NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of corneal implants for the correction of refractive error

Short-sightedness is the inability to see clearly at a distance. Eyesight can usually be corrected by wearing spectacles or contact lenses. The insertion of clear plastic implants into the cornea is an interventional procedure aiming to improving vision in short-sightedness.

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 November 2006

Procedure name

- Corneal implants for the correction of refractive error

Specialty societies

- Royal College of Ophthalmologists

Description

Indications

Myopic refractive error. Myopia occurs when light from a distant object is brought into focus in front of the retina, rather than on it. This is usually because the eye is too long, but it may be due to the cornea being too steeply curved (this may be due to keratoconus for which a separate overview and guidance has been produced). Near objects are seen clearly but more distant ones are blurred. This procedure may not be suitable for patients with a high degree of astigmatism.

Current treatment and alternatives

Focusing (refractive) errors are usually corrected by wearing spectacles or contact lenses, both of which correct visual acuity and are acceptable solutions to the majority of patients. In addition, surgical treatments can be used to treat myopia, including photorefractive keratectomy (PRK) and laser in situ keratomileusis (LASIK).

What the procedure involves

Corneal implants are flexible, crescent-shaped rings of polymethyl methacrylate that are inserted in the periphery of the cornea. They affect refraction in the eye by physically changing the shape of the cornea, flattening 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.

Efficacy

The key efficacy outcomes for this procedure that were identified by specialist advisers were visual acuity (both uncorrected and best spectacle-corrected), accuracy of correction, reduced astigmatism, ocular topography, and contrast sensitivity.

Outcomes used to measure visual acuity varied between studies, making comparisons difficult. Similarly length of follow up varied between studies, and it was not always clear how many patients (or eyes) were available at each time point.

Visual Acuity

In matched case analysis, uncorrected visual acuity (UCVA) one day after the procedure was reported to be 20/20 or better in 24% (20/82) of eyes receiving corneal implants, and 55% (73/133) of eyes undergoing Laser in Situ Keratomileusis (LASIK). At three months of follow-up the proportion of eyes with 20/20 acuity or better was 75% (58/77) and 67% (84/126) respectively - statistical significance was not reported[1].

Following insertion of corneal implants UCVA of 20/20 or better was reported in 74% of eyes at one year in a case series study (absolute numbers not provided)[2]. In another case series study 43% (35/79) of eyes had 20/20 vision or better (uncorrected) at one year follow up, rising to 64% (27/42) at five years[3]. Sixty-three percent (83/132) of eyes had Best Corrected Visual Acuity (BCVA) of 20/20 or better at one year in a third case series study[4]. In a fourth case series study acuity had improved, with the ratio of postoperative UCVA to baseline UCVA being 0.77 at 6 months[5].

One case series of 159 eyes receiving corneal implants found that the change in manifest refraction spherical equivalent (one type of measurement of visual acuity) was 0.32 (±0.79) dioptres (D) between one and three months of follow-up, but only 0.01 (± 0.58) between six and 12 months follow up[4].

The proportion of eyes in which correction of vision was within 1.0 D of intended ranged between 68% (28/42), 92% (absolute numbers not provided)[2], and 100% (16/16)[5], and the proportion corrected to within 0.5 D ranged from 41% (17/42), 69% (absolute numbers not provided)[2], and 81% (13/16)[5].

Patient satisfaction

One case series found that patient satisfaction with the result of the implant of corneal segments was rated as excellent by 47% of patients at one year of follow-up, good by 41%, fair in 9%, and poor by 2% of 104 patients surveyed[6].

Surgical parameters

One case series found that the mean operative time was 17 (±10) minutes, in 159 eyes treated[4]. Another case series 4% (absolute numbers not provided) of patients required a secondary surgical intervention following insertion of corneal implants[2].

Safety

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

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

Across the studies identified, the rate of corneal perforations ranged from between 0% (0/21)[5], <1% (3/452)[2], and 2% (3/163)[6]. The timing of these complications is not defined. One case series reported one incident of infectious keratitis in 452 patients treated[2].

A number of sight complications were reported following insertion of corneal implants, including poor night vision in 5% of patients (absolute numbers not

provided)[2], glare in between 1% of patients (absolute numbers not provided)[2] and 2% (2/104)[6], halos in between 1% (absolute numbers not provided)[2] and 2% (2/104)[6], and photophobia in between <1% (absolute numbers not provided)[2] and 1% (1/104).[6], although degree of severity varied between studies.

One case report described a patient in whom partial extrusion of an implant occurred following thinning of the corneal stroma at five years of follow-up. The implants were successfully removed and best spectacle corrected visual acuity recovered to 20/25 at 4 weeks[7].

A loss of two or more lines of visual acuity of best spectacle corrected visual acuity was reported in 5% (4/79) eyes at one year follow-up and 7% (3/42) of eyes at five year follow-up in one case series[3]. In a second case series two lines were lost in 4% (5/138) of eyes, and more than two lines in 2% (3/138) of eyes, although none of these patients requested removal of implants[4]. Among eyes receiving corneal implants 9% (7/76) demonstrated a decrease of two or more lines compared to 1% (1/126) of LASIK treated eyes at three months follow up in a matched case analysis[1].

One case report described a patient where linear opacities in the anterior central stroma of both eyes at 4 year follow up[8]. Microscopic study showed highly reflective crystalline-like structures in the anterior stroma of both central corneas, microbiology studies showed no bacterial growth. The segments were explanted and there was no evidence of bacterial colonisation on the segments, and after a further 8 months follow up the clinical appearance of the cornea remained unchanged.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to corneal implants for the correction of refractive error. Searches were conducted via the following databases, covering the period from their commencement to the 26/09/06 and updated to 15/01/07: 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, laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising methodology.
Patient	Patients with refractive error (myopia)
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 one case series report of a multicentre trial[2], one case matched comparison[1], three further case series (four reports[3,5,6,4]), and two case reports[7,8].

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

Existing reviews on this procedure

One systematic review by the American academy of ophthalmology was found during literature searching. The details of this study are extracted in table 2.

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:

IPG164 Photorefractive (laser) surgery for the correction of 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 the correction of refractive error

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Rapuano C J (2001)[2] **Case series – pooled data** USA (international studies) Study period: not stated **n = 452 Patients** from an unspecified number of phase II and III trials Population: Male = 49%, Age =39 years. UCVA ≤20/125 = 43%, UCVA 20/50 to 20/100 = 44%, UCVA 20/25 to 20/40 = 11%. Indications: Myopia in range -1.00 to -3.50 D, stable for 6 months. Corneal diameter <10 mm, corneal curvature >40D and <46D Technique: Intacs insertion, techniques varied between studies. **Follow-up: 12 months** Conflict of Interest: not stated.	**Surgical parameters** A total of 447 implants were successfully placed in 452 patients at the first attempt. In 4 patients implantation was not successful due to intraoperative complications. Dissatisfaction requesting removal was reported in 11 patients A total of 9% (37/449) of patients had the inserts explanted with no clinically significant complications reported. A total of 3.8% of patients required a secondary surgical intervention (not otherwise defined) (absolute numbers not provided). **Visual acuity** 97% of patients had UCVA of 20/40 or better at 1 year follow up (absolute numbers not provided) 74% of patients had UCVA of 20/20 or better at 1 year follow up. 92% of patients had correction to within ±1D of intended correction, and 69% to within ±0.5D. There was a change in of ≤1D in scores between the 3 months and 6 months examination in 97% of patients.	**Operative complications** Corneal surface perforation <1% (3/452) Chemosis <1% (1/452) **Subsequent complications** At 12 months follow up Reduced central corneal sensation ≥ 20mm 5.5% Induced cylinder >1 to 2 D 3.7% Deep neovascularisation (not affecting visual acuity or function) 1.2% Loss of >2 lines of BSCVA 1.0% Persistant epithelial defect 0.2% Iritis / uveitis 0.2% Any ocular complication 11% (45/410) Intrastromal tunnel deposits (no significant visual consequence) 68% (213/312) Absolute numbers were not provided unless where stated Adverse events (serious or permanent if untreated) Infectious keratitis n=1 Shallow placement of segment n=1 Loss of 2 lines of BSCVA over two consecutive visits n=1 Anterior chamber perforation n=2	The search was undertaken in Medline only between the dates 1990 and 2000 and limited to English language articles Ophthalmic professionals and industry were also contacted to identify articles. All studies were assigned a rating based on study design, but no quality appraisal was undertaken. Abstracts from meeting presentations that were not subject to peer review were not included in the analysis 91% follow up at 1 year (410/449), patients with unsuccessful implantation and those without an examination were not included in final analyses. The total number of patients who had visual symptoms was not described The study reports significant differences in safety and efficacy results for three different Intacs thicknesses, data not extracted here.

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Rapuano C J (2001) Cont.		**Visual Symptoms** Symptoms rated as 'Always or severe' at 12 months follow up (n=314) Poor night vision 5.1% Blurry vision 2.9% diplopia 1.6% Glare 1.3% halos 1.3% Fluctuating distance vision 1.0% Fluctuating near vision 0.3% Photophobia 0.3%	Authors state that although the efficacy and safety of Intacs appear comparable to PRK and LASIK, the technology has not been embraced by surgeons or patients, probably because the refractive indications are more limited.

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Suiter B G (2000)[1] **Non randomised controlled trial (matched case series)** USA Study period: not stated **n = 215 eyes (82 Intacs)** Population: Characteristics not stated Indications: Binocular vision with BSCVA of 20/20 or better, and Myopia in range -1.00 to -3.50 D, with astigmatic refraction of 1.00 D or less Technique: Intacs insertion, or LASIK, no further details provided. **Follow-up: 3 months** Conflict of Interest: trial supported by manufacturer and one author is a paid consultant for manufacturer	**Visual acuity** UCVA on day 1 of follow up Corneal implants / LASIK ≥ 20/40: 87% (71/82) / 95% (126/133) ≥ 20/20: 24% (20/82) / 55% (73/133) ≥ 20/16: 6% (5/82) / 14% (8/133) Statistical significance not stated UCVA at 3 months follow up Corneal implants / LASIK ≥ 20/40: 99% (76/77) / 95% (120/126) ≥ 20/20: 75% (58/77) / 67% (84/126) ≥ 20/16: 38% (29/77) / 29% (37/126) Statistical significance not stated 70% (45/77) of eyes with corneal implants and 82% (103/126) of LASIK treated eyes were within 0.5 D of intended correction at 3 months follow up. 99% (76/77) of implant treated and 965 (121/126) of LASIK treated eyes were within1.0 D of intended correction at the same time point. The mean MRSE in the implant group changed from -2.28 (± 0.65) D at baseline to -0.17 (± 0.47) D at 3 months. In the LASIK treated eyes MRSE decreased from -2.70 (± 0.71) D at baseline to -0.11 (± 0.44) D at 3 months. Visual function score at 3 months Corneal implants / LASIK Excellent: 90% (69/77) / 78% (98/126) Good: 10% (8/77) / 18% (23/126) Fair: 0% / 4% (5/126) Poor: 0% / 0% Statistical significance not stated	**BSCVA** Corneal implants / LASIK Decreased 2 or more lines: 9% (7/76) / 1% (1/126) Unchanged: 45% (34/76) / 46% (56/126) Increased 1 line: 26% (20/76) / 37% (46/126)	Retrospective study Matched LASIK cases from the same surgeon with similar age, preoperative myopia, astigmatism characteristics, where full correction was intended and a single intervention was undertaken. **Independent clinicians obtained outcomes data.** **Different charts were used to evaluate UCVA between the two groups.** Follow up data are available on 95% of the LASIK patients and 94% of the Intacs treated patients at 3 months. No statistical comparison in scores or changes of scores from baseline between the groups is presented. Baseline characteristics of patients are not provided, nor is a description of case matching procedure. Authors state that each different thickness of corneal implant segment achieved an additional 0.7 D refractive change where as LASIK can be programmed for 0.01 D increments

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Schwartz A P (2006)[3] **Case series** International Study period: 1993 to 1994 **n = 72 patients (113 eyes)** Population: Characteristics not stated Indications: Myopia in range -0.75 to -4.50 D, and BSCVA of 20/20with a central corneal thickness >0.48 mm Technique: Intacs insertion under topical anaesthesia, with postoperative combination antibiotic and steroid eye drops. **Follow-up: up to 5 years.** Conflict of Interest: Not clear	**Visual acuity** UCVA 1 year 5 years ≥ 20/40 88% (71/79) 83% (35/42) ≥ 20/20 43% (35/79) 64% (27/42) BSCVA At no stage throughout follow up did any eye have BSCVA worse then 20/40 68% (28/42) of eyes with corneal implants were within 1 D of intended correction at 5 years follow up compared to 71% (56/79) eyes at 1 year. 41% (17/42) of eyes with corneal implants were within 0.5 D of intended correction at 5 years follow up compared to 38% (30/79) eyes at 1 year. **Astigmatism** No patient had astigmatism of >2.0 D at 5 years follow up, although 5% (2/42) of eyes showed an induced astigmatism > 1.0 D.	**BSCVA loss** There was a loss of more than two lines of visual acuity in 5% (4/79) eyes after 1 year of follow up, which increased to 7% (3/42) eyes at 5 years follow up. **Optical complications** Slitlamp biomicroscopy at both 1 and 5 years found non-progressive faint diffuse haze in the stromal tunnel created during implantation, with minimal white deposits, and clinically insignificant epithelial iron lines and inclusion cysts.	Study refers to the intervention being a 360 degree ring, although the description of insertion is similar to that of ring segments. 42 eyes available for 5 year follow up. The patients may also be included in the review by Rapuano (2001) but data extracted here to demonstrate 5-year outcomes. No details provided of case selection process.

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Wijdh R H (2000)[5] **Case series** Holland Study period: May 1997 - Nov 1998 **n = 15 patients (21 eyes)** Population: Male =46%, Age =36 years. Patients with mean myopia of -3.0D and range -1.5 D to -4.1 D. mean UCVA 0.08, mean BSCVA =1.1. Indications: Patients with manifest cylinder of <1.0 D and a central corneal thickness >0.50 mm Technique: Intacs (various thicknesses) insertion at a depth of 75% of the corneal thickness under topical anaesthesia, with postoperative antibiotic NSAID and prednisolone eye drops. **Follow-up: 6 months.** Conflict of Interest: None	**Visual acuity** UCVA 3 months / 6 months 1.0 or better: 44% (8/18) / 43% (7/16) 0.5 or better: 94% (17/18) / 100% (16/16) Ratio of postoperative UCVA to preoperative UCVA: 0.74 / 0.77 BSCVA 3 months / 6 months 1.0: 100% (18/18) / Not reported Ratio of postoperative BSCVA to preoperative BSCVA: 1.0 / 0.96 94% (17/18) of eyes with corneal implants were within 1 D of intended correction at 3 months and 61% (11/18) eyes were within 0.5 D of intended correction. 100% (16/16) of eyes with corneal implants were within 1 D of intended correction at 6 months and 81% (13/16) eyes were within 0.5 D of intended correction.	**Refractive complications** 3 months / 6 months Overcorrection > 1.0 D: 0% / 0% Induced astigmatism: 1.03 D (± 0.75) / 1.0 D (± 0.5) **Complications** No intraoperative complications were reported Small epithelial defects occurred around the incision site in almost all patients which responded well to eye drops and all resolved within 1 week outcome / rate Conjuntival haemorrhage (no discomfort): 13% (2/15) Corneal perforations: 0% Lamellar channel deposits: 'almost all' Glare or halos, particularly in the dark: 'almost all' Migration of ring segment into opposite channel, and neovascularisation at week 7: 7% (1/15) High postoperative astigmatism: 7% (1/15) Explantation of implant, due to poor quality of vision: 7% (1/15)	Prospective series 18 eyes available for follow up at 3 months and 16 eyes at 6 months. No details provided about method of case selection of accrual. Two operators undertook all the procedures. Authors state that there was no relationship between refractive outcome and thickness of ring segments implanted.

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Ruckhofer J (2001)[6,4] **Case series** European multicentre Study period: May 1996 - Dec 1997 **n = 107 patients (159 eyes)** Population: Male =44%, Age =33 years. Patients with UCVA 20/20 to 20/800, worse then 20/40 in 98%. Indications: Patients with myopia in range -1.0 D to -6.0 D stable for 6 months (<0.5 D change) and astigmatic component of no more than + 1.0 D, and a central corneal thickness >0.40 mm, no ocular condition predisposing to complications or history of glaucoma. Technique: Intacs rings (various thicknesses) insertion at a depth of 75% of the corneal thickness under general anaesthesia (32%) or IV conscious sedation. An antibiotic-steroid ointment applied at the end of the procedure to the eye and postoperative antibiotic NSAID and prednisolone eye drops given. **Follow-up: 12 months.** Conflict of Interest: None	**Surgical parameters** Mean operative time was 17 (± 10) minutes. The implants were successfully placed in 98% (159/163) attempts 11 implants were removed and one was exchanged then removed. 3 months after removal of the implants the MRSE was within 1.0 D of baseline value in all patients and within 0.5 D in 73% (8/11) of patients at 3 months follow up. The implants were repositioned in 4 eyes. Epithelia defect had healed in 85% (132/156) of patients at 1 week. **Visual acuity** UCVA 		1 day	3 months	12 months
Worse than 20/40	NR	NR	4% (5/132)
20/40 or better	67% (103/154)	92% (133/144)	96% (127/132)
20/20 or better	25% (38/154)	49% (71/144)	63% (83/132)
20/16 or better	NR	NR	32% (42/132) | Overall (for all thicknesses) 82% (84/114) of eyes were within 1 D of intended correction in cycloplegic refraction spherical equivalent at 12 months and 49% (56/114) eyes were within 0.5 D of intended correction. Stability of correction The mean change in manifest refraction spherical equivalent was 0.32 (± 0.79) D between months 1 and 3, 0.08 (± 0.53) D between months 3 and 6, and 0.01 (± 0.58) D between months 6 and 12.	**Refractive complications** The mean baseline manifest refraction astigmatism was 0.36 (± 0.38) D. At 12 months follow up it was 0.28 (± 0.69) D. Specifically 25% (34/138) of eyes had an induced cylinder of more than 0.5 D, 11% (15/138) >1.0 D, 6% (8/138) >1.5 D, and 2% (3/128) >2.0D. There was no significant difference in induced cylinder between implant thickness. At 12 months 4% (5/138) of eyes had lost 2 lines of BSCVA, and 2% (3/138) had lost more than 2 lines. None of these patients requested removal of the implants At 12 months the mean intra-ocular pressure was 1.5 (±2.5) mm Hg lower than at baseline. **Complications** Posterior corneal micro-perforations <1% (1/163) Anterior corneal surface perforation 2% (3/163) All 4 perforations healed without clinically meaningful sequelae Incisional gapes n=2 Channel infection (cornel recovered with high dose topical antibiotics n=1 Mild subconjunctival haemorrhage due to vacuum centring) 56% (64/114)	**12 eyes in which the implants were removed, and 1 where a different thickness was implanted were excluded from analysis**. 7 patients were lost to follow up and 1 missed the 12 month evaluation leaving 138 eyes analysed at 12 months. Data for baseline UCVA score not presented in a similar fashion to that at follow up, making comparison difficult. No statistical comparison in scores or changes of scores from baseline between the groups is presented. **Study cohort represents patients in which the implants were successfully implanted**. Not always clear what number of patients were available for evaluation of many of the safety outcomes.

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Ruckhofer J (2001) Cont.	**Patient satisfaction** Good or excellent satisfaction with the results of implantation was reported by 88% of patients at 12 months follow up.	**Complications**	

Satisfaction grade	1 day	1 month	6 months	12 months
Excellent	9%	18%	48%	47%
Good	36%	46%	36%	41%
Fair	37%	25%	12%	9%
Poor	11%	10%	3%	2%
n=	158	156	136	104

Mild aqueous flare at 1 day	64% (73/114)
Stromal thinning at 2 months	1% (2/156)
Epithelial inclusion cysts at up to 3 months	7% (11/156)
Epithelial inclusion cysts at 12 months	1% (1/104)
Entral corneal cloudiness	0%
Mild to moderate postoperative pain	68% (107/158)
Severe postoperative discomfort	13% (20/158)
Mild to moderate foreign body sensation / sctratchiness / photophobia to 48 hours	58% (91/158)
Severe foreign body sensation / sctratchiness / photophobia to 48 hours	10% (16/158)
Mild photophobia (12 months)	9% (9/104)
Moderate photophobia (12 months)	1% (1/104)

Vision outcomes at 12 months n=104

Outcome	None	Mild	moderate	severe
Fluctuating distance vision	65%	25%	8%	0%
Halos	93%	3%	2%	0%
Glare	87%	9%	2%	0%
Double vision	78%	13%	6%	1%

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Bourges J L (2003)[7] Case report France Study period: Not stated **n = 1 patient (1 eye)** Population: Male =0%, Age =41 years. Patient with BSCVA 20/20, -2.25 D refractive error. Indications: not stated. Technique: Intacs ring segments (0.35 mm thickness) inserted at a depth of 70% of the corneal thickness under topical anaesthesia. **Follow-up: 5 years.** Conflict of Interest: None	**Visual acuity** 3 months / 12 months / 5 years UCVA 20/32 / 20/20 / NR BSCVA 20/25 / 20/20 / 20/32* * With + 1.00 and +0.50 X 90.	**Complications** No operative or immediate postoperative complications occurred Mild persistent halos reported with no clinical discomfort at 1 year, with lamellar channel deposits. At five years follow up the patient reported progressive eye discomfort, foreign body sensation, and blurring of vision. The upper and anterior parts of the corneal stroma in front of the implant had thinned, and patrial extrusion of the segment was observed. The implant was removed surgically under topical anaesthesia. Analysis showed no infection of the corneal bed or implant. However antibiotic therapy was given for 1 week, followed by polyvinyl alcohol treatment for 6 weeks Four weeks after removal BSCVA returned to 20/25 with -2.00 -2.00 X 25. Two tracks of lamellar haze and a few channel deposits were noted and a temporal extended scar at the level of the stromal necrosis was recorded. At 9 months after removal the visual acuity and biomicroscopic condition had not changed. The patient reported mild photophobia and persistent foreign body sensation.	It is not stated how many implant procedures had been undertaken at the centre where this complication was reported. No details provided of antibiotic regimen (if any) employed after implantation. Not clear when onset of symptoms that required removal first began The operator experience is not reported.

Abbreviations used: D – dioptre, UCVA – uncorrected visual acuity, LASIK – Laser in situ keratomileusis, BSCVA – Best spectacle corrected visual acuity, MRSE – manifest refraction spherical equivalent

Study details	Key efficacy findings	Key safety findings	Comments
Katsoulis K (2006)[8] Case report Switzerland Study period: Not stated **n = 1 patient (2 eyes)** Population: Male =0%, Age =45 years. Patient with BSCVA 20/20, -3.5 to -3.75 D refractive error. Indications: Myopia (not otherwise specified). Technique: Intacs ring segments. (not otherwise specified) **Follow-up: 4 years+.** Conflict of Interest: None	**Visual acuity** At 4 months follow up UCVA was recorded as 20/16 bilaterally	**Complications** At 4 month follow up deposits along the channels containing the corneal ring segments were noted. At 40 months follow up in the left eye and 48 months follow up in the right eye the patient complained of 'decreased and blurred vision with halos' At 4 year follow up BSCVA was 20/30 in the right eye and 20/16 in the left eye. The channel deposits had become more dense and visible and there were linear opacities in the anterior central stroma of both eyes. Microscopy showed highly reflective crystalline-like structures in the anterior stroma of both central corneas, microbiology studies showed no bacterial growth. The segments were explanted and there was no evidence of bacterial colonisation or biofilm production on the surface of the ring segments. Eight months following explantation the clinical appearance of the central cornea was unchanged. BSCVA was 20/16 and 20/20 in the right and left eye respectively.	It is not stated how many implant procedures had been undertaken at the centre where this complication was reported. The operator experience is not reported. Antibiotic and steroid regimen following the index procedure were not described.

Validity and generalisability of the studies

- Significant publication duplication of patients in FDA trials, every effort has been taken to ensure that patients have not been double counted in Table 2 unless where stated.
- There is considerable variation within and between studies in the degree of myopia permitted for patient inclusion.
- It is unclear from the studies the proportion of all patients that had abnormally shaped corneas, or myopia due to other abnormality. Curvature / abnormal shape of the cornea appears to have been variably measured in the few studies that report this characteristic.
- None of the available case series undertook a statistical analysis of change in outcome variables from baseline.
- 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 could be subject to considerable degree of placebo effects.
- Overall, the degree of myopia of the patients included in the studies does not appear to have been severe.

Specialist advisers' 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 B Beigi, Mr S Daya.

- Advisers were asked to comment on this procedure for correction of refractive errors. However, they also suggested that the procedure can be used in Keratoconus and iatrogenic ectasia. These indications will be considered in a second overview.
- The Advisers were split in their consideration of the current status of this procedure. Two thought it to be an established procedure, and one that it was novel and of uncertain safety and efficacy.
- The expected benefits of the procedure are a correction of low myopia with a rapid recovery time and minimal ocular morbidity.
- Although there is 10 years of work demonstrating the safety and efficacy of this procedure for myopia of up to -3.0 D it has been not widely taken up due to simultaneous development of laser correction technology.
- Adverse events that have been reported include photophobia, glare, foreign body sensation, extrusion, corneal perforation, and infection these may lead to implant removal.
- Additional theoretical adverse events cited by advisers included ring erosion, inflammation, corneal melt, damage to retina or optical nerve through increased intraocular pressure, and loss of effect over time.
- Advisers noted that the procedure is reversible as the implants can be removed.

- Training should consist of education about the procedure, wet lab training, and early cases may be undertaken with a trainer present.
- One adviser suggested that there may be a difference between method of corneal channel creation between mechanical and femtosecond laser techniques.
- Advisers were divided in their opinion as to how widely this procedure would be available if it were found to be safe and efficacious.

Issues for consideration by IPAC

- The procedure is intended to be reversible and adjustable
- In April 1999 Intacs were approved by the FDA for use in adults 21 years or older who have mild myopia (-1.00 to -3.00 D of spherical equivalent at the spectacle plane) with mild astigmatism (+1.00 D or less) and whose vision has been stable for the past year, as demonstrated by a change of ≤0.50 D for at least 12 months before the preoperative examination.

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

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2 Rapuano CJ, Sugar A, Koch DD et al. (2001) Intrastromal corneal ring segments for low myopia: a report by the American Academy of Ophthalmology. *Ophthalmology* 108: 1922-1928.

3 Schwartz AP, Tinio BO, Babayan A et al. (2006) Intrastromal corneal ring implantation (360 degrees ring) for myopia: a 5-year follow-up. *Eye & Contact Lens: Science & Clinical Practice* 32: 121-123.

4 Ruckhofer J, Stoiber J, Alzner E et al. (2001) One year results of European Multicenter Study of intrastromal corneal ring segments. Part 1: refractive outcomes. *Journal of Cataract & Refractive Surgery* 27: 277-286.

5 Wijdh RH and van Rij G. (2000) Intrastromal corneal ring segments (ICRs): three- and six months results. *Documenta Ophthalmologica* 100: 27-37.

6 Ruckhofer J, Stoiber J, Alzner E et al. (2001) One year results of European Multicenter Study of intrastromal corneal ring segments. Part 2: complications, visual symptoms, and patient satisfaction. *Journal of Cataract & Refractive Surgery* 27: 287-296.

7 Bourges JL, Trong TT, Ellies P et al. (2003) Intrastromal corneal ring segments and corneal anterior stromal necrosis. *Journal of Cataract & Refractive Surgery* 29: 1228-1230.

8 Katsoulis K, Sarra GM, Schittny JC et al. (2006) Bilateral central crystalline corneal deposits four years after intacs for myopia. *Journal of Refractive Surgery* 22: 910-913.

Appendix A: Additional papers on Corneal implants for the correction of refractive error 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	Direction of conclusions	Reasons for non-inclusion in Table 2
Asbell PA, Ucakhan OO. Long-term follow-up of Intacs from a single center. Journal of Cataract & Refractive Surgery 2001; 27(9):1456-1468.	n=72 (113 eyes) FU = 17.5 months	UCVA 20/40 or better in 95% of eyes	Same patients as Rupuano (2001) as included in table 2
Baikoff G, Maia N, Poulhalec D, Fontaine A, Giusiano B. Diurnal variations in keratometry and refraction with intracorneal ring segments.[see comment]. Journal of Cataract & Refractive Surgery 1999; 25(8):1056-1061	n=10 (eyes) FU = to 2 years	At 1 year corneal implant treated eyes had a tendancy toward an evening myopic shift	Larger series are included in table 2
Bourcier T, Borderie V, Laroche L. Late bacterial keratitis after implantation of intrastromal corneal ring segments. Journal of Cataract & Refractive Surgery 2003; 29(2):407-409	n=1 FU = 3 months	Case report of bacterial keratitis infection	Larger series are included in table 2
Holmes-Higgin DK, Burris TE, Lapidus JA, Greenlick MR. Risk factors for self-reported visual symptoms with Intacs inserts for myopia. Ophthalmology 2002; 109(1):46-56.	n=263 FU = 1 years	Implanted eyes showed a tendancy towards an evening myopic shift	Larger series are included in table 2
Holmes-Higgin DK, Burris TE, Asbell PA, Durrie DS, Schanzlin DJ. Topographic predicted corneal acuity with intrastromal corneal ring segments. Journal of Refractive Surgery 1999; 15(3):324-330.	n=93 FU – 3 months	Predicted corneal acuity did not change significantly from baseline in eyes implanted with corneal ring segments.	Same patients as Rupuano (2001) as included in table 2
Kessler D, El Shiaty AF, Wachler BS. Evaluation of tear film following Intacs for myopia. Journal of Refractive Surgery 2002; 18(2):127-129.	n=10 (17 eyes) FU = 1month	There was a transient dry eye period following insertion, but tear film quality was restored within 1 week	Larger series are included in table 2
Nagy Z, Krasznai G, Modis L, Jr., Sefcsik I, Furka I, Miko I. Intrastromal corneal ring, a new refractive surgical technique to decrease myopia. Experimental and clinical results. Acta Chirurgica Hungarica 1997; 36(1-4):248-250.	n=3 FU = 3 to 10 months	The desired optical results proved permanent to up to 10 months	Larger series are included in table 2
Nose W, Neves RA, Burris TE, Schanzlin DJ, Belfort JR. Intrastromal corneal ring: 12-month sighted myopic eyes. Journal of Refractive Surgery 1996; 12(1):20-28.	n=10 (10 eyes) FU = 1 year	Cornael implants can correct 1.5 to 3.0 D of myopia, and maintain BSCVA	Larger series are included in table 2
Rau M, Dausch D. Intrastromal corneal ring implantation for the correction of myopia: 12-month follow-up. Journal of Cataract & Refractive Surgery 2003; 29(2):322-328.	n=9 (15 eyes) FU = 1 year	At twelve months all eyes were within 1.0 D of intended manifest refraction	Larger series are included in table 2
Schanzlin DJ. Studies of intrastromal corneal ring segments for the correction of low to moderate myopic refractive errors. Transactions of the American Ophthalmological Society 1999; 97:815-890	n=89 eyes FU=12 months	68% of patients had correction not within 0.5 D of intended	Same patients as Rupuano (2001) as included in table 2

Schanzlin DJ, Abbott RL, Asbell PA, Assil KK, Burris TE, Durrie DS et al. Two-year outcomes of intrastromal corneal ring segments for the correction of myopia. Ophthalmology 2001; 108(9):1688-1694.	n=452 FU = to 24 months	93% of patients within 1.0 D of intended correction at 2 years	Same patients as Rupuano (2001) as included in table 2
Schanzlin DJ, Asbell PA, Burris TE, Durrie DS. The intrastromal corneal ring segments. Phase II results for the correction of myopia. Ophthalmology 1997; 104(7):1067-1078.	n=102 FU = 3 months	99 patients had UCVA of 20/'40 or better	Same patients as Rupuano (2001) as included in table 2 Series with longer FU are included in table 2
Schwartz, A. R., Tinio, B. O., Esmail, F., Babayan, A., Naikoo, H. N., and Asbell, P. A. Ten-year follow-up of 360 degrees intrastromal corneal rings for myopia. Journal of Refractive Surgery 22 (9) 878-883.2006	n=10 FU = 10 years	No statistically significant difference between UCVA at 1 year and 10 years. 90% had BSCVA of ≤20/25 at 10 years.	Same patients as Schwartz (2006) as included in table 2 Larger series are included in table 2
Sugar A. Correction of spherical myopia with a single 150-degree intrastromal corneal ring segment. Journal of Cataract & Refractive Surgery 2004; 30(5):1127-1129.	n=1 FU = 1 week	Report of a successful removal of 1 of 2 intacs segment	Larger series are included in table 2
Twa MD, Hurst TJ, Walker JG, Waring GO, Schanzlin DJ. Diurnal stability of refraction after implantation with intracorneal ring segments. Journal of Cataract & Refractive Surgery 2000; 26(4):516-523	n=67 (134 eyes) FU = 6 months	95% of eyes were within 1 line of BSCVA from morning to evening	Same patients as Rupuano (2001) as included in table 2 Larger series are included in table 2
Twa MD, Karpecki PM, King BJ, Linn SH, Durrie DS, Schanzlin DJ. One-year results from the phase III investigation of the KeraVision Intacs. Journal of the American Optometric Association 1999; 70(8):515-524	n=95 FU = 12 months	99% of patients had 20/40 vision or better at 1 year	Same patients as Rupuano (2001) as included in table 2
Twa MD, Ruckhofer J, Shanzlin DJ. Surgically induced astigmatism after implantation of intacs intrastromal corneal ring segments. Journal of Cataract & Refractive Surgery 2001; 27(3):411-415	n=449 (eyes) FU = 12 months	Mean induced astigmatism was 0.13 D at 2 monhts	Same patients as Rupuano (2001) as included in table 2

Appendix B: Related published NICE guidance for Corneal implants for the correction of refractive error

Guidance programme	Recommendation
Interventional procedures	**IPG164** Photorefractive (laser) surgery for the correction of refractive error 1.1 Current evidence suggests that photorefractive (laser) surgery for the correction of refractive errors is safe and efficacious for use in appropriately selected patients. 1.2 Clinicians undertaking photorefractive (laser) surgery for the correction of refractive errors should ensure that patients understand the benefits and potential risks of the procedure. Risks include failure to achieve the expected improvement in unaided vision, development of new visual disturbances, corneal infection and flap complications. These risks should be weighed against those of wearing spectacles or contact lenses. 1.3 Clinicians should audit and review clinical outcomes of all patients who have photorefractive (laser) surgery for the correction of refractive errors. Further research will be useful and clinicians are encouraged to collect longer-term follow-up data. 1.4 Clinicians should have adequate training before performing these procedures. The Royal College of Ophthalmologists has produced standards for laser refractive surgery (www.rcophth.ac.uk/docs/ publications/RefractiveSurgeryStandardsDec2004.pdf)
Technology appraisals	None applicable
Clinical guidelines	None applicable
Public health	None applicable

Appendix C: Literature search for Corneal implants for the correction of refractive error

IP: 371 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