KERALINK

Corneal cross-linking versus standard care in children with keratoconus; a randomised, multicentre, observer-masked trial of efficacy and safety.

Version	4.0
Date	23.12.2016
Sponsor	University College London (UCL)
Comprehensive Clinical Trials Unit Trial Adoption Group #	15/0599
Trial registration #	ISRCTN17303768
CTA #	20363/0363/001
EudraCT #	2016-001460-11
NRES#	16/LO/0913

Authorisation: Chief Investigator

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Role	Consultant ophthalmologist
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Date	

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1 Administrative information

This document was constructed using the Comprehensive Clinical Trials Unit (CCTU) at UCL Protocol template Version 4. It describes the Keralink trial, sponsored by UCL and co-ordinated by CCTU.

It provides information about procedures for entering participants into the trial, and provides sufficient detail to enable: an understanding of the background, rationale, objectives, trial population, intervention, methods, statistical analyses, ethical considerations, dissemination plans and administration of the trial; replication of key aspects of trial methods and conduct; and appraisal of the trial's scientific and ethical rigour from the time of ethics approval through to dissemination of the results. The protocol should not be used as an aide-memoire or guide for the treatment of other patients. Every care has been taken in drafting this protocol, but corrections or amendments may be necessary. These will be circulated to registered investigators in the trial. Sites entering participants for the first time should confirm they have the correct version through a member of the trial team at CCTU.

CCTU supports the commitment that its trials adhere to the SPIRIT guidelines. As such, the protocol template is based on an adaptation of the Medical Research Council CTU protocol template (2012) and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2012 Statement for protocols of clinical trials [1]. The SPIRIT Statement Explanation and Elaboration document [2] can be referred to, or a member of CCTU Protocol Review Committee can be contacted for further detail about specific items.

1.1 Compliance

The trial will be conducted in compliance with the approved protocol, the Declaration of Helsinki (2008), the principles of Good Clinical Practice (GCP) as laid down by the Commission Directive 2005/28/EC with implementation in national legislation in the UK by Statutory Instrument 2004/1031 and subsequent amendments, the Human Tissue (Quality and Safety for Human Application) Regulations 2007, the UK Data Protection Act, and the National Health Service (NHS) Research Governance Framework for Health and Social Care (RGF). Agreements that include detailed roles and responsibilities will be in place between participating sites and CCTU.

Participating sites will inform CCTU as soon as they are aware of a possible serious breach of compliance, so that CCTU can fulfil its requirement to report the breach if necessary within the timelines specified in the UK Clinical Trials Regulations (currently 7 days). For the purposes of this regulation a 'serious breach' is one that is likely to affect to a significant degree:

- The safety or physical or mental integrity of the subjects in the trial, or
- The scientific value of the trial.

1.2 Sponsor

UCL is the trial sponsor and has delegated responsibility for the overall management of the Keralink trial to CCTU. Queries relating to UCL sponsorship of this trial should be addressed to the CCTU Director or via the trial team.

1.3 Structured trial summary

Primary Registry and Trial Identifying Number	ISRCTN17303768
Date of Registration in Primary Registry	10 Nov 2016
Secondary Identifying Numbers	2016-001460-11
Source of Monetary or Material Support	National Institute of Health Research (EME)
Sponsor	University College London with sponsor responsibilities delegated to CCTU.
Contact for Public Queries	Keralink Trial Manager UCL Comprehensive Clinical Trials Unit Gower Street, London, WC1E 6BT 02035495448 07464498627 ctu.keralink@ucl.ac.uk ctu.enquiries@ucl.ac.uk
Contact for Scientific Queries	Mr Frank Larkin Consultant Ophthalmologist Moorfields Eye Hospital 162 City Road, London, EC1V 2PD Tel: 020 75662045 Email: f.larkin@ucl.ac.uk
Public Title	Keralink
Scientific Title	Corneal cross-linking versus standard care in children with keratoconus; a randomised, multicentre, observer-masked trial of efficacy and safety
Countries of Recruitment	Three sites in the UK
Health Condition(s) or Problem(s) Studied	Keratoconus
Intervention(s)	Experimental intervention: Corneal collagen cross-linking (CXL) in one or both eyes (according to whether progression is confirmed in one eye or both), under general or local anaesthesia as applicable, followed by standard management Control Intervention: Standard management alone to include provision of glasses and/or contact lenses as required for best corrected visual acuity
Key Inclusion and Exclusion Criteria	Inclusion criteria: • Age 10-16 years with keratoconus progression confirmed in one or both eyes using Pentacam or other topography. Progression for eligibility is defined as an increase of at least 1.5 dioptres in K_{max} on corneal topography between two examinations done using the same scanning technique at least 3

	months apart. • Patients and their parents/guardians must be sufficiently fluent in English to provide assent and informed consent and to complete the patient reported outcome measures • Patients must be willing to attend for follow up visits. Exclusion criteria: • Advanced keratoconus as determined by apex corneal scarring • Apex corneal thickness <400µ • Maximum corneal curvature (K_{max}) >62 dioptres • Rigid contact lens wear in both eyes and unable to abstain for 7 days pre-examinations • Corneal comorbidity • Down's syndrome • Any clinical condition which the investigator considers would make the patient unsuitable for the trial, including pregnancy • Participation in other clinical trials which would materially impact on the Keralink study
Study Type	This is a multicentre, UK based, randomised controlled trial comparing the efficacy and safety of cross linking surgery with standard clinical care in patients aged 10-16 years with progressive keratoconus.
Date of First Enrolment	October 2016
Target Sample Size	60
Primary Outcome(s)	Primary outcome measure is K_{max} in the study eye at 18 months post randomisation NB. The **study eye** is defined as the eye with the more advanced keratoconus at randomisation, where both eyes are eligible. The same intervention will be offered for the second eye for patients with progression in both eyes, unless the patient does not wish to receive the same intervention.
Key Secondary Outcomes	(a) Keratoconus progression (yes/no) defined as >1.5D increase in K_{max} from baseline (randomisation) to 18 months or requirement for change from spectacle to rigid contact lens correction of vision (b) Time to Keratoconus progression (defined as >1.5D increase in K_{max} from baseline) (c) uncorrected and best corrected visual acuity (measured as logMAR using EDTRS chart) (d) refraction (measured in dioptres of myopia and astigmatism) (e) central corneal thickness (ultrasound) (f) quality of life as assessed by CHU9D and CVAQC questionnaires

1.4 Roles and responsibilities

These membership lists are correct at the time of writing; please see terms of reference documentation in the TMF for current lists.

1.4.1 Protocol contributors

Name	Affiliation	Role
Frank Larkin	Moorfields Eye Hospital NHS Foundation Trust	Chief Investigator
Caroline Doré	UCL CCTU	Head of Statistics UCL CCTU
Susan Tebbs	UCL CCTU	Deputy Director UCL CCTU
Victoria McCudden	UCL CCTU	Clinical Project Manager UCL CCTU
Kashfia Chowdhury	UCL CCTU	Statistician UCL CCTU
Stephen Tuft	Moorfields Eye Hospital NHS Foundation Trust	Principal Investigator Moorfields Eye Hospital
Matthew Edwards	Sheffield Teaching Hospitals NHS Foundation Trust	Principal Investigator Sheffield
Mathew Raynor	Sheffield Teaching Hospitals NHS Foundation Trust	Co-Investigator Sheffield
Colin Willoughby	University of Liverpool & Royal Liverpool & Broadgreen Hospitals NHS Trust	Principal Investigator Liverpool
Jennifer Burr	University of St Andrews	Co-applicant
Catey Bunce	Kings College London	Co-applicant; Applied ophthalmic statistics expertise

1.4.2 Role of trial sponsor and funders

Name	Affiliation	Role
UCL	N/A	Regulatory Trial Sponsor. Represented by UCL Comprehensive Clinical Trials Unit
UCL CCTU	UCL	Specific functions have been delegated to the UCL CCTU by the sponsor. A Clinical Project Manager (CPM) at the UCL CCTU will oversee the Trial Manager (TM) and other operations staff who will be responsible for the day-to-day management of the trial and for providing support to the site staff. The CCTU staff will be involved in approaching sites, case report form development, database construction, protocol and participant information in collaboration with the Trial Management Group, and site initiation training. Training will be provided on all aspects of the trial including the informed consent process and safety reporting as well as aspects of good clinical practices which will be updated regularly. The CCTU staff will be responsible for routine and triggered monitoring visits

		with oversight by the CPM as well as auditing, if necessary, which will be provided by a member of CCTU staff independent of the trial. Feedback will be via a formal reporting process regarding trial progress and site quality.
NIHR EME	NIHR	Funder

1.4.3 Trial Team

Name	Affiliation	Role and responsibilities
Frank Larkin	Moorfields Eye Hospital NHS Foundation Trust	Chief Investigator
Susan Tebbs	UCL CCTU	Co-applicant and Deputy Director UCL CCTU
Caroline Doré	UCL CCTU	Co-applicant and Head of statistics UCL CCTU
Kashfia Chowdhury	UCL CCTU	Trial Statistician
Emilia Caverly	UCL CCTU	Clinical Project manager
Haripriya Tumuluri	UCL CCTU	Trial Manager

1.4.4 Trial Management Group

Name	**Affiliation**	**Role and responsibilities**
Frank Larkin	Moorfields Eye Hospital NHS Foundation Trust	Chief Investigator
Susan Tebbs	UCL CCTU	Deputy Director UCL CCTU
Caroline Doré	UCL CCTU	Head of statistics UCL CCTU
Emilia Caverly	UCL CCTU	Clinical Project Manager UCL CCTU
Stephen Tuft	Moorfields Eye Hospital NHS Foundation Trust	Principal Investigator Moorfields Eye Hospital
Prof. Colin Willoughby	University of Liverpool & Royal Liverpool & Broadgreen Hospitals NHS Trust	Principal Investigator Liverpool
Mr. Mathew Raynor	Sheffield Teaching Hospitals NHS Foundation Trust	Principal Investigator Sheffield
Mr. Matthew Edwards	Sheffield Teaching Hospitals NHS Foundation Trust	Co-Investigator Sheffield
Jennifer Burr	University of St. Andrews	Co-applicant
Catey Bunce	Moorfields Eye Hospital NHS Foundation Trust	Ophthalmic statistics expertise
Haripriya Tumuluri	UCL CCTU	Trial Manager
Kashfia Chowdhury	UCL CCTU	Trial Statistician UCL CCTU

Anne Klepacz	Trustee, UK Keratoconus Self Help and Support Organisation	Lay member

1.4.5 Trial Steering Committee

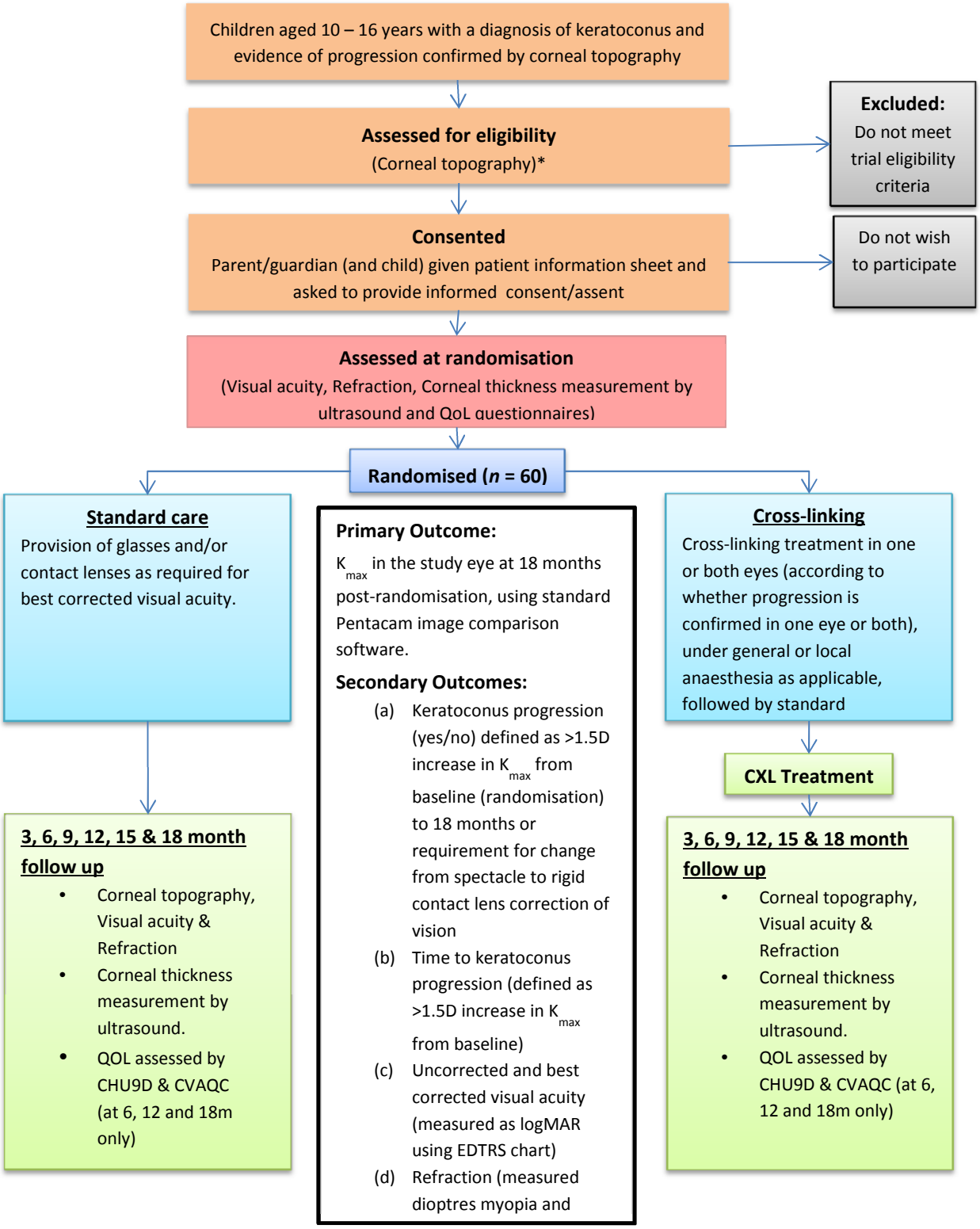
Name	Affiliation	Role and responsibilities
Prof Augusto Azuara-Blanco	Queen's University Belfast	Chair
Ms Suzanne Webber	Royal Gwent Hospital, Newport	Independent member
Mike Oliver	UK Keratoconus Self Help and Support Organisation	Lay member

1.4.6 Independent Data Monitoring Committee

Name	Affiliation	Role and responsibilities
Dr Irene Stratton	Gloucestershire Royal Hospital	Chair
Prof Madhavan Rajan	Addenbrooke's Hospital, Cambridge	Independent member
Dr Tom Margrain	School of Optometry & Vision Sciences, Cardiff University	Independent member
Dr Jonathan Jackson	Royal Victoria Hospital, Belfast	Independent member

2 Trial Diagram

Flow diagram: Keralink: Efficacy and Safety of cross-linking in children with Keratoconus



** The K_{max} value obtained using Pentacam assessment at trial centre prior to randomisation will be used as the baseline K_{max} for outcome assessment.*

3 Abbreviations

AE	Adverse Event
AR	Adverse Reaction
CCTU	Comprehensive Clinical Trials Unit
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
CXL	Corneal cross-linking
DSUR	Development Safety Update Report
EU	European Union
FDA	(US) Food and Drug Administration
FWA	Federal Wide Assurance
GCP	Good Clinical Practice
ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IRB	Institutional Review Board
ITT	Intention to Treat
K_{max}	Maximum corneal curvature measured on corneal topography
MHRA	Medicines and Healthcare products Regulatory Agency
PI	Principal Investigator
PIS	Participant Information Sheet
QA	Quality Assurance
QC	Quality Control
QoL	Quality of life
QMMP	Quality Management and Monitoring Plan
R&D	Research and Development
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAR	Serious Adverse Reaction
SPC	Summary of Product Characteristics
SSA	Site Specific Approval
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
TMG	Trial Management Group
TMT	Trial Management Team
ToR	Terms of Reference
TSC	Trial Steering Committee
UCL	University College London
VA	Visual Acuity

4 Glossary

K_{max}: Steepest anterior corneal curvature on Pentacam topography in dioptres

Baseline K_{max}: K_{max} at randomisation

5 Introduction

5.1 Background and rationale

Keratoconus is characterised by thinning and distortion of the cornea that results in visual loss from complex refractive error and corneal opacification. It is usually bilateral but very asymmetric. The prevalence in Europe is 1:12,000, rising to 1 in 450 in South Asians, with an estimated 50,000 affected individuals in the UK (cited in Gore et al[3]). The age at initial referral is teens and 20s, with progression until the early 30s in most affected eyes. Keratoconus is often more advanced if it is first diagnosed in childhood, rather than in adults, with faster subsequent disease progression. Patients with a suspected or confirmed diagnosis of keratoconus are usually referred to hospital clinics immediately or following initial dispensing of spectacles. 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, until increasingly irregular astigmatism requires correction with rigid contact lenses for best vision. Lenses may not be well tolerated for significant periods of the day because of the irregular shape of the cornea and the common association of keratoconus with severe allergic eye disease. Without lenses these individuals can effectively be blind. This has major implications for quality of life (QoL), schooling and career opportunities for children and young adults. Patients with more advanced keratoconus lose contact lens-corrected visual acuity on account of corneal opacification and require corneal transplant surgery. In one large multicentre report, transplantation was eventually necessary in at least one eye of 21% of patients. While the standard care described above involves treatment of the refractive consequences of keratoconus or replacement of the diseased cornea, the concept of stabilising keratoconus and arresting its progression at a stage when there is still good unaided or spectacle-corrected vision is relatively recent.

The most important parameters used in the assessment of keratoconus are the curvature of the cornea (measured as mm radius but presented as dioptre power (K)), corneal thickness (µm), refraction, and best-corrected visual acuity. Even very early disease can be detected by corneal topography, a non-invasive imaging technique which demonstrates thinning and steepening and irregularity of corneal curvature. Quantification of steepness of the corneal curvature in horizontal, vertical and multiple oblique meridians identifies the meridian of maximum corneal steepness, termed K_{max}. In hospital clinics corneal topography has become the standard of care for the examination of keratoconus suspects and follow-up of patients with a confirmed diagnosis. Topography instruments are also becoming more widely used by optometrists in the community.

No study has addressed QoL in children/adolescents with keratoconus. In a preliminary survey in Moorfields, the most frequently reported difficulties in young patients were poor vision, discomfort and light sensitivity, associated in particular with contact lens wear. Without lenses these patients can effectively be blind. Associated parental anxiety is striking. Keratoconus is a lifelong condition which is a significant health burden in working age adults. Keratoconus patients are entitled to out-patient management including contact lens provision and surgery funded by the NHS. The proportion of keratoconus patients requiring corneal transplantation is around 20% [4], accounting for >1000 corneal transplants p.a. in the UK.

Cross-linking (CXL) is a procedure conceived to increase the stiffness of the cornea and stop progression of Keratoconus. Epithelium-off cross-linking is a procedure that involves surgical

removal of the outer layer of the cornea prior to administration of riboflavin eye drops and exposure of the cornea to UV light. The Keralink trial has been designed to investigate efficacy and safety of the established epithelium-off CXL, henceforth termed CXL, in the paediatric age group in which no RCT has been undertaken.

Current evidence on safety and efficacy of CXL

(i) Reported CXL outcomes in adults

CXL has been reported to be efficacious in the majority of treated adult eyes in a number of non-randomised studies (including Henriquez et al 2011[5], Hersh et al 2011[6]) and two randomised controlled trials (RCTs) (O'Brart et al 2011[7], Wittig-Silva et al 2014[8]). The age range treated in these randomised studies was 21-42[7] and 16-50[8] years respectively. In the larger study by Wittig-Silva et al a significant difference in progression of K_{max} between CXL and control eyes was reported: an improvement in CXL-treated eyes with flattening of K_{max} by -1.03 ± 0.19 D compared to an increase in K_{max} for control eyes of +1.75 ± 0.38 D at 36 months.

Data from RCTs are reported in an updated Cochrane review comparing CXL with standard care for Keratoconus[9]. Overall the studies were deemed to be at high risk of bias. Data were not pooled due to differences in measuring and reporting outcomes. There was limited evidence on the risk of progression, data suggested that eyes given CXL were less likely to have an increase in maximum keratometry of 1.5D or more at 12 months compared to eyes given no treatment. Other data reported suggested that on average treated eyes had a less steep cornea (approximately 2D less steep) (mean difference [MD] -1.92, 95% CI -2.54 to -1.30; participants = 94; studies = 1, low quality evidence) and better uncorrected visual acuity (approximately 2 lines or 10 letters better) (MD -0.20, 95% CI -0.31 to -0.09; participants = 94; studies = 1, low quality evidence); but the quality of the evidence was deemed low as it was largely derived from one trial at high risk of bias. The data on corneal thickness were inconsistent. There were no data available on QoL. Adverse effects were not uncommon but mostly transient, including corneal oedema, anterior chamber inflammation and recurrent corneal erosions.

(ii) CXL in children and young patients

In younger subjects only two observational studies of CXL in keratoconus patients <19 years have been published, each with limitations but each reporting effectiveness. Caporossi et al reported an uncontrolled study of 152 keratoconus patients ranging in age from 10 to 18 years, of whom follow up post-CXL was available on only 61% of patients[10]. In addition to short-term follow-up, the inclusion criteria included several parameters which are well recognised to be characterised by high inter-test variability. In this treated patient group, a statistically significant reduction of K_{max} by -0.4 D was found. Vinciguerra et al reported 40 CXL-treated eyes in patients with progressive keratoconus aged 9-18 (mean 14.2) years in a non-randomised prospective study[11]. Findings included improved visual acuity, reduced myopic spherical equivalent on refraction testing and flattening on keratometry readings compared to pre-CXL. Of note, no randomised trial has been undertaken in young patients.

Although the findings from these studies suggested a beneficial effect of CXL, more robust evidence is required to inform practice, particularly in children and adolescents in whom published outcomes are very sparse.

5.1.1 Explanation for choice of comparators

The standard treatment for adolescents with keratoconus is provision of glasses. If spectacle-corrected visual acuity is poor, contact lenses are provided and visual acuity is reviewed every 6 months. Those patients with advanced disease and poor spectacle- and lens-corrected visual acuity are offered corneal transplantation. This standard care pathway is the comparator arm of the Keralink study, but children with advanced keratoconus will not be randomized into the study.

5.2 Objectives

The aim of KERALINK is to establish clear evidence on whether CXL is efficacious in stabilising the progression of keratoconus and safe in children and young patients between the age of 10 and 16 years. The specific objectives are to assess: *(i)* change in corneal shape (steepest keratometric meridian on topography), *(ii)* visual acuity, *(iii)* refraction and *(iv)* corneal thickness. Patient reported effects on quality of life will be explored.
Patients will be followed up for 18 months following randomization.

5.3 Trial design

Multi-centre, observer-masked randomised controlled trial, comparing CXL treatment with standard care. All outcome assessments will be done by an optometrist masked as to the patient's randomisation.

6 Methods

6.1 Site selection

The trial sponsor has overall responsibility for site and investigator selection and has delegated this role to CCTU.

6.1.1 Study setting

This trial will be conducted in three secondary care NHS clinics in the UK: Moorfields Eye Hospital NHS Foundation Trust, Royal Liverpool & Broadgreen Hospitals NHS Trust and Sheffield Teaching Hospitals NHS Foundation Trust.

6.1.2 Site/Investigator eligibility criteria

To participate in the Keralink trial, investigators and trial sites must fulfil a set of criteria that have been agreed by the Keralink Trial Management Group (TMG) and are defined below.

Eligibility criteria:

- A named clinician is willing and appropriate to take Principal Investigator responsibility
- Suitably trained staff are proficient in CXL and have access to the trial device.
- Suitably trained staff are available to recruit participants

Trial sites meeting eligibility criteria and that are accepted by the TMG as being suitable to recruit to the trial, will be issued with documentation from the Keralink Trial Master File (TMF) to use when applying for NHS Permissions or local institutional approval as applicable.

6.1.2.1 Principal Investigator's (PI) qualifications and agreements

The Principal Investigator (PI) must be willing to sign a CCTU Clinical Trial Agreement and an Investigator Agreement to comply with the trial protocol (confirming their specific roles and responsibilities relating to the trial, and that their site is willing and able to comply with the requirements of the trial). This includes confirmation of appropriate qualifications, familiarity with the appropriate use of any investigational products, agreement to comply with the principles of GCP, to permit monitoring and audit as necessary at the site, and to maintain documented evidence of all staff at the site that have been delegated significant trial related duties.

6.1.2.2 Resourcing at site

The investigator(s) have demonstrated a potential for recruiting the required number of suitable subjects within the agreed recruitment period (i.e. the investigator(s) regularly treat(s) the target population). They also have an adequate number of qualified staff and facilities available for the foreseen duration of the trial to enable them to conduct the trial properly and safely.

Sites will be expected to complete a delegation of responsibilities log and provide staff contact details.

The site should have sufficient facilities to store and manage the riboflavin drops and be available for audit on request by the sponsor. Please see section 6.4.1.1 for more information.

The site should have sufficient data management resources to allow prompt data return to CCTU.

6.2 Site approval and activation

On receipt of the signed Clinical Trial Agreement and Investigator Agreement, approved delegation of responsibilities log and staff contact details, written confirmation will be sent to the site PI. The trial manager or delegate will notify the PI in writing of the plans for site initiation. Sites will not be permitted to recruit any patients until an activation letter has been issued. The Trial Manager or delegate will be responsible for issuing this after a green light to recruit process has been completed.

The site must conduct the trial in compliance with the protocol as agreed by the Sponsor and, by the regulatory authority(ies) (as appropriate), and which was given favourable opinion by the Research Ethics Committee (REC) and/or Institutional Review Board (IRB). The PI or delegate must document and explain any deviation from the approved protocol, and communicate this to the trial team at the CCTU.

A list of activated sites may be obtained from the Trial Manager.

6.3 Participants

6.3.1 Eligibility Criteria

6.3.1.1 Participant selection

The eligibility criteria for this trial have been carefully considered and are the standards used to ensure that only medically appropriate participants are entered. Participants not meeting the criteria should not be entered into the trial for their safety and to ensure that the trial results can be used as an appropriate basis to make future treatment decisions on other patients with keratoconus. It is therefore vital that exceptions are not made to these eligibility criteria.

Participants will be considered eligible for enrolment in this trial if they fulfil all the inclusion criteria and none of the exclusion criteria as defined below.

There will be NO EXCEPTIONS (waivers) to eligibility requirements at the time of randomisation. Questions about eligibility criteria should be addressed PRIOR to attempting to randomise the participant.

Patients will still be considered for recruitment if they should speak English but their parents/guardians do not. We will use translators where appropriate, as is common in the clinical trial sites. There is no current intention to translate patient information into other languages but this will be considered as needed. If translation does occur it will be back-translated and verified prior to use. Where translators are used for the consent process or questionnaire completion, their witness signature will be recorded on consent forms and questionnaire forms.

6.3.1.2 Participant inclusion criteria

- Age 10-16 years with keratoconus progression confirmed in one or both eyes using Pentacam or other topography. Progression for eligibility is defined as an increase of at least 1.5 dioptres in K_{max} on corneal topography between two examinations done using the same scanning technique at least 3 months apart.
- Patients and their parents/guardians must be sufficiently fluent in English to provide assent and informed consent and to complete the patient reported outcome measures.
- Patients must be willing to attend for follow up visits.

6.3.1.3 Participant exclusion criteria

- Advanced keratoconus as determined by apex corneal scarring
- Apex corneal thickness <400µ
- Maximum corneal curvature (K_{max}) >62 dioptres
- Rigid contact lens wear in both eyes and unable to abstain for 7 days pre-examinations
- Corneal comorbidity
- Down's syndrome
- Any clinical condition which the investigator considers would make the patient unsuitable for the trial, including pregnancy
- Participation in other clinical trials which would materially impact on the Keralink study

6.3.1.4 Eligibility criteria for individuals performing the interventions

All surgeons should be proficient in the use of CXL linking treatment and will have performed at least 20 procedures.

6.3.1.5 Co-enrolment guidance

The Principal Investigator or Co-Investigator(s) at trial sites will be responsible for ascertaining whether the patient is currently taking part in a clinical trial. Patients may not be enrolled in any other interventional trial without permission of the Chief Investigator. Co-enrolment in observational studies is acceptable. All patients will only be enrolled once into the trial. The investigator will be responsible for checking the patient notes against the screening/enrolment log at site prior to screening to ensure that the patient is not already enrolled in the trial.

6.3.1.6 Screening procedures and pre-randomisation investigations

Written informed consent to enter and be randomised into the trial must be 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 are performed. The only procedures that may be performed in advance of written informed consent being obtained are those that would be performed on all patients in the same situation as a usual standard of care.

6.4 Interventions

Arm A: Experimental intervention: cross-linking in one or both eyes
Arm B: Control Intervention: standard management, provision of glasses

6.4.1 Arm A

6.4.1.1 Cross-linking

Cross-linking in one or both eyes (according to whether progression is confirmed in one eye or both eyes), under general or local anaesthesia as applicable, followed by standard management. Following removal of corneal epithelium and administration of riboflavin drops, ultraviolet light will be administered according to standardised parameters of 10mW/cm^2 for a 5.4J/cm^2 total energy dose.

Like adults, children and young adults will experience some levels of stress and anxiety when undergoing medical treatment involving a surgical procedure. Special care, assistance and information will be provided to the children to alleviate their concerns. In bilateral cases in which there is randomisation to cross-linking the interval between procedures on the 1st and 2nd eye will be discussed with the patient and parents/guardians, and the preferred schedule will be decided on a case by case basis. To help patients for cross-linking feel more at ease during the procedure, they will be offered to choose between three different forms of anaesthesia: local anaesthesia with eye drops alone, drops with sedation and general anaesthesia. The 'Guidance on clinical research involving infants, children and young people: an update for researchers and research ethics committees' (2014) from the Royal College of Paediatrics and Child Health acknowledges that sedating active infants and children may be essential for some procedures which of themselves are of minimal risk. It states that sedation in healthy infants and children carries minimal additional risk and is usually associated with no more than occasional vomiting or short-lived disturbance of sleep. Only children who by themselves or their parents wish to do so will be sedated. General anaesthesia will only be performed in the youngest children, in whom the CXL procedure would not otherwise be feasible.

Sedation and general anaesthesia will be performed by experienced anaesthetic staff in the trial centre hospitals, who possess the necessary experiences, competencies, and skills to carry out the procedures and to deal immediately with any adverse effects. Participants will be monitored during and for approx. 2 hours after the procedure before being discharged home. One week following the CXL procedure, and subsequently as necessary, participants will have an eye examination to confirm corneal re-epithelialisation.

Riboflavin drops are procured as regular hospital stock following local site procedure. Sites should request and be able to provide a certificate of conformity or analysis for any batch of riboflavin used

for the trial and this should be kept within the investigator site file. According to regulatory requirements set out by the MHRA, all drops that are used for the purpose of the trial need to be labelled as 'for local use only'.

6.4.2 Arm B

6.4.2.1 Standard management

Standard management alone, including refraction testing with provision of glasses and/or specialist contact lens fitting. Glasses or contact lenses to be provided for one or both eyes as required for best corrected visual acuity. Those patients who develop advanced disease and poor spectacle- and lens-corrected visual acuity during the course of the trial will be offered corneal transplantation.

6.4.3 Treatment schedule

Patients randomised to cross-linking will be added to a surgical list following enrolment and a letter will be sent to the patient with confirmation of the surgery date. Patients randomised to CXL will receive treatment no later than 4 weeks following randomisation but as soon as is feasible in all cases.

For participants with both eyes eligible, management of the second eye will be according to the randomised allocation for the first eye, unless there is a specific patient preference not to do so. The eye with the more advanced keratoconus at the time of randomisation will be categorised as the study eye for the primary analysis. Participants with both eyes eligible and who are randomised to CXL, can choose whether to have the procedure on both eyes at the same time. For participants with only one eye eligible at the time of randomisation, if during the course of the study the second eye has progressive keratoconus then management will be according to the randomised allocation.

Those participants with keratoconus progression identified on the basis of clinically significant worsening of vision during the study follow up will be offered further management on a patient-by-patient basis. Those participants who are randomised to CXL but choose not to have the surgery will be managed according to standard care.

6.4.4 Concomitant care

For patients on pre-existing treatment for allergic conjunctivitis, this will be continued as required for the treatment of the respective condition.

All concomitant medication taken by patients will be reviewed during enrolment and advice given as to whether this can be continued during the trial. It is likely that this will already be covered by the existing exclusion criteria.

6.4.5 Protocol treatment discontinuation

In consenting to the trial, participants are consenting to trial treatments, trial follow-up and data collection. As participation in the trial is entirely voluntary, the participant may choose to discontinue trial treatment at any time without penalty or loss of benefits to which they would otherwise be entitled. Although not obliged to give a reason for discontinuing their trial treatment, a reasonable effort should be made to establish this reason, whilst remaining fully respectful of the participant's rights.

Participants who discontinue protocol treatment, for any of the above reasons, should remain in the trial for the purpose of follow up and data analysis. They will be particularly encouraged to attend the 18 month follow-up visit.

6.5 Outcomes

6.5.1 Primary outcome

Primary outcome measure will be K_{max}* in the study eye at 18 months post-randomisation.

6.5.2 Secondary Outcomes

a) Keratoconus progression (yes/no) defined as >1.5 dioptre increase in K_{max}* from baseline (at randomisation) to 18 months **or** requirement for change from spectacle to rigid contact lenses correction of vision, as the latter precludes reliable topography measures
b) Time to keratoconus progression (defined as >1.5D increase in K_{max} from baseline)
c) Uncorrected and best corrected visual acuity (measured as logMAR using EDTRS chart)
d) Refraction (measured dioptres spherical equivalent, myopia and astigmatism)
e) Apical corneal thickness measurement (ultrasound) **
f) Quality of life as assessed by CHU9D and CVAQC questionnaires

* We will use Pentacam K_{max} measurements as the indicator of disease progression. The probability is high that K_{max} increases >1.5D would discriminate a true change in the steepest corneal meridian from artefact. A change of this magnitude is clinically significant, indicating a likelihood of improved visual acuity with correction of the refractive change; for example benefit from spectacle provision in an eye that previously had good unaided vision, a change in spectacle lens correction, or progression from spectacle wear to contact lens correction. K_{max} will be measured 3 times by a masked observer at each visit during the trial and the mean value used in analyses.

** Apical corneal thickness measurement:
Biomechanical and ultrastructural studies to date have not been able to demonstrate the mechanisms by which CXL stiffens the cornea. The Keralink study will examine changes in thickness of the cornea by ultrasound as topography measurements do not provide accurate and reproducible thickness measurements. Cone apex thickness measurements will be correlated with changes in corneal shape and visual parameters. This will confirm whether arrest of keratoconus progression following CXL is accompanied by arrest in progressive thinning.

Keratoconus disease progression criteria:

(i) At six months following randomisation and each subsequent follow up visit, corneal topography (using Pentacam) in each eye will be reviewed for possible progression, defined as a K_{max} increase >1.5D from baseline.

(ii) Bearing in mind the inter- and intra-test variation in topography analysis, any patient found to have >1.5D increase in K_{max} will need to have this confirmed at a subsequent visit (i.e. 3 months later). Participants who have unconfirmed progression at the 18 month follow-up visit will need this confirmed at a further visit at 21 months.

6.5.3 Compliance and adherence

Investigators and staff at site should follow local procedures for ensuring informed consent for CXL has been given, and that all patients have had sufficient opportunity to ask questions about the surgery.

Patients in CXL and standard care groups will be required to comply with the follow up schedule. All patients will be followed-up at 3, 6, 9, 12, 15 & 18 months from randomisation. However, if a participant first shows signs of progression at the 18 month follow-up visit, this would need to be confirmed at an additional 21 month visit. Site staff will be responsible for booking these appointments and contacting any patients who do not attend to rearrange the appointment. No additional research visits will be required for patients needing surgery for their second eye.

6.6 Participant timeline

Table 1. Schedule of enrolment, interventions, and assessments.*

			Months post randomisation						
Study parameter	Consent, Screening, Randomisation	Treatment	3	6	9	12	15	18	21**
Clinical examination and general eligibility assessment	x								
Informed consent and eligibility screening	x								
Corneal topography (Pentacam*)	x		x	x	x	x	x	x	x
Visual acuity (unaided, spectacle- and contact lens-corrected as applicable)	x		x	x	x	x	x	x	x
Refraction (measured dioptres myopia and astigmatism)	x		x	x	x	x	x	x	x
Corneal thickness (ultrasound)	x		x	x	x	x	x	x	x
Confirmation of eligibility	x								
Randomisation	x								
CXL Treatment		x ***							
CHU9D and CVAQC (QoL)	x			x		x		x	
Adverse Events	x	x	x	x	x	x	x	x	x

All follow up visits will have a window of ±28 days. CXL treatment should be undertaken within 4 weeks randomisation.

* Pentacam or other topography measurements prior to enrolment are used as the comparator for confirmation of keratoconus progression and thereby trial eligibility. For feasibility reasons, if patients referred for trial evaluation have had at least two measures of topography using the same instrument in the community or in referring eye clinics, these measurements will be used to assess trial eligibility.

Pentacam measurements for confirmation of trial eligibility and for outcome assessment will be by standardised methodology. To improve repeatability, three measurements of each eye will be taken by a masked observer at each trial examination from randomization onwards and the mean used to determine progression.

The K_{max} value obtained using Pentacam assessment at trial centre prior to randomisation will be used as the baseline K_{max} for outcome assessment.

** Only participants with unconfirmed progression at the 18 month visit will have an additional 21 month visit to confirm progression.
*** All patients undergoing CXL treatment will have a non-research 1 week follow up appointment as standard of care.

6.6.1 Early Stopping of Follow-up

Participants will be followed up for 18 months from randomisation.

If a participant chooses to discontinue from the study care pathway, they should continue to be followed up as closely as possible to the schedule defined in the protocol, providing they are willing. They should be encouraged and facilitated not to leave the whole trial, even though they no longer wish to comply with the study follow up schedule. If, however, the participant exercises the view that they no longer wish to be followed up either, this view must be respected and the participant withdrawn entirely from the trial. CCTU should be informed of the withdrawal in writing using the appropriate Keralink trial documentation. Data already collected will be kept and included in analyses according to the intention-to-treat principle for all participants who stop follow up early. If a patient is only willing to return for one follow up visit, then this should be the 18 month visit.

Participants who stop trial follow-up early will not be replaced.

6.6.2 Participant Transfers

If a participant moves from the area making continued follow up at their consenting centre inappropriate, every effort should be made for them to be followed at another participating trial centre. Written consent should be taken at the new centre and then a copy of the participant's CRFs should be provided to the new centre. Responsibility for the participant remains with the original consenting centre until the new consent process is complete.

Alternatively if a patient requires general anaesthetic which is not available at one site but is available at another site then a transfer for surgery will be accepted but all subsequent follow up appointments should be conducted at the original recruitment site.

6.6.3 Loss to Follow-up

All participants will be asked to provide contact details for, and consent to contact where necessary, a "best alternative contact" such as a relative or close friend. Every effort will be made to maintain contact with all patients.

6.6.4 Trial Closure

The end of the trial will be defined as when the last patient recruited has reached their 18 month follow up visit, all data chases have been completed and all data queries have been resolved.

The REC and MHRA will be notified within 90 days of the end of the trial. A summary report of the research will be sent to the REC and MHRA within 12 months of the end of the trial.

6.7 Sample Size

We have calculated our sample size as follows:

A difference between the groups in the change in K_{max} of 1.5D from randomisation to 18 months would be viewed as a clinically important difference (based on Wittig-Silva RCT of CXL in adults [8]). A

K_{max} increase >1.5D would discriminate a true change in the steepest corneal meridian from 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 SD of 1.5D. The total sample size has been increased to 60 patients (30/group) to allow for up to 24% loss to follow-up. These estimates are based on 12 and 24 month data reported by Wittig-Silva et al[8] from which we estimate a pooled SD of the changes of 1.476D.

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

6.8 Recruitment and Retention

6.8.1 Recruitment

We aim to recruit a total of 60 patients over the 12 month recruitment period from UK NHS sites as described in section 6.1.1: Moorfields Eye Hospital NHS Foundation Trust, Sheffield Teaching Hospitals NHS Foundation Trust and Royal Liverpool & Broadgreen Hospitals NHS Trust. We expect ~50% patients to be recruited in Moorfields, ~25% in Sheffield and ~25% in Liverpool. Patients attending a consultant clinic in one of the three trial centres in whom progressive keratoconus is confirmed may initially have been referred by an optometrist in the community or an ophthalmologist in a hospital eye clinic. These potential participants will be invited to participate in the Keralink trial and provided further information by consultant ophthalmologist principal investigators or authorized suitably trained members of the clinical care teams in the trial centre.

Screening, recruitment and randomisation will be undertaken by qualified individuals at site, and this will be documented on the site delegation log. Individuals taking consent will have received appropriate training.

We expect to recruit 4-6 patients per month across the three sites.

Screening logs, recruitment rates, cross over rates and loss to follow up rates will be reviewed at monthly meetings of the Trial Management Group. Any barriers to recruitment will be investigated and mechanisms put in place to correct them.

6.8.2 Retention

The follow up period for the Keralink trial is 18 months. All participants will be required to attend clinic at 3, 6, 9, 12, 15 and 18 months from randomisation. However, if a participant first shows signs of progression at the 18 month visit, they will need an additional 21 month visit to confirm progression. A visit window of 28 days has been deemed sufficient to allow for the target population to attend follow up visits without this interfering with their school timetables.

Site teams will attempt to book all follow up visits when the patient attends for treatment and they will also routinely contact the patient or parent/guardian prior to each follow up visit as a reminder.

6.9 Assignment of Intervention

6.9.1 Allocation

6.9.1.1 Sequence generation

Patients will be randomised in a 1:1 ratio to CXL or to standard care, via the Sealed Envelope.com website. Sealed Envelope is a randomisation service provider that provides a proven, reliable and centralised computer generated randomisation system. The system will be custom designed to the trial requirements. This will use minimisation with stratification by (a) treatment centre and (b) whether progression is confirmed in one eye or both eyes at randomisation. A random trial arm allocation will be computer generated. Sealed Envelope will provide the randomised treatment for each participant.

6.9.1.2 Allocation concealment mechanism

On the day of randomisation, delegated staff at site will enter the patient's initials, gender, date of birth, date of consent, eligibility criteria fulfilment, treatment centre, and whether progression is confirmed in one or both eyes into the SealedEnvelope.com secure website, which will then allocate the randomised treatment. The treatment allocation will not be concealed from the investigator and the trial participant, however treatment allocation will be concealed from optometrists or delegated staff obtaining the outcome measures. Usernames and passwords for Sealed Envelope will be provided to site staff during the site activation procedure.

6.9.1.3 Allocation Implementation

The responsibility for enrolling and randomising participants into the trial lies with the Principal Investigator and staff at site.

Individuals at participating centres will be provided with a secure login to the sealedenvelope.com website, according to a delegation of responsibilities log. The users will be required to log into the website and answer eligibility questions before entering stratification data and being permitted to randomise. The randomisation result will be shown directly online, with an email confirmation to the user and also to the Trial Manager.

6.9.2 Masking

Although the initial K_{max} measurement may be performed in the facility from which the patient is referred, at all subsequent examinations K_{max} will be measured 3 times by a masked observer. Principal Investigator or treating clinician will be masked to the Kmax values measured during the follow up assessments (3, 6, 9, 12, 15 18 and 21 month follow up). Due to the nature of the intervention, neither the trial participants nor the treating clinician or site staff will be masked to the treatment allocation, but optometrists performing outcome assessments will be unaware of treatment allocation.

6.9.3 Emergency unmasking

As the trial participants and site clinicians will have access to the treatment allocation, emergency unmasking will not be necessary.

6.10 Data Collection, Management and Analysis

6.10.1 Data collection methods

Each participant will be given a unique trial Participant Identification Number (PIN). Data will be collected at the time-points indicated in the Trial Schedule (Table 1).

Pseudo-anonymised data will be collected from the trial sites using paper Case Record Forms (CRFs) and transferred to CCTU. The data will be entered into the MACRO database by a member of the Keralink trial team and stored on secure servers based at UCL. Training on paper CRF completion and storage for site staff listed on the delegation of responsibilities log will be provided at the site initiation meeting(s).

Data collection, data entry and queries raised by a member of the Keralink trial team will be conducted in line with the CCTU and trial specific Data Management Standard Operating Procedure.

Identification logs, screening logs and enrolment logs will be kept at the trial site in a locked cabinet within a secured room.

Clinical trial team members will receive trial protocol training. All data will be handled in accordance with the Data Protection Act 1998.

6.10.2 Data Management

Data will be entered in the approved Keralink database by a member of the Keralink trial team at CCTU and protected using established CCTU procedures.

Pseudo-anonymised data: Participants will be given a unique trial Participant Identification Number (PIN). Data will be entered under this identification number onto the central database stored on the servers based at CCTU. The database will be password protected and only accessible to members of the Keralink trial team at CCTU, and external regulators if requested. The servers are protected by firewalls and are patched and maintained according to best practice. The physical location of the servers is protected by CCTV and security door access.

The database and coding frames have been developed by the Clinical Trial Manager in conjunction with CCTU. The database software provides a number of features to help maintain data quality, including; maintaining an audit trail, allowing custom validations on all data, allowing users to raise data clarification requests, and search facilities to identify validation failure/ missing data.

After completion of the trial the database will be retained on the servers of UCL for on-going analysis of secondary outcomes.

The identification, screening and enrolment logs, linking participant identifiable data to the Participant Identification Number, will be held locally by the trial site. This will either be held in written form in a locked filing cabinet or electronically in password protected form on hospital computers. After completion of the trial, the identification, screening and enrolment logs will be stored securely by the sites for 5 years unless otherwise advised by CCTU.

6.10.3 Non-adherence and non-retention

Trial teams should encourage patients and the parent/guardians to attend all follow up visits. If a patient or parent/guardian wishes to withdraw consent this should be documented in the Withdrawal CRF. Once consent has been withdrawn follow-up will cease.

If however a patient has been deemed lost to follow up, all effort should be made to encourage that participant to attend all remaining trial visits.

6.10.4 Statistical methods

6.10.4.1 Statistical analysis plan

Patient characteristics at the time of randomisation will be summarised using mean and standard deviation for continuous variables which are approximately normally distributed, median and interquartile range for variables which are not normally distributed, or by frequencies and percentages for categorical variables.

All statistical tests will use a 2-sided *p*-value of 0.05 unless otherwise specified. All confidence intervals presented will be 95 % and two-sided. A detailed statistical analysis plan will be developed for approval by the Trial Steering Committee and review by the Independent Data Monitoring Committee and finalised before the first statistical analysis of unmasked data. All statistical analyses will be performed using Stata (StataCorp, College Station TX, USA).

6.10.4.2 Statistical Methods – Outcomes

For each patient the eye with the more advanced keratoconus at the time of randomisation will be defined as the study eye for the primary analysis, unless that eye has previously been treated by CXL or corneal transplantation. The analysis of the primary outcome will be performed using a linear mixed model fitted to all K_{max} values recorded after randomisation. K_{max} at randomisation, treatment group, follow-up time, the interaction between treatment and time, and the stratifying variables centre and whether each patient has only one eye eligible will be included as fixed effects and patient will be included as a random effect. This analysis is equivalent to modelling the change in K_{max} adjusting for K_{max} values at randomisation. Model assumptions will be assessed, and a logarithmic transformation used if this improves normality of the residuals. The impact of missing K_{max} values due to the unreliability of topography measurements in patients who are unable to abstain from wearing lenses for 7 days pre-examination following rigid contact lens wear will be mitigated by applying appropriate multiple imputation methods to estimate these values.

Similar linear mixed models will be fitted for continuous outcomes such as uncorrected and best corrected visual acuity measured at randomisation and on more than one occasion during follow-up. Uncorrected and best corrected visual acuity will be measured in logMAR using an ETDRS chart at a distance of 4 metres.

In patients for whom both eyes show progression at the time of randomisation, information from both eyes will be included in a secondary analysis including eye as a fixed effect and patient as a random effect.

Cox survival analysis method will be used to estimate time to Keratoconus progression in each treatment group. Analysis will be stratified by the stratifying variables, centre and whether each

patient has only one eye eligible, and patients who do not progress during the course of the trial will be censored at their last follow-up visit.

We will also explore how health and visual disability in children and young patients with keratoconus relate to changes in K_{max}. CHU9D is a nine-question paediatric generic preference based measure of health outcome which provides a descriptive health profile as well as a utility score and has been validated for self-completion in an adolescent population (11-17 years)[12]. CVAQC is a 25-item vision specific questionnaire designed for children[13].

Fisher's exact test will be used to compare proportions.
Two sample t tests or Mann Whitney U tests, depending on the distribution of the data, will be used for continuous outcomes measured only at the end of the trial.

6.10.4.3 Additional Analyses - Subgroup

An interaction between the number of eyes with progression at randomisation and CXL treatment will be added to the primary efficacy outcome analysis mixed model to investigate whether the effect of CXL differs between patients who had progression at randomisation in one or both eyes.

We will also investigate possible interactions between treatment effect and ethnicity, family history of Keratoconus and atopy as pre-specified subgroup analyses by adding interaction terms to the regression model for the primary outcome.

6.10.5 Analysis Population and Missing Data

The primary analysis will be conducted following the intention to treat (ITT) principle where all randomised patients are analysed in their allocated group whether or not they receive their randomised treatment. However, in the event of cross-over from the randomised arm to the other, we will perform two analyses of the primary outcome, the primary ITT analysis and a per protocol analysis. The per-protocol analysis will exclude any information collected from a patient after cross-over. Any cross-over or other treatment deviations will be summarised with reasons.

An ITT analysis will be performed for all secondary outcomes. The impact of missing data will be mitigated against by incorporating information from earlier timepoints using a mixed model approach.

6.11 Data Monitoring

6.11.1 Independent Data Monitoring Committee

Details of the roles and responsibilities of the Independent Data Monitoring Committee (IDMC), including membership, relationships with other committees, decision making processes, and the timing and frequency of interim analyses (and description of stopping rules and/or guidelines where applicable) are described in detail in the Keralink DMC Terms of Reference (ToR).

6.11.2 Interim Analyses

No formal interim analysis is planned, but reports concerning patient safety and key efficacy outcomes will be prepared for review by the Independent Data Monitoring Committee (IDMC) who may request an interim analysis if a report raises concern.

The IDMC will also be asked to review all the assumptions used for the sample size calculation before the end of recruitment.

6.11.3 Data Monitoring for Harm

6.11.3.1 Safety reporting

Definitions of harm of the EU Directive 2001/20/EC Article 2 based on the principles of ICH GCP apply to this trial.

Table 1: Adverse Event Definitions

Adverse Event (AE)	Any untoward medical occurrence in a patient or clinical trial participant administered a medicinal product and which does not necessarily have a causal relationship with this product.
Adverse Reaction (AR)	Any untoward and unintended response to an investigational medicinal product related to any dose administered
Unexpected Adverse Reaction (UAR)	An adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. Investigator's Brochure for an unauthorised product or summary of product characteristics (SPC) for an authorised product.
Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)	Any AE or AR that at any dose: • results in death • is life threatening* • requires hospitalisation or prolongs existing hospitalisation** • results in persistent or significant disability or incapacity • is a congenital anomaly or birth defect • or is another important medical condition***
Serious Unexpected Serious Adverse Reaction (SUSAR)	A serious adverse reaction, the nature and severity of which is not consistent with the information about the medical product in question set out: • in the care of a product with a marketing authorisation, in the summary of product characteristics for that product • in the case of any other investigational medicinal product, in the investigator's brochure relating to the trial question

* the term life threatening here refers to an event in which the patient is at risk of death at the time of the event; it does not refer to an event that might hypothetically cause death if it was more severe (e.g. a silent myocardial infarction)

** Hospitalisation is defined as an in-patient admission, regardless of length of stay, even if the hospitalisation is a precautionary measure for continued observation. Hospitalisation for pre-existing conditions (including elective procedures that have not worsened) do not constitute an SAE

*** Medical judgement should be exercised in deciding whether an AE or AR is serious in other situations. Important AEs or ARs that may not be immediately life threatening or result in death or hospitalisation, but may seriously jeopardise the participant by requiring intervention to prevent one of the other outcomes listed in the table (eg a secondary malignancy, an allergic bronchospasm requiring intensive emergency treatment, seizures or blood dyscrasias that do not require hospitalisation, or development of drug dependency).

In addition to the definition above, Adverse Events (AEs), include but are not limited to the following:

- An exacerbation of a pre-existing illness
- A condition (regardless of whether PRESENT prior to the start of the trial) that is DETECTED after trial drug administration. (This does not include pre-existing conditions recorded as such at randomisation – as they are not detected after trial drug administration.
- Any reversible or short-term corneal abnormality, e.g. eye pain prolonged >48 hours, delayed corneal epithelialisation, transient corneal oedema.

AEs do not include:

- Pre-existing disease or a condition present before treatment that does not worsen
- Medical or surgical procedures: the condition that leads to the procedure is the adverse event
- Hospitalisation where no untoward or unintended response has occurred e.g. elective cosmetic surgery
- Overdose of medication without signs or symptoms

In addition to the definition above, Serious Adverse Events (SAEs), include but are not limited to the following:

- Requiring hospitalisation or prolongation of existing hospitalisation;
- Resulting in persistent or significant disability, including *(i)* corneal stromal scarring subsequent to CXL or secondary to post-CXL corneal infection;
- Is otherwise considered medically significant by the investigator.

6.11.3.2 Other Notifiable Adverse Events

Pregnancy

Pregnancy is a contraindication to CXL on account of possible confounding effects of hormonal change on corneal shape. Subjects known to be pregnant will not be recruited. If a participant becomes pregnant during follow-up they will not be withdrawn; data will be collected until completion of the follow-up period.

6.11.3.3 Procedures to follow in the event of female participants becoming pregnant

Participants, who become pregnant during the trial should be allowed to remain in the trial. The participant should continue to be followed up as detailed above.

6.11.3.4 Investigator responsibilities relating to safety reporting

All non-serious AEs and ARs, whether expected or not, should be recorded in the patient's medical notes and reported in the AE CRF and sent to the CCTU ideally within 7days. SAEs and SARs should be notified to CCTU as soon as the investigator becomes aware of the event.

6.11.3.4.1 Seriousness assessment

When an AR occurs, the investigator responsible for the care of the participant must first assess whether or not the event is serious using the definition given in Table 1. If the event is classified as

'serious' then an SAE form must be completed and CCTU (or delegated body) notified immediately (within 24 hours) of investigator becoming aware of the event.

6.11.3.4.2 Severity or grading of Adverse Events

The severity of all ARs (serious and non-serious) in this trial should be graded using the Common Terminology Criteria for Adverse Events (CTCAE).

Grade 1 Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2 Moderate; minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living (ADL)*.
Grade 3 Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL**.
Grade 4 Life-threatening consequences; urgent intervention indicated.
Grade 5 Death related to AE

*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self-care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

6.11.3.4.3 Causality

The investigator must assess the causality of all serious events or reactions in relation to the trial therapy using the definitions in Table 2.

Table 2: Causality definitions

Relationship	Description	Event type
Unrelated	There is no evidence of any causal relationship	Unrelated SAE
Unlikely to be related	There is little evidence to suggest that there is a causal relationship (e.g. the event did not occur within a reasonable time after administration of the trial medication). There is another reasonable explanation for the event (e.g. the participant's clinical condition or other concomitant treatment)	Unrelated SAE
Possibly related	There is some evidence to suggest a causal relationship (eg because the event occurs within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (eg the participant's clinical	SAR

	condition or other concomitant treatment)	
Probably related	There is evidence to suggest a causal relationship and the influence of other factors is unlikely	SAR
Definitely related	There is clear evidence to suggest a causal relationship and other possible contributing factors can be ruled out.	SAR

If an SAE is considered to be related to trial treatment, refer to the relevant interventions sections of the protocol.

6.11.3.4.4 Expectedness

If there is at least a possible involvement of the trial medications (including any comparators), the Investigator and Sponsor must assess the expectedness of the event. An unexpected adverse reaction is one that is not reported in the current IB or SPC, or one that is more frequently reported or more severe than previously reported. If a SAR is assessed as being unexpected it becomes a SUSAR (suspected, unexpected, serious adverse reaction) MHRA and REC reporting guidelines apply (see Notifications sections of the protocol). In this trial the IMP, which is the riboflavin drops, is currently categorised as a CE-marked device and therefore does not hold the usual reference safety information as would a standard IMP under investigation. For this trial as there is no IB or SPC for the riboflavin drops, we have sought advice on expected events/reactions from several sources and results were as follows.

In the last three years the CXL procedure has been performed on more than 1000 patients at Moorfields Eye Hospital, and no adverse effects occurred which could be attributed to the riboflavin drops.

Reports were reviewed on the drug analysis prints from the MHRA website and again we could not find any attributed to the riboflavin drops, (http://www.mhra.gov.uk/drug-analysis-prints/).

A recent systemic review and meta-analysis did not report any adverse effects http://www.ncbi.nlm.nih.gov/pubmed/26751990).

Participants undergoing CXL treatment will be expected to experience variable discomfort/pain for the first 1-2 days post-procedure. The eye may be red and sensitive to light for several days. Some patients report little discomfort and others report bad pain in the CXL-treated eye. However pain control is not usually a problem and should be well controlled through provision of eye drops or analgesic tablets as needed. There may be some blurring of vision which clears over the first few days and weeks.

Serious complications such as infection are rare. The studies that NICE reviewed involved about 2500 patients in different reported cohorts undergoing CXL which reported serious complications in 39 (1.5%) out of the 2500 patients: infection; inflammation (redness, swelling, heat and pain), which in

a small number of cases led to scarring or loss of eyesight and the need for a corneal transplant; scarring; fluid build‑up causing corneal oedema. Very few patients have been reported to lose vision in the treated eye as a result of haze, scarring or infection. If symptoms suggestive of possible infection do occur, participants will be asked to contact the treating principal investigator or attend the hospital's A&E service.

One specified expected complication is listed, categorised as a SAE. Corneal stromal scarring subsequent to CXL itself or secondary infection post-CXL is rare. As ~30 trial participants will be randomised to CXL, no more than one CXL-treated participant would be expected to have this complication.

AE	Severity	Frequency	Duration
Discomfort/pain	Mild	25%	1-2 days
Discomfort/pain	Moderate	75%	1 day
Blurred vision	Mild	50%	1-2 weeks
Infection	severe	<1%	2 weeks
Corneal stromal scarring	severe	<1%	Long term

6.11.3.5 Notifications

6.11.3.5.1 Notifications by the Investigator to CCTU

CCTU must be notified of all SAEs immediately (within 24 hours) of the Investigator becoming aware of the event.

Investigators should notify CCTU of any SAEs and other Notifiable Adverse Events (NAEs, such as adverse effects from topical eye medication) occurring from the time of randomisation until 30 days after the last protocol treatment administration. SARs and SUSARs must be notified to CCTU until trial closure. Any subsequent events that may be attributed to treatment should be reported to the MHRA using the yellow card system (https://yellowcard.mhra.gov.uk/the-yellow-card-scheme/).

The SAE form must be completed by the investigator (the consultant named on the delegation of responsibilities list who is responsible for the participant's care) with attention paid to the grading, causality and expectedness of the event. In the absence of the responsible investigator, the SAE form should be completed and signed by a member of the site trial team and emailed as appropriate within the timeline. The responsible investigator should check the SAE form at the earliest opportunity, make any changes necessary, sign and then email securely to CCTU. Detailed written reports should be completed as appropriate. Systems will be in place at the site to enable the investigator to check the form for clinical accuracy as soon as possible.

The minimum criteria required for reporting an SAE are the trial number and date of birth, name of reporting investigator and sufficient information on the event to confirm seriousness. Any further

information regarding the event that is unavailable at the time of the first report should be sent as soon as it becomes available.

The SAE form must be scanned and sent by encrypted email to the trial team at CCTU on

ctu.keralink@ucl.ac.uk

Participants must be followed up until clinical recovery is complete and laboratory results have returned to normal or to values measured at randomisation, or until the event has stabilised. Follow-up should continue after completion of protocol treatment and/or trial follow-up if necessary. Follow-up SAE forms (clearly marked as follow-up) should be completed and emailed to CCTU as further information becomes available. Additional information and/or copies of test results etc. may be provided separately. The participant must be identified by trial number, date of birth and initials only. The participant's name should not be used on any correspondence and should be blacked out and replaced with trial identifiers on any test results.

6.11.3.5.2 CCTU responsibilities

Medically qualified staff at CCTU and/or the Chief Investigator (CI or a medically qualified delegate) will review all SAE reports received. In the event of disagreement between the causality assessment given by the local investigator and the CI, both opinions and any justifications will be provided in subsequent reports.

The delegated staff at CCTU will review the assessment of expectedness and, based on possible wider knowledge of the reference material for the treatment or comparator, and after discussion with the CI, may over-rule the investigator assessment of expectedness for the purposes of onward reporting.

UCL CCTU is undertaking the duties of trial sponsor and is responsible for the reporting of SUSARs to the regulatory authorities (MHRA) and the REC as appropriate. Fatal and life threatening SUSARs must be reported to the competent authorities within seven days of CCTU becoming aware of the event; other SUSARs must be reported within 15 days.

CCTU will keep investigators informed of any safety issues that arise during the course of the trial.

The trial manager or delegate at CCTU will submit Development Safety Update Reports (DSURs) to competent authorities.

6.11.4 Quality Assurance and Control

6.11.4.1 Risk Assessment

The Quality Assurance (QA) and Quality Control (QC) considerations for the Keralink trial are based on the standard CCTU Quality Management Policy that includes a formal Risk Assessment, and that acknowledges the risks associated with the conduct of the trial and proposals of how to mitigate them through appropriate QA and QC processes. Risks are defined in terms of their impact on: the rights and safety of participants; project concept including trial design, reliability of results and institutional risk; project management; and other considerations.

QA is defined as all the planned and systematic actions established to ensure the trial is performed and data generated, documented and/or recorded and reported in compliance with the principles of

GCP and applicable regulatory requirements. QC is defined as the operational techniques and activities performed within the QA system to verify that the requirements for quality of the trial related activities are fulfilled.

6.11.4.2 Central Monitoring at CCTU

CCTU staff will review Case Report Form (CRF) data for errors and missing key data points. The trial database will also be programmed to generate reports on errors and error rates. Essential trial issues, events and outputs, including defined key data points, will be detailed in the Keralink trial Data Management Plan.

6.11.4.3 On-site Monitoring

The frequency, type and intensity of routine and triggered on-site monitoring will be detailed in the Keralink Quality Management and Monitoring Plan (QMMP). The QMMP will also detail the procedures for review and sign-off of monitoring reports. In the event of a request for a trial site inspection by any regulatory authority UCL CCTU must be notified as soon as possible.

6.11.4.3.1 Direct access to participant records

Participating investigators must agree to allow trial related monitoring, including audits, REC review and regulatory inspections, by providing access to source data and other trial related documentation as required. Participant consent for this must be obtained as part of the informed consent process for the trial.

6.11.4.4 Trial Oversight

Trial oversight is intended to preserve the integrity of the trial by independently verifying a variety of processes and prompting corrective action where necessary. The processes reviewed relate to participant enrolment, consent, eligibility, and allocation to trial groups; adherence to trial interventions and policies to protect participants, including reporting of harms; completeness, accuracy and timeliness of data collection; and will verify adherence to applicable policies detailed in the Compliance section of the protocol. Independent trial oversight complies with the CCTU trial oversight policy.

In multi-centre trials this oversight is considered and described both overall and for each recruiting centre by exploring the trial dataset or performing site visits as described in the Keralink Quality Management and Monitoring Plan.

6.11.4.4.1 Trial Management Team

The Trial Management Team (TMT) will be set up to assist with developing the design, co-ordination and day to day operational issues in the management of the trial, including budget management. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMT terms of reference.

6.11.4.4.2 Trial Management Group

A Trial Management Group (TMG) will be set up to assist with developing the design, co-ordination and strategic management of the trial. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TMG terms of reference.

6.11.4.4.3 Independent Trial Steering Committee

The Independent Trial Steering Committee (TSC) is the independent group responsible for oversight of the trial in order to safeguard the interests of trial participants. The TSC provides advice to the CI, CCTU, the funder and sponsor on all aspects of the trial through its independent Chair. The membership, frequency of meetings, activity (including trial conduct and data review) and authority will be covered in the TSC terms of reference.

6.11.4.4.4 Independent Data Monitoring Committee

The Independent Data Monitoring Committee (IDMC) is the only oversight body that has access to unmasked accumulating comparative data. The IDMC is responsible for safeguarding the interests of trial participants, monitoring the accumulating data and making recommendations to the TSC on whether the trial should continue as planned. The membership, frequency of meetings, activity (including review of trial conduct and data) and authority will be covered in the IDMC terms of reference. The IDMC will consider data in accordance with the statistical analysis plan and will advise the TSC through its Chair. The IDMC will meet regularly throughout the trial to monitor the accumulating evidence on both efficacy and harm, and can recommend to the Trial Steering Committee at any stage that the trial is stopped and all patients are offered CXL.

6.11.4.4.5 Trial Sponsor

The role of the sponsor is to take on responsibility for securing the arrangements to initiate, manage and finance the trial. UCL is the trial sponsor and has delegated the duties as sponsor to CCTU via a signed letter of delegation.

7 Ethics and Dissemination

7.1 Research Ethics Approval

Before initiation of the trial at any clinical site, the protocol, all informed consent forms and any material to be given to the prospective participant will be submitted to the relevant REC for approval. Any subsequent amendments to these documents will be submitted for further approval. Before initiation of the trial at each additional clinical site, the same/amended documents will be submitted to the local Research and Development (R&D) for NHS permissions.

7.2 Competent Authority Approvals

This protocol will be submitted to the UK regulatory authority (MHRA).

This is a Clinical Trial of an Investigational Medicinal Product (IMP) as defined by the EU Directive 2001/20/EC. Therefore, a CTA is required in the UK.

The progress of the trial, safety issues and reports, including expedited reporting of SUSARs, will be reported to the MHRA.

7.3 Other Approvals

The protocol will be submitted by those delegated to do so to the relevant R&D department of each participating site or to other local departments for approval as required in each country. A copy of the local R&D approval (or other relevant approval as above) and of the Participant Information

Sheet (PIS) and consent form on local headed paper must be forwarded to the co-ordinating centre before participants are randomised to the trial.

The protocol has received formal approval and methodological, statistical, clinical and operational input from the CCTU Protocol Review Committee.

7.4 Protocol Amendments

The CCTU will ensure that the trial protocol, patient information sheet, consent form, GP letter and submitted supporting documents have been approved by the research ethics committee and site Research & Development department prior to any patient recruitment. The protocol and all agreed substantial protocol amendments, will be documented and submitted for ethical and regulatory approval prior to implementation.

7.5 Consent or Assent

Potential trial patients will be identified following confirmation of diagnosis and progression of keratoconus in the trial centres. We will ensure that CXL, standard care and the rationale behind the study are clearly explained to parents and patients without bias, and that the process of randomisation is fully understood. Children will be invited to read an age appropriate information sheet and to give their written assent. Information sheets have been written for (i) 10-12 year old patients, (ii) 13-16 year old patients and (iii) parents/guardians. Information presented to the child and parent will explain what will happen; what is being asked of the child; that the child may or may not agree to take part without adverse consequences and may withdraw at any time; and be given in clear language at a level that the child can understand, using visual aids if necessary. Careful thought has been given to 'translating' this information as appropriate for the age of the patients.

Following a discussion with a medically qualified investigator or suitable trained and authorised delegate, any questions will be satisfactorily answered and if the participant is willing to participate, written informed consent will be obtained. The rights of the participant to refuse to participate in the trial without giving a reason will be respected.

Consent will be re-sought if new information becomes available that affects the participant's consent in any way. This will be documented in a revision to the patient information sheet and the participant will be asked to sign an updated consent form. These will be approved by the ethics committee prior to their use. Consent will also be re-sought in the event that a child's carer changes. Children or adolescents will be asked to assent or agree. Participation will be refused in the event that assent is not given. A copy of the approved consent form is available from the CCTU trial team. After the participant has entered the trial, the clinician remains free to give alternative treatment to that specified in the protocol, at any stage, if s/he feels it to be in the best interest of the participant. The reasons for doing so will be recorded. After randomisation the participant will remain within the trial for the purpose of follow up and data analysis according to the treatment option to which they have been allocated. However, the participant remains free to change their mind at any time about the protocol treatment and follow-up without giving a reason and without prejudicing their further treatment.

7.6 Confidentiality

Data protection and information governance principles will be followed throughout the study, which will be overseen by the Trial Manager and Clinical Project Manager based at CCTU. Any confidentiality concerns expressed by potential patients will be addressed prior to providing informed consent.

Patients will be assigned a trial number upon randomisation. This number will be used on all trial-related documentation in place of personal identifiable data and used to identify patients on the CRFs. Patient identifiable information will be held securely at the sites and will be removed from documents and replaced with the trial number in the event of being sent off-site. Patient names will not be passed to anyone outside the research team who is not involved in the trial.

The records obtained during the trial, as well as related health records, will remain strictly confidential at all times. The information will be held securely on paper and electronically at the treating hospital under the provisions of the 1998 Data Protection Act. Information will be transferred from hospital sites to UCL CCTU on CRFs to enable analysis of the trial results to be undertaken. Patient names will only appear on their consent form, which will be kept at the hospital site in the medical notes, a copy will not be sent to the CCTU.

Patient records will be available to people authorised to work on the trial within NHS Trusts but may also need to be made available to people authorised by the Sponsor for monitoring and audit purposes. By signing the consent form patients agree to this access for the Keralink trial and any further research that may be conducted in relation to it, even if they withdraw from the trial. When a patient withdraws consent from the trial, unless they object, their data will remain on file and will be included in the final trial analysis.
All trial staff will have a duty of confidentiality to participants in the Keralink trial

7.7 Declaration of Interests

The investigators named on the protocol have no financial or other competing interests that impact on their responsibilities towards the scientific value or potential publishing activities associated with the trial.

7.8 Indemnity

UCL holds insurance to cover participants for injury caused by their participation in the clinical trial. Participants may be able to claim compensation if they can prove that UCL has been negligent. However, as this clinical trial is being carried out in a hospital, the hospital continues to have a duty of care to the participant in the clinical trial. UCL does not accept liability for any breach in the hospital's duty of care, or any negligence on the part of hospital employees. This applies whether the hospital is an NHS Trust or not. This does not affect the participant's right to seek compensation via the non-negligence route.

Participants may also be able to claim compensation for injury caused by participation in this clinical trial without the need to prove negligence on the part of UCL or another party. Participants who sustain injury and wish to make a claim for compensation should do so in writing in the first instance to the Chief Investigator, who will pass the claim to UCL's insurers, via the Sponsor's office.

Hospitals selected to participate in this clinical trial shall provide clinical negligence insurance cover for harm caused by their employees and a copy of the relevant insurance policy or summary shall be provided to UCL, upon request.

7.9 Finance

Keralink is fully funded by an NIHR EME grant number 14/23/18. It is not expected that any further external funding will be sought unless it is decided to extend follow-up beyond 18 months.

7.10 Archiving

The investigators agree to archive and/or arrange for secure storage of Keralink trial materials and records for a minimum of 5 years after the close of the trial unless otherwise advised by the CCTU.

7.11 Access to Data

Requests for access to trial data will be considered, and approved in writing where appropriate, after formal application to the TMG/TSC. Considerations for approving access are documented in the TMG/TSC Terms of Reference.

7.12 Ancillary and Post-trial Care

Once the trial has come to an end any further treatment to trial participants will be provided as per the standard of care at the local sites.

7.13 Publication Policy

7.13.1 Trial Results

The results of the trial will be disseminated regardless of the direction of effect and reported in accordance with the CONSORT guidance.

Trial findings will be disseminated to all potential beneficiaries of the research including patients, carers and relatives, and also doctors, advisory bodies and health care Commissioners. This will take the form of papers in high impact open access (included in the budget) medical journals and also presentations at national and international medical conferences. We will seek publication of the trial protocol once finalised. Trial results will also be disseminated to the trial patients in a one-page summary written in lay language.

7.13.2 Authorship

Publications generated from the trial will be attributed to the Keralink Trial Management Group, which will consist of all those who have wholeheartedly collaborated in the trial. The main report will be drafted by the TMG, and the final version will be reviewed by the TSC before submission for publication. TMG members will be named and their affiliations listed in the main report. All publications will be in compliance with the CCTU Publication Policy.

8 Ancillary Studies

There are no ancillary studies. Any proposal for ancillary studies will need to be approved by the TSC.

9 Protocol Amendments

Amendment 1

In response to REC and MHRA feedback after initial submissions. Updates made to expected events and use of translators.

Amendment 2: Summary of Changes to Protocol V3.0 dated 05 August 2016

1.	Section 1.3 and 6.3.1.2 – Change to inclusion criteria to include patients with Pentacam and non-Pentacam topography scanning technique to record progression
2.	Section 1.3 and 6.3.1.2 - Added text to the Inclusion Criteria: Patients and their parents/guardians must be sufficiently fluent in English to provide assent and informed consent and to complete the patient reported outcome measures.
3.	Section 1.3 and 6.3.1.3 – Change to exclusion criteria 3. Maximum corneal curvature (Kmax)>62 dioptres
4.	Section 1.3 and 6.5.1 – Primary Outcome: Clarified the definition of study eye
5	Section 1.3 and 6.5.2 – Secondary Outcome: Clarified Time to Keratoconus progression
6.	Section 6.9.2 – Added text to Masking: Principal Investigator or treating clinician will be masked to the Kmax values measured during the follow up assessments (3,6,9,12,15,18 and 21 month follow up)
7	Section 6.11.3.1 - Clarification on reporting of SAE's and AE's and their definitions.
8.	Administrative changes throughout the protocol

10 References

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