National Institute for Health and Clinical Excellence

[IP724/2] – [Photochemical corneal cross linkage using riboflavin and ultraviolet A for keratoconus and keratectasia]

Consultation Comments table

IPAC date: [Thursday July 11th 2013]

Com. no.	Consultee name and organization	Sec. no.	Comments	Response Please respond to all comments
1	Consultee 1 Royal College of Ophthalmologists	**1**	While available publications are encouraging and indicate potential benefits of treatment, efficacy is not proven and the guidelines should draw attention to important limitations of studies; there are relatively few in total, sample sizes are small and in many, follow up is short. Trial design can be poor with some being no more than observational case series. Also, the criteria analysed are mostly parameters of corneal shape with unproven relevance to patient benefit - particularly the anticipated long-term aim of preventing corneal surgery. Study numbers are bolstered by combining keratoconus and kerectasia without regard to potentially different underlying mechanisms. In conclusion, a definitive controlled trial based on patient benefit with attention to appropriate treatment protocols is required before cross linkage can be classified as effective.	Thank you for your comment. The Committee considered your comment and chose not to amend the guidance recommendations. The recommendations (1.1 & 1.2) in the guidance are based on a full systematic review of literature commissioned by NICE. This review acknowledged several limitations of the current evidence base for the efficacy and safety of epithelium-off CXL alone, in combination with therapies designed to improve visual acuity and transepitheial (epithelium-on) CXL. IPAC took into account the overall evidence on efficacy and safety and came up with the current recommendations. In 1.6 of the guidance NICE also encourages further research on CXL procedures.

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2	Consultee 1 Royal College of Ophthalmologists	**1.4**	1.4 There is uncertainty about repeatability of measurements. Until this work is completed it is difficult to define ‘progression’.	Thank you for your comment. The Committee considered the use of the terms ‘progressive’ and ‘adequate’ in 1.4 and amended it to state that ‘Patient selection should include assessment of corneal thickness and consideration of the likelihood of disease progression’.
3	Consultee 2 Patient	**1.4**	On para 1.4, the definition of 'progressive' might be difficult. In some advanced keratoconus cases CXL on a stable but steep eye; could allow the use of contact lenses where otherwise a transplant would be the only option.	Thank you for your comment. IPAC values hearing comments from patients. Please see response to comment 2 for amended version of 1.4.
4	Consultee 3 NHS Professional	**1.4**	I'm interested that the terms "progressive keratoconus" and "adequate corneal thickness" have no numerical values attached. Should NICE define what is meant by "progressive" and "adequate"?	Thank you for your comment. Please see response to comment 2 for amended version of 1.4.
5	Consultee 4 NHS professional	**1.4**	1.4 Defining criteria for disease progression is problematic (see Gore DM, Shortt AJ, Allan BD. New clinical pathways in keratoconus. Eye 2013 Mar;27(3):329-39.) Our current criteria at Moorfields based on repeatability limits for Pentacam tomography include: >1.5D increase (Kmax or K2), >13Âµm thinning. Rigid CLs out 2 weeks; soft CLs 1 week prior to each review to reduce corneal warpage. Alternate criteria are needed for patients who cannot manage without contact lenses.	Thank you for your comment. Please see response to comment 2 for amended version of 1.4. Gore et al is a review which was found in our update search. It contained no unique outcome data so not included in the systematic review. However, this was used as a background paper for the report and referenced. We did not look into clinical pathways aspect in our guidance.
6	Consultee 1 Royal College of Ophthalmologists	**1.5**	1.5 It can be performed by a qualified nurse/technician under supervision.	Thank you for your comment. The Committee considered your comment and amended 1.5 to state that ‘The procedures should only be carried out by ophthalmologists with expertise in managing corneal disease and specific training in the use of ultraviolet light or by appropriately trained staff under their supervision’.

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7	Consultee 4 NHS professional	**1.5**	A large number of patients are eligible for CXL and the procedure can be performed safely by appropriately trained nursing staff provided that clear protocols are in place. We are working towards a nurse led pooled CXL service at Moorfields and such a service already exists in Liverpool. Utilising appropriately trained nursing staff should help reduce the cost of the procedure to the NHS and help to avoid diverting busy corneal surgeons away from more complex work in order to absorb the additional workload created. The important caveat is that work should be carried out in specialist units with appropriate expert back-up and arrangements for monitoring vision/corneal shape pre & post CXL.	Thank you for your comments. Please see response to comment 6 for amended version of 1.5. The Committee considered the wording in 1.5 adequately addresses the need for supervision and support.
8	Consultee 5 Private Sector Professional	**1.5**	The procedure has been used successfully down to 250 microns with hypotonic riboflavin. Complications are more likely with thinner corneas, but eyes can change in weeks so treatment could be offered after informed discussion with patients. All doctors who have trained in Zurich on the CXL course should be allowed to undertake the treatment. The specialist register should not be a requirement for this treatment. Doctors on the specialist register have shown by their obstruction that this is a poor guideline.	Thank you for your comments. The Committee considered that paragraph 1.3 details the information that should be passed to patients and their carers about the uncertainty surrounding the safety and efficacy of the procedures in the long term. Please see response to comment 6 for amended version of paragraph 1.5. Paragraph 1.5 currently refers the need for training but IPAC does not specify any training courses. The arrangement for training staff in the use of UV light is for the relevant unit to arrange.

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9	Consultee 1 Royal College of Ophthalmologists	**1.6**	1.6 Further work is required to confirm equivalence of difference treatment protocols for epithelium on and off	Thank you for your comment. Paragraph 1.6 is an encouragement to further research, especially on epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures. The Committee considered your comment and amended 1.6 to state **'**NICE encourages further research into CXL using riboflavin and UVA for keratoconus and keratectasia, especially epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures. Details of the techniques used should be clearly described. Reported outcomes should include visual acuity, corneal topography and quality of life Data on long-term outcomes for all types of CXL using riboflavin and UVA for keratoconus and keratectasia would be useful– specifically data about prevention of progression to corneal transplantation and about repeat procedures and their efficacy'.
10	Consultee 6 Patient	**1**	If progression can be halted with CXL then this is very good news for patients with progressive disease who can just still manage with spectacles or contact lenses as it will significantly improve their chances of remaining in employment and with a good quality of life.	Thank you for your comment. IPAC values hearing comments from patients. It is helpful to hear the potential benefit of this procedure in terms of quality of life and employment. Please also see the Committee's response to comment 12.

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11	Consultee 7 Keratoconus Group	**1**	The Keratoconus Group welcomes the revised guidelines which should ensure that all eligible patients will have access to this procedure on the NHS. In the last few years, very few patients have had access to NHS treatment so it has been largely confined to those who can afford private treatment. This despite many NHS specialists recommending the treatment to their patients, but only able to offer it privately as they have been unable to secure funding. Private health insurers have also been refusing to cover CXL on the grounds that NICE considered it to be 'experimental'. 1.6 We also welcome the encouragement of research into the less invasive epi-on procedure.	Thank you for your comments which support the recommendations of IPAC.

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12	Consultee 7 Keratoconus Group	**2**	Keratoconus can severely affect quality of life, impacting on education, career choices, employment prospects and job retention. While contact lenses can improve the vision, issues such as light sensitivity, halos, ghosting, multiple images mean that vision is still often significantly compromised for many with KC. Limitations on wear time, combined with contact lens dependence (vision no longer improved by glasses) also impact on education, employment and social activities. We have members who have lost their jobs through no longer being able to drive (especially after dark) and difficulties working at a PC screen for extended hours. Halting progression can avoid these problems and the depression that often accompanies them. ICRS only helps a proportion of those with KC. CXL has the potential to avoid the need for corneal surgery and the likelihood of regrafts being needed for young transplant recipients 20 or more years later. Ideally, CXL would be offered before the patient becomes contact lens dependent.	Thank you for your comments. The Committee considered your comment and added a Committee comment (6.4) in section 6 of the guidance as follows: Paragraph 6.4 The Committee noted commentary from a patient group describing the serious impact that can have on employment and quality of life. The Committee recognised the potential benefits that these procedures might offer, if further evidence supports their efficacy.
13	Consultee 1 College of Ophthalmologists	**2.2**	Intra corneal ring segments are rarely used in severe keratoconus, as suggested, but in relatively early disease when there is contact lens intolerance.	Thank you for your comments. The Committee considered your comment and amended 2.2 to state that 'In mild to moderate keratoconus, visual acuity can be corrected using spectacles, contact lenses and in some cases intracorneal ring segment (ICRS) implantation. Keratectasia can be managed by using contact lenses or ICRS. In advanced disease, corneal surgery, including deep lamellar keratoplasty or penetrating keratoplasty, may be needed.

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14	Consultee 3 NHS Professional	**2**	What does "natural degeneration" mean? Keratoconus is a disorder or disease of the cornea. Should there be a brief statement on the known associations, i.e. genetic, allergy, eye rubbing behaviour? - because management of these aspects is vital to good overall care of the sufferer. This section should contain a clear statement that the indication for CXL is stabilisation of vision, with improvement in vision a secondary aim.	Thank you for your comments. Section 2 is intended to be summary of the indications and current treatments and alternatives and it is not intended to include all relevant information. The Committee considered your comment and deleted the word “natural” in 2.1 of the guidance. The Committee considered your comment and included a comment about the aim of the procedure in section 6 as follows: Paragraph6.2 The Committee noted that the primary aim of the procedures is to stabilise vision by halting progression of keratoconus or keratectasia but that many of the studies reported improvement of vision as a secondary outcome**.**
15	Consultee 8 NHS Professional	**3.1**	3.1 CXL can be performed under general anaethesia for progressive Keratoconus in smaller children, patients with intellectual disability or learning difficulties, or other cases when topical or local anaesthesia is not possible. There is no limitation of where it can be performed as outpatient or inpatient, main theatre /day case or in outpatient clinic. However, clean environment and sterility of surgical field is essential.	Thank you for your comment. This section is intended to be a summary of the procedure. The Committee considered your comment and amended 3.1 to state that “The CXL procedures are normally done as outpatient procedures using topical anaesthesia, and typically take 60–90 minutes”.

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16	Consultee 1 Royal College of Ophthalmologists	**3.2**	3.2 With new accelerated protocols the treatment can take less than half an hour. However, there are now several different protocols for performing cross-linking and the original 'Dresden' protocol is not generally used now. For example, there is as yet no evidence that changing the irradiance of the ultraviolet irradiation by a factor of 10 for 'accelerated treatment' to give a shorter treatment time will give a similar outcome. 3.2 The application of riboflavin is usually for a minimum of 20 minutes. There is no evidence as to the efficacy of repeat treatment.	Thank you for your comments. Section 3 is intended to be a summary of the procedure and does not include all the different treatment protocols. Most of the published evidence is around epithelium-off CXL where UV exposure time is usually 30 minutes. Therefore, 3.2 is a description about the epithelium-off CXL method. Also, the evidence on the length of time that riboflavin is applied varied between studies. The Committee considered your comments and amended 3.2 and added a sentence about new accelerated protocols to section 3.2 as follows: In epithelium-off CXL, the epithelium is first abraded with a blunt spatula to allow penetration of riboflavin into the corneal tissue. Riboflavin eye drops are applied to the corneal surface before the procedure and intermittently during the procedure. The corneal surface is exposed to UVA radiation: precise timings and treatment protocols vary. Postoperatively, topical antibiotics and anti-inflammatory drops are normally prescribed, with topical steroids if necessary. In some cases, a bandage contact lens may also be used for a few days. The procedure is done on 1 eye at a time and may also be repeated if needed.
17	Consultee 5 Private Sector Professional	**3.2**	The epithelium can first be loosened with ethanol In some cases, particularly with higher levels of ectasia further progression can occur some years later	Thank you for your comments. Section 3 is a summary of procedure and does not include all the different treatment protocols. Also, see the response to comment 16 for the amended version of 3.2.

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18	Consultee 3 NHS Professional	**3.2**	It appears accelerated protocols for cross linking are gaining popularity. It might be helpful to speak of the approximate total dose of ultraviolet (if this can be stated from current research) required rather than a time period of UV exposure.	Thank you for your comments. See the response to comment 16 for amended version of 3.2.
19	Consultee 8 NHS Professional	**3.2**	3.2 What about accelerated or express CXL which can reduce time of exposure to UVA to 4-10 minutes (depending on the study)? 3.2 This is not accurate: Riboflavin is installed prep either to saturation or with a specified number of drops (every 2 -5 minutes for 30 minutes prior to treatment). please see systematic review for evidence. I also believe that the degree of saturation and frequency of drops pre-operatively can influence the results; this might need to be clarified or reviewed again in the systematic review.	Thank you for your comments. Section 3 is a summary of procedure and does not include all the different treatment protocols. See also the response to comment 16 for the amended version of 3.2.

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20	Consultee 4 NHS Professional	**3.2 & 3**	Soak times and UV exposure parameters vary with some evidence that newer, rapid protocols may be at least as effective as the 30 min soak, 30mins UV at 3mW/cm2 'classic' protocol. Rapid protocols are certainly a more efficient use of clinical time; but most of the evidence base is for the 'classic' protocol. We need to collect good longer term data on newer protocols. In other words, patients need to be monitored at least annually post treatment for 5 years and need to be aware that CXL may need to be repeated if initial treatment fails to halt progression. There is a strong case for developing a national registry of CXL outcomes (similar to corneal transplant outcome registries) to help the evidence base keep up with technical developments in CXL.	Thank you for your comments. Section 3 is a summary of procedure and does not include all the different treatment protocols. See also the response to comment 16 for the amended version of 3.2. Paragraph 1.6 is an encouragement to further research especially on epithelium-on (transepithelial) CXL and the combination (CXL-plus) procedures, and includes a call for long term data. See response to comment 9 for the amended version of 1.6. The Committee also added a Committee comment about newer treatment protocols in section 6 as follows: 6.3 The Committee noted that CXL techniques and precise treatment regimens are continuing to develop and evolve. NICE would welcome steps towards the development of a register.
21	Consultee 1 - Royal College of Ophthalmologists	**3.3**	3.3 and 3.4 Epithelium on treatment is rarely performed in isolation without an additional step to make the epithelium more permeable to riboflavin. This is usually achieved by scratching the corneal epithelium or by the use of drops to chemically disrupt the intercellular boundaries. Thus, although the epithelium is left on, it is usually damaged in some way.	Thank you for your comment. The Committee considered your comment and amended 3.3 to state that ‘In epithelium-on (transepithelial) CXL, the corneal epithelial surface is left intact (or may be partially disrupted) and a longer riboflavin loading time is needed.

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22	Consultee 2 Patient	**3.4**	On para 3.4, to group together multiple 'CXL-plus' procedures seems overly simplistic since they are fairly different. Unless it is to be used as an exclusion term from the main advice?	Thank you for your comment. The techniques were grouped together based on expert clinical advice. The grouping is not intended to suggest that these are similar procedures. The focus in this guidance was on CXL with or without adjunctive procedures and the grouping was to differentiate the studies which used adjunctive procedures.
23	Consultee 8 NHS Professional	**3.4**	3.4 How about CXL with Keraflex and LASIK?	Thank you for your comments. 3.4 lists some examples of adjunctive procedures used in combination with CXL. The Guidance is not intended to be an exhaustive list of available options and variations.
24	Consultee 1 - Royal College of Ophthalmologists	**3.5**	3.5 The mechanism of action is unknown, although it has been proposed that it causes bonding between components of the cornea. The nature of these bonds is unknown.	The Committee considered your comment and amended paragraph 3.5 to state: “The mechanism of action of CXL procedures is not fully understood; they may increase the number of ‘anchors’ that bond collagen fibres together and strengthen the cornea. This is expected to stop the progression of the disease but the duration of benefit is uncertain”.
25	Consultee 8 NHS Professional	**3.5**	3.5 I do not think the mechanism of action of the procedure description is accurate. We still do not fully understand how it works and there are various theories (see Prof Meek and Dr Hersh work)	Thank you for your comment. Please see response to comment 24 for amended version of 3.5.

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26	Consultee 1 Royal College of Ophthalmologists	**4**	In the analysis no distinction made between a change in parameters as a result of cross-linking as opposed to changes caused by the supplementary therapies (laser or lens implantation). Inserting an intraocular lens will obviously change the vision. This distinction needs to be made more clearly.	Thank you for your comments. The systematic review has considered the outcomes from combination procedures delivered either sequentially or simultaneously as a composite intervention and not attributed benefit to the individual components. Thus the outcomes reported are those after treatment with the combined procedures. In several studies which undertook the procedures on the same day, no results were reported for the individual component procedures.
27	Consultee 5 Private Sector Professional	**4**	Epithelium on treatment shows a shallower, lesser effect than epithelium off and was initially used as a way to get around FDA guidelines on this being designated a surgical procedure. While there has been some benefit with some formulae, it is widely accepted that there is less benefit with epithelium on.	Thank you for your comments. The Committee considered the efficacy and safety of both epithelium-off and epithelium-on procedures based on a systematic review of the published literature.
28	Consultee 8 NHS Professional	**4.2**	4.2 It is extremely important to take into consideration the variability in keratomery measurements from visit to visit even when using the same topographer/topographer/keratometer. The error is estimated to be up to +/-1.5 diopter in Kmax i.e. the change of Kmax measurement at 12 month by -1.5 D might not be significant or indicative of improvement.	Thank you for your comments. The variability in keratometry measurements is indeed a limiting factor in interpreting data within each study. The meta-analysis is seeking to provide a quantitative synthesis of the reported means and standard deviations or standard errors reported across 18 studies. It is reporting statistically significant change to provide readers with a descriptive statistic on the direction and magnitude of change and the likelihood that it arose because of the procedure. The changes may or may not be clinically significant.
29	Consultee 8 NHS Professional	**4.4**	4.4 The same principle apply here, refraction or measurement of astigmatism can be variable in keratoconus patients and a change of 0.5 D would not be significant.	Thank you for your comments. See response to comment 28.

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30	Consultee 8 NHS Professional	**4.5**	4.5 Is 14.4 micrometer a significant change in pachymetry? Also the systematic review describes poor evidence in relation to IOP and no conclusion can be drawn.	Thank you for your comments. Yes, change was statistically significant; the 95% confidence intervals were -25.9 to -3 micrometres.
31	Consultee 7 Keratoconus Group	**4.5**	Is 4.5 (a decrease in corneal thickness) correct?	Thank you for your comments. Yes, the value quoted is correct. 'The meta-analysis included 6 studies and reported a significant decrease of -14.4 micrometres in central corneal thickness. There was considerable variation across the studies, the 95% confidence intervals were -25.9 to -3 micrometres'.
32	Consultee 8 NHS Professional	**4.6**	4.6 Any significant change of VA has to be ≥0.2 logMar	Thank you for your comments. See response to comment 28.
33	Consultee 3 NHS Professional	**4.12**	Here the specialist advisers are clear that efficacy should be measured in terms of stabilisation but a statement on the likelihood of visual improvement from the published papers would be helpful.	Thank you for your comments. Section 4.12 is the list of efficacy outcomes stated by the specialist advisers. Visual acuity was mentioned throughout section 4.
34	Consultee 7 Keratoconus Group	**5**	As well as being made aware of the risks of CXL, patients need to be made aware that in a small proportion of cases (3% according to current research) CXL may result in a loss of visual acuity, not a gain.	Thank you for your comments. The adverse effect listed is covered in the published literature included in the guidance (in section 5.1 & 5.2).

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35	Consultee 5 Private Sector Professional	**5**	I have seen one corneal perforation in 8 years. The cornea was initially 360 microns thick at its minimum and the patient washed the eye against instructions in the immediate post-operative period. No bacteria or acanthamoeba was grown. I have also seen occasional scarring, but this nearly always fades after a few months.	Thank you for your comments. This adverse event was not reported in any of the published literature. Therefore, the Committee considered your comment and added a sentence about this anecdotal event **'corneal perforation'** to section 5.9 in the guidance as follows: 'In addition a specialist provided information about a single occurrence of corneal perforation after the procedure'. 'Occasional scarring' listed is covered in the published literature included in the guidance (in section 5.2 & 5.3).
36	Consultee 3 NHS Professional	**5**	A key measure of safety is the incidence of loss of lines of best corrected visual acuity (BCVA).	Thank you for your comments. BCVA outcomes following an adverse event were reported in the published literature included in the guidance. Further details are available in the systematic review.
37	Consultee 7 Keratoconus Group	**6.1**	We are aware of one case where CXL was successfully performed on a young adult with Downs Syndrome (the procedure was carried out under a general anaesthetic).	Thank you for your comments.
38	Consultee 1 Royal College of Ophthalmologists	**6.1**	The wording of this statement is unclear. If cross-linking works then it could potentially prevent some patients with mild keratoconus progressing to a stage where contact lenses are required. However, there is not any evidence to show that it can be useful in patients who are unable to wear contact lenses to allow them to wear their lenses. The suggestion as it stands is that it can restore something that has been lost.	Thank you for your comments. The Committee considered your comment and amended paragraph 6.1 to state that 'The Committee noted that these procedures may be useful for disabled people who have keratoconus or keratectasia and whowould need to wear contact lenses but are unable to do so.'.

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39	Consultee 5 Private Sector Professional	**6.1**	I have seen several people get out of contact lenses after this procedure. However, it is mainly a protective procedure and should not be regarded as a refractive procedure.	Thank you for your comments. See response to comment 38 for amended version of 6.1.
40	Consultee 8 NHS Professional	**6.1**	6.1 Can this be clarified? Are you implying that CXL is a way to improve vision in those who are unable to wear contact lenses. This also contradicts what was mentioned in the indication section. If you are referring to combined procedures i.e. CXL-Plus then this has to be made clear.	Thank you for your comments. Paragraph 6.1 does not imply that CXL is a way to improve vision in those who are unable to wear contact lenses. This also doesn't contradict with related statement in 2.2. See response to comment 38 which addresses the changes made in the amended version of paragraph 6.1.
41	Consultee 3 NHS Professional	**6.1**	Such patients may also be problematic to treat with CXL! While possibly true in some cases, the statement seems to raise unreasonable hopes of contact lens independence whereas the primary aim of CXL is surely stabilisation as discussed above.	Thank you for your comments. See response to comment 38 which addresses the changes made in the paragraph 6.1. The Committee added a Committee comment about the aim of the procedure in section 6 as follows: Paragraph 6.2 The Committee noted that the primary aim of the procedures is to stabilise vision by halting progression of keratoconus or keratectasia but that many of the studies reported improvement of vision as a secondary outcome.
42	Consultee 4 NHS Professional	**6**	The essential aim in CXL is to stabilise keratoconus before patients become contact lens dependent. Evidence from the CLEK study shows quality of life deteriorates as corneal shape and contact lens fit get worse. CXL+ type interventions, aimed at rehabilitating good spectacle corrected vision and unaided vision probably have a highly beneficial effect on QoL measures and this is an important area for further study.	Thank you for your comments. Paragraph 1.6 in the guidance states that quality of life is an important area for further study.

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43	Consultee 8 NHS Professional	**7**	**7.1** Do you mean normal arrangements or special arrangements? **7.2** I suggest the title of the document to state keratoconus and keratectasia. Thank you for your hard work, time, and efforts.	Thank you for your comments. 7.1 Is relevant to procedures with special arrangements recommendations. The Committee amended 7.1 to state 'This guidance requires that clinicians undertaking the epithelium-on (transepithelial) CXL and combination (CXL-plus) procedures make special arrangements for audit. NICE has identified relevant audit criteria and is developing an audit tool [add URL] (which is for use at local discretion). Paragraph 7.2 was moved as a review statement to the beginning of the guidance as follows: 'This document replaces previous guidance on Photochemical corneal collagen cross-linkage using riboflavin and ultraviolet A for keratoconus (interventional procedure guidance 320)'. This is a standard statement for any guidance reviewed after publication and will not be changed.