractive astigmatism in the study eye at 18 months, compared with 88% of standard care patients. There was no significant difference in the odds of having astigmatism between the two groups ($p = 0.50$).

Patients' quality of life improved in the CXL group from baseline to 18 months, as measured using the CVAQC-25 and CHU9D questionnaires, but there was no significant difference between treatment groups at 18 months ($p = 0.22$ and 0.14, respectively).

Two patients (7%) in the CXL group experienced keratoconus progression in the study eye, compared with 12 (43%) in the standard-care group, during the trial follow-up period. The unadjusted analysis shows that, on average, the probability of progression in the study eye within 18 months was 90% (odds ratio 0.1, 95% CI 0.02 to 0.48; $p = 0.004$) lower in the CXL group than in the standard-care group.

Cox proportional hazards regression analysis also suggests that eyes in the CXL group had an 87% lower hazard of progression than those in the standard-care group. *Figure 7* shows the Kaplan–Meier plot of time to progression in the two treatment groups.

Ancillary analyses

Subgroup analysis

The subgroup analysis for the primary outcome is presented in *Table 6*. We explored a possible interaction with ethnicity – Asian/Asian British compared with all other ethnic groups. There was no significant interaction ($p = 0.95$), that is, there is no evidence that the effect of treatment differed between ethnic groups. Ten patients (33%) in the CXL group reported a history of atopy, compared with 13 (53%) in the standard-care group. In both subgroups (i.e. in patients with and patients without a history of atopy), K2 in the study eye at 18 months was lower than that in standard care. However, the interaction with a history of atopy was not significant.

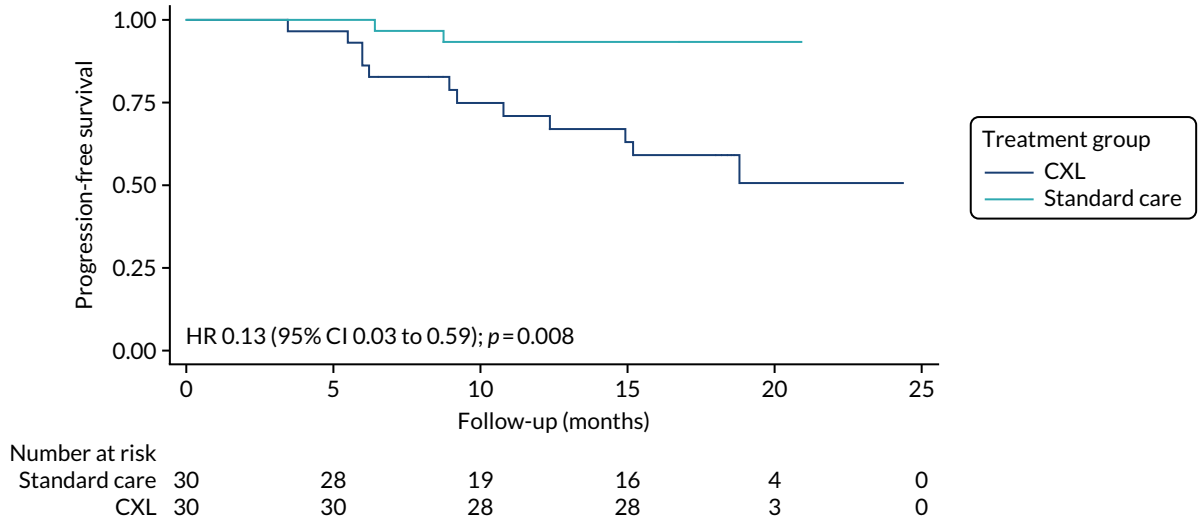

FIGURE 7 Kaplan–Meier plot showing time to progression by treatment group. Reproduced with modification and permission from Larkin *et al.*[27] This is an Open Access article distributed in accordance with the terms of the Creative Commons Attribution (CC BY-ND 4.0) license, which permits others to distribute this work, for commercial use, provided the original work is properly cited. See: https://creativecommons.org/licenses/by-nd/4.0/.

TABLE 6 Subgroup analysis

Subgroup	Treatment group (*n*)		Adjusted coefficient (95% CI)	Interaction *p*-value
	CXL	Standard care		
Ethnicity				
All other ethnic groups[a]	20	11	−2.73 (−4.35 to −1.11)	0.95
Asian or Asian British	10	12	−3.07 (−6.28 to 0.15)	
History of atopy				
No	20	10	−2.70 (−5.26 to −0.31)	0.59
Yes	10	13	−3.86 (−6.90 to −0.82)	

a Includes patients who identify as white/white British, black/black British or as being of mixed or other ethnicity.

Post hoc comparison of those patients with and without progression in the study eye by age and ethnicity showed that there was no difference in average age between the groups ($p = 0.31$) and that there was no significant association between progression and ethnicity (χ^2 test, $p = 0.21$). We also compared time to progression pre randomisation with time to progression post randomisation in those who progressed while in the trial. There was no significant correlation ($p = 0.50$).

Exploratory outcome

Table 7 shows that the mean K_{max} in the study eye at 18 months post randomisation was 57 D (SD 6.2 D) in the CXL group and 60 D (SD 7.7 D) in the standard-care group. The adjusted difference in K_{max} in the study eye at 18 months was −2.11 D (95% CI −4.81 to 0.60 D) and the *p*-value was 0.13. There was no statistically significant difference in K_{max} at 18 months between the two treatment groups as the 95% CI for the difference included zero. *Figure 8* shows the K_{max} across the trial follow-up period by treatment group in the ITT population and in the population of patients including measurements from red-flagged scans (*Figure 9*). The finding that K_{max} values in the two groups did not significantly differ indicates that this parameter does not have the precision of K2 as a measure of progression.

Harm

No serious adverse events were reported during the trial. A total of six patients (10%) experienced at least one adverse event during the trial (*Table 8*) – four patients in the CXL group and two in the standard-care group. A total of 13 adverse events were reported – seven in the CXL group and six in the standard-care group. However, no adverse events were considered to be related to treatment.

TABLE 7 Exploratory outcome analysis

	Treatment group					
	CXL		Standard care			
Outcome	*n*	Mean (SD)	*n*	Mean (SD)	Adjusted coefficient (95% CI)[a]	*p*-value
K_{max} (D) at 18 months	30	57.0 (6.2)	22	60.3 (7.7)	−2.11 (−4.81 to 0.60)	0.13

a Adjusted for baseline K_{max} and minimisation factors, site and number of eyes progressed.

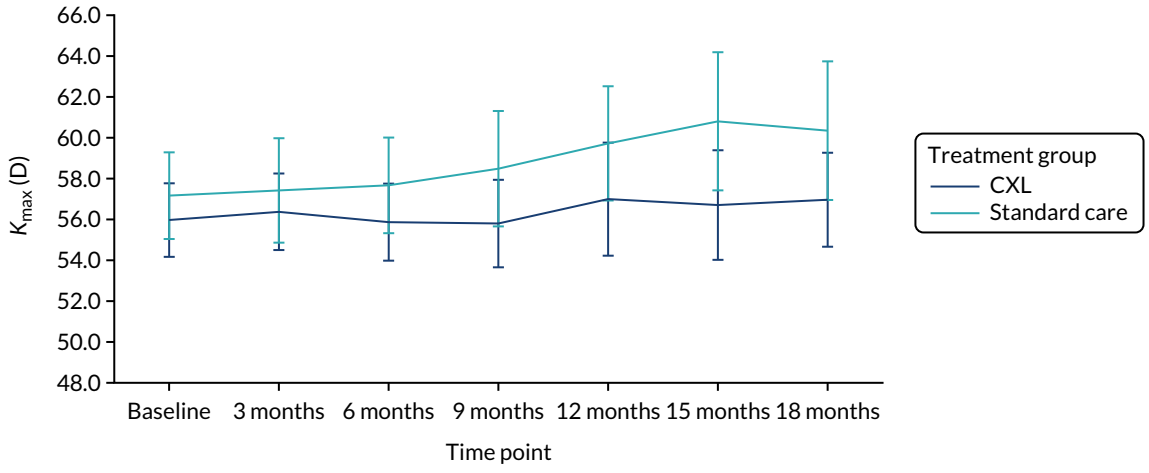

FIGURE 8 K_{max} in the study eye in the ITT population (primary outcome population) by treatment group.

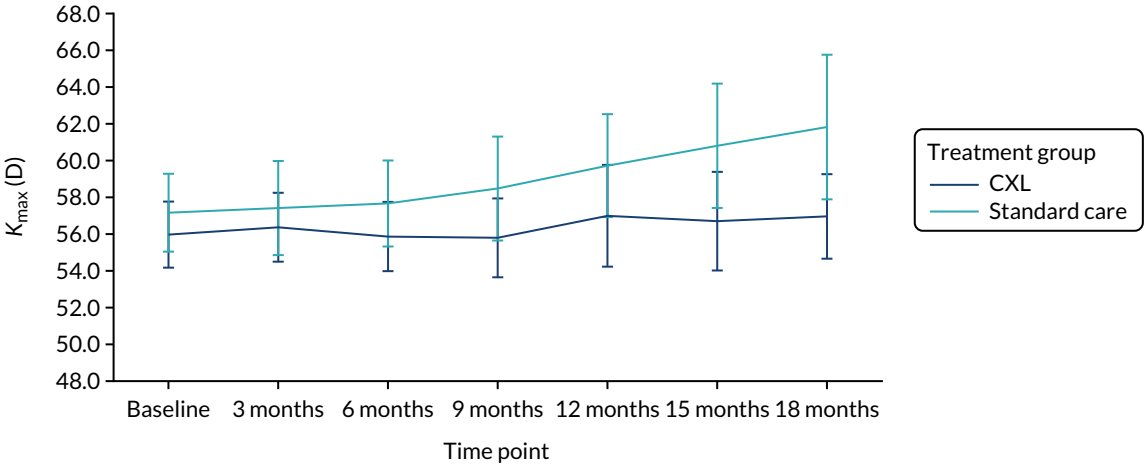

FIGURE 9 K_{max} in the population including red-flagged measures from patients with advanced disease at 18 months by treatment group

TABLE 8 Adverse events and serious adverse events by treatment group

Adverse event	Treatment group (*n*)		Total (*N* = 30) (*n*)
	CXL (*N* = 30)	Standard care (*N* = 30)	
Number of patients reporting at least one adverse event	4	2	6
Total number of adverse events	7	6	13
Attention deficit hyperactivity disorder	0	1	1
Cyst on right eyebrow	1	0	1
Flu-like symptoms	1	0	1
Hay fever	0	1	1
Tonsillitis	2	0	2
Right eye pain on blinking	1	0	1
Autistic spectrum disorder	0	1	1
Right eye lump on cornea	1	0	1
Anxiety disorder	0	1	1
Hypermobility	0	1	1
Clavicle pain post fracture	0	1	1
Loose suture to graft (non-study eye)	1	0	1

There was no clinical significance arising from reported adverse effects in right eye.

Chapter 4 Discussion

Main findings

In this observer-masked RCT involving children and young people aged 10–16 years, we found that, on average, at 18 months post randomisation participants randomised to CXL and standard care were less likely to have clinically significant progressive keratoconus in the study eye than those treated with standard care alone, and had better vision in that eye. The primary trial outcome finding was the demonstration that, on average, at 18 months post randomisation, corneal power in the steepest meridian (K2) was 3 D (95% CI −4.93 to −1.08 D) lower in patients who underwent CXL in the study eye than in those who had received standard care. This difference is statistically significant ($p = 0.002$). In addition, the 95% CI for the difference included the clinically important difference of 1.5 D, which was the trial protocol definition of keratoconus progression. Several secondary outcomes demonstrate that the efficacy of CXL in halting keratoconus progression in this trial age group was also clinically significant:

- The finding of significant differences in uncorrected ($p = 0.002$) and best corrected visual acuity ($p = 0.002$) between the trial groups indicates that patients randomised to CXL had significantly better vision in the study eye at 18 months without and with spectacle correction.
- Keratoconus progression in the study eye by 18 months occurred in only two patients (7%) randomised to CXL, compared with 12 (43%) randomised to standard care. Time-to-event analysis indicated that the risk of progression was 87% lower in the CXL group ($p = 0.008$).

Taken together, these primary and secondary trial outcomes provide clear evidence of efficacy of CXL in stabilising keratoconus progression in 10- to 16-year-olds with progressive keratoconus. No adverse events were considered to be treatment related, suggesting that this is a relatively safe intervention.

Putting our findings into context with existing evidence

Keratoconus progression and visual acuity

These findings are in keeping with results from RCTs in adult patients reported in a Cochrane review comparing CXL with standard care for keratoconus and also reduce the uncertainty.[11] The three trials eligible for inclusion in that review provided limited evidence on the risk of progression, although the data suggested that eyes treated by CXL were less likely than eyes treated with standard care only to exhibit an increase in K_{max} of ≥ 1.5 D at 12 months. Other data reported suggested that, on average, treated eyes had a less steep cornea (approximately 2 D less steep) and better uncorrected visual acuity (approximately two lines or 10 letters better) (mean difference −0.20 D, 95% CI −0.31 to −0.09 D; participants = 94; studies = 1, low-quality evidence). The quality of the evidence was deemed to be low as it was largely derived from a single trial rated as being at a high risk of bias. The data on corneal thickness were inconsistent. Adverse effects were not uncommon but mostly transient. It is important to note that, to our knowledge, no randomised trials in young patients have been reported, which was the principal justification for the KERALINK trial. A number of observational studies of CXL in keratoconus patients aged < 19 years have been published, each with limitations but each reporting effectiveness.[12,13,15,16] Caporossi *et al.*[12] reported an uncontrolled study of 152 keratoconus patients ranging in age from 10 to 18 years, on whom follow-up post-CXL data were available on only 61% of patients. In addition to short-term follow-up, the inclusion criteria included several parameters that are well recognised to be characterised by high inter-test variability. In this treated patient group, a statistically significant reduction of K2 by −0.4 D was found. Vinciguerra *et al.*[13] reported 40 CXL-treated eyes in patients with progressive keratoconus aged 9–18 years (mean 14.2 years)

in a non-randomised prospective study. Findings included improved visual acuity, reduced myopic spherical equivalent on refraction testing and flattening on keratometry readings compared with pre-CXL treatment.

Corneal thickness

Our finding that apical corneal thinning continued after baseline in the CXL-treated trial group, although to a lesser extent than in the standard-care group, is in keeping with other reports.[10,11,16]

Quality of life

Patients' quality of life improved in the CXL group at 18 months from baseline, but there was no significant difference between trial groups. The impact of keratoconus on quality of life is known to be influenced by whether one or both eyes are affected,[28] and best corrected visual acuity in the better eye has been reported to be associated with reduced vision-associated quality-of-life utilities.[29] For this reason, a major determinant of quality of life in the trial is likely to be vision in the non-study eye, which in most cases was the eye with better vision. It is noteworthy that patient-reported outcomes are not routinely collected in keratoconus studies, despite the fact that they may be a sensitive measure of progression, along with changes in vision or keratometry, and despite their possible value in allowing clinicians to make more informed risk-versus-benefit decisions on interventions, such as CXL, by considering the effects that are meaningful to patients.[30] Quality-of-life analysis has not been undertaken in prospective trials of CXL and may be of particular interest in the case of young patients such as the KERALINK trial population. Although we did not find important differences between the trial groups at 18 months, it is important to examine quality of life over a longer follow-up period, in this case 4 years. We consider this a strength of our study.

Strengths of this trial

Age group of participants

On account of the known poorer long-term visual prognosis in those keratoconus patients who are younger at disease onset, the greatest need is to identify the efficacy of CXL in paediatric patients. We therefore restricted trial recruitment to an upper age limit of 16 years, in contrast to previous observational studies in young people, which included patients up to the age of 19 years. This age restriction aligns with paediatric services in the NHS and will allow targeting of dissemination of the trial results in the UK. Demonstration of efficacy in young patients is of additional importance as measurement of corneal topography is becoming more widely available in the community, which will in turn lead to a reduction in the mean age at diagnosis and increased referrals to secondary care clinics.

Randomisation

As far as we are aware, this is the first randomised evidence of efficacy of CXL in young patients. Considering that recruitment to the KERALINK trial commenced in 2016, 4 years later than reports of CXL efficacy in the first uncontrolled case series of CXL in keratoconus in young patients,[12,13] this is a valuable study and provides high-quality evidence.

Precision in measurement of corneal power

A further strength of our study was the use of methods that directly addressed the key problem of measurement variability in corneal topography, the standard imaging technique for assessing progression of keratoconus.[19] Repeatability of most topographic parameters is good in normal corneas and in patients with mild keratoconus but worsens as the disease progresses; this is particularly true of the single steepest point corneal power measurement K_{max}.[18] To obtain data reliably identifying change (1) we measured K2, the mean corneal power in the steepest corneal meridian, rather than K_{max} as the primary outcome; (2) we used the means of triplicate readings for all analyses – at trial eligibility screening, baseline and outcome examinations; and (3) our definition of progression post randomisation, K2 increase > 1.5 D, corresponded to a change in corneal power of visual significance.

These methodological strengths give validity to the finding of differences in the primary and clinically important secondary outcomes between the two trial groups. Our results on longitudinal measurement of K_{max} and K2 demonstrate for the first time that K_{max} has insufficient precision to identify clinically important progression. This is an important observation that must call into question the use of this parameter to monitor keratoconus progression to aid clinical decision-making and for research purposes.

Trial limitations

An unanticipated measurement problem that emerged during our trial was that our measurements of K2 in those eyes with most significant progression were in some cases marked with a red flag by Pentacam device software. This usually occurs if there are data gaps following imaging of the cornea. Although not specified in the trial protocol, in routine clinical practice data identified in this way are usually regarded as suspect and repeat measurements taken if feasible. Individual red-flagged measurements during the trial could be excluded from the triplicate values used in calculation of mean values; however, in two patients in the standard-care group, measurements from all three scans taken at the 18-month follow-up assessment were red flagged. Exclusion from primary outcome analysis of red-flag Pentacam scan data on these two patients with the most significant progression is a source of potential bias. To deal with this, our primary outcome analysis of K2 has been presented excluding (*Figure 2a*) and including (*Figure 2b*) the data from these examinations.

Generalisability

UK

Our upper age limit for eligibility for recruitment of 16 years corresponds to the upper age in paediatric services in the majority of NHS ophthalmology clinics. This will assist dissemination of our trial results by allowing us to specifically target those health-care personnel providing eye care in paediatric services.

International

As there is known international variation in the prevalence of severe keratoconus, a limitation of our study may be the lack of applicability of our findings to some international regions and populations. Nevertheless, it is of interest that Asian ethnicity, known to be strongly associated with keratoconus in the UK,[31] accounted for 45% of patients recruited in this trial, a very significant over-representation compared with UK census statistics. However, on analysis of patients with Asian ethnicity, compared with all others, we found no evidence that the effect of CXL differed in Asian patients, and a post hoc comparison found no significant association between progression and ethnicity.

Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence

This trial has provided, to our knowledge, the first randomised evidence of CXL efficacy in arresting progression of keratoconus in young patients. In addition, we encountered no safety problems associated with CXL. On the basis of results at 18 months post randomisation, CXL should be offered as a first-line treatment for keratoconus in young patients with progression affecting vision, supporting a change in clinical practice.

Although significant differences in outcomes were found in the CXL group, our finding of significant progression, as defined by K2 change > 1.5 D over an 18-month period, in only 43% of subjects receiving standard care is of interest. Moreover, this statistic under-represents the proportion of keratoconus patients who may have spontaneous stabilisation of keratoconus or clinically insignificant disease

progression: eligibility for trial randomisation required prior evidence of progression and 64 patients with progressive keratoconus who were screened for eligibility had insufficient progression. Earlier reports from uncontrolled studies of effectiveness of CXL in halting keratoconus progression in young patients could now be re-evaluated in the light of this observation so that children with non-progressive keratoconus were not unnecessarily treated by CXL. It is possible that some CXL-treated keratoconus patients in these uncontrolled studies[12,13] reported to have not progressed might have spontaneously stabilised without intervention.

Conclusions

Clinical significance and effects on patient care and policy

Our data support consideration of a change in practice such that CXL could be considered for disease stabilisation in young patients with evidence of keratoconus progression. In such patients with early-onset keratoconus, in whom there is potential for further progression to the end of the third decade, there may be particular benefit in avoiding the later requirement for contact lens wear or corneal transplantation. The clinical and health economic benefits of CXL in children and young people may exceed those in adult patients.

For a policy change one might need a large-scale effectiveness RCT and a trial-based economic evaluation. However, a larger effectiveness trial is now unlikely to be possible, as it will be difficult to randomise patients as the KERALINK trial has clearly demonstrated efficacy.

Recommendations for research

Key questions are to investigate whether or not the arrest of keratoconus progression induced by CXL is maintained in the long term and whether or not the proportion of those in the standard-care group who experience significant progression increases with time. Longer follow-up, to 4 years, of our trial population is already under way and will allow us to address these questions. A health economic analysis of the impact of CXL, beyond the scope of our trial, is now warranted. The KERALINK trial has shown that CXL is an effective and safe intervention that stabilises keratoconus progression in young patients; in the event that stabilisation is sustained, our findings may be the first line of evidence justifying screening for keratoconus in young patients with astigmatism.

Further research to define keratoconus progression is needed and would have important value as a threshold in guidelines for clinician decision-making on patients being monitored. Our selection of K2 increase by 1.5 D as the definition in this trial was primarily prompted by a concern to ensure that true progression was indicated rather than insignificant change that may be influenced by poor repeatability. We believe that K2 is a more representative marker of corneal power than K_{max}; however, the numerical change of 1.5-D corneal power warrants rigorous evaluation.

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See www.journalslibrary.nihr.ac.uk/programmes/eme/142318/#/ for further project information.

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Publications

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Chowdhury K, Doré CJ, Bunce C, Larkin DFP. Corneal cross-linking versus standard care in children with keratoconus – a randomised, multicentre, observer-masked trial of efficacy and safety (KERALINK): a statistical analysis plan. *Trials* 2020;**21**:523.

Larkin DFP, Chowdhury K, Burr JM, Raynor M, Edwards M, Tuft SJ, *et al.* Effect of corneal cross-linking versus standard care on keratoconus progression in young patients. *Ophthalmology* 2021; in press.

Data-sharing statement

All data requests should be submitted to the corresponding author for consideration. Access to anonymised data may be granted following review.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Recruiting sites

TABLE 9 Recruiting sites, local PIs and screening start and end dates

Site	Local PI	Screening start date	Screening end date
Moorfields Eye Hospital NHS Foundation Trust	Professor Frank Larkin	October 2016	September 2018
Sheffield Teaching Hospital NHS Foundation Trust	Mr Mathew Raynor Mr Matthew Edwards	December 2016	September 2018
Royal Liverpool & Broadgreen University Hospitals NHS Trust	Professor Colin Willoughby Professor Stephen Kaye	May 2017	September 2018
Aneurin Bevan University Health Board	Ms Sue Webber Mr Karim Tourkmani	March 2018	September 2018
Manchester University NHS Foundation Trust	Mr Susmito Biswas	May 2018	September 2018

Appendix 2 Protocol amendments summary

Amendment 1

- Replaced use of the Visual Function Index (VF)-14 with the CVAQC-25, which is a validated questionnaire for use in children and more appropriate than the VF-14 questionnaire.
- Measurement of corneal thickness changed from central to apical.
- Clarified that the ophthalmologist will be blinded to the K_{max}, and subsequent K2, values measured by the optometrist. The ophthalmologist's assessment will therefore be based on clinically significant worsening of vision.
- The secondary outcome measure was amended from 'time to keratoconus progression' to 'time to keratoconus progression (defined as >1.5 D increase in K_{max})'. This was to provide greater clarity for the researchers.

Amendment 2

- Inclusion criterion 1 updated to include patients with Pentacam topography or other topography scanning techniques to record keratoconus progression.
- Added text to inclusion criterion 2 to become: 'patients and their parents/guardians must be sufficiently fluent in English to provide assent and consent and to complete the patient reported outcomes'.
- Exclusion criterion 3 updated with the following: 'maximum corneal curvature (K_{max}) > 62 D'.
- A definition was added to the secondary outcome of 'time to keratoconus progression'. Progression was to be 'defined as > 1.5 D increase in K_{max} from baseline'.
- Further clarification was provided as to the masking of the PI (or treating clinician), to the K_{max} value, during the course of the trial.

Amendment 3

- Changing the primary outcome measure from K_{max} to K2 throughout the protocol. K2 has better repeatability and an increasing proportion of keratoconus researchers are using K2 in conference communications and publications.
- Inclusion criterion 1 updated to 'progression for eligibility is defined as an increase of at least 1.5 D in K2 or K_{max} on Pentacam corneal topography (or equivalent other topography devices)'.
- Exclusion criterion 3 amended to 'steepest corneal meridian (K2) > 62 D and maximum corneal curvature (K_{max}) > 70 D on Pentacam topography at screening'.

Amendment 4

- Addition of a long-term follow-up study allowing the original patients to consent to be followed up to 4 years post randomisation.

Appendix 3 Sample questionnaires

Child Health Utility 9D questionnaire

QUALITY OF LIFE (CHU9D)

By placing a tick in one box in each group below, please indicate which statements best describe your own level of satisfaction today.

1. WORRIED	
I don't feel worried today	☐
I feel a little bit worried today	☐
I feel a bit worried today	☐
I feel quite worried today	☐
I feel very worried today	☐

2. SAD	
I don't feel sad today	☐
I feel a little bit sad today	☐
I feel a bit sad today	☐
I feel quite sad today	☐
I feel very sad today	☐

3. PAIN	
I don't have any pain today	☐
I feel a little bit of pain today	☐
I feel a bit of pain today	☐
I feel quite a lot of pain today	☐
I have a lot of pain today	☐

4. TIRED	
I don't feel tired today	☐
I feel a little bit tired today	☐
I feel a bit tired today	☐
I feel quite tired today	☐
I feel very tired today	☐

5. ANNOYED	
I don't feel annoyed today	☐
I feel a little bit annoyed today	☐
I feel a bit annoyed today	☐
I feel quite annoyed today	☐
I feel very annoyed today	☐

QUALITY OF LIFE (CHU9D)

By placing a tick in one box in each group below, please indicate which statements best describe your own level of satisfaction today.

6. SCHOOL/HOMEWORK (e.g. reading, writing, doing lessons etc)	
I have no problems with school/ homework today	☐
I have a few problems with school/ homework today	☐
I have some problems with school/ homework today	☐
I have many problems with school/ homework today	☐
I can't do my school/homework to-day	☐

7. SLEEP	
I had no problems sleeping last night	☐
I had a few problems sleeping last night	☐
I had some problems sleeping last night	☐
I had many problems sleeping last night	☐
I couldn't sleep at all last night	☐

8. DAILY ROUTINE	
I have no problems with my daily routine today	☐
I have a few problems with my daily routine today	☐
I have some problems with my daily routine today	☐
I have many problems with my daily routine today	☐
I can't do my daily routine today	☐

9. ABLE TO JOIN IN ACTIVITIES (e.g. playing with friends, doing sports, joining activities)	
I can join in with all activities today	☐
I can join in with most activities today	☐
I can join in with some activities today	☐
I can join in with a few activities today	☐
I can join in with no activities today	☐

Cardiff Visual Ability Questionnaire for Children

VISUAL IMPAIRMENT ABILITY QUESTIONNAIRE FOR CHILDREN-25 (CVAQC-25)

How would your rate your ability to do the following activities? Please make a tick.

		Very easy	Easy	Difficult	Very Difficult	Don't do for other reason or not interested in doing this
1	How difficult do you find your maths lessons?					
2	How difficult do you find your science lessons?					
3	How difficult do you find your geography lessons?					
4	How difficult do you find your language lessons?					
5	How difficult do you find reading text books and work sheets you are given in					
6	How difficult do you find reading the smallest print in your text books?					
7	How difficult do you find drawing, colouring or painting?					
8	How difficult do you find reading text messages on your mobile phone?					

		Very easy	Easy	Difficult	Very Difficult	Don't do for other reason or not interested in doing this
9	How difficult do you find it to read restaurant menus?					
10	How difficult do you find reading the board in your class room?					
11	How difficult do you find it to watch television?					
12	How difficult do you find it to watch films at the cinema?					
13	How difficult do you find it going out alone in the day light?					
14	How difficult do you find it to walk in a crowded place?					
15	How difficult do you find using public transport (bus/train)?					
16	How difficult do you find reading bus or train time tables on a screen at a station?					
17	How difficult do you find it to chat with your friends?					

		Very easy	Easy	Difficult	Very Difficult	Don't do for other reason or not interested in doing this
18	How difficult do you find recognising faces or identifying your friends sitting					
19	How difficult do you find seeing your friends in a playground?					
20	How difficult do you find it to use a Playstation?					
21	How difficult do you find it to play computer games ?					
22	How difficult do you find using your IPOD/MP3/MP4 players?					
23	How difficult do you find swimming?					
24	How difficult do you find it to take part in athletics?					
25	How difficult do you find it to play ball games?					

Appendix 4 Summary of protocol deviations

TABLE 10 Summary of protocol deviations

Deviation category	Number of deviations	Deviation classification	Comments/details
Follow-up visit performed outside the 28-day window	53	Minor	
Missed follow-up visits	36	25 minor, 1 major	Major deviation: KER30 did not attend the month 18 follow-up visit. KER42 missed visits at months 3, 6, 9, 12 and 15, and came back for the month 18 visit. KER50 missed visits at months 6, 12 and 15. Came for visits at months 9 and 18
Study assessments	12	Minor	Questionnaires not completed (8), treatment visit not performed in the 4-week window (1), topography assessments issues (3)
Study eye assignment	4	Minor	1. KER15 both eyes were eligible, but participant's least-progressed eye was selected as study eye 2. KER03, KER31 and KER35 had one eye eligible on MACRO, two eyes eligible on SE
Investigator's accidental unmasking to topography results	2	Major	
Exclusion criteria not met	2	Critical	For two participants (KER08, KER18) K_{max} values were greater than the upper limit defined at the then-approved protocol. CI, CPM, CCTU QA concluded in protocol amendment; K_{max} value updated and participants considered eligible
Inclusion criteria not met	1	Major	Inclusion criterion 1 was not met for participant KER13. This was later discovered while reviewing the source data. Participant completed all the follow-up visits
Data monitoring	1	Minor	Trial statistician looking into the sample size calculation after the participant recruitment ended, and not before as stated in the protocol
Consent	1	Major	KER32 was consented by non-study clinician

CCTU, Comprehensive Clinical Trials Unit; CPM, clinical programme manager; QA, quality assurance; SE, source clinical notes.

Appendix 5 Study oversight

Trial Steering Committee

The TSC was the independent group responsible for the oversight of the KERALINK trial to safeguard the interests of trial participants. Professor Augusto Azuara-Blanco, TSC chairperson, is an experienced clinical trials researcher and was joined by a lay member from the Keratoconus Patient Group, Mr Mike Oliver, and an ophthalmologist with special interest in keratoconus and the CXL procedure, Ms Seema Anand. The chief investigator and members of the TMG were invited to report as required. The TSC met at least annually and minutes were taken and forwarded to the funder.

Independent Data Monitoring Committee

The IDMC was the only oversight body to have access to unmasked accumulating comparative data. The IDMC was responsible for safeguarding the interests of the trial participants, monitoring the data and making recommendations to the TSC on the continuation of the trial. Dr Irene Stratton, IDMC chairperson, is an independent senior statistician and was joined by one ophthalmologist, Professor Madhavan Rajan, and two optometrists with an interest in keratoconus, Professor Jonathan Jackson and Professor Tom Margrain. The IDMC met at least annually and provided feedback to the TSC.

Patient and public involvement

Before the study the NIHR Moorfields Biomedical Research Centre hosted a Cornea Patient Day, attended by > 100 participants, including young keratoconus patients and parents. A session was devoted to research on CXL in keratoconus and an active discussion was held on the design of the KERALINK trial. The patient day was followed by a smaller meeting with the founder of the UK Keratoconus Self Help and Support Association. The founder of this patient group agreed to be a trial co-applicant and a member of the TMG. Patient group representatives were involved in the funding application, the TMG and the TSC and will be involved in dissemination of the trial results.

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