NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of insertion of a subretinal prosthesis system for retinitis pigmentosa

Retinitis pigmentosa is a disease that affects light-sensitive cells in the back layer of the eye (retina), typically leading to progressive loss of vision and sometimes blindness. In this procedure a light-sensitive microchip is implanted behind the retina to take on the function of damaged cells and help the person to see basic images.

Introduction

The National Institute for Health and Care Excellence (NICE) has prepared this interventional procedure (IP) overview to help members of the Interventional Procedures Advisory Committee (IPAC) make 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 IP overview was prepared in January 2015

Procedure name

- Insertion of a subretinal prosthesis system for retinitis pigmentosa

Specialist societies

- Royal College of Ophthalmologists
- British and Eire Association of Vitreoretinal Surgeons

Description

Indications and current treatment

Retinitis pigmentosa is the encompassing term for a group of degenerative eye conditions that cause progressive loss of retinal photoreceptors. The disease is often inherited. Patients initially experience ring scotoma and night vision problems which in most cases slowly progress, leading to the loss of peripheral vision. Central vision is usually preserved until late stages of the disease, but can be lost earlier with severe disease.

Conservative treatment strategies are aimed at early identification and treatment of complications such as cataract or macular oedema. Some newer treatments aim to slow the progression of the condition. Surgical treatments are being developed; including subretinal and epiretinal prostheses, as well as optic nerve implants, to restore basic sight.

What the procedure involves

Retinitis pigmentosa causes loss of retinal photoreceptors but inner retinal cells (ganglion and bipolar cells) remain intact. Subretinal prosthesis systems aim to restore perception of light, movement, and shapes by surgically implanting a microchip behind the retina. The microchip mimics the function of damaged outer retinal photoreceptors by absorbing light and converting it into retinotopically correct electrical pulses that stimulate the overlying bipolar cell layer. The bipolar cells propagate the signal to downstream retinal cells, which send visual information to the brain.

Implantation of the microchip is done with the patient under general anaesthesia. A vitrectomy is performed and the microchip is implanted underneath the macula using a transscleral, then subretinal approach. The microchip connects to a thin cable that exits the eye at the equator, through the choroid and sclera, and runs under the skin to a power source which is fixed to bone in the retroauricular region. This, in turn, connects to an external power source/control unit via a removable, surface mounted induction loop.

Outcome measures

Visual acuity

Visual acuity is usually tested by asking people to read a letter chart presented at a set distance. The level of visual acuity relates to the angle that the letters subtend at the retina, which in turn relates to the size of the letter and its distance from the person. The Snellen chart is commonly used and is expressed as a fraction where 6/6 (in metres) or 20/20 (in feet) is normal vision, and lower values (for example, 20/200 [in feet]) correspond to subnormal vision. Other charts

quantify vision in: logMAR (logarithm of the minimum angle of resolution) units, where lower values represent better vision; or Early Treatment of Diabetic Retinopathy study (ETDRS) charts where higher letter scores reflect better vision. If people cannot see the eye chart letters they may be able to count fingers presented in front of them, see hand movement or perceive changes in light intensity (light perception).

The logMAR scale can be converted to the Snellen scale as shown below.

Vision	logMAR	Snellen
Superior vision	–0.3	20/10
	–0.2	20/12.5
	–0.1	20/16
Normal vision	0.0	20/20
Worse than normal	0.1	20/25
		20/30
	0.2	20/32
	0.3	20/40
	0.4	20/50
	0.5	20/63
		20/70
	0.6	20/80
	0.7	20/100

The level of vision obtained with retinal prostheses is often quite rudimentary, and the traditional clinical vision tests listed above may therefore be inappropriate for many patients. Consequently other, sometimes novel, tests are used to assess visual function. These tests are performed to determine whether the patient: perceives light, is able to locate or count objects, is able to indicate directions of motion, is able to specify the orientation of shapes/patterns, or is able to identify objects.

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to insertion of a subretinal prosthesis system for retinitis pigmentosa. The following databases were searched, covering the period from their start to 17 December 2014: 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). Relevant published studies identified during consultation or resolution that are published after this date may also be considered for inclusion.

The following selection criteria (table 1) were applied to the abstracts identified by the literature search. Where selection 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 a laboratory or animal study. Conference abstracts were also excluded because of the difficulty of appraising study methodology, unless they reported specific adverse events that were not available in the published literature.
Patient	Patients with retinitis pigmentosa.
Intervention/test	Insertion of a subretinal prosthesis system
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 IP overview

This IP overview is based on 44 patients from 6 case series; but, there may be considerable overlap between studies.

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.

Table 2 Summary of key efficacy and safety findings on insertion of a subretinal prosthesis system for retinitis pigmentosa

Study 1 Stingl K (2013)

Details

Study type	**Case series**
Country	Germany
Recruitment period	Not reported
Study population and number	Patients with severe profound loss of vision caused by retinitis pigmentosa n=**9**
Age and sex	Mean age, 46.9 years; 55.5% (5/9) male
Patient selection criteria	Inclusion criteria: patients with light perception without correct light source localisation or complete blindness (no light perception) caused by retinitis pigmentosa and other hereditary retinal diseases were included. Exclusion criteria: not reported
Technique	A 3 mm x 3 mm x 70 micrometer-sized micro-photodiode array, with 1500 autonomously operating units, was implanted between the neuroretina and pigment epithelium in the macular area of 1 eye in each patient.
Follow-up	**Maximum of 9 months**
Conflict of interest/source of funding	Authors state that the trial was 'supported' by the manufacturer; however no further details were provided.

Analysis

Follow-up issues: One patient was excluded from analysis due to an intraoperative adverse event: the tip of the implant touched the head of the optic nerve resulting in device failure.

Study design issues: The small sample size means the study may lack sufficient statistical power to detect changes in outcome measures.

Study population issues: Eight patients had retinitis pigmentosa and 1 patient had cone-rod dystrophy. Potential overlap with other studies included in table 2 (Kitiratschky, 2014; Peters, 2013; Zrenner, 2010)

Other issues:

- Light perception test: the patient was placed 60 cm away from a black screen and asked to indicate whether they saw light when the screen was briefly illuminated with 1 or 2 flashes.
- Light source localisation test: the patient was placed in front of a black screen and asked to focus on a white dot. After an auditory cue, the patient was asked to indicate the direction of the pointed end of a white wedge that appeared: directed up, down, right or left.
- Direction of motion test: the patient was placed in front of a black screen and asked to indicate the direction of a white polka-dot pattern that moved across the screen at a randomly chosen angle.
- Basic Grating acuity test: the patient was placed in front of a screen and was asked to indicate the grid orientation of a black and white striped pattern that was presented at spatial frequencies ranging from 0.1 to 3.3 cycles per degree (cpd).
- Landolt C visual acuity test: the patient was place in front of a black screen and asked to indicate the orientation of a white ring which had a gap, similar to the letter 'C' that appeared in 1 of 4 orientations (up, down, right or left). The size of the C and its gap were reduced until the participant made a specified number of errors. No further details were provided
- Table tasks: the patient was seated in front of a black table and asked to identify 4 of 6 possible geometric objects (square, circle, triangle, rectangle, ring or crescent) and 4 of 6 possible tableware objects (small and medium-sized plates, cup, fork, spoon and knife). The patient was asked to report the number of objects, locate them and name them. The performance scores for each question ranged from 0 to 4.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **8**

Screen tasks

	Patient							
Outcome	1	2	3	4	5	6	7	8
Light perception	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Light source localisation	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes
Direction of motion (degrees per second)	No	No	3	No	7	5	35	5
Grating acuity (cycles per degree)	No	No	0.33	0.1	0.3	0.5	3.3	1.0
Landolt C visual acuity (logMAR)	No	No	No	2	No	No	1.43	No

- All patients were able to perceive light when their prosthesis systems were switched on; usually described as bright tilted square. Light perception thresholds were considerably better when prosthesis systems were switched on compared against when they were switched off. No further details were provided.
- Seven patients correctly indicated the direction in which the wedge was pointing when their prosthesis systems were switched on.
- Five patients were able to detect the direction of motion of polka dot patterns using their prosthesis systems.
- Grating acuity was successfully measured in 6 patients when their prosthesis systems were switched on, up to a maximum of 3.3 cycles per degree.
- Visual acuity was assessable, using Landolt C rings, in 2 patients when their prosthesis systems were switched on; their visual acuities were 1.43 and 2 logMAR respectively.

Table task scores (scores ranged between 0 and 4 with a point given for each correct answer)

	Mean score		
Outcome	System on	System off	p value
Counting shapes	2.8	0.5	0.012
Localisation of shapes	2.2	0.5	0.012
Discrimination of shapes	1	0.1	0.018
Counting tableware	2.9	0.5	0.012
Localisation of tableware	2.5	0.5	0.012
Discrimination of tableware	1.3	0.25	0.012

NB: results were obtained from a graph

Other outcome measures

- Three patients were able to read several letters. No further details were provided.
- Five patients were able to recognise facial characteristics, such as smiles and the presence/absence of glasses, and differentiate patterns on clothes. These patients stated that they were also able to localise and distinguish objects such as telephones, cutlery, red/white wine, door knobs, washbasins and wastebaskets.
- In relation to far-vision, patients were able to find the line of the horizon, and objects along the line of the horizon such as houses and trees. Cars on the street were localised by their surfaces reflecting light, during the day, or by their headlights. One patient reported being able to see the contours of heads, while another patient was able to read the letters of restaurant signs and store names.

Safety

Authors only reported the occurrence of serious adverse events. Other adverse events are believed to be reported in another article by the same research group (Kitiratschky, 2014 – See study 2)

- Postoperative bleeding which resulted in increased intraocular pressure was reported in 1 patient. This resolved without sequelae.
- An intraoperative touch of the operative nerve head by the tip of the implant resulted in the patient being unable to perceive light via the implant.

Study 2 Kitiratschky BD (2014)

Details

Study type	Case series
Country	Germany
Recruitment period	Not reported
Study population and number	Patients with severe profound loss of vision caused by retinitis pigmentosa **n=9**
Age and sex	Age and sex ratio not reported
Patient selection criteria	Inclusion criteria: patients who were 'fully blind' (no light perception) or unable to localise light correctly, due to retinitis pigmentosa or other hereditary outer layer degenerations, were included. Exclusion criteria: not reported
Technique	A 3 mm x 3 mm x 70 micrometer-sized micro-photodiode array, with 1500 autonomously operating units, was implanted between the neuroretina and pigment epithelium in the macular area of 1 eye in each patient.
Follow-up	**1 year**
Conflict of interest/source of funding	The study was funded by the manufacturer.

Analysis

Follow-up issues: Patients were followed-up at 2 and 4 weeks, as well as 2, 3, 6, 9 and 12 months. One patient had part of the subretinal prosthesis system explanted before the final 12 month follow-up assessment: the patient was still followed-up for12 months.

Study design issues: Authors reported the occurrence of all adverse events, related or unrelated to the insertion of the subretinal prosthesis. Adverse events that were observed during follow-up appointments, experienced by participants between each visit, or observed by general physicians, ophthalmologists or other physicians, were included.

Study population issues: Seven patients had retinitis pigmentosa, 1 patient had progressive cone dystrophy and 1 patient had Leber congenital amaurosis. Potential overlap with other studies included in table 2 (Stingl, 2013; Peters, 2013; Zrenner, 2010).

Other issues: Adverse events were classified as follows:

- Mild – asymptomatic or mild symptoms; clinical or diagnostic symptoms; clinical or diagnostic observations only; intervention not required.
- Moderate – minimal, local or non-invasive intervention required; limiting age-appropriate instrumental activities of daily living (preparing meals, shopping for groceries, using the telephone, managing money).
- Severe – Severe or medically significant, but not immediately life threatening; hospitalisation or prolongation of hospitalisation required; disabling; limiting self-care activities of daily living (bathing, dressing, feeding, using the toilet, taking medications).

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Key efficacy and safety findings

Safety

Number of patients analysed: **9 patients (75 adverse events)**

Adverse event	Proportion of all adverse events n (%) N=75	Relationship to the device (n)				Outcome (n)		
		Certain	Probable	Possible	No relation-ship	Resolved without sequelae	Unresolved	Unknown
Diseases of the blood and blood-forming organs								
Eosinophilia	1 (1)				1		1	
Diseases of the nervous system								
Polyneuropathy	1 (1)				1		1	
Diseases of the eye and adnexa								
Mucopurulent conjunctivitis	1 (1)	1				1		
Conjunctival hyperaemia	6 (8)	6				6		
Conjunctival erosions above the external part of the cable and suture erosions through the conjunctiva	12 (16)	11		1		12		
Peripheral corneal dent	1 (1)	1				1		
Acute iritis	1 (1)			1		1		
Retinal detachment with retinal break	1 (1)	1				1 [a]		
Retinal break without detachment	2 (3)	2					2	
Retinal vascular leakage and neovascularisation	10 (13)	1	7		2 [b]		9	1
Retinal haemorrhage	7 (9)	2	5			7		
Ocular hypertension	8 (11)	1	2	5		8 [a]		
Ocular pain	1 (1)		1			1		
Diseases of the circulatory system								
Thrombophlebitis of lower extremity	1 (1)				1	1		
Diseases of the respiratory system								
Acute nasopharyngitis	2 (3)				2	2		
Diseases of the musculoskeletal system and connective tissue								
Internal derangement of the knee	1 (1)				1	1		
Symptoms, signs, and abnormal clinical and laboratory findings								
Epistaxis	2 (3)				2	2		
Paraesthesia of skin	3 (4)	1		1	1	3		
Rash and other non-specific skin eruption	2 (3)			1	1	2		
Dizziness	1 (1)			1		1		
Headache	1 (1)			1		1		
Chronic pain	1 (1)			1		1		
Malaise and fatigue	2 (3)			2		2		
Localised oedema	2 (3)	1			1	2		
Raised C-reactive protein	1 (1)		1			1		
Injury, poisoning and other consequences of external causes								
Contusion of the eyelid and periocular area	1 (1)				1	1		
Postoperative bleeding	1 (1)	1				1		
Intraoperative perforation of the choroid	1 (1)	1				1 [c]		
Intraoperative contact of the optic nerve head with the implant	1 (1)	1				1 [c]		

[a] Severe adverse events were reported in 2 patients: ocular hypertension in 1 patient and a retinal detachment with retinal break in another. All other adverse events were classified as mild or moderate.

[b] Retinal leakage was present in 2 patients before implantation of the subretinal prosthesis system.
[c] Adverse events occurred in the same patient and 'resolved with sequelae': residual vision was lost in the study eye.

Study 3 Peters T (2013)

Details

Study type	**Case series**
Country	Germany
Recruitment period	Not reported
Study population and number	Patients with severe profound loss of vision caused by retinitis pigmentosa **n=9**
Age and sex	Mean age, 45 years; 100% (9/9) male
Patient selection criteria	Inclusion criteria: patients with no useful vision for up to 20 years who previously had a visual acuity of greater than 20/200 were included. Bright light stimulation mediated limited light perception, without any recognition of shapes, in all study participants. Exclusion criteria: not reported
Technique	A micro-photodiode array was implanted in 1 eye of each patient. No further details were provided.
Follow-up	**Mean of 6 weeks**
Conflict of interest/source of funding	Authors state that the trial was 'supported' by the manufacturer; however no further details were provided.

Analysis

Follow-up issues: Patients were meant to be followed-up for 4 weeks, at which point the subretinal prosthesis system was explanted. 6 patients completed the study as planned, 1 patient had the device removed at 8 weeks, another patient at 20 weeks, and 1 patient refused to have the device removed.

Study design issues: All patients received 1 psychological counselling session at screening. Additional counselling sessions were given to 8 out of the 9 study participants during the follow-up period; 1 patient declined to receive counselling. When possible, each patient received counselling from the same psychiatrist.

Study population issues: Potential overlap with other studies included in table 2 (Kitiratschky, 2014; Stingl, 2013; Zrenner, 2010).

Other issues: The Brief Symptom Inventory (BSI) is a 53-item questionnaire that assesses mental wellbeing using 9 domains: somatisation, obsession-compulsion, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation and psychoticism. Scores range from 0 to 100 with higher scores indicating worsening mental health. Three summary indexes can be calculated: the General Severity Index, a weighted frequency based on the sum of the ratings that the patient has assigned to each symptom; the Positive Symptom Total, a count of the number of the subjects' symptoms; the Positive Symptom Distress Index, a score reflecting the intensity of distress, corrected for the number of symptoms. A worsening of the condition can be stated only if scores lie above the normal limit of 63.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **9**

Mean Brief Symptom Inventory scores

Symptom dimensions	Pre-implant	Number of patients who had scores above the normal limit (>63 points)	pre-explant	Number of patients who had scores above the normal limit (>63 points)
Somatisation	47.67±7.97	0	54.44±11.05	3
Obsession-compulsion	46.22±11.05	1	42.78±11.73	1
Interpersonal sensitivity	51.22±9.58	1	45.44±9.15	1
Depression	49.44±10.91	1	48.11±10.21	1
Anxiety	52.89±5.40	0	46.67±9.74	0
Hostility	47.89±10.64	1	48.11±10.63	1
Phobic anxiety	48.89±6.37	0	55.33±10.35	1
Paranoid ideation	46.89±11.15	1	52.56±10.31	1
Psychoticism	48.11±11.88	1	47.67±11.47	1

- Global Severity Index: Only 1 patient had a score above the normal limit before implantation. The patient's Global Severity Index score remained above 63 throughout the follow-up period.
- Positive Symptom Total: Only 1 patient had a score above the normal limit before implantation. The patient's Positive Symptom Total score remained above 63 throughout the follow-up period.
- Positive Symptom Distress Index: 3 patients had scores above the normal limit before implantation. All patients had Positive Symptom Distress Index scores below the normal limit at final follow-up.

Safety

Investigators did not actively monitor the occurrence of adverse events.

Abbreviations used: SD, standard deviation

Study 4 Geruschat D (2012)

Details

Study type	**Case series**
Country	USA
Recruitment period	2000 to 2001
Study population and number	Patients with severe profound loss of vision caused by retinitis pigmentosa **n=8**
Age and sex	Male mean age, 49; female mean age, 43.5; 50% (4/8) male
Patient selection criteria	Inclusion criteria: patients with reduced visual acuity and visual field, due to retinitis pigmentosa were included.
Technique	A 2 mm diameter, 25 micrometer thick micro-photodiode array, with 5,000 autonomously operating units, was implanted in the superior to superior temporal subretinal space (approximately 20º off axis from the macula) in the right eyes of all patients.
Follow-up	**6 months**
Conflict of interest/source of funding	Not reported.

Analysis

Follow-up issues: Two patients refused to wear an eye patch for monocular mobility tests: thus, the sample size was 6 for binocular vision and 8 for monocular vision.

Study design issues: The purpose of the study was to evaluate the effect of subretinal implants on mobility.

Study population issues: Four patients usually travelled using a long cane, 1 with a guide dog, and 3 patients usually travelled without a mobility aid but required a sighted guide in unfamiliar or crowded areas. 2 of the 3 patients who travelled without mobility aids had visual acuities of 20/125 and 20/80, respectively, and were able to drive to and from work on a daily basis.

Other issues:

- Visual acuity was measured in the patient's treated and untreated eye using Early Treatment of Diabetic Retinopathy Study (EDTRS) charts: 3 measurements were obtained per eye.

- Contrast sensitivity is the ability to distinguish between objects and their background. It was assessed in the patient's treated and control eye: 3 measurements were obtained per eye. Authors state that 'contrast sensitivity thresholds were measured using forced-choice orientation discrimination of computer-generated square wave gratings'. Gratings were presented at a size twice as large as the patient's grating visual acuity resolution limit. Contrast sensitivity was measured in logarithmic contrast sensitivity values with higher values indicating better outcomes.

- Mobility tests were performed 2 weeks before device implantation and at 3, 6, 9, 12 and 15 month follow-up visits. The patient was asked to walk along an empty hallway, without their mobility aid, at their normal walking speed. The patient was then seated out of sight of the hallway while obstacles were placed: obstacles were either hung from the ceiling or placed on the floor. The patient was asked to walk along the hallway while avoiding contact with any obstacles they came across. They were not told the number, location or type of obstacle they might encounter. Upon completion of the walking course, the patient was asked to turn around and complete the reverse route. Patients were tested 3 times with a randomised viewing sequence: treated eye, control eye or both eyes. For each visual condition, patients walked 36.6 metres and experienced a total of 24 obstacles.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **8**

Measures of visual function

	Mean visual acuity measurements (Snellen scale)				Mean contrast sensitivity measurements (LogCS)		Visual field (degrees)	
Patient number	VA in the treated eye at baseline	VA in the untreated eye at baseline	VA in the treated eye at 6 months	VA in the untreated eye at 6 months	CS in the treated eye 3 to 6 months after surgery	CS in the untreated eye 3 to 6 months after surgery	Visual field diameter 3 to 6 months after surgery	Type of mobility aid usually used
1	20/500	20/500	20/800	20/500	0.38	0.30	<5	None
2	20/110	20/160	20/1280	20/160	0.38	0.08	<5	Cane
3	20/460	20/125	20/640	20/110	0.98	1.13	20	None
4	20/950	20/1280	20/800	20/1280	0.45	0.45	<5	Dog
5	20/720	20/240	20/1600	20/240	0.90	0.98	<50	Cane
6	20/80	20/60	20/80	20/60	1.20	1.28	30	Cane
7	20/160	20/80	20/160	20/80	0.83	0.83	40	None
8	20/500	20/600	20/320	20/600	0.68	0.53	Not measurable	Cane

Mobility course

	Time taken to walk the course, in seconds (mean±SD)		
Follow-up	Binocular vision (n=8)	Treated eye (n=6)	Untreated eye (n=6)
Baseline	38.5±14.7	40.4±16.1	42.0±16.1
3 months	36.9±10.9	39.1±10.7	34.4±9.4
6 months	41.6±13.6	43.5±14.7	40.4±13.5
p value	0.32	0.56	0.36

	Number of obstacles touched (mean±SD)		
Follow-up	Binocular vision (n=8)	Treated eye (n=6)	Untreated eye (n=6)
Baseline	10.9±8.4	8.5±6.7	9.7±7.0
3 months	7.6±5.5	9.3±5.3	10.0±6.8
6 months	11.3±6.5	8.8±5.0	7.8±7.1
p value	0.20	0.19	0.47

Abbreviations used: CS, contrast sensitivity; VA. Visual acuity;

Study 5 Chow AY (2004)

Details

Study type	**Case series**
Country	USA
Recruitment period	2000 to 2001
Study population and number	Patients with severe profound loss of vision caused by retinitis pigmentosa **n=6**
Age and sex	Mean age, 63 years; sex ratio not reported
Patient selection criteria	Inclusion criteria: patients aged ≥40 years, who had retinitis pigmentosa with a Snellen visual acuity of 20/800 or worse, or less than 15º of the visual field (determined by Humphrey automatic visual field tests) were included. All patients were able to perceive electrically induced phosphenes. Exclusion criteria: patients with unrealistic expectations, unstable personality traits or other significant psychiatric conditions were excluded.
Technique	A 2 mm diameter, 25 micrometer thick micro-photodiode array, with 5000 autonomously operating units, was implanted in the superior to superior temporal subretinal space (approximately 20º off axis from the macula) in the right eyes of all patients.
Follow-up	**2 years**
Conflict of interest/source of funding	Authors state that the trial was 'supported' by the manufacturer; however no further details were provided.

Analysis

Follow-up issues: No patients were lost to follow-up.

Study design issues: None identified.

Study population issues: Three patients (patients A, C and F) were pseudophakic before the prosthesis was implanted. Cataracts were removed in 3 patients (patients B, D and E): 2 of these patients (patients B and D) were left aphakic after and 1 patient (patient E) underwent secondary anterior chamber intraocular lens implantation 1 month after prosthesis implantation.

Other issues:

- 9-sector visual threshold test: in a room with 'less than 0.1 foot-candle illumination', an optical fibre halogen light-source was placed 10 cm away from the patient's eye at the following 9 locations (from the patient's perspective): right-upper, right-middle, right-lower, middle-upper, middle middle, middle-lower, left-upper, left-middle, left-lower. All positions, except middle-middle, were located approximately 45º from the optical axis. The threshold was established in each sector by crossing it at least 3 times in an ascending and descending staircase paradigm.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **6** **Visual acuity (using the ETDRS chart)** • Improvements in visual acuity were reported in 3 patients. The smallest ETDRS letters identified improved from a Snellen equivalent of 20/800 to 20/200 in patient E, at 6 month follow-up. Visual acuity improved from 20/1600 to 20/400 in patient F at 6 month follow-up. Patient C was unable to read ETDRS letters preoperatively but had a visual acuity of 20/1600 at 18 month follow-up. **9-sector visual threshold test** • Improvements in 9-sector test results were reported in the operated eyes of 2 patients compared against the unoperated eyes, at 1 year follow-up. In patient A, the threshold sensitivity improved by 1000% to 1500% in all sectors and was consistent with the patient's perception that the entire visual field was better in the implanted eye. In patient B, the threshold sensitivity improved by 5000% to 10, 000% in 3 of the 9 sectors. **Colour perception** • A substantial improvement in colour perception was reported in 1 patient (patient E) who was able to see multiple colours in his surroundings; such as highway signs, stop signs, green grass and tablecloth colours.	Investigators did not actively monitor the occurrence of adverse events. • Elevated intraocular pressure was reported in 50% (3/6) of patients within the first week of surgery. This was attributed to steroids contained in antibiotic steroid drops and was treated by medication. • A scratching sensation was reported in the operated eye of several patients (numbers not stated). This resolved after approximately 6 weeks. • Aniseikonia was reported in 1 patient when they used glasses. This was treated by implantation of an anterior chamber intraocular lens. • Syneresis of images, seen from the implanted eye, was reported in 1 patient. This was believed to be related to syneresis of a previously implanted posterior chamber intraocular lens. Symptoms improved after replacement of the lens with a stable anterior chamber intraocular lens.
Abbreviations used: ETDRS, early treatment of diabetic retinopathy study	

Study 6 Zrenner E (2011)

Details

Study type	**Case series**
Country	Germany
Recruitment period	Not reported
Study population and number	Patients with severe profound loss of vision caused by hereditary retinal degeneration **n=3**
Age and sex	Mean age, 40.6 years; 33.3% (1/3) male
Patient selection criteria	Inclusion criteria: patients with severe loss of vision caused by hereditary retinal degeneration who had lost their reading ability for at least 5 years were included. In all patients, bright light stimulation mediated limited light perception without recognition of shapes. Exclusion criteria: not reported.
Technique	A 3 mm x 3 mm x 70 micrometer-sized micro-photodiode array, with 1500 autonomously operating units, was initially implanted close to the foveola; however, improved surgical technique conferred the placement of the micro-photodiode array under the macula.
Follow-up	**Not reported**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: No patients were lost to follow-up.

Study design issues: Patient B was the only patient who had the prosthesis system implanted under the macula. Table tasks were assessed by an independent professional mobility trainer.

Study population issues: Two patients had retinitis pigmentosa and 1 patient had choroideraemia but had good central vision previously. Potential overlap with other studies included in table 2 (Kitiratschky, 2014; Stingl, 2013; Peters, 2013).

Other issues:

- Light perception test: the patient was placed 60 cm away from a black screen and asked to indicate whether they saw light when the screen was briefly illuminated with 1 or 2 flashes.
- Light source localisation test: the patient was placed in front of a black screen and asked to focus on a white dot. After an auditory cue, the patient was asked to indicate the direction of a white wedge that appeared: directed up, down, right or left.
- Direction of motion test: the patient was placed in front of a black screen and asked to indicate the direction of a white polka-dot pattern that moved across the screen at a randomly chosen angle.
- Basic grating acuity test: the patient was placed in front of a screen and was asked to indicate the grid orientation of a black and white striped pattern that was presented at spatial frequencies ranging from 0.1 to 3.3 cycles per degree (cpd).
- Landolt C test: the patient was place in front of a black screen and asked to indicate the orientation of a white ring which had a gap, similar to the letter ‘C’ that appeared in 1 of 4 orientations (up, down, right or left). The size of the C and its gap were reduced until the participant made a specified number of errors. No further details were provided.
- Table tasks: the patient was seated in front of a black table and asked to identify geometric objects, common tableware objects (small and medium-sized plates, cup, fork, spoon and knife) and some fruit. The patient was asked to locate and name them.

Key efficacy and safety findings

<table>
<tr><td>Efficacy</td><td>Safety</td></tr>
<tr><td>Number of patients analysed: 3

• Improved pupillary reflexes were reported in all patients when the retinal prosthesis systems were switched on

Screen tasks
<table><tr><td></td><td colspan="3">Patient</td></tr><tr><td>Outcome</td><td>A</td><td>B</td><td>C</td></tr><tr><td>Light perception</td><td>Yes</td><td>Yes</td><td>Yes</td></tr><tr><td>Light source localisation</td><td>Yes</td><td>No</td><td>Yes</td></tr><tr><td>Direction of motion</td><td>Yes</td><td>No</td><td>Yes</td></tr><tr><td>Grating acuity (cycles per degree)</td><td>No</td><td>0.46</td><td>0.22</td></tr><tr><td>Landolt C visual acuity (logMAR)</td><td>No</td><td>1.69</td><td>No</td></tr></table>• The mean success rate for the light localisation test was 94% when prosthesis systems were switched on, compared against 0% when they were switched off (p<0.05).

Table tasks
• Patient A was able to locate a saucer, a square and a cup. No further details were provided.
• Patient B was able to locate and identify square, diamond, triangular, circular and rectangular shapes. The patient was also able to localise and identify a spoon, a knife, a cup, a banana and an apple.
• Patient C was able to locate and differentiate a large saucer from a small saucer.

Optional tasks
• Patient B was able to distinguish 16 different white letters (5-8 cm high, Tahoma font), placed on a black table. The patient was able to perceive individual letters and identify words. He was also able to identify spelling mistakes in his name.
• Patient B was able to indicate clock times set to full quarter hours (o’clock, quarter past, half past, quarter to); the dimensions of the clock’s hour and minute hands were 6 x 1.5 cm and 12 x 1.5 cm respectively.</td><td>Investigators did not actively monitor the occurrence of adverse events.

• Patients reported high sensitivity to infrared light. No further details were provided.</td></tr>
<tr><td colspan="2">Abbreviations used:</td></tr>
</table>

Efficacy

Visual acuity

In a case series of 6 patients, improvements in visual acuity (measured by the smallest Early Treatment of Diabetic Retinopathy study [ETDRS] letters that could be read) were reported in 3 patients. Visual acuity improved in 1 patient from a Snellen equivalent of 20/800 before the procedure to 20/200 at 6 month follow-up. In the second patient, visual acuity improved from 20/1600 before the procedure to 20/400 at 6 month follow-up. The third patient had been unable to read ETDRS letters before the procedure but had a visual acuity of 20/1600 at 18 month follow-up[5].

In a case series of 9 patients, visual acuity was assessable, using Landolt C rings, in 2 patients when their prosthesis systems were switched on; their visual acuities were 1.43 and 2 logMAR respectively at a maximum follow-up of 9 months. Grating acuity was successfully measured in 6 patients when their prosthesis systems were switched on, up to a maximum of 3.3 cycles per degree[1].

Light perception

In a case series of 9 patients, light perception thresholds were considerably better when prosthesis systems were switched on compared against when they were switched off. All patients were able to perceive light when their prosthesis systems were switched on, at maximum follow-up of 9 months. No further details were provided[1].

Light source localisation

In the case series of 9 patients, patients were asked to indicate the direction (up, down, left or right) of the pointed end of a white wedge on a black screen. Seven patients correctly indicated the direction in which the wedge was pointing when their prosthesis systems were switched on, at maximum follow-up of 9 months[1].

Direction of motion tests

In the case series of 9 patients, patients were asked to indicate the direction of a white polka dot pattern that moved across a black screen. Five patients were able to detect the direction of motion using their prosthesis systems, at maximum follow-up of 9 months[1].

Counting, locating and discriminating shapes.

In the case series of 9 patients, patients were asked to count, identify and localise 4 of 6 possible geometric shapes that were placed on a black table cloth. The mean number of shapes counted was 2.8 when prosthesis systems were switched on, compared against 0.5 when prosthesis systems were switched off, at maximum follow-up of 9 months (p=0.012). The mean number of shapes located was 2.2 when prosthesis systems were switched on, compared against

0.5 when prosthesis systems were switched off (p=0.012). The mean number of shapes correctly identified was 1 when prosthesis systems were switched on, compared against 0.1 when prosthesis systems were switched off (p=0.018). [1].

Mobility tests

In a case series of 8 patients, patients were asked to walk along a corridor while avoiding objects that were placed on the floor or hung from the ceiling. The mean time taken to complete the course, when patients used binocular vision, improved from 38.5 seconds at baseline to 41.6 seconds at 6 month follow-up (p=0.32). The mean time taken to complete the course, when patients only used their treated eye, improved from 40.4 seconds at baseline to 43.5 seconds at 6 month follow-up (p=0.56). The mean time taken to complete the course, when patients only used their untreated eye, decreased from 42.0 seconds at baseline to 40.4 seconds at 6 month follow-up (p=0.36)[4].

Emotional wellbeing

In a second case series of 9 patients, mean brief symptom inventory scores (scores range from 0 to 100 with higher scores indicating worsening mental health) were recorded before prosthesis implantation and at mean follow-up of 6 weeks. Somatisation, obsession-compulsion, interpersonal sensitivity subscores changed from 47.7 to 54.4, 46.2 to 42.8 and 51.2 to 45.4 respectively (no p values reported). Depression, anxiety and hostility subscores changed from 49.4 to 48.1, 52.9 to 46.7 and 47.9 to 48.1 respectively. Phobic anxiety, paranoid ideation and psychoticism subscores changed from 48.9 to 55.3, 46.9 to 52.6 and 48.1 to 47.7 respectively[3].

Safety

In a case series of 9 patients, 75 adverse events occurred within 1 year of prosthesis implantation.

'Retinal break' without detachment was reported twice (3% of adverse events). Neither case resolved (no further details provided)[2].

Conjunctival erosions above the external part of the cable and/or suture erosions through the conjunctiva were reported 12 times (16% of adverse events). All cases resolved without sequelae (no further details provided) [2].

Conjunctival hyperaemia was reported 6 times (8% of adverse events). All cases resolved without sequelae (no further details provided) [2].

Retinal vascular leakage and neovascularisation was reported 10 times (13% of adverse events). Two patients had a retinal vascular leakage before device implantation. Nine cases did not resolve. In 1 patient, retinal vascular leakage resulted in damage to eye structures and loss of light perception (no further details provided)[2].

Retinal haemorrhage was reported 7 times (9% of adverse events). All cases resolved without sequelae (no further details provided) [2].

Ocular hypertension was reported 8 times (11% of adverse events). All cases resolved without sequelae (no further details provided) [2].

Paraesthesia of the skin (unspecified location) was reported 3 times (4% of adverse events). All cases resolved without sequelae (no further details provided) [2].

Epistaxis was reported twice (3% of adverse events). All cases resolved without sequelae (no further details provided) [2].

Localised oedema was reported twice (3% of adverse events). Both cases resolved without sequelae (no further details provided) [2].

In the case series of 9 patients, a single occurrence of each of the following was reported within 1 year of prosthesis implantation: intraoperative perforation of the choroid, intraoperative contact of the optic nerve head with the implant, postoperative bleeding, contusion of the eyelid and periocular area, mucopurulent conjunctivitis, a peripheral corneal dent, acute iritis, retinal detachment with a retinal break, ocular pain, dizziness, headache, and chronic pain (unspecified location). Intraoperative perforation of the choroid and intraoperative contact of the optic nerve head with the implant both occurred in the same patient and resulted in loss of residual vision in the study eye. All other adverse events resolved without sequelae.

Aniseikonia was reported in 1 patient in a case series of 6 patients (the timing of occurrence was not reported). This was treated by implantation of an anterior chamber intraocular lens[5].

Validity and generalisability of the studies

- All studies included in this overview appear to be feasibility studies.
- There is a high degree of overlap between included studies because the same authors and treatment centres were involved in each study [1, 2, 3, 6].
- Some studies included patients with other forms of retinal dystrophy, such as choroideraemia[1,2, 6].
- There were no standardised methods of evaluating the efficacy of the intervention in relatively small samples of patients.
- No comparative studies were available that compared subretinal prostheses with appropriate alternatives. This is likely to be because alternative treatments are still in early development.

- No studies demonstrated that the small improvements in visual function resulted in considerable improvements in quality of life.

Existing assessments of this procedure

There were no published assessments from other organisations identified at the time of the literature search.

Related NICE guidance

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

Interventional procedures

- Insertion of an epiretinal prosthesis for retinitis pigmentosa (in development). NICE interventional procedure guidance number is yet to be confirmed (2015). Available from http://www.nice.org.uk/guidance IPGXXX

Specialist advisers' opinions

Specialist advice was sought from consultants who have been nominated or ratified by their Specialist Society or Royal College. The advice received is their individual opinion and is not intended to represent the view of the society. The advice provided by Specialist Advisers, in the form of the completed questionnaires, is normally published in full on the NICE website during public consultation, except in circumstances but not limited to, where comments are considered voluminous, or publication would be unlawful or inappropriate. Six Specialist Advisor Questionnaires for insertion of a subretinal prosthesis system for retinitis pigmentosa were submitted and can be found on the NICE website [INSERT HYPER LINK TO MAIN IP PAGE].

Patient commentators' opinions

NICE's Public Involvement Programme was unable to gather patient commentary for this procedure.

Issues for consideration by IPAC

Ongoing trials

- NCT01024803: Safety and Efficacy of Subretinal Implants for Partial Restoration of Vision in Blind Patients; location: Multicentre - Germany,

Hungary, Italy, United Kingdom; type: RCT; estimated enrolment: 45; estimated primary completion date: December 2015.

References

1. Stingl K, Bartz-Schmidt KU, Besch D, et al. (2013) Artificial vision with wirelessly powered subretinal electronic implant alpha-IMS. Proceedings of the Royal Society of Biological Sciences 280 (1757): 20130077. doi: 10.1098/rspb.2013.0077.
2. Kitiratschky VB1, Stingl K, Wilhelm B, et al. (2014) Safety evaluation of "retina implant alpha IMS"-a prospective clinical trial. Graefe's Archive of Clinical and Experimental Ophthalmology. [Epub ahead of print]. doi: 10.1007%2Fs00417-014-2797-x
3. Peters T, Klingberg S, Zrenner E, Wilhelm B. (2013) Emotional wellbeing of blind patients in a pilot trial with subretinal implants. Graefe's Archive of Clinical and Experimental Ophthalmology 251(6):1489-93. doi: 10.1007/s00417-012-2210-6.
4. Geruschat DR, Bittner AK, Dagnelie G. (2012) Orientation and mobility assessment in retinal prosthetic clinical trials. Optometry and vision science 89 (9): 1308-15. doi: 10.1097/OPX.0b013e3182686251.
5. Chow AY, Chow VY, Packo KH, et al. (2004) The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. Archives of Ophthalmology 122(4):460-9.
6. Zrenner E, Bartz-Schmidt KU, Benav H, et al. (2011) Subretinal electronic chips allow blind patients to read letters and combine them to words. Proceedings of the Royal Society of Biological Sciences 278 (1711): 1489-97. doi: 10.1098/rspb.2010.1747.

Appendix A: Additional papers on insertion of a subretinal prosthesis system for retinitis pigmentosa

The following table outlines the studies that are considered potentially relevant to the IP 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	Number of patients/follow-up	Direction of conclusions	Reasons for non-inclusion in table 2
Chuang AT, Margo CE, Greenberg PB. (2014) Retinal implants: a systematic review. British Journal of Ophthalmology 98 (7) 852-856.	Narrative Review	This review compared selected models by examining publications describing five representative retinal prostheses: Argus II, Boston Retinal Implant Project, Epi-Ret 3, Intelligent Medical Implants (IMI) and Alpha-IMS (Retina Implant AG).	The journal article is a narrative review that discussed recent developments in subretinal and epiretinal implants.
Besch, D, Sachs, H, Szurman, P, et al. (2008) Extraocular surgery for implantation of an active subretinal visual prosthesis with external connections: feasibility and outcome in seven patients. British Journal of Ophthalmology 92 (10) 1361-1368.	Case series n=7 Follow-up: 4 weeks	All implantations were performed as planned without complications, and no serious adverse events occurred in the postoperative period. Fixation of the implants was stable throughout the entire study duration of 4 weeks; permanent skin penetration proved to be uncomplicated. Motility was minimally restricted in downgaze and ab-/adduction. Explantation was uneventful	This was a pilot study that described the surgical procedure. No appropriate efficacy outcomes were reported.
Kusnyerik A, Greppmaier U, Wilke R, et al. (2012) Positioning of electronic subretinal implants in blind retinitis pigmentosa patients through multimodal assessment of retinal structures. Investigative Ophthalmology & Visual Science 53 (7) 3748-3755	Case series n=10 Follow-up: Not reported	The mean light sensitivity ratio between the area actually covered by the chip and that of the planned position was 90.8% with an SD of 11.4%. In two cases with almost perfect positioning, the computed ratio was 100%. Measurements showed that to achieve a 95% sensitivity rate the difference between the planned and achieved chip position must be less than 1.7 mm. Preoperative calculations of the intraocular cable length	This was a feasibility study that described the surgical procedure. No appropriate efficacy outcomes were reported.

		proved accurate in all cases	
Stingl, K., Bartz-Schmidt, K. U., Gekeler, F., et al. (2013) Functional outcome in subretinal electronic implants depends on foveal eccentricity. Investigative Ophthalmology & Visual Science 54 (12) 7658-7665	Case series n=2 Follow-up: Not reported	Patients with non-foveal placement of prosthesis systems implant could perceive and locate light sources. No patient was able to determine the direction of motion or pass Landolt C-ring tests. When the implant was placed subfoveally, patients could perceive light, locate light sources, determine the direction of motion and pass Landolt C-ring test with a decimal visual acuity of up to 20/546 (logMAR 1.43)	Minimal reporting of outcome measures.
Stingl K, Gekeler F, Bartz-Schmidt KU, et al. (2013) Fluorescein angiographic findings in eyes of patients with a subretinal electronic implant. Current Eye Research 38 (5) 588-596.2013.	Case series n=11 Follow-up: 4 weeks	Fluorescein angiography revealed regions of capillary loss, calibre alterations of the capillaries, retinal neovascularisation and leakage.	The study was a pilot study that analysed retinal fluorescein angiography findings of the implant area
Wilke R, Gabel VP, Sachs H, et al (2011) Spatial resolution and perception of patterns mediated by a subretinal 16-electrode array in patients blinded by hereditary retinal dystrophies. Investigative Ophthalmology & Visual Science 52 (8) 5995-6003.	Case series n=11 Follow-up: Not reported	On single-electrode activation, percepts were generally described as round spots of light of distinguishable localisation in the visual field. On activation of a pattern of electrodes, percepts matched that pattern when electrodes were activated sequentially. Patterns such as horizontal or vertical bars were identified reliably; the most recent participant was able to recognize simplified letters presented on the 16-electrode array. The smallest distance between sites of concurrent retinal stimulation still yielding discernible spots of light was assessed to be 280,µm; corresponding to a logMAR of 1.78	The study was a feasibility study that assessed action potentials and stimulus thresholds.

Appendix B: Related NICE guidance for insertion of a subretinal prosthesis system for retinitis pigmentosa

Guidance	Recommendations
Interventional procedures	**Insertion of an epiretinal prosthesis for retinitis pigmentosa (in development). NICE interventional procedure guidance number is yet to be confirmed (2015).** **Provisional recommendations**. 1.1 Current evidence on the safety and efficacy of insertion of an epiretinal prosthesis for retinitis pigmentosa is limited in quality and quantity. Therefore, this procedure should only be used in the context of research. 1.2 NICE encourages further research on this potentially beneficial technology. Outcomes should include the impact on quality of life and activities of day-to-day living, and durability of implants. NICE may update the guidance on publication of further evidence.

Appendix C: Literature search for insertion of a subretinal prosthesis system for retinitis pigmentosa

Databases	Date searched	Version/files
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	17/12/2014	Issue 12 of 12, December 2014
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	17/12/2014	Issue 4 of 4, October 2014
HTA database (Cochrane Library)	17/12/2014	Issue 4 of 4, October 2014
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	17/12/2014	Issue 11 of 12, November 2014
MEDLINE (Ovid)	17/12/2014	1946 to November Week 3 2014
MEDLINE In-Process (Ovid)	17/12/2014	December 11, 2014
EMBASE (Ovid)	17/12/2014	1974 to 2014 Week 50
PubMed	17/12/2014	n/a
BLIC	17/12/2014	n/a

Trial sources searched on 7 November 2014:

- National Institute for Health Research Clinical Research Network Coordinating Centre (NIHR CRN CC) Portfolio Database
- Current Controlled Trials *meta*Register of Controlled Trials – *m*RCT
- Clinicaltrials.gov

Websites searched on 7 November 2014:

- National Institute for Health and Care Excellence (NICE)
- NHS England
- Food and Drug Administration (FDA) - MAUDE database
- French Health Authority (FHA)
- Australian Safety and Efficacy Register of New Interventional Procedures – Surgical (ASERNIP – S)
- Australia and New Zealand Horizon Scanning Network (ANZHSN)
- Conference websites
- General internet search

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

1	Visual prosthesis/
2	((Subretin* or retin* or visual* or vision* or eye*) adj4 (prosth* or microchip* or chip* or implant*)).tw.
3	((Artificial or enhance* or augment* or boost* or bionic* or second*) adj4 (sight* or vision* or eye*)).tw.
4	or/1-3
5	Retinitis Pigmentosa/
6	(Retinitis adj4 pigment*).tw.
7	RP.tw.
8	Retinal Degeneration/
9	(Retin* adj4 (degenerat* or decay* or dystroph* or declin*)).tw.
10	Blindness/su
11	Choroideremia/
12	Choroideremia.tw.
13	Usher syndromes/
14	(Usher adj4 syndrome*).tw.
15	Bardet-Biedl syndrome/
16	((Bardet-Biedl or "Bardet Biedl") adj4 syndrome*).tw.
17	Laurence-Moon Syndrome/
18	((Laurence-Moon or "Laurence Moon") adj4 Syndrome*).tw.
19	(Leber* adj4 congen* adj4 amaurosis*).tw.
20	((Cone* or rod* or cone-rod*) adj4 dystroph*).tw.
21	Vision, Low/
22	((severe* or progres*) adj4 (low* or loss* or less* or reduce* or diminish* or subnormal*) adj4 (vision* or sight*)).tw.
23	or/5-22
24	4 and 23
25	Alpha IMS.tw.
26	"Artificial Silicon Retina*".tw.
27	(ASR adj4 (microchip* or chip*)).tw.
28	(Optobionics adj4 (microchip* or chip*)).tw.
29	or/24-28
30	animals/ not humans/
31	29 not 30
32	limit 31 to english language