NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of corneal implants for keratoconus

Keratoconus is a disease of the cornea which affects the shape of the eyeball and causes refractive errors, some of which cannot be corrected by spectacles or contact lenses. The insertion of clear plastic implants into the cornea is an interventional procedure aiming to restore eyesight in patients with this condition.

Introduction

This overview has been prepared to assist members of the Interventional Procedures Advisory Committee (IPAC) in making recommendations about the safety and efficacy of an interventional procedure. It is based on a rapid review of the medical literature and specialist opinion. It should not be regarded as a definitive assessment of the procedure.

Date prepared

This overview was prepared in January 2007.

Procedure name

- Corneal implants for corneal disease

Specialty societies

- Royal College of Ophthalmologists

Description

Indications

Keratoconus

Keratoconus is a progressive disease in which the normally round corneal surface becomes thinner and begins to bulge into a cone-like shape. This changes the normal physical properties of the cornea, and affects refraction.

Keratoconus is often associated with astigmatism. Patients should have clear central corneas in order for them to be suitable candidates for the insertion of corneal implants.

Several scales and instruments have been used to grade the severity of keratoconus: these include: the Amsler-Krumeich scale which grades keratoconus severity from grade I mild, to grade IV severe.

This procedure can also be used for pellucid marginal degeneration, a non-inflammatory, peripheral corneal thinning disorder characterised by thinning of the peripheral band of the inferior cornea. It is not known whether pellucid marginal degeneration and keratoconus are distinct diseases or different manifestations of the same disorder. The cornea within and adjacent to the thinned area is ectatic.

It is not known whether pellucid marginal degeneration and keratoconus are distinct diseases or different manifestations of the same disorder.

Current treatment and alternatives

In the mild to moderate keratoconus, spectacles or a range of contact lenses may help, although as the corneal shape continues to deteriorate contact lenses may become intolerable due to ill-fitting, and refractive correction becomes difficult. In more severe disease other treatments may include collagen cross-linking riboflavin eye drops which can be used to strengthen corneal tissue and limit bulging of the eye's surface.

Invasive procedures include penetrating keratoplasty to modify the shape of the cornea. Ultimately a corneal transplant may be required in some patients.

What the procedure involves

Corneal implants are flexible, crescent-shaped rings of polymethyl methacrylate that are placed in the periphery of the cornea. They effect refraction in the eye by physically changing the shape of the cornea, to flatten the front of the eye.

The procedure is undertaken under local or general anaesthesia. An incision is made in the cornea at the 12 o’clock position, of approximately 1.2mm length (vertically) and two-thirds of the corneal thickness. Either a lamellar dissector is introduced at the incision and rotated to create a channel in either direction, or a channel is created using a femtosecond laser. One corneal implant segment is introduced to each channel and a suture may be used to close the original incision. A number of implants have been employed for this procedure, and a range of implant thicknesses are available for different degrees of correction.

Postoperative care consists of steroid and antibiotic treatment for a few days or weeks, and a bandage soft contact lens may be worn for a few days.

If required the procedure is reversible with minimal permanent visual effect, and it is unlikely to impact on future corneal transplant procedures.

Efficacy

The key efficacy outcomes for this procedure identified by the specialist advisers were uncorrected visual acuity (UCVA), best spectacle-corrected visual acuity (BSCVA), refractive error and ocular topography or keratometry measurements. Outcomes used to measure visual acuity varied between studies, making comparisons difficult. Length of follow-up also varied between studies, and it was not always clear how many patients (or eyes) were available at each time point.

Visual acuity

One case series (n = 34 eyes) reported that BSCVA had improved significantly at 6 months after insertion of corneal ring segments; 3% of eyes gained 6–8 lines, 59% gained 2–5 lines, 32% had no change and 6% lost 2 or more lines ($p < 0.001$).[1] In this study UCVA also improved significantly: 24% (8/34) of eyes had a score of 20/40 or better at 12 months' follow-up compared with 4% (2/53) of eyes at baseline ($p < 0.001$).

A second case series reported that UCVA had improved by 2 lines or more in 72% (53/74) of eyes and BSCVA in 45% (33/74) of eyes at 9 months' follow-up.[2] A third case series of 31 eyes reported that BSCVA improved by 2 lines or more in 87% (27/31 eyes) and UCVA by the same amount in 81% (25/31 eyes) at 12 months' follow-up).[3]

Mean UCVA improved significantly in 58 eyes undergoing corneal ring implantation, the score improving from 20/200 at baseline to 20/50 at 12 months' follow-up ($p < 0.001$). The change in BSCVA over the same period was not statistically significant, however.[4]

In one case series of 8 eyes treated with intercorneal ring segments for pellucid marginal degeneration, the UCVA improved in all 8 eyes from a mean score of 20/325 at baseline to 20/50 at 12 months follow up. The mean BSCVA improved from a mean score of 20/45 at baseline to 20/30 at 12 months follow up[5].

Resolution of keratoconus-related astigmatism

In one case series of 51 eyes, the mean refractive astigmatism decreased from 3.69 ± 2.20 D (dioptres) at baseline to 2.21 ± 1.96 D after surgery ($p < 0.01$) (follow-up not stated).[6] One case series of 13 eyes treated with corneal ring implants reported that average keratoconus improved from 48.46 ± 3.72 D at baseline to 45.32 ± 3.01 D at 6 months' follow-up, although this was not sustained at 3 years' follow-up (47.00 ± 3.57 D).[7] A third case series of 100 eyes reported that mean keratometry improved from 50.1 ± 5.6 D at baseline to 46.6 ± 5.3 D at one year and 46.8 ± 4.9 at 2 years ($p<0.001$ for both).

Contact lens compatibility

In one case series of 13 eyes with 3 years' follow-up, all patients who were contact-lens intolerant at baseline were able to wear a contact lens after surgery.[7]

Surgical parameters

One case series reported successful corneal segment implantation in 98% (58/59) of eyes.[1] Adjustment of the implants was required in 10% (6/58) of eyes in a second series.[4] In a third series, poor-quality vision required penetrating keratoplasty in 6% (2/36) of eyes.[3]

Safety

The Specialist Advisers considered the following outcomes to be the most important in considering the safety of this procedure: infection, infiltration, pain, implant extrusion and anterior chamber perforation.

The safety outcomes reported and the definitions used varied between the studies. It was not always clear how many patients (or eyes) were included in the analysis of safety outcomes.

Intra-operative complications

One case series of 57 eyes reported that there were no intraoperative complications, and any postoperative complications were not considered to be clinically significant.[1] In another case series, creation of a superficial channel perforated Bowman's layer in 1% (1/74) of eyes, although this was successfully re-channelled and the implant fitted.[2]

Extrusion rates

Implant segment extrusion occurred in 0%,[4] 1% (1/74),[2] 14% (5/36)[3] and 20% (10/51) of eyes.[6] Bacterial infection following corneal implant procedures occurred in 0%,[2] 0%[7], 2% (1/51),[6] and 3% (1/36)[3] of eyes.

Miscellaneous adverse events

One case series reported that there was a feeling of discomfort in 2% (1/57) of eyes,[1] and in a second series, chronic foreign body sensation required removal of the implants in 4% (3/74) of eyes.[2] In a third case series, corneal channel deposits were found in 31% (4/13) of eyes, although these did not affect visual outcome.[7]

Various visual disturbances were reported, the most common being halos or glare, which occurred in between 3% (2/74)[2] and 5% (3/57)[1] of eyes.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to corneal implants for corneal disease. Searches were conducted via the following databases, covering the period from their commencement to 26/09/06 and updated to 14/11/06: Medline, PreMedline, EMBASE, Cochrane Library and other databases. Trial registries and the Internet were also searched. No language restriction was applied to the searches. (See Appendix C for details of search strategy.)

The following selection criteria (Table 1) were applied to the abstracts identified by the literature search. Where these criteria could not be determined from the abstracts the full paper was retrieved.

Table 1 Inclusion criteria for identification of relevant studies

Characteristic	Criteria
Publication type	Clinical studies were included. Emphasis was placed on identifying good-quality studies. Abstracts were excluded where no clinical outcomes were reported, or where the paper was a review, editorial or laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patients	Patients with corneal disease (including keratoconus, ectasia or pellucid marginal degeneration)
Intervention/test	Corneal implants
Outcome	Articles were retrieved if the abstract contained information relevant to the safety and/or efficacy.
Language	Non-English-language articles were excluded unless they were thought to add substantively to the English-language evidence base.

List of studies included in the overview

This overview is based on nine case series.[1-8,10] and one non randomised controlled trial [9]

Other studies that were considered to be relevant to the procedure but were not included in the main extraction table (Table 2) are listed in Appendix A.

Existing reviews on this procedure

There were no published reviews identified at the time of the literature search.

Related NICE guidance

Below is a list of NICE guidance related to this procedure. Appendix B details the recommendations made in each piece of guidance listed below.

Interventional procedures

IPG XXX corneal implants for refractive error

Technology appraisals
None applicable.

Clinical guidelines
None applicable.

Public health
None applicable.

Table 2 Summary of key efficacy and safety findings on corneal implants for Keratoconus

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Colin J (2007)[8] **Case series** France **n= 82 (100 eyes)** Study period: 2001 to 2003 Population: Mean age = ? years, Male = 65%, Keratoconus grade I n = 16 eyes, grade II n=26, grade III n= 40. Indications: patients with Amsler-Krumeich grade I to III keratoconus with clear central cornea, and contact lens intolerance. Intervention: Under general or local anaesthesia a 1.0 mm incision was made to 70% of the corneal depth. Semi circular tunnels were created using specialised dissectors, and Intacs ring segment s of various thicknesses were inserted. The incision was closed without sutures, and postoperative topical antibiotics and steroids were prescribed. **Follow up: 24 months.** Conflict of interest: First author is a consultant to manufacturer, no author has a proprietary or financial interest in any material or method described.	**Operative success.** Ring segments were successfully implanted in 100% (100/100) of eyes enrolled to the study. **Visual outcomes** BSCVA Outcome / Baseline / 1 year / 2 years <0.1: 3.7% / 0% / 0% 0.1 to 0.2: 30.5% / 18.3% / 13.4% 0.6 to 0.4: 43.9% / 30.5% / 32.9% ≥ 0.5: 22.0% / 51.2% / 53.7% P<0.001at both 1 and 2 years Vs baseline. 68% of eyes gained 1 or more lines, 17% of eyes were unchanged and 15% of eyes lost 1 or more lines. UCVA Outcome / Baseline / 1 year / 2 years <0.1: 43.9% / 4.9% / 0% 0.1 to 0.2: 45.1% / 60.5% / 68.5% 0.6 to 0.4: 8.5% / 22.2% / 22.0% ≥ 0.5: 2.4% / 12.4% / 9.8% P value not stated 81% of eyes gained 1 or more lines, 13% of eyes were unchanged and 5% of eyes lost 1 or more lines. Outcome / Baseline / 1 year / 2 years / p= MRSE (D): -6.93 ± 3.91 / -4.01 ± 3.16 / -3.80 ± 2.73 / <0.001 both Vs baseline Mean Keratometry (D): 50.1 ± 5.6 / 46.6 ± 5.3 / 46.8 ± 4.9 / <0.001 both Vs baseline Of 44 patients who required contact lenses for residual myopia and or astigmatism 89% (39/44) were still tolerant at 1 year and 84% (37/44) at 2 years.	**Complications** Complication / Rate (n=82) Secondary displacement or migration / 0% Vascularisation at incision site / 0% Non-progressive epithelial cysts / 26% (21/82) White-yellow channel deposits (no effects on vision) / 27% (22/82)	Prospective study. All procedures undertake by one experiences surgeon. Outcome assessments were not undertaken by independent clinicians. Patients were discontinued from the study if they had reason to remove the implants (4 eyes), or an operative or post operative event occurred. 82 eyes of 68 patients were available for 2 year follow up. 14% (14/100) eyes were lost to follow up. 2 year BSCVA and UCVA results were within 2 lines of those reported at 1 year in 89% of eyes, demonstrating stability over time.

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Colin J (2006)[1] **Case series** European – 5 sites **n = 57 eyes** Study period: Sept 1999 to Mar 2002 Population: Mean age = not stated years, Male = not stated, mean UCVA = 'slightly worse than' 20/200, mean BSCVA = 20/50 Indications: patients with moderate-to-severe keratoconus with clear central cornea Intervention: Under general or local anaesthesia, a 1.2 mm incision was made to 70% of the corneal depth. Semi-circular tunnels were created using a pocketing hook, and Intacs ring segments of various thicknesses were inserted. The incision was closed with one suture, and postoperative topical antibiotics and steroids were prescribed. In some cases either a unilateral segment was implanted, or a thicker implant was used on one side. **Follow up: 12 months** Conflict of interest: None stated	**Operative success** Ring segments were successfully implanted in 98% (58/59) of patients enrolled to the study. **Visual outcomes** Outcome / Baseline / 6 months / 12 months / p value Intraocular pressure – from baseline: N/A / 0.2 ± 2.4 (n = 15) / –0.7 ± 2.8 (n = 7) / N/R UCVA 20/40 or better: 4% (2/53) / 17% (5/29) / 24% (8/34) / <0.001 BSCVA improved significantly from baseline at 6 months;3% gained 6–8 lines, 59% gained 2–5 lines, 32% had no change, and 6% lost ≥ 2 lines ($p < 0.001$) (n = 34). 84% of eyes had a stable BSCVA (no more than 2 lines change between visits) for all intervals from 1 to 12 months. The mean MRSE value improved significantly from –4.6 ± 3.5 D at baseline to 3.1 ± 2.5 D at 6 months ($p < 0.001$) (n = 30). Changes to refractive astigmatism were evaluated by the absolute value of the manifest refraction cylinder, which decreased significantly from 4.40 ± 2.40 D at baseline to –1.52 ± 1.60 D at 6 months ($p < 0.001$). Patient-reported quality of vision / Baseline / 6 months Poor: 69% (27/39) / 24% (5/21) Fair: 21% (8/39) / 29% (6/21) Good: 10% (4/39) / 38% (8/21) Excellent: 0% / 10% (2/21) Statistical significance N/R.	**Complications** No intraoperative complications were reported. The most common outcomes were intrastromal deposits on or near the inserts, and haze in the incision area, rates N/R. At 6 months, 16% (9/57) of patients reported moderate or severe visual symptoms. Three patients reported glare (5% of eyes), and 1 patient (2% of eyes) reported discomfort, itching, burning, photophobia, difficulty with night vision or fluctuating vision. Dissatisfaction with the procedure leading to request for implant removal occurred in 12% (7/57) of patients.	Prospective study Eyes were excluded from the study if the implant was explanted in the first year or where there was an operative of postoperative adverse event. One patient was lost to follow-up. Complication rates were calculated on the assumption that procedures were carried out on one eye in each patient. It is not clear how visual acuity outcomes were analysed, whether it was based on the proportion of patients at each level of acuity across all outcome times. The authors state that if outcome is not acceptable following insertion of ring segments, they can be removed and corneal transplantation performed.

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Boxer Wachler BS (2003)[2] **Case series** USA **n = 50 (74 eyes)** Study period: Dec 1999 to May 2001 Population: Mean age = 35 years; male = 84% Indications: patients with keratoconus with severity ranging from forme fruste to advanced cones with scarring, intolerant to rigid gas-permeable contact lenses Intervention: Anaesthesia type not reported. An incision was made to 66% of the corneal depth, often in the same meridian as the axis of the positive cylinder. Intacs inserts of various thicknesses were implanted. The incision was not sutured. Topical antibiotics and steroids were prescribed for up to 7 days postoperatively. In some cases a thicker implant was used on the inferior side. **Follow up: 9 months** Conflict of interest: None stated	**Visual outcomes** Outcome / Improved ≥ 2 lines / No change / worsened ≥ 2 lines BSCVA: 45% (33/74) / 51% (38/74) / 4% (3/74) UCVA: 72% (53/74) / 19% (14/74) / 9% (7/74) Post-hoc analysis found that eyes that had gained lines of both BSCVA and UCVA had worse scores at baseline than those that showed no change ($p < 0.0001$ and $p < 0.001$ respectively). The mean refraction spherical equivalent was reduced from –3.89 ± 5.16 D at baseline to –1.46 ± 4.11 D after surgery (significance and length of follow up N/R) ***Visual acuity by cylinder sub-group*** Preoperative cylinder / Baseline BSCVA / Postoperative BSCVA / p value 0–3 D (n = 33) / 0.29 (± 0.24) / 0.18 (± 0.23) / 0.006 3–6 D (n = 31) / 0.48 (± 0.55) / 0.28 (± 0.40) / 0.006 > 6 D (n = 10) / 0.53 (± 0.65) / 0.29 (± 0.24) / 0.23 . Preoperative cylinder / Baseline UCVA / Postoperative UCVA / p value 0-3 D (n = 33) / 0.92 (± 0.49) / 0.48 (± 0.47) / < 0.0001 3-6 D (n = 31) / 1.12 (± 0.38) / 0.72 (± 0.52) / 0.0004 > 6 D (n = 10) / 1.32 (± 0.32) / 0.72 (± 0.62) / 0.42	**Complications** ***Perioperative complications*** A superficial channel dissection with perforation of the anterior Bowman's layer occurred in one eye (1%). This was successfully rechannelled and a ring segment inserted. Complication / Rate Transient inflammatory reaction to epithelium in the incision / 3% (2/74) Segment migration and externalisation (1 day follow-up) explanted / 1% (1/74) Chronic foreign body sensation requiring explantation / 4% (3/74) Halos around lights / 3% (2/74) Keratolysis infection / 0% Anterior chamber perforation / 0% One patient required refractive adjustment in both eyes because sight had become hyperopic; the superior segments in each eye were explanted.	Retrospective study All procedures were undertaken by the same surgeon. Length of follow-up for outcome evaluation was not well reported. It is assumed to be 9 months, the stated mean follow-up period. The units used for visual acuity outcomes were not reported. Baseline and follow-up outcomes were assessed unmasked. Refractive changes may have been missed because outcomes at follow-ups of different lengths were grouped together.

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Kwitko S (2004)[6] **Case series** Brazil **n = 47 (51 eyes)** Study period: Not stated Population: Mean age = ? years, male = ?, inferior keratoconus = 27 eyes, central keratoconus = 24 eyes Indications: patients with stage II or III keratoconus on the Amsler –Krumeich classification with clear central cornea. Intolerant to contact lenses and awaiting penetrating keratoplasty. Intervention: Under local anaesthesia, two incisions of 5.0 mm and 6.0 mm were made to 70–80% of the corneal depth at 180° degrees to each other. Semi-circular tunnels were created using a purpose-designed spatula, and Ferrara ring segments of various thickness were inserted. One incision was closed with one suture. Topical antibiotics and steroids were prescribed for 30 days postoperatively. **Follow up: 13 months** Conflict of interest: None stated	**Visual outcomes** UCVA improved in 86% (44/51) of eyes, there was no change in 8% (4/51*), and it worsened in 6% (3/51). *figure reported in paper was 3 eyes but this does not tally with either the total sample size or the fraction stated. BSCVA improved in 86% (44/51) of eyes, there was no change in 2% (1/51), and it worsened in 12% (6/51). The mean refractive spherical equivalent decreased from –6.08 ± 5.01 D at baseline to –3.81 ± 3.99 D at 13 months ($p < 0.01$) The mean refractive astigmatism decreased from –3.69 ± 2.20 D at baseline to 2.21 ± 1.96 D 'postoperatively' ($p < 0.01$). The mean corneal curvature decreased from 48.76 ± 3.97 D at baseline to 43.17 ± 4.79 D at 13 months ($p < 0.001$). Outcomes of topographic astigmatism, spherical equivalent and refraction cylinder were better among eyes with central keratoconus than among those with inferior keratoconus ($p < 0.05$ for each). However, there were no significant differences in outcomes of central corneal curvature, surface regularity index, surface asymmetry index, UCVA or BSCVA.	**Complications** Additional penetrating keratoplasty was required in 25% (13/51) of eyes: 3 because of no improvement in BSCVA, 5 because of segment extrusion, 4 because of poor-quality visual acuity, and 1 because of segment decentration. ***Other postoperative complications*** Outcome — Rate Ring decentration — 4% (2/51) Ring extrusion — 20% (10/51) Diciform keratitis adjacent to the segment (resolved with topical prednisolone) — 2% (1/51) Presumed bacterial keratitis after extrusion (cleared after removal and intense topical ofloxacin and cephalothin) — 2% (1/51)	All procedures were undertaken by one surgeon. Visual acuity outcomes were not analysed quantitatively against baseline scores. Individual patient (eye) data were presented but have not been extracted here. Patients' previous operative experience was not reported. No details were provided of method of case selection or accrual. No details were provided of independent outcome assessment.

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Levinger S (2005)[4] **Case series** Israel **n = 43 (58 eyes)** Study period: Mar 2001 to Aug 2002 Population: Mean age = 36 years; male = 58% Forme fruste stage = 7 eyes definitive keratoconus = 51 eyes Indications: patients with keratoconus of varying severity (diagnosed by slitlamp signs or video keratography) who were intolerant to rigid contact lenses. Patients with pupils >7.0 mm were not excluded. Intervention: Under local anaesthesia, a 1.8 mm radial incision was made at the steepest meridian of the cornea to 66% of the corneal depth. Intacs inserts of various thicknesses were implanted. The incision was closed with one suture. Topical antibiotics, steroids and artificial tears were prescribed for up to 3 weeks posoperatively. In some cases, a thicker implant was used on the inferior side. **Follow up: 12 months** Conflict of interest: None stated	**Operative success** Adjustment of the implants(removal, exchange, addition or shifting) was required in 10% (6/58) of eyes. **Visual outcomes** Outcome: Mean UCVA — Baseline (n = 58): 20/200 (± 0.1 line) — Postoperative (n = 58): 20/50^{-3} (± 3.1 lines) — p = < 0.001 Outcome: Mean BSCVA — Baseline (n = 58): 20/30^{-1} (± 0.23 lines) — Postoperative (n = 58): 20/32 (± 0.18 lines) — p = 0.75 Snellen line equivalents Most eyes with baseline BSCVA > 0.2 (20/32) fell into the fair or good outcome group. Mean manifest spherical equivalent (D): Baseline (n = 58) –3.88 (± 1.64) — Postoperative (n = 58) –1.04 (± 1.51) — p value < 0.001 Mean manifest astigmatic correction (D): Baseline (n = 58) –3.34 (± 2.32) — Postoperative (n = 58) –1.97 (± 1.51) — p value < 0.001 Multiple regression analysis of the effect of baseline characteristics on postoperative UCVA found that baseline BSCVA and degree of astigmatism were independent predictors of visual outcome. There were no significant difference in UCVA, BSCVA, refraction, corneal topography or patient-satisfaction outcomes between eyes treated with symmetric implants and those treated with asymmetric implants.	**Complications** Patients completed a brief questionnaire regarding sight disturbance at 9–12 months' follow-up. These are not reported in the study paper. Increased astigmatism: 7% (4/58) Increased hyperopia: 2% (1/58) Insufficient correction requiring a second implant: 2% (1/58) Superficial corneal 'buttonholing': 0% Segment extrusion: 0%	Retrospective study Outcomes were evaluated at 1 day, 1 week, 1, 3, 6 and 12 months. No details were provided of method of case selection or accrual. No details were provided of independent outcome assessment. Analysis was based on outcomes and included 6 eyes where adjustment surgery was required.

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Miranda D (2003)[3] **Case series** Brazil **n = 35 (36 eyes)** Study period: Not stated Population: Mean age = 26 years; male = 51% Keratoconus grade III or IV = 100% Indications: patients with severe keratoconus, defined as highly disabling spectacle or contact lens visual acuity, total intolerance of contact lenses, and a previous indication for penetrating keratoplasty; minimum corneal thickness 400 µm Intervention: Under local anaesthesia and with topical antiseptic solution applied, two incisions of 1.0 mm were made to 80% of the corneal depth at 180° to each other. Semi-circular tunnels were created using a purpose-designed spatula, and Ferrara ring segments of various thicknesses were inserted. No sutures were used. A bandage contact lens was placed. Topical antibiotics and steroids were prescribed for 30 days postoperatively. **Follow up: 12 months** Conflict of interest: One author has a financial interest in the implant manufacturers.	**Visual outcomes** 12-month outcome (n = 31 eyes) Outcome: Improved ≥ 2 lines; No change; worsened ≥ 2 lines BSCVA: 87% (27/31); 13% (4/31); 0% UCVA: 81% (25/31); 19% (6/31); 0% Snellen lines Outcome: Baseline (n = 36); 1 month (n = 36); 12 months (n = 30) MRSE (D): –7.29 (± 3.12); –5.57 (± 3.13); –4.80 (± 3.04) Meaurement of preoperative refraction was difficult because of the severity of keratoconus. Penetrating keratoplasty was undertaken in 6% (2/36) of eyes because of symptoms of poor-quality vision. ***Corneal topography*** Mean (and range) flat keratometric power (D): Baseline (n = 21); 12 months (n = 21) EyeSys test: 58.1 (46.6–77.9); 50.6 (38.6–70.0) Orbscan test: 51.9 (55.0–68.4); 49.8 (39.8–61.2) Mean (and range) steep keratometric power (D): Baseline (n = 21); 12 months (n = 21) EyeSys test: 62.3 (50.9–81.8); 52.7 (41.2–71.3) Orbscan test: 60.1 (50.6–74.4); 54.9 (43.4–67.2) Mean central corneal curvature decreased ‘significantly’ from the preoperative to the last postoperative examination (p values not stated).	**Postoperative complications** Outcome: Rate (n = 36) Segment decentration: 3% (1/36) Segment asymmetry: 6% (2/36) Inadequate implant depth: 6% (2/36) Segment migration: 6% (2/36) Segment extrusion: 14% (5/36) Conjunctivitis: 3% (1/36) Hydrops (not otherwise defined): 3% (1/36) Infection (*Nocardia* Sp.): 3% (1/36)	Outcomes were evaluated at 1, 3, 6 and 12 months. 5/40 patients (13%) were lost to follow-up, one who had segments removed because of severe irritation, two who had penetrating keratoplasty, and two who were unavailable for examination. No quantitative analysis of change in visual acuity from baseline was reported. Keratoconus grades based on the stage of the cone evolution (no further details given)

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Alió J L (2006)[7] **Case series** Spain / Egypt **n = 11 (13 eyes)** Study period: Apr 2000 to Dec 2001 Population: Mean age = 28 years; male = ? Amsler –Krumeich keratoconus grade I = 31%, grade II = 46%, grade III = 23%, grade IV = 0% Indications: patients with keratoconus (no further details) Intervention: Under local anaesthesia, a 1.8 mm incision was made to 70% of the corneal depth. Semi-circular pockets were created using a semi-automated device, and Intacs ring segments were inserted. The incision was closed with one suture. Topical antibiotics and steroids were prescribed for 10 days postoperatively. The decision to undertake asymmetrical implantation was made according to corneal topography, in these cases either a unilateral segment was implanted, or a thicker implant was used on one side. **Follow up: 3 years** Conflict of interest: None stated	***Visual outcomes and Corneal topography*** Parameter / Baseline (n = 13) / 6 months (n = 13) / 3 years (n = 13) Sphere (D): –2.84 ± 3.78 / –2.80 ± 3.86 / –3.19 ± 4.96 Cylinder (D): –5.5 ± 3.19 / –3.67 ± 1.34 / –3.36 ± 1.26 Spherical equivalent (D): –5.40 ± 4.11 / –4.65 ± 4.06 / –4.86 ± 5.09 BSCVA: 0.46 ± 0.20 / 0.66 ± 0.18* / 0.62 ± 0.18† Keratoconus maximum (D): 51.07 ± 3.62 / 47.15 ± 3.45 / 48.92 ± 3.53 Keratoconus minimum (D): 45.84 ± 3.48 / 43.50 ± 2.86 / 45.08 ± 3.73 Average keratoconus (D): 48.46 ± 3.27 / 45.32 ± 3.01* / 47.00 ± 3.57 Statistical differences not reported unless stated. *p ≤ 0.001 vs baseline. †p ≤ 0.5 vs 6 months. There were no significant differences in increase in BSCVA score at 6 months between patients treated with two or one ring segments. **Contact lens tolerance** All patients who were contact-lens intolerant at baseline were able to use a contact lens after surgery.	**Complications** Outcome / Rate Corneal channel deposits (not affecting visual outcome): 31% (4/13) Superficial revascularisation at incision site and peripheral corneal tunnel at 6 months (regressed at 24 months): 15% (2/13)	Retrospective study 7/26 eyes (27%) were excluded from the original study cohort because the implant was explanted in the first year of follow-up, and 6 eyes because of loss to follow-up. The authors state that the extrusion rate may have been a reflection of a learning curve for this procedure, although advanced keratoconus may be a factor, as 3/7 eyes where extrusion occurred had advanced disease. Clinical complications were reported by an independent observer. Keratoconus was graded on the Amsler–Krumeich scale. All operations were undertaken by one surgeon. The authors state that an increase in mean keratoconus between 6-month and 3-year outcomes may reflect the progressive nature of the disease.

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Mularoni A (2005)[5] **Case series** Italy **n = 8 (8 eyes)** Study period: not reported Population: Mean age = 55 years; male = 50 Indications: patients with bilateral PMD unsatisfied with spectacle or contact lens correction (no further details) Intervention: Under local anaesthesia, a 1.8 mm incision was made to 70% of the corneal depth. Semi-circular pockets were created using specialised instruments and asymmetrical insertion of Intacs ring segments was undertaken with thicker segment placed inferiorly. The incision was closed with one suture. Topical antibiotics and steroids were prescribed for 15 days postoperatively. **Follow up: 25 months** Conflict of interest: None	**Visual outcomes** The UCVA improved in all 8 eyes from a mean score of 20/325 at baseline to 20/50 at 12 months follow up. The mean BSCVA improved from a mean score of 20/45 at baseline to 20/30 at 12 months follow up. 4 patients received a prescription for glasses, 1 patient could tolerate contact lenses again, and 3 were satisfied without correction. The mean MRSE improved from -4.75 ± 3.56 D at baseline to -1.36 ± 3.24 at 12 months follow up The mean cylinder improved from -6.31 ± 1.81 D at baseline to -1.72 ± 6.20 at 12 months follow up The mean keratometry improved from 43.95 ± 2.08 D at baseline to 42.46 ± 1.84 at 12 months follow up	**Complications** Outcome — Rate White channel deposits — 50% (4/8)	All procedures undertaken by one surgeon. No patients were lost to follow up The eye with greater astigmatism was treated in each patient. No measures of statistical significance between baseline and follow up scores are reported. Although mean follow up was 25 months, and final visual acuity outcomes are reported for each patient, mean scores for the group are only reported to 12 months.

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Rodriguez L A (2007)[9] **Non randomised controlled study** Venezuela **n = 17 (17 eyes keratoplasty 17 eyes corneal ring segments)** Study period: not reported Population: Mean age = 30 years; male = 77% Indications: patients with keratoconus (no further details). Patients with other ocular disease were excluded from the study. Intervention: an 1.8 mm incision was made to 80% of the corneal depth. Semi-circular pockets were created using specialised instruments, and intacs inserted. The incision was closed with one or two sutures. Postoperative antibiotics and steroids were prescribed for 14 days. Or penetrating keratoplasty 2 to 10 years previously. **Follow up: 10 months (ring segments)** Conflict of interest: None	**Visual outcomes** Asymmetrical keratoconus Keratoplasty n=4 FU 2 years minimum Outcome / Baseline / Final follow up / P value BSCVA / 1.41 (± 0.61) / 0.42 (± 0.32) / <0.0001 UCVA / 1.71 (± 0.43) / 0.69 (± 0.34) / <0.0001 intacs n=4 FU 10 months minimum Outcome / Baseline / Final follow up / P value BSCVA / 0.30 (± 0.33) / 0.50 (± 0.16) / 0.33 UCVA / 0.91 (± 0.49) / 0.50 (± 0.30) / 0.0088 Symmetrical Keratokonus UCVA was significantly different at all follow up points and better with intacs than keratoplasty (p=0.0046)	**Complications** No intraoperative complications occurred in either group.	In the asymmetrical keratoconus group baseline visual acuity was worse in patients undergoing keratoplasty than intacs, as the eye with severe corneal ectasia was chosen for treatment. In the asymmetrical keratoconus group no analysis was undertaken to compare intacs vs keratoplasty

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments
Kymionis G D (2006)[10] **Case series** USA **n = 15 (17 eyes)** Study period: not reported Population: Mean age = 34 years; male = 53% Indications: patients with keratoconus with clear central corneas and contact lens intolerance Intervention: Under local anaesthesia, a 0.9 mm incision was made to 70% of the corneal depth. Semi-circular pockets were created using specialised instruments and Intacs ring segments (0.45 mm). The incision was closed with one suture. Topical antibiotics and steroids were prescribed for 14 days postoperatively. **Follow up: 67 months** Conflict of interest: None	**Visual outcomes** Spherical equivalent error was significantly reduced from -5.54 ± 5.02 D baseline to -3.02 ± 2.65 at 5 years follow up (P=0.01). The mean UCVA improved by 2.8 Snellen lines at final follow up The mean BSCVA improved by 1.4 Snellen lines at final follow up The mean keratometry value was reduced significantly from 49.95 ± 5.10 D at baseline to 48.02 ± 4.99 at final follow up (p=0.009). Mean keratometricadn topographic astigmatism values remained stable between the 6 month and 5 year follow up. **Patient satisfaction** In 35% (6/17) of eyes contact lenses were tolerated following ring segment insertion. Patients were asked to rate overall satisfaction with the procedure on a 1 to 5 scale (5 best), 82% (14/17) of eyes received a score of 5.	**Complications** All procedures were uneventful Superficial wound site neovascularisation and channel deposits were found in 69% (12/17) eyes at 5 year follow up. These outcomes were clinically insignificant with no loss to BSCVA	This study cohort is taken from 28 patients who were initially entered in a clinical trial. 5 patients asked for Intacs to be removed, and 8 patients were lost to follow up

Abbreviations used: BSCVA – best spectacle-corrected visual acuity; D – dioptre; LASIK – laser in situ keratomileusis; MRSE – manifest refraction spherical equivalent; N/R – not reported; UCVA – uncorrected visual acuity; PMD – pellucid marginal degeneration.

Study details	Key efficacy findings	Key safety findings	Comments

Validity and generalisability of the studies

- None of the studies was a randomised controlled trial. It is well known from other ophthalmological procedures assessed against sham/placebo interventions that visual acuity outcomes can be subject to considerable placebo effects.
- Overall, the degree of myopia of the patients included in the studies does not appear to have been severe.
- Variation in the severity of keratoconus between studies makes comparison difficult.
- Although one of the intended benefits of corneal implants is that they may allow patients to wear contact lenses, only one study reported directly on this outcome.

Specialist adviser's opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College.

Mr D O'Brart, Mr M Leyland, Mr S Daya.

- Two specialist advisers thought that this was an established procedure, and no longer new, while one considered it to be novel and of uncertain safety and efficacy.
- The procedure aims to reduce astigmatism in keratoconus and reduce the need for corneal transplant, with a rapid recovery time and little ocular morbidity.
- The procedure is performed in an attempt to delay corneal transplantation which would be the inevitable next step.
- Theoretical adverse events include occasional ring erosion, and inflammation around the ring segments, as well as intraoperative damage to the retina / optic nerve due to increased intraocular pressure, and a loss of effect over time.
- There is some unreliability of effect from patient to patient.
- Wet-laboratory training is required before the procedure is undertaken.
- The implants can be removed easily and the effect is reversible.
- In advanced cases of keratoconus the refractive effect may be too small to be useful.
- The procedure may have a moderate impact on the NHS; 1 in 2000 people suffer from keratoconus, of whom up to 50% may be suitable for implantation of corneal ring segments.

Issues for consideration by IPAC

- The procedure is intended to be reversible and adjustable.
- Intacs inserts were approved by the US FDA in July 2004 for use in adults aged 21 years or older who have clear central corneas and a corneal

thickness of 450 μm or thicker at the site of incision, who have experienced a progressive deterioration in their vision, such that they can no longer achieve adequate functional vision on a daily basis with their contact lenses or spectacles, and who have corneal transplantation as the only remaining option to improve their functional vision.
http://www.fda.gov/cdrh/pdf4/h040002a.pdf

A summary of the benefits and safety data relating to this decision is available at http://www.fda.gov/cdrh/pdf4/h040002b.pdf

References

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2 Boxer Wachler BS, Christie JP, Chandra NS et al. (2003) Intacs for keratoconus.[erratum appears in Ophthalmology. 2003 Aug;110(8):1475]. *Ophthalmology* 110: 1031-1040.

3 Miranda D, Sartori M, Francesconi C et al. (2003) Ferrara intrastromal corneal ring segments for severe keratoconus. *Journal of Refractive Surgery* 19: 645-653.

4 Levinger S and Pokroy R. (2005) Keratoconus managed with intacs: one-year results. *Archives of Ophthalmology* 123: 1308-1314.

5 Mularoni A, Torreggiani A, di Biase A et al. (2005) Conservative treatment of early and moderate pellucid marginal degeneration: a new refractive approach with intracorneal rings. *Ophthalmology* 112: 660-666.

6 Kwitko S and Severo NS. (2004) Ferrara intracorneal ring segments for keratoconus. *Journal of Cataract & Refractive Surgery* 30: 812-820.

7 Alio JL, Shabayek MH, and Artola A. (2006) Intracorneal ring segments for keratoconus correction: long-term follow-up. *Journal of Cataract & Refractive Surgery* 32: 978-985.

8 Colin J and Malet FJ. (2007) Intacs for the correction of keratoconus: Two-year follow-up. *Journal of Cataract & Refractive Surgery* 33: 69-74.

9 Rodriguez LA, Guillen PB, Benavides MA et al. (2006) Penetrating keratoplasty versus intrastromal rign segments to correct bilateral corneal ectasia:Preliminary study. *Journal of Cataract Refractive Surgery* 33: 488-496.

10 Kymionis GD, Siganos CS, Tsiklis NS et al. (2006) Long-term Follow-up of Intacs in Keratoconus. *American Journal of Ophthalmology* 143: 236-244.

Appendix A: Additional papers on corneal implants for Keratoconus not included in summary Table 2

The following table outlines the studies that are considered potentially relevant to the overview but were not included in the main data extraction table (Table 2). It is by no means an exhaustive list of potentially relevant studies.

Article title	Number of patients/ follow-up (FU)	Direction of conclusions	Reasons for non-inclusion in Table 2
Alio JL, Artola A, Hassanein A, Haroun H, Galal A. One or 2 Intacs segments for the correction of keratoconus. Journal of Cataract & Refractive Surgery 2005; 31(5):943–953.	Case series n = 26 eyes FU = to 1 year	Spherical equivalent error and refractive astigmatism were significantly reduced.	Larger studies are included in Table 2. Most outcomes compare subgroups treated with unilateral or bilateral implants.
Alio JL, Shabayek MH, Belda JI, Correas P, Feijoo ED. Analysis of results related to good and bad outcomes of Intacs implantation for keratoconus correction. Journal of Cataract & Refractive Surgery 2006; 32(5):756–761.	Case series n = 25 eyes FU = 6 months	Poor results can be anticipated in advanced keratoconus (K reading $\geq$ 55 D).	Larger studies are included in Table 2.
Barbara A, Shehadeh-Masha'our R, Zvi F, Garzozi HJ. Management of pellucid marginal degeneration with intracorneal ring segments. Journal of Refractive Surgery 2005; 21(3):296-298.	Case report n = 1 FU = 12 months	UCVA improved from 2/60 to 6/60, and completely eliminated myopia of -8.00 D. Irregularity of astigmatism was improved although magnitude was not.	Larger studies are included in table 2
Chalita MR, Krueger RR. Wavefront aberrations associated with the Ferrara intrastromal corneal ring in a keratoconic eye. Journal of Refractive Surgery 2004; 20(6):823–830.	Case report n = 1 FU = 1 month	Ring implant notably increased higher-order aberrations compared with the fellow eye.	Larger studies are included in Table 2. Largely surrogate outcomes were used.
Chan-Colin-C-K, Wachler-Brian-S-Boxer. Reduced best spectacle-corrected visual acuity from inserting a thicker intacs above and thinner intacs below in keratoconus. *JOURNAL OF REFRACTIVE SURGERY*, 2007, V23, N1, JAN, pp 93-95	Case report n=1 FU=N/S	Correction of insert thickness produced improved visual acuity	Case series from these authors is described in table 2. This report does not highlight additional safety outcomes
Colin J, Cochener B, Savary G, Malet F, Holmes-Higgin D. INTACS inserts for treating keratoconus: one-year results. Ophthalmology 2001; 108(8):1409–1414.	Case series n = 10 FU = 12 months	Corneal steepening and associated astigmatism was reduced.	Larger studies are included in Table 2.
Ertan, A. and Bahadir, M. Topography-guided vertical implantation of Intacs using a femtosecond laser for the treatment of keratoconus. *Journal of Cataract & Refractive Surgery*, 2007, 33 (1) 148-151.	Case report n=2	No further details available	Larger studies are included in Table 2.
Ertan-A, Bahadir-M. Intrastromal ring segment insertion using a femtosecond laser to correct pellucid marginal corneal	Case series n=6 (9 eyes)	Successful implantation in all eyes. Significant	Larger studies are included in Table 2.

degeneration. *JOURNAL OF CATARACT AND REFRACTIVE SURGERY*, 2006, V32, N10, OCT, pp 1710-1716	FU=6 months	difference between the preoperative and postoperative UCVA	
Hellstedt T, Makela J, Uusitalo R, Emre S, Uusitalo R. Treating keratoconus with intacs corneal ring segments. Journal of Refractive Surgery 2005; 21(3):236–246.	Case series n = 37 (50 eyes) FU = 6 months	92% operative success Patient satisfaction with vision improved from 24% to 88%.	Studies with longer follow-up are included in Table 2.
Hofling-Lima AL, Branco BC, Romano AC, Campos MQS, Moreira H, Miranda D et al. Corneal infections after implantation of intracorneal ring segments. Cornea 2004; 23(6):547–549.	Case series n = 8 FU = to 22 months	Infectious keratitis reported in all cases,, onset 1– 22 months after insertion. Two patients required penetrating keratoplasty to control the infection.	Larger studies are included in Table 2.
Kanellopoulos AJ, Pe LH, Perry HD, Donnenfeld ED. Modified intracorneal ring segment implantations (INTACS) for the management of moderate to advanced keratoconus: efficacy and complications. Cornea 2006; 25(1):29–33	Case series n = 15 (20 eyes) FU = 6– 12 months	Segment implantation improved UCVA and BSCVA significantly. There was one case of anterior chamber perforation.	Larger studies are included in Table 2. Studies with longer follow-up are included in Table 2.
Kymionis GD, Aslanides IM, Siganos CS, Pallikaris IG. Intacs for early pellucid marginal degeneration. Journal of Cataract & Refractive Surgery 2004; 30(1):230–233.	Case report n = 1 FU = 11 months	UCVA improved to 20/200 from counting fingers at baseline. BSCVA improved from 20/50 to 20/25. Corneal topography was improved.	Larger studies are included in Table 2.
McAlister JC, Ardjomand N, Ilari L, Mengher LS, Gartry DS. Keratitis after intracorneal ring segment insertion for keratoconus. Journal of Cataract & Refractive Surgery 2006; 32(4):676–678.	Case report n = 1 FU = 1 month	A case of sterile keratitis was reported, which resolved within a few days of implant removal.	Larger studies are included in Table 2.
Siganos CS, Kymionis GD, Kartakis N, Theodorakis MA, Astyrakakis N, Pallikaris IG. Management of keratoconus with Intacs. American Journal of Ophthalmology 2003; 135(1):64–70.	Case series n = 26 eyes FU = 11 months	Ring segments improved UCVA and BSCVA in the majority of patients.	Larger studies are included in Table 2. Studies with longer follow-up are included in Table 2.
Siganos D, Ferrara P, Chatzinikolas K, Bessis N, Papastergiou G. Ferrara intrastromal corneal rings for the correction of keratoconus. Journal of Cataract & Refractive Surgery 2002; 28(11):1947–1951	Case series n = 26 FU = 6 months	Corneal implants reduced corneal steepening and reduced astigmatism in eyes where the rings were left in place. Two rings were removed because they had been placed incorrectly.	Larger studies are included in Table 2. Studies with longer follow up are included in Table 2.

Appendix B: Related published NICE guidance for corneal implants for Keratoconus

Guidance programme	Recommendation
Interventional procedures	IPG XXX corneal implants for refractive error In production.
Technology appraisals	None applicable
Clinical guidelines	None applicable
Public health	None applicable

Appendix C: Literature search for corneal implants for corneal disease

IP: 391 Semi-circular corneal implants		
Database	**Date searched**	**Version searched**
Cochrane Library	26/09/06	2006 Issue 3
CRD databases (DARE & HTA)	26/09/06	2006 Issue 3
Embase	26/09/06	1980 to 2006 Week 38
Medline	26/09/06	1966 to September Week 2 2006
Premedline	26/09/06	September 25, 2006
CINAHL	26/09/06	1982 to September Week 4 2006
British Library Inside Conferences	26/09/06	-
NRR	26/09/06	2006 Issue 3
Controlled Trials Registry	26/09/06	-

The following search strategy was used to identify papers in Medline. A similar strategy was used to identify papers in other databases.

1	intacs.tw.	74
2	keravision.tw.	24
3	(cornea$ adj3 (implant$ or insert$ or ring$ or disc$ or disk$)).tw.	1082
4	(intrastromal adj3 (implant$ or insert$ or ring$ or disc$ or disk$)).tw.	120
5	(ferrara adj3 (implant$ or insert$ or ring$ or disc$ or disk$)).tw.	10
6	(prescription adj3 (implant$ or insert$ or ring$ or disc$ or disk$)).tw.	300
7	icrs.tw.	135
8	or/1-7	1526
9	Myopia/	9145
10	Keratoconus/	1864

11	myop$.tw.	24250
12	keratoconus.tw.	1869
13	nearsighted$.tw.	50
14	shortsighted$.tw.	62
15	Astigmatism/	3969
16	astigmatism.tw.	4048
17	(refractive adj3 (error$ or defect$ or disorder$)).tw.	3482
18	Refractive Errors/	4938
19	Dilatation, Pathologic/	6180
20	((cone or conical) adj3 (ectasia or cornea)).tw.	14
21	or/9-20	42648
22	8 and 21	320
23	animals/	4094980
24	humans/	9775865
25	23 not (23 and 24)	3098534
26	22 not 25	306
27	limit 26 to english language	256