GIG CYMRU NHS WALES

Pwyllgor Gwasanaethau Iechyd Arbenigol Cymru (PGIAC)

Welsh Health Specialised Services Committee (WHSSC)

Specialised Services Commissioning Policy: CP271

Corneal Cross-linking for Keratoconus in Children (from birth until their 16th birthday)

October 2023

Version 1.0

PARCH - RESPECT

PARTNERIAETH - PARTNERSHIP

GWELLA AC ARLOESI - IMPROVEMENT & INNOVATION

Document information	
Document purpose	Commissioning Policy
Document name	**Corneal Cross-linking for Keratoconus in Children (from birth until their 16th birthday)**
Author	Welsh Health Specialised Services Committee
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Commissioning Team	Women & Children
Target audience	Chief Executives Medical Directors Directors of Finance Consultant Ophthalmologists
Description	NHS Wales will routinely commission this specialised service in accordance with the criteria described in this policy
Document No	CP271
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Contents

Policy Statement

Welsh Health Specialised Services Committee (WHSSC) will commission corneal cross-linking for children (aged under 16 years) with keratoconus in accordance with the criteria outlined in this document.

In creating this document WHSSC has reviewed this clinical condition and the options for its treatment. It has considered the place of this treatment in current clinical practice, whether scientific research has shown the treatment to be of benefit to patients, (including how any benefit is balanced against possible risks) and whether its use represents the best use of NHS resources.

Welsh Language

WHSSC is committed to treating the English and Welsh languages on the basis of equality, and endeavour to ensure commissioned services meet the requirements of the legislative framework for Welsh Language, including the Welsh Language Act (1993), the Welsh Language (Wales) Measure 2011 and the Welsh Language Standards (No.7) Regulations 2018.

Where a service is provided in a private facility or in a hospital outside of Wales, the provisions of the Welsh language standards do not directly apply but in recognition of its importance to the patient experience the referring health board should ensure that wherever possible patients have access to their preferred language.

In order to facilitate this, WHSSC is committed to working closely with providers to ensure that in the absence of a Welsh speaker, written information will be offered and people have access to either a translator or 'Language-line' if requested. Where possible, links to local teams should be maintained during the period of care.

Decarbonisation

WHSSC is committed to taking assertive action to reducing the carbon footprint through mindful commissioning activities. Where possible and taking into account each individual patient's needs, services are provided closer to home, including via digital and virtual access, with a delivery chain for service provision and associated capital that reflects the WHSSC commitment.

Disclaimer

WHSSC assumes that healthcare professionals will use their clinical judgment, knowledge and expertise when deciding whether it is appropriate to apply this policy.

This policy may not be clinically appropriate for use in all situations and does not override the responsibility of healthcare professionals to make

decisions appropriate to the circumstances of the individual patient, in consultation with the patient and/or their carer or guardian, or Local Authority.

WHSSC disclaims any responsibility for damages arising out of the use or non-use of this policy.

1. Introduction

This commissioning policy has been developed as a Policy Position for the planning and delivery of corneal cross-linking for keratoconus for children (from birth until their 16th birthday) who are resident in Wales. This service will only be commissioned by the Welsh Health Specialised Services Committee (WHSSC) and applies to residents of all seven Health Boards in Wales.

WHSSC only has commissioning responsibility for paediatric ophthalmology, and therefore this policy only covers children from birth until their 16th birthday. Health Boards are responsible for commissioning corneal cross-linking for keratoconus for adults and young people aged 16 years and above.

1.1 Plain Language Summary

Keratoconus is an eye condition characterised by a progressive thinning and distortion of the cornea, causing a cone-shaped bulge to develop. The cornea is the major focussing surface of the eye. This results in vision problems such as short-sightedness, blurred vision, astigmatism or light sensitivity[1]. The condition typically develops in children and young adults and can progress over time. If left untreated, progressive keratoconus may ultimately require corneal transplantation.

Corneal cross-linking uses ultraviolet light with riboflavin dye to stiffen the cornea[1]. It works by creating new chemical linkages within and between the proteins in the corneal stroma (a layer of the cornea)[2],[3].

1.2 Aims and Objectives

This policy aims to define the commissioning position of WHSSC on the use of corneal cross-linking for children (from birth until their 16th birthday) with keratoconus.

[1] Wollensak G, Spoerl E, Seiler T. (2003). Stress-strain measurements of human and porcine corneas after riboflavin-ultraviolet-A-induced cross-linking. Journal of Cataract and Refractive Surgery. 29(9): 1780-5

[2] Hayes S, Kamma-Lorger CS, Boote C, Young RD, Quantock AJ, et al. The Effect of Riboflavin/UVA Collagen Cross-linking Therapy on the Structure and Hydrodynamic Behaviour of the Ungulate and Rabbit Corneal Stroma. PLOS ONE. 2013; 8(1):e52860. https://doi.org/10.1371/journal.pone.0052860

[3] Zhang Y, Conrad AH, Conrad GW. Effects of ultraviolet-A and riboflavin on the interaction of collagen and proteoglycans during corneal cross-linking. J Biol Chem. 2011 Apr 15;286(15):13011-22. doi: 10.1074/jbc.M110.169813

The objectives of this policy are to:

- ensure commissioning for the use of corneal cross-linking is evidence based
- ensure equitable and timely access to corneal cross-linking
- define criteria for people with keratoconus to access treatment
- improve outcomes for people with keratoconus

1.3 Epidemiology

There are no universal criteria for keratoconus diagnosis, meaning it is challenging to assess its prevalence. Furthermore, there are no direct estimates of the incidence or prevalence of the disease in Wales. Two recent studies in Australia[4] and the Netherlands[5] estimated prevalence of keratoconus as 1.2% and 0.27% respectively. Both estimates are higher than previous population estimates, although they are based on newly diagnosed cases and it is not clear what proportion of all keratoconus cases are progressive. It is not known whether this is attributable to an increasing incidence of the condition or better recognition and reporting. Keratoconus may be more common in ethnic groups such as Indian and Pakistani populations, and family history is also associated with the condition, suggesting that genetic factors may be involved[6]. Environmental factors such as allergies, asthma, eczema and chronic eye rubbing, are also associated with keratoconus. Several reports also describe an association with Down's syndrome, Leber's congenital amaurosis (a degenerative retinal disease) and mitral valve prolapse.

1.4 Current Treatment

Treatment options available for progressive keratoconus are limited. In early or mild keratoconus, changes to the vision can be corrected with glasses. As the condition progresses, frequent spectacle prescription changes are common, and in more advanced cases only soft or rigid gas permeable contact lenses can correct irregular astigmatism. In the UK, these lenses are often only supplied in a hospital contact lens service, requiring a minimum of annual follow up in clinic. Additionally, lenses are not universally tolerated and can be considered uncomfortable. Both these factors can have an adverse effect on quality of life, while placing significant burden on the hospital eye service since these patients require lifelong follow up.

[4] Chan E, Chong EW, Lingham G, et al. (2021). Prevalence of keratoconus based on Scheimpflug imaging: The Raine Study. Ophthalmology. 128(4): 515-21

[5] Godefrooij DA, de Wit GA, Uiterwaal CS, et al. (2017a). Age-specific incidence and prevalence of keratoconus: a nationwide registration study. American Journal of Ophthalmology. 175: 169-72

[6] Rabinowitz YS. (1998). Keratoconus. Survey of Ophthalmology. 42(4): 297-319

If left untreated, and where vision can no longer be corrected with glasses or contact lenses, progressive keratoconus can lead to cornea scarring and may ultimately require corneal transplantation. This involves grafting a cornea from a donor, of which there are a shortage in the UK[7]. Some eyes (estimates suggest around 50%) still require the use of rigid contact lenses after corneal transplantation[8]. As keratoconus affects relatively young people, multiple repeat grafts may be required during their lifetime, and there is a reduction in graft survival with each successive graft[9].

Reported estimates of the proportion of untreated eyes with keratoconus that require corneal transplant range from 8% to 32%; reports of mean time from referral to corneal surgery range from 3 to 8 years. As with progression, time to and requirement for transplant were found to be dependent on age, and also initial disease severity[10].

1.5 Proposed Treatment

Corneal cross-linking (CXL) is a procedure that is used to treat keratoconus that is progressive. Riboflavin (vitamin B2) drops are administered to the cornea in conjunction with ultraviolet light, making a photochemical reaction that stiffens and stabilise the corneal tissue. The aim of the procedure is to stop or at least slow the progression of keratoconus[11]. If disease progression continues after CXL, the treatment can be repeated.

The standard CXL procedure usually follows the Dresden protocol[12]. This is an 'epithelium-off' procedure: the epithelium of the cornea is removed to allow penetration of riboflavin into the corneal tissue. The Dresden protocol involves anaesthetising the eye, removing the central 8-10mm of the epithelium and applying a riboflavin solution to the corneal surface 30 minutes before irradiation and at 5 minutes intervals during the course of a 30 minute exposure to 370 nm UVA with an irradiance of 3 mW/cm^2.

More recently, an accelerated treatment protocol has been introduced which uses higher intensity UV light (9 mW/cm^2) but a shorter irradiation duration (10 minutes). This accelerated treatment protocol maintains the total radiant exposure within a shortened time period. This accelerated protocol has become more preferable in paediatric patients as it enables

[7] Romano V, Dinsdale M, Kaye S. (2019). Compensating for a shortage of corneal donors after Brexit. Lancet. 394(10200): 732

[8] Geerards AJ, Vreugdenhil W, Khazen A. (2006). Incidence of rigid gas-permeable contact lens wear after keratoplasty for keratoconus. Eye & Contact Lens. 32(4): 207-10

[9] Aboshiha J, Jones MNA, Hopkinson CL, Larkin DFP. Differential Survival of Penetrating and Lamellar Transplants in Management of Failed Corneal Grafts. *JAMA Ophthalmol.* 2018;136(8):859–865. doi:10.1001/jamaophthalmol.2018.1515

[10] Ferdi AC, Nguyen V, Gore DM, et al. (2019). Keratoconus natural progression: a systematic review and meta-analysis of 11 529 eyes. Ophthalmology. 126(7): 935-45

[11] Maier P, Reinhard T, Kohlhaas M. (2019). Corneal collagen cross-linking in the stabilization of keratoconus. Deutsches Arzteblatt International. 116(11): 184-90

[12] Pediatric Crosslinking: Current Protocols and Approach - PubMed (nih.gov)

treatment of very young patients under topical anaesthesia. In a recent retrospective comparison, the accelerated approach was equally as effective as the conventional protocol to treat paediatric keratoconus[13].

After treatment, antibiotic eye drops are applied and a therapeutic soft contact lens with good oxygen transmissibility is placed upon the eye to decrease pain without decreasing the quality of the re-growing epithelium. Application of topical antibiotics is required for one week after the operation and mild steroids may also be prescribed. Patients are usually pain-free within 5 to 7 days, when the contact lens is removed.

1.6 What NHS Wales has decided

WHSSC has carefully reviewed the evidence of CXL for keratoconus. We have concluded that there is enough evidence to fund the use of CXL within the criteria set out in section 2.1.

1.7 Relationship with other documents

This document should be read in conjunction with the following documents:

- **NHS Wales**
  - All Wales Policy: Making Decisions in Individual Patient Funding requests (IPFR).

- **Other published documents**
  - Health Technology Wales Guidance 002-2 Corneal cross-linking to treat adults and children with keratoconus March 2021

[13] https://pubmed.ncbi.nlm.nih.gov/28864070/

2. Criteria for Commissioning

The Welsh Health Specialised Services Committee approve funding of corneal cross-linking for children (from birth until their 16th birthday) with keratoconus in line with the criteria identified in this policy.

2.1 Inclusion Criteria

- Age <16 years old; **and**
- Confirmed progression on analysis of serial corneal tomography in one or more of the indices of corneal shape in Table 1 below for both early keratoconus and moderate to advanced keratoconus. Where possible, the mean of three scans at each visit should be considered when making comparisons.

Table 1: Indices of corneal shape[14]

Early keratoconus (K_{MAX} <55D)	**Mod./Advanced keratoconus (K_{MAX} ≥55D)**
≥ 1D increase K_{MAX}	≥ 2.5D increase K_{MAX}
≥ 1D increase anterior K2 or K1	≥ 2.5D increase anterior K2 or K1
≥ 0.5D increase posterior K2	≥ 22 µm decrease minimum thickness
≥ 16 µm decrease minimum thickness	

Other valid inclusion criteria in the absence of progression on shape indices alone:

- Confirmed progression following interpretation of elevation data (for example, tomography maps), even in the absence of progression of the indices in Table 1
- History of progression described in the referral letter based on serial topography/tomography or loss of corrected vision
- Previous Laser-Assisted In-Situ Keratomileusis (LASIK) with ectasia
- Minimum corneal thickness <400um at presentation
- Advanced fellow eye that either:
    - has had previous hydrops
    - has had previous corneal graft
    - is too thin for treatment

[14] KC Clinic Protocol v4.0.pdf

2.2 Exclusion Criteria

- aged 16 years and above
- poor visual potential (e.g., significant scarring)
- corneal thickness of <325 microns
- severely uncontrolled ocular atopy
- pregnancy
- breastfeeding

2.3 Acceptance Criteria

The service outlined in this policy is for patients ordinarily resident in Wales, or otherwise the commissioning responsibility of the NHS in Wales. This excludes patients who whilst resident in Wales, are registered with a GP practice in England, but includes patients resident in England who are registered with a GP Practice in Wales.

2.4 Patient Pathway

Referrals to the corneal cross-linking service will be accepted in line with the inclusion criteria listed in 2.1 above from opticians, GPs or other eye units.

2.5 Transition Arrangements

Transition arrangements should be in line with Transition from children's to adults' services for young people using health or social care services NICE guidance NG43 and the Welsh Government Transition and Handover Guidance.

Transition involves a process of preparation for young people and their families for their transition to adulthood and their transition to adult services. This preparation should start from early adolescence 12-13 year olds. The exact timing of this will ideally be dependent on the wishes of the young person but will need to comply with local resources and arrangements.

The transition process should be a flexible and collaborative process involving the young person and their family as appropriate and the service.

The manner in which this process is managed will vary on an individual case basis with multidisciplinary input often required and patient and family choice taken into account together with individual health board and environmental circumstances factored in.

2.6 Designated Centre

To be determined.

2.7 Exceptions

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If the patient wishes to be referred to a provider outside of the agreed pathway, an IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

2.8 Clinical Outcome and Quality Measures

The Provider must work to written quality standards and provide monitoring information to the lead commissioner.

The Provider must enable the patient's, carer's and advocate's informed participation and be able to demonstrate this. Provision should be made for patients with communication difficulties and for children and teenagers. Data on the following key outcomes should be routinely collected and reported to WHSSC:

- Changes in maximal keratometry
- Changes in corneal power/thickness
- Changes in (corrected or uncorrected) visual acuity
- Health related quality of life
- Rate of disease progression
- Time to requiring further treatment
- Adverse events

2.9 Responsibilities

Referrers should:

- inform the patient that this treatment is not routinely funded outside the criteria in this policy, and
- refer via the agreed pathway.

Clinicians considering treatment should:

- discuss all alternative treatments with the patient;
- advise the patient of any side effects and risks of the potential treatment
- inform the patient that treatment is not routinely funded outside of the criteria in the policy, and
- confirm that there is contractual agreement with WHSSC for the treatment.

In all other circumstances an IPFR must be submitted.

3. Evidence

WHSSC is committed to regularly reviewing and updating all of its commissioning policies based upon the best available evidence of both clinical and cost effectiveness.

The evidence of clinical and cost effectiveness to support the decision by WHSSC to commission corneal crosslinking (CXL) to treat children with keratoconus was based on guidance published by Health Technology Wales (HTW) in May 2021[15].

The HTW evidence review was presented to the WHSSC Prioritisation Panel in July 2021 who recommended CXL to treat children with keratoconus as a high priority. Funding was approved in the 2022-2025 WHSSC Integrated Commissioning Plan.[16]

HTW guidance evidence summary

HTW searched for and appraised evidence on the clinical and cost effectiveness of CXL in people with progressive keratoconus. Evidence on CXL procedures that involve removing the corneal epithelium (to allow eye drops to penetrate the cornea) during the procedure (known as 'epithelium-off' CXL) was considered. Two systematic reviews of randomised controlled trials provided evidence on outcomes after CXL compared to no treatment.

The results suggest keratoconus progression is less likely after CXL than in untreated eyes at 18 or 36 months. The same sources of evidence suggest that 12 months after treatment, CXL-treated eyes have improvements in maximum keratometry (Kmax, a measurement of corneal curvature frequently used as an indicator of disease progression) and visual acuity compared to untreated eyes. These results suggest that in addition to changes in disease progression, CXL may reduce distortion of the cornea and thereby improve vision, although the design of the studies and reliability of the evidence means these conclusions should be interpreted cautiously

Evidence on outcomes beyond 36 months (the maximum follow-up time used in the randomised controlled trials) was assessed using observational studies. These reported rates of progression ranging from 0 to 20% in adults and 0 to 25% in children following CXL treatment, with follow up times ranging from 3 to 10 or more years. The majority of observational studies also reported that mean improvements in Kmax and visual acuity after CXL were sustained in the long term.

[15] https://healthtechnology.wales/reports-guidance/corneal-cross-linking/
[16] https://whssc.nhs.wales/publications/integrated-commissioning-plan/integrated-commissioning-plan-2022-2025/integrated-commissioning-plan-2022-2025/

An economic analysis developed by HTW to consider the cost-effectiveness of CXL in the UK NHS setting found CXL to be more effective but more costly than standard care. Whether CXL can be considered cost-effective in cost per QALY terms was found to be heavily dependent upon the assumption around the duration of treatment effect with CXL. In the base case, where it was assumed that patients would progress as if untreated after 10 years, CXL was not found to be cost-effective at a threshold of £20,000 per QALY. However, threshold analysis showed that CXL became cost-effective at £20,000 per QALY, with a CXL treatment effect duration of 14 years or more.

3.1 Date of Review

This document is scheduled for review in 2026, where we will check if any new evidence is available. If no new evidence or intervention is available, the review date will be progressed.

If an update is carried out the policy will remain extant until the revised policy is published.

4. Equality Impact and Assessment

The Equality Impact Assessment (EQIA) process has been developed to help promote fair and equal treatment in the delivery of health services. It aims to enable Welsh Health Specialised Services Committee to identify and eliminate detrimental treatment caused by the adverse impact of health service policies upon groups and individuals for reasons of race, gender re-assignment, disability, sex, sexual orientation, age, religion and belief, marriage and civil partnership, pregnancy and maternity and language (Welsh).

This policy has been subjected to an Equality Impact Assessment in line with guidance contained in CPL-026[17].

The Assessment demonstrates the policy is robust and there is no potential for discrimination or adverse impact. All opportunities to promote equality have been taken.

[17] https://whssc.nhs.wales/publications/corporate-policies-and-procedures/corp-026-eqia-policy/

5. Putting Things Right:

5.1 Raising a Concern

Whilst every effort has been made to ensure that decisions made under this policy are robust and appropriate for the patient group, it is acknowledged that there may be occasions when the patient or their representative are not happy with decisions made or the treatment provided.

The patient or their representative should be guided by the clinician, or the member of NHS staff with whom the concern is raised, to the appropriate arrangements for management of their concern.

If a patient or their representative is unhappy with the care provided during the treatment or the clinical decision to withdraw treatment provided under this policy, the patient and/or their representative should be guided to the LHB for NHS Putting Things Right. For services provided outside NHS Wales the patient or their representative should be guided to the NHS Trust Concerns Procedure, with a copy of the concern being sent to WHSSC.

5.2 Individual Patient Funding Request (IPFR)

If the patient does not meet the criteria for treatment as outlined in this policy, an Individual Patient Funding Request (IPFR) can be submitted for consideration in line with the All Wales Policy: Making Decisions on Individual Patient Funding Requests. The request will then be considered by the All Wales IPFR Panel.

If an IPFR is declined by the Panel, a patient and/or their NHS clinician has the right to request information about how the decision was reached. If the patient and their NHS clinician feel the process has not been followed in accordance with this policy, arrangements can be made for an independent review of the process to be undertaken by the patient's Local Health Board. The ground for the review, which are detailed in the All Wales Policy: Making Decisions on Individual Patient Funding Requests (IPFR), must be clearly stated

If the patient wishes to be referred to a provider outside of the agreed pathway, and IPFR should be submitted.

Further information on making IPFR requests can be found at: Welsh Health Specialised Services Committee (WHSSC) | Individual Patient Funding Requests

Annex ii Codes

Code Category	Code	Description
ICD-10	H18.6	Keratoconus
OPCS-4	C51.8	Other specified operation on cornea

Annex iii Abbreviations and Glossary

Abbreviations

CXL Corneal Cross-Linking

IPFR Individual Patient Funding Request

LASIK Laser-Assisted In-Situ Keratomileusis

WHSSC Welsh Health Specialised Services Committee

Glossary

Individual Patient Funding Request (IPFR)
An IPFR is a request to Welsh Health Specialised Services Committee (WHSSC) to fund an intervention, device or treatment for patients that fall outside the range of services and treatments routinely provided across Wales.

Welsh Health Specialised Services Committee (WHSSC)
WHSSC is a joint committee of the seven local health boards in Wales. The purpose of WHSSC is to ensure that the population of Wales has fair and equitable access to the full range of Specialised Services and Tertiary Services. WHSSC ensures that specialised services are commissioned from providers that have the appropriate experience and expertise. They ensure that these providers are able to provide a robust, high quality and sustainable services, which are safe for patients and are cost effective for NHS Wales.