Technoleg Iechyd Cymru
Health Technology Wales

HEALTH TECHNOLOGY WALES (HTW) GUIDANCE 002-2 (March 2021)

Corneal cross-linking to treat adults and children with keratoconus

HTW Guidance:

The evidence supports the routine adoption of corneal cross-linking (CXL) for children and adults with progressive keratoconus. Compared to standard care, CXL slows disease progression and may improve visual acuity. It may also reduce or delay the need for corneal transplantation.

Economic modelling suggests that CXL is cost effective on the basis of an assumed sustained clinical benefit for at least 14 years.

HTW recommends the acquisition of real word data to capture long-term outcomes (including patient-reported outcomes measures) in people who have CXL for keratoconus.

The status of HTW guidance is that NHS Wales should adopt this guidance or justify why it has not been followed. HTW will evaluate the impact of its guidance.

Why did Health Technology Wales (HTW) appraise this topic?

Keratoconus is an eye condition characterised by progressive thinning and distortion of the cornea, causing a cone-shaped bulge to develop. This can lead to blurred vision, short-sightedness and sensitivity to light or glare. It typically develops in children and young adults and can deteriorate over time. If this deterioration continues and is untreated, some people with keratoconus require corneal transplantation to restore their vision. Corneal cross-linking (CXL), is a procedure that uses riboflavin eye drop medication combined with ultraviolet light treatment to stiffen and strengthen the cornea, and slow or stop progression of keratoconus.

HTW originally issued Guidance on CXL to treat keratoconus in February 2018. HTW Guidance is periodically updated when necessary. Following consultation with Optometry Wales and the UK Cross-linking Consortium, HTW agreed it was appropriate to issue updated Guidance, due to substantial changes to the evidence base since the original Guidance was issued.

Evidence Summary

Refer to Evidence Appraisal Report 002-2 (EAR002-2) for a full report of the evidence supporting this Guidance.

HTW researchers 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.

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.

The appropriate mechanism for patient engagement was determined and the patient perspective was considered via a written submission from the Keratoconus Group.

Appraisal Panel considerations

- The Appraisal Panel learnt about experiences collected from patients with keratoconus through a patient organisation. These highlighted the challenges of living with keratoconus and its negative impact on quality of life as a result of reduced visual acuity, such as loss of independence and inability to work, as well as the difficulty and discomfort involved in wearing specialist contact lenses to correct impaired visual acuity.
- The Appraisal Panel heard from clinical experts about the challenges associated with managing keratoconus. They explained that if people do not have access to CXL, the symptoms of keratoconus can only be managed by vision correction (specialist glasses and contact lenses), which can be difficult due to the specialist nature of the lenses needed, the requirement to update these as disease progresses, and the discomfort associated with their use.
- Experts informed the panel that CXL is a relatively simple procedure that can usually be performed as an outpatient procedure and requires minimal follow up after treatment. Experts advised that if keratoconus is left untreated, corneal transplantation may eventually be needed to restore and preserve visual acuity. This is a more complex procedure and relies

on the availability of donor corneas, of which there is a shortage. Experts also emphasised that patients may be reluctant to undergo corneal transplantation due to the risks of the surgery.

- The Appraisal Panel considered the likely duration of treatment effect after CXL, which was found to be a key consideration in determining cost effectiveness. Experts explained that the mechanistic treatment effect of CXL in structurally stabilizing the cornea is unlikely to reverse with time. The Panel noted that this is consistent with the evidence available from long-term observational studies up to 10 years after treatment which indicate that benefits are sustained in most patients. The Appraisal Panel concluded that while it may not be possible to estimate the timing or rate of disease progression with precision following CXL in individual patients, it is reasonable to assume that this is durable and that long-term benefits will be achieved beyond 14 years.
- The Appraisal Panel considered the criteria for treatment of keratoconus with CXL from the evidence and were also advised by the clinical experts about this. It was noted that most of the evidence was gathered in people with keratoconus in whom disease progression was confirmed before they were deemed eligible for treatment, but that there are no universally accepted criteria for determining keratoconus progression. Experts also explained that in their clinical practice, some cases of keratoconus are treated as soon as they are detected rather than waiting to confirm progression. One example is in children, in whom disease progression is usually rapid. On balance, the Appraisal Panel concluded that CXL should be offered to patients in whom disease progression has been established.
- The Appraisal Panel considered the use of CXL to treat children as well as adults with keratoconus. Whilst there is less evidence available on the effectiveness of CXL in children, the experts advised that mechanistically, there is no reason to believe CXL is any less effective in children than in adults. The Panel concluded that CXL treatment should be offered to children as well as adults with progressive keratoconus.
- The Appraisal Panel concluded that the current evidence supports the clinical effectiveness of CXL to treat keratoconus in children and adults and that the treatment benefits are likely to be sustained in most patients. Furthermore, on the assumption of a benefit beyond 14 years, the Panel concluded that this is likely to be a cost effective treatment through the avoidance of the need for future treatments including corneal transplantation.
- The Appraisal Panel discussed the need for further research into the effectiveness of CXL. It was agreed that long term effectiveness should be monitored as this is a key consideration in determining clinical and cost effectiveness and some uncertainty remains about this. The Appraisal Panel recommend that real world data be accumulated to monitor the long-term effectiveness of CXL and that patient reported outcome measures should be included in data collected.

Responsibilities for consideration of this Guidance

Health Technology Wales (HTW) was established by Ministerial recommendation[1,2] to support a strategic, national approach to the identification, appraisal and adoption of non-medicine health technologies into health and care settings. The HTW Appraisal Panel comprises senior representation from all Welsh boards with delegated authority to produce guidance 'from NHS Wales, for NHS Wales'. The status of HTW guidance is 'adopt or justify'. There is an expectation from Welsh Government that HTW guidance is implemented with adoption regularly audited by HTW.[3]

The guidance in this document is intended to assist Welsh care system decision makers to make evidence-informed decisions when determining the place of health technologies and thereby improve the quality of care services.

The content of this HTW guidance was based upon the evidence and factors available at the time of publication. An international evidence base was reviewed and external topic experts and HTW committee members consulted to contextualise available evidence to Wales. Readers are asked to consider the generalisability of the evidence reviewed to NHS Wales and that new trials and technologies may have emerged since first publication and the evidence presented may no longer be current. It is acknowledged that evidence constitutes only one of the sources needed for decision making and planning.

This guidance does not override the individual responsibility of health professionals to make decisions in the exercise of their clinical judgment in the circumstances of the individual patient, in consultation with the patient and/or guardian or carer.

No part of this guidance may be used without the whole of the guidance being quoted in full. This guidance represents the view of HTW at the date noted. HTW guidance is not routinely updated. It may, however, be considered for review if requested by stakeholders, based upon the availability of new published evidence which is likely to materially change the guidance given.

Standard operating procedures outlining HTWs evidence review methods and framework for producing its guidance are available from the HTW website.

Acknowledgements. HTW would like to thank the individuals and organisations who provided comments on the draft Evidence Appraisal Report or HTW guidance.

Declarations of interest were sought from all reviewers. All contributions from reviewers were considered by HTWs Assessment Group. However, reviewers had no role in authorship or editorial control and the views expressed are those of Health Technology Wales.

Chair, Health Technology Wales Appraisal Panel

1. National Assembly for Wales, Health and Social Care Committee. Access to medical technologies in Wales. December 2014.
2. Response to Recommendations from the Health & Social Care Committee: Inquiry into Access to Medical Technologies in Wales. February 2015.
3. Gething, V. Letter to all Health Board Chairs re Funding for Sacral Nerve Stimulation in Wales. VG_01655_17. September 2017.