NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

INTERVENTIONAL PROCEDURES PROGRAMME

Interventional procedure overview of insertion of an epiretinal prosthesis 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 and sometimes severe loss of vision. In this procedure small electrodes are implanted onto the retina. A camera, mounted on a pair of glasses, sends information to the electrodes, which stimulate healthy cells in the retina 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 July 2014 and updated in December 2014

Procedure name

Insertion of an epiretinal prosthesis 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 and lead to the loss of all 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. Insertion of an epiretinal prosthesis aims to restore perception of light, movement and shapes by surgically implanting an array of electrodes onto the retina. The electrodes emit electrical impulses to stimulate the sensory neurons of surviving retinal cells, which send visual information to the brain.

An epiretinal prosthesis system has 2 key components: an eye implant and external camera system. The eye implant consists of an episcleral receiver unit and an epiretinal electrode array. The external camera system comprises an eyeglass-mounted video camera and a small patient-worn computer (video processing unit [VPU]).

Insertion of the eye implant is performed with the patient under general anaesthesia, usually in 1 procedure that may take several hours. The surgeon performs core and peripheral vitrectomies, followed by dissection of any epiretinal membrane in the area where the electrode array will be placed. The electrode array is then inserted through a temporal sclerotomy and secured onto the retina using a retinal tack. It is connected to the receiver unit by a cable that penetrates the sclera in the pars plana.

After surgery, when the implant is set up and fully functional, the video camera records real-time images and sends them to the VPU. The VPU converts the images into data that are wirelessly transmitted to the episcleral receiver unit. The episcleral receiver unit relays the data to the electrode array, which produces electrical impulses that bypass damaged photoreceptors and stimulate the

retina's remaining cells. Visual information is then transmitted by the optic nerve to the brain, creating a visual percept.

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

Tests that assess perception of light and movement

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 some patients. Consequently other, sometimes novel, tests are used to assess visual function. The following tests were commonly used to assess the efficacy of epiretinal prostheses in studies that are included in this overview.

Square localisation test: the patient was placed 12 inches away from a touchscreen monitor. A white square appeared in a random location on the monitor. When prompted, the patient scanned the monitor and attempted to locate the square by touching the centre of the square. Unless otherwise stated, 40 trials were attempted with the prosthesis system turned on and then off (80 trials in total).

Direction of motion test: the patient was asked to maintain eye and head fixation on the centre of a 19–inch touchscreen monitor, located 12 inches in front of them. After an audio prompt a 1.4–inch white bar swept across the screen in a randomly chosen angle (0º to 360º in 1º increments). Bar speeds varied across participants according to their best performance. After each trial the patient was asked to draw, on the touchscreen, the direction of motion they perceived the white bar to have travelled. Correct or satisfactory results were noted if the patient's perception of motion was within 15º of the stimulus angle. Unless otherwise stated, 40 trials were attempted with the prosthesis system turned on and then off (80 trials in total).

Literature review

Rapid review of literature

The medical literature was searched to identify studies and reviews relevant to insertion of an epiretinal prosthesis for retinitis pigmentosa. Searches were conducted of the following databases, covering the period from their commencement to 31 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 an epiretinal prosthesis
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 129 patients from 7 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 an epiretinal prosthesis for retinitis pigmentosa

Study 1 Humayun MS (2012)

Details

Study type	**Case series**
Country	Multicentre: USA, Switzerland, Mexico, UK, France
Recruitment period	Not reported
Study population and number	Patients with outer retinal degeneration **n=30**
Age and sex	Median 57.5 years; 70% (21/30) male
Patient selection criteria	Inclusion criteria: patients with retinitis pigmentosa or other form of outer retinal degeneration (1 patient had Leber congenital amaurosis and another had choroideremia) with bare or no light perception and visual acuity worse than 2.9 logMAR in both eyes were included. Exclusion criteria: not clearly defined.
Technique	Patients were implanted with an epiretinal prosthesis (60-electrode stimulating array) in 1 eye. An allograft or suitable alternative was draped and sutured over the episcleral receiver unit to minimise the risk of conjunctival irritation.
Follow-up	**Up to 2.7 years**
Conflict of interest/source of funding	The manufacturer contributed to the design of the study and participated in data collection, data management, data analysis, as well as preparation and review of the final manuscript.

Analysis

Follow-up issues: None identified.

Study design issues: Patients were recruited from 10 participating centres. Authors described the study as a multicentre feasibility study. Patients were allowed to use the prosthesis system outside outpatient clinical setting, in their daily lives, once it had been individually programmed and they had completed training.

Two orientation and mobility tests were performed in an empty 20 foot by 20 foot room:

- Door finding test: the patient was placed either in the centre, offset left by 3 feet, or offset right by 3 feet of a room and asked to place their hand on a rectangular door 20 feet away. The distance between the patient's hand and the edge of the door was recorded. The test was deemed a success if the patient touched any part of the door. The test was repeated twice in each position (total of 6 trials).
- Follow the line test: the patient was asked to walk along high contrast 20 foot line, in one of three directions, as quickly and safely as possible. The distance between the patient's feet and line was recorded. The test was deemed a success if the patient was standing on the line at the end.

Study population issues: potential overlap with other studies included in table 2 (da Cruz, 2013; Dorn, 2013; Ahuja, 2011) as the same group of clinicians and treatment centres were involved in each study. In this study, 33% (10/30) of patients had undergone previous cataract removal surgery in the eye with the implant. One patient had several previous ocular procedures in the eye with the implant. The last 15 patients were implanted with a slightly modified prosthesis.

Other issues: Poor reporting of moderate adverse events. Authors stated a range of values in which moderate adverse events had occurred; the top end of the range is reported.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **30;** however, numbers varied depending on the outcome measure that was assessed

Visual acuity
Improvements in visual acuity were reported in 23.3% (7/30) of patients; visual acuity improved from worse than 2.9 logMAR to between 2.9 and 1.6 logMAR (no p value reported).

Full-field light threshold
No significant difference was observed between stimulus thresholds before and after implantation.
No change in light perception was reported in the eyes of 93% (28/30) of patients after implantation.
An improvement from no light perception to bare light perception was reported in the eye of 1 patient after implantation.
A decline from bare light perception to no light perception was reported in the eye of 1 patient after implantation (timing not clear but followed up to 2.7 years).

Light perception upon electrical stimulation (without video camera input)
All patients were able to perceive light when their prostheses were stimulated (thresholds were measurable on at least 1 electrode).

Outside- outpatient use
The mean duration of prosthesis use, outside a clinical setting, was 15.8±9.7 months.

Square localisation test (n=28)
Significantly better square localisation test results were reported in 96% (27/28) of patients when their prosthesis systems were switched on.

Direction of motion test (n=28)
Significantly better direction of motion test results were observed in 57% (16/28) of patients when their prosthesis systems were switched on.

Door finding test (mean success rate[%])

	12 months	18 months [a]	24 months [a]
System on	52	53	60
System off	44	21	5

[a] Statistically significant differences were observed in success rates when prostheses were switched on compared against when prostheses were switched off ($p<0.05$).

Follow the line test (mean success rate[%])

	12 months	18 months	24 months
System on	63	82	54
System off	25	23	15

[a] Statistically significant differences were observed in success rates when prostheses were switched on compared against when prostheses were switched off, at all follow-up assessments ($p<0.05$)

Safety

Adverse events (n=30)

Serious adverse events (as reported by the authors)

NB: No serious adverse events were reported in 70% (21/30) of patients)

Adverse event	%
Conjunctival dehiscence [a]	10.0 (3/30)
Conjunctival erosion	6.7 (2/30)
Presumed endophthalmitis [b]	10.0 (3/30)
Hypotony [c]	10.0 (3/30)
Replacement of a retinal tack [d]	6.7 (2/30)
Retinal detachment – rhegmatogenous [e]	3.3 (1/30)
Retinal detachment – tractional [f]	3.3 (1/30)
Retinal tear	3.3 (1/30)
Uveitis - inflammatory	3.3 (1/30)

[a] The majority of cases were treated by additional sutures and/or placement of additional tissue.
[b] Presumed cases of endophthalmitis were treated by antibiotic therapy.
[c] All cases of hypotony occurred within 1 year of implantation and required surgical treatment: two patients required intraocular silicone tamponades whereas 1 patient required device removal
[d] Replacement of a retinal tack was required within the first few days of implantation because the tack was not securely implanted in the initial operation. No clinical implications were reported.
[e] Rhegmatogenous retinal detachment occurred at 5-month follow-up and required surgical repair.
[f] Tractional retinal detachment occurred after blunt trauma to the implanted eye, 5 months following implantation. This was repaired by vitrectomy, partial retinectomy and silicone oil.

Non-serious adverse events

- Conjunctival oedema was reported in up to 33.3% (10/30) of patients.
- Intraocular inflammation, hypotony without choroidal detachments, suture irritation and ocular pain were reported in 23.3% (7/30) of patients.
- Inflammatory conjunctivitis, corneal filaments, epiretinal membrane, high intraocular pressure (controlled by anti-glaucoma medications), epiphora, mild hyphema, inflammatory uveitis with few keratic precipitates and mild vitreous haemorrhage were reported in up to 10.0% (3/30) of patients. Patients had more than 1 adverse events; however no further details were provided.
- A single occurrence each of limited conjunctival dehiscence, corneal abrasion, mild peripheral corneal vascularisation, cystoid macular oedema, decrease in light perception, dry eye, transient headache, iris vessel engorgement that receded secondary to surgery, a stable tractional retinal detachment, transient nausea, transient increased nystagmus, scleritis or transient vertigo was reported.

Study 2 da Cruz L (2012)

Details

Study type	**Case series**
Country	Multicentre: USA, Switzerland, Australia, UK, France
Recruitment period	Not reported
Study population and number	Blind patients with outer retinal dystrophies **n=30**
Age and sex	Mean 58 years; 70% (21/30) male
Patient selection criteria	Inclusion criteria: patients with retinitis pigmentosa or other form outer retinal degeneration (one patient had choroideraemia) with bare or no light perception and visual acuity worse than 2.9 logMAR in both eyes were included. Exclusion criteria: not reported.
Technique	Patients were implanted with a 60-electrode stimulating array on the macula. It is assumed that an epiretinal prosthesis was implanted in 1 eye.
Follow-up	**Mean of 19.9 months**
Conflict of interest/source of funding	At least one of the co-authors was an employee of the manufacturer.

Analysis

Follow-up issues: There were inconsistencies in the total number of patients analysed in the study: authors stated that 9 patients were not included in efficacy analysis.

Study design issues: Patients were recruited from multiple clinical centres around the world.

- Letter identification test: patients were sat in a darkened room and asked to identify white letters on a black background on a LCD screen. Each letter size was 41.27º. Patients were assessed in 3 groups: Group A was assessed on horizontal and vertical components (for example, H,I); Group B was assessed on oblique components involving the full height of the letter (for example, A,M,W) or letters with a minor variation on a circle (for example, O,D,C). Group C was assessed on letters with an oblique or curved element involving half the letter height (for example, K,R). Researchers presented letters in a random order, 1 at a time 4 times each, both with the prosthesis on and off.

- Word recognition test: patients were asked to identify 2-, 3- and 4–letter words on the LCD screen. There were 10 words per trial. Letter spacing was standard for the font size with no additional spacing between letters. The test was performed with prosthesis set to 1 of 3 settings: off, on (where the prosthesis was set to a normal function) and scrambled; where the electrode array was fully functional but the signal input would result in the electrodes being stimulated in a random scattered pattern. Patients also had to take the test under 2 eye conditions: eyes 'patched' (where both eyes would be taped closed) or 'unpatched'.

Study population issues: Potential overlap between other studies included in table 2 (Humayun, 2012; Dorn, 2013; Ahuja, 2011) as the same group of clinicians and treatment centres were involved in each study. One patient had choroideraemia.

Other issues: None identified.

Key efficacy and safety findings

Efficacy

Number of patients analysed: **21; however, numbers in each group varied.**

Letter identification test (n=21)

	Mean percentage correct		
Group	System on	System off	Average time taken to correctly identify letters with the system on (seconds)
A	72.3±24.6	17.7±12.9	47.7
B	55.0±27.4	11.8±10.7	68.6
C	51.7±28.9	15.3±7.4	63.9

Word recognition test (n=4): mean percentage correct

	System setting				
	Off	On		Scrambled	
Number of letters	-	Unpatched	Patched	Unpatched	Patched
2	7.5	75	80	2.5	2.5
3	5	62.5	67.5	5	0
4	2.5	57.5	65	2.5	2.5

Results were calculated by the NICE Interventional Procedures team

Safety

Adverse events (n=30)

- Conjunctival erosion requiring device removal was required in 1 patient.
- Retinal detachment was reported in 1 patient.
- Hypotony was reported in 1 patient.
- Replacement of a retinal tack was required in 1 patient.
- All patients (n=28) with a prosthesis implanted at the final assessment reported the occurrence of visual phosphenes.

Study 3 Dorn JD (2013)

Details

Study type	**Case series**
Country	Multicentre: USA, Switzerland, Mexico, UK, France
Recruitment period	Not reported
Study population and number	Blind patients with retinitis pigmentosa **n=30**
Age and sex	Mean 59.5 years; 71.4% (20/28) male
Patient selection criteria	Inclusion criteria: patients with retinitis pigmentosa with bare light perception in at least 1 eye and visual acuity worse than 2.9 logMAR (Snellen 20/15887) in both eyes were included. Exclusion criteria: not reported
Technique	A 60–electrode array (in a 6 x 10 electrode grid) was surgically implanted over the macula of 1 eye of each patient. The array covered an area of the retina corresponding to about 20º in visual angle, assuming 293 micrometre on the retina equates to 1º of visual angle. Stimulation settings were customised for each patient with current amplitude values based on the patient's perceptual thresholds for each electrode. The pulse frequency was fixed for each patient, ranging from 3Hz to 60 Hz.
Follow-up	**Up to 36 months**
Conflict of interest/source of funding	The principal investigator and 2 co-authors were employed by the manufacturers. One co-author held stock in the manufacturer's company.

Analysis

Follow-up issues: One patient had their prosthesis removed prior to assessment due to recurrent conjunctival erosion. Another patient was unavailable for assessment due to the treatment centre's review board's reluctance to approve testing.

Study design issues: Potential overlap between other studies included in table 2 (Humayun, 2012; da Cruz, 2013; Ahuja, 2011) as the same group of clinicians and treatment centres were involved in each study. Patients were recruited from and treated at multiple clinical centres around the world. Authors described the study as a phase 1 feasibility study.

Study population issues: None identified.

Other issues: None identified.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **28** **Direction of motion test** • Smaller mean errors were reported in 53.5% (15/28) of patients when their prosthesis systems were switched on, compared against when their prosthesis systems were switched off. • Smaller mean errors were reported in 7.1% (2/28) of patients when their prosthesis systems were switched **off** compared against when their prosthesis systems were switched on. • 39.3% (11/28) of patients were unable to perform the direction of motion test with or without the system.	Study did not actively assess the occurrence of adverse events. • Recurrent conjunctival erosion was reported in 1 patient, resulting in the need for prosthesis removal.

Study 4 Ahuja AK (2012)

Details

Study type	**Case series**
Country	Multicentre: USA, Switzerland, Mexico, UK, France
Recruitment period	Not reported
Study population and number	Blind patients with severe profound retinitis pigmentosa **n=27**
Age and sex	Mean 58 years; 70% (19/27) male
Patient selection criteria	Inclusion criteria: patients with retinitis pigmentosa with bare light perception and visual acuity worse than 2.9 logMAR (worse than Snellen 20/15887) in both eyes were included. Exclusion criteria: not reported.
Technique	Patients were implanted with a 60–electrode stimulating array on the macula. It is assumed that the retinal prosthesis was implanted in 1 eye.
Follow-up	**Mean of 14 months**
Conflict of interest/source of funding	The principal investigator and 3 co-authors were employees of the manufacturer and had a financial interest in the company

Analysis

Follow-up issues: none identified.

Study design issues: patients were recruited from multiple clinical centres around the world. Study appears to be a feasibility study.

- Square localisation test – the task was deemed a success if the patient touched anywhere on the square or 'close' if the patient touched within 100 pixels (2.9 cm) of the edge of the square.

Study population issues: Potential overlap between other studies included in table 2 (Humayun, 2012; da Cruz, 2013; Dorn, 2013) as the same group of clinicians and treatment centres were involved in each study.

Other issues: None identified.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **27** • Significantly better square localisation test results were reported in 96% (26/27) of patients when their prosthesis systems were switched on. • The mean distance from the square when prostheses were switched on was 149±50 pixels; compared against 323±94 pixels when prostheses were switched off ($p<0.05$).	Study did not actively monitor the occurrence of adverse events.

Study 5 Barry MP (2014)

Details

Study type	**Case series**
Country	Multicentre: USA, Switzerland, UK
Recruitment period	Not reported
Study population and number	Patients with late stage retinitis pigmentosa **n=21**
Age and sex	Not reported
Patient selection criteria	Inclusion criteria: patients with retinitis pigmentosa with bare light perception and visual acuity worse than 2.9 logMAR (Snellen 20/15887) in both eyes were included. Exclusion criteria: not reported
Technique	A 60–electrode array (in a 6 x 10 electrode grid) was surgically implanted over the macula of 1 eye of each patient.
Follow-up	**Not reported**
Conflict of interest/source of funding	The study was funded by the manufacturer

Analysis

Follow-up issues: None identified.

Study design issues: Patients were asked to trace paths on a touchscreen. Sets of paths were divided into 3 categories: right-angle/single-turn, mixed-angle/single-turn, and mixed-angle/two-turn. Paths were presented in a random order. Patients trained on paths by using prosthetic vision and auditory feedback, and then were tested without auditory feedback, with and without prosthetic vision (prosthesis on then off). Custom software recorded position and timing of any contact that patients made with the touchscreen. The area between the correct path and the trace, and the elapsed time to trace a path were used to evaluate each patient's performance.

Study population issues: None identified.

Other issues: Authors did not report absolute values for tracing errors when prosthesis systems were switched on and off; instead they reported the mean.

Key efficacy and safety findings

Efficacy	Safety
Number of patients analysed: **21;** however numbers varied according to the type of test performed **Overall results** • Overall, tracing errors reduced by a mean of 60% and tracing times increased by a mean of 211% when prosthesis systems were switched on (p values<0.001). **Right-angle tests** • Tracing errors reduced by a mean of 63% and tracing times increased by a mean of 156% when prosthesis systems were switched on (p values<0.001). • A reduction in tracing errors was reported in 43% (9/21) of patients when prosthesis systems were switched on. **Mixed, single-angle tests** • Tracing errors reduced by a mean of 53% and tracing times increased by a mean of 184% when prosthesis systems were switched on (p values<0.001). • A reduction in tracing errors was reported in 56% (9/16) of patients when prosthesis systems were switched on. **Two-turn tests** • Tracing errors reduced by a mean of 38% and tracing times increased by a mean of 252% when prosthesis systems were switched on (p values<0.001). • A reduction in tracing errors was reported in 55% (5/9) of patients when prosthesis systems were switched on.	Study did not actively monitor the occurrence of adverse events.

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Study 6 Kotecha A (2014)

Details

Study type	**Case series**
Country	UK
Recruitment period	Not reported
Study population and number	Blind patients with outer retinal dystrophies **n=6**
Age and sex	Mean 70.9 years; 83.3% (5/6) male
Patient selection criteria	Inclusion criteria: patients with retinitis pigmentosa or other form outer retinal degeneration (1 patient had choroideraemia) were included. No further details were provided. Exclusion criteria: not reported
Technique	A 60–electrode array (in a 6 x 10 electrode grid) was surgically implanted over the macula of 1 eye of each patient. The array covered an area of the retina corresponding to about 20º in visual angle.
Follow-up	**3 years**
Conflict of interest/source of funding	Not reported

Analysis

Follow-up issues: none identified.

Study design issues: potential overlap between other studies included in table 2. Authors described the study as a feasibility study.

- Number of successful grasps – each patient was asked to reach out and grasp a high contrast cuboid object placed in 1 of 4 positions on a black matt. Patients were given 30 seconds to successfully grasp the cuboid object. The prosthesis was set to 1 of 3 settings: off, on (where the prosthesis was set to a normal function) and scrambled; where the electrode array was fully functional but the signal input would result in the electrodes being stimulated in a random scattered pattern. The prosthesis settings presented in a randomised order and patients were masked. Patients had to take the test under 2 eye conditions: eyes 'patched' (where both eyes would be taped closed) or 'unpatched'. Participants performed 48 reach and grasp tasks in total: 3 prosthesis settings, 2 eye conditions and 8 repetitions. Each patient was retested 4-6 weeks later.

Study population issues: One patient had choroideraemia.

Other issues: None identified.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>Number of patients analysed: 6

Successful grasps
<table>
<tr><td></td><td colspan="2">Mean percentage successful</td></tr>
<tr><td>System setting</td><td>1st Assessment</td><td>Retest (4-6 weeks)</td></tr>
<tr><td>Off</td><td>0</td><td>0</td></tr>
<tr><td>On</td><td>69</td><td>69</td></tr>
<tr><td>Scrambled</td><td>59</td><td>28</td></tr>
<tr><td>Chi-square p value</td><td>0.04</td><td>0.02</td></tr>
</table>

There were no significant differences between patched and unpatched eye conditions within each prosthesis setting.
There were no significant differences in times to object contact between on and scrambled settings at each visit.
</td><td>Study did not actively monitor the occurrence of adverse events.</td></tr>
</table>

Study 7 Rizzo S (2014)

Details

Study type	**Case series**
Country	Italy
Recruitment period	Not reported
Study population and number	Blind patients with retinitis pigmentosa **n=6**
Age and sex	Mean 45 years; 83.3% (5/6) male
Patient selection criteria	Inclusion criteria: patients with retinitis pigmentosa with residual light perception and visual acuity worse than 2.9 logMAR (Snellen 20/15887) in both eyes were included. Patients were required to have some visual sensation and no electroretinographic response Exclusion criteria: patients a history of cystic macular oedema, uncontrolled systemic disease or another ocular disease that might interfere with device function or inhibit postoperative device visualisation were excluded
Technique	A 60–electrode array (in a 6 x 10 electrode grid) was surgically implanted over the macula of 1 eye of each patient. After surgery 1 mg of vancomycin and 2.25 mg cefazolin were injected into the vitreous cavity of the implanted eye. Topical medications were used for 2 weeks following surgery: they included moxifloxacine (1 drop, 3 times a day); dexamethasone (1 drop, 4 times a day); and 1% atropine (1 drop, twice a day) Patients also took prednisolone (60 mg, once a fay) for 2 weeks.
Follow-up	**12 months**
Conflict of interest/source of funding	None reported

Analysis

Follow-up issues: 1 patient was lost to follow-up.

Study design issues: All surgeries were performed by a single surgeon.

- Square localisation test – The distance between the patient's finger and the centre of the square were recorded. The experiment was repeated 40 times for each patient.

Study population issues: None identified.

Other issues: None identified.

Key efficacy and safety findings

<table>
<tr><th>Efficacy</th><th>Safety</th></tr>
<tr><td>
Number of patients analysed: 5

Operative results
• The mean operative time was 174.1±36.9 minutes.

Square localisation tests (mean distance from the square)
<table>
<tr><td></td><td colspan="2">Mean distance (cm)</td></tr>
<tr><td>Patient</td><td>Baseline</td><td>12 months</td></tr>
<tr><td>1</td><td>14</td><td>6.9</td></tr>
<tr><td>2</td><td>5.4</td><td>3.1</td></tr>
<tr><td>3</td><td>7.6</td><td>4.4</td></tr>
<tr><td>4</td><td>6.1</td><td>4.7</td></tr>
<tr><td>5</td><td>3.6</td><td>3.9</td></tr>
</table>
• Square localisation tests improved in 4 patients after implantation.

Direction of motion tests (number of correct responses)
<table>
<tr><td></td><td colspan="2">Mean distance (cm)</td></tr>
<tr><td>Patient</td><td>Baseline</td><td>12 months</td></tr>
<tr><td>1</td><td>8</td><td>10</td></tr>
<tr><td>2</td><td>19</td><td>54</td></tr>
<tr><td>3</td><td>17</td><td>55</td></tr>
<tr><td>4</td><td>16</td><td>10</td></tr>
<tr><td>5</td><td>49</td><td>18</td></tr>
</table>
</td><td>
• Elevated ocular pressure was reported in 1 patient on the day after implantation: it was controlled medically without the need for surgery.
• Choroidal detachment was reported in 1 patient on the day after implantation. The choroidal detachment spontaneously resolved and did not require medical or surgical treatment.
</td></tr>
</table>

Efficacy

Visual acuity

In a case series of 30 patients implanted with an epiretinal prosthesis, improvements in visual acuity were reported in 23.3% (7/30) of patients at follow-up of up to 2.7 years. Visual acuity improved from worse than 2.9 logMAR (logarithm of the minimum angle of resolution) to between 2.9 and 1.6 logMAR[1].

Full-field light threshold (Light Perception)

In the case series of 30 patients, no changes in light perception were reported in the eyes of 93% (28/30) of patients after prosthesis implantation. In the same study, an improvement from no light perception to bare light perception was reported in the eye of 1 patient[1].

Square localisation tests

In the case series of 30 patients, patients were asked to locate a white square that randomly appeared on a black LCD touchscreen. Significantly better square localisation test results were reported in 96% (27/28) of patients when their prosthesis systems were switched on. No further details were provided[1].

Direction of motion tests

In the case series of 30 patients, patients were asked to indicate the path of a white bar that swept across a black LCD touchscreen. Significantly better direction of motion test results were observed in 57% (16/28) of patients when their prosthesis systems were switched on. No further details were provided[1].

Door finding test

In the case series of 30 patients, patients were asked to stand in the centre of a room, or offset left of centre by 3 feet, or offset right of centre by 3 feet. They were asked to find a rectangular ‘door’ 20 feet away and to place their hand on it. The mean success rate was 60% when the prostheses were switched on compared against 5% when the prostheses were switched off, at 24-month follow-up[1].

Letter identification

In a second case series of 30 patients implanted with an epiretinal prosthesis, patients were asked to identify 2-, 3- and 4-letter words when prostheses were switched ‘off’, ‘on and patched’ (both eyes be taped closed) and ‘on and unpatched’. The mean success rates for 2-letter words when prostheses were switched ‘off’, ‘on and patched’ and ‘on and unpatched’ were 7.5%, 80% and 75%, respectively. The mean success rates for 3-letter words were 5%, 67.5% and 62.5%, respectively. The mean success rates for 4-letter words were 2.5%, 65% and 57.5%, respectively. NB: results were calculated by the IP team[2].

Successful grasps

In a case series of 6 patients, the mean percentage of successful grasps of a white cube placed on a black surface when prostheses were switched on was 69% compared against 0% when prostheses were switched off at 3-year follow-up. There was no significant difference between the proportion of successful grasps when patients' eyes were 'patched' (both eyes taped closed) or 'unpatched'[6].

Safety

All the adverse events presented to the Committee came from a single case series of 30 patients; each affected patient may have experienced more than 1 adverse event.

Serious adverse events

Serious retinal complications were reported in 10% (3/30) of patients in a case series of 30 patients. A retinal tear was reported in 1 patient (timing not reported and no further details were provided). Rhegmatogenous retinal detachment, that needed surgical repair, was reported in 1 patient. Tractional retinal detachment was reported in 1 patient at 5-month follow-up: the patient had incurred blunt trauma to the eye with the implant resulting in proliferative vitreoretinopathy which progressed to retinal detachment. This was repaired by vitrectomy, partial retinectomy and silicone oil[1].

Replacement of retinal tacks was needed, within the first few days of implantation, in 7% (2/30) of patients[1].

Conjunctival dehiscence was reported in 10% (3/30) of patients. Neither the timing nor the clinical significance of these dehiscences was described. They were treated by additional sutures with or without placement of additional tissue[1].

Conjunctival erosion was reported in 7% (2/30) of patients. Timing of occurrence was not reported[1].

Presumed endophthalmitis was reported, within 8 weeks of surgery, in 10% (3/30) of patients. This resolved in all cases with antibiotic treatment[1].

Hypotony was reported in 10% (3/30) of patients, within 1 year of implantation. All cases of hypotony needed surgical treatment: 2 patients needed intraocular silicone tamponades and 1 patient had the device removed[1].

Severe inflammatory uveitis was reported in 1 patient. Timing of occurrence was not reported and no further details were provided[1].

Non-serious adverse events

Conjunctival oedema was reported in 33% (10/30) of patients in the case series of 30 patients[1].

Intraocular inflammation, hypotony without choroidal detachment, suture irritation and ocular pain were reported in up to 23% (7/30) of patients. No exact figures were reported, timing of occurrence was not reported, and no further details were provided[1].

Inflammatory conjunctivitis, corneal filaments, epiretinal membrane, high intraocular pressure (controlled by anti-glaucoma medications), epiphora, mild hyphaema, inflammatory uveitis with few keratic precipitates and mild vitreous haemorrhage were reported in up to 10% (3/30) of patients. No exact figures were reported, timing of occurrence was not reported, and no further details were provided[1].

A single occurrence was reported of each of the following: limited conjunctival dehiscence; corneal abrasion; mild peripheral corneal vascularisation; cystoid macular oedema; decrease in light perception; dry eye; transient headache; iris vessel engorgement; a stable tractional retinal detachment; transient nausea; transient increased nystagmus; scleritis; and transient vertigo[1].

Validity and generalisability of the studies

- The longest follow-up period reported in included studies was 3 years.
- There is a high degree of overlap between included studies because the same authors and treatment centres were involved in each study.
- The majority of included studies appear to be feasibility studies[1,3,4,5,6,7].
- Some studies included patients with other forms of retinal dystrophy, such as choroideraemia[1,2,6].
- No comparative studies were available that compared epiretinal prostheses with appropriate alternatives. This is likely to be because alternative treatments are still in early development.
- There were no standardised methods of evaluating the efficacy of the intervention in relatively small samples of patients.

Existing assessments of this procedure

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

Related NICE guidance

There is currently no NICE guidance related to this procedure.

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 does not represent the view of the society.

Mr G W Aylward, Mr Lyndon da Cruz, Mr Moin Mohamed, Mr Stephen Winder, Mr Wai Hung Woon (Royal College of Ophthalmologists)

- Four specialist advisers have never performed the procedure. One specialist adviser has performed the procedure at least once.
- Two specialist advisers described the procedure as novel and of uncertain safety and efficacy while the other 3 specialist advisers described insertion of an epiretinal prosthesis as the first in a new class of procedure.
- All specialist advisers stated that fewer than 10% of specialists engaged in this area of work.
- All specialist advisers stated that there are currently no comparators to the procedure.
- Specialist advisers did not highlight any additional adverse events reported in the literature.
- Specialist advisers did not highlight any anecdotal adverse events additional to those reported in the literature.
- Specialist advisers listed theoretical adverse events as loss of residual existing vision, phthisis bulbi, suprachoroidal haemorrhage, secondary neovascularisation, allergic reaction to the implant, failure of the implant, extrusion of the implant, and complications associated with vitrectomies.

- Specialist advisers listed key efficacy outcomes as improvement in vision (recognition of words or objects, as well as perception of light, movement or direction), performance in spatial or motor tasks and improved quality of life.
- Specialist advisers stated that an uncertainty about the efficacy of the procedure is related to a low resolution within the active visual field due to the small number of pixels generated by the prosthesis. They highlighted that studies have not demonstrated that the small improvements in vision translate to improved quality of life. One specialist adviser stated that the previous status of the eye is an important variable in determining efficacy. He also highlighted that there are concerns that current evidence on efficacy may represent test-retest variations or may be due to training of patients. Another specialist adviser noted that the lifespan of the prosthesis may pose some concern; the longest period that epiretinal prostheses have remained implanted in patients is approximately 6 years.
- One specialist adviser stated that the procedure would have a moderate impact on the NHS whereas the other 3 specialist advisers stated that the procedure would have a minor impact on the NHS.

Patient commentators' opinions

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

Issues for consideration by IPAC

Ongoing trials:

- NCT00407602: Argus II Retinal Stimulation System Feasibility Protocol; location: United States; type: Case series; estimated enrolment: 30; estimated primary completion date: August 2019.
- NCT01999049: Observational Study of the Argus II Retinal Prosthesis System; location: United States; type: Case series; estimated enrolment: 10; estimated primary completion date: January 2016.

- NCT01490827: Argus® II Retinal Prosthesis System Post-Market Surveillance Study; location: Multicentre - Germany, Italy; type: Case series; estimated enrolment: 45; estimated primary completion date: May 2016.
- NCT01860092: New Enrolment Post-Approval Study of the Argus® II Retinal Prosthesis System; location: United States; type: Case series; estimated enrolment: 53; estimated primary completion date: August 2018.
- NCT00279500: Feasibility Study of a Chronic Retinal Stimulator in Retinitis Pigmentosa: United States; type: Case series; estimated enrolment: 6; estimated primary completion date: December 2016.

References

1. Humayun, M. S., Dorn, J. D., da, Cruz L., Dagnelie, G., Sahel, J. A., Stanga, P. E., Cideciyan, A. V., Duncan, J. L., Eliott, D., Filley, E., Ho, A. C., Santos, A., Safran, A. B., Arditi, A., Del Priore, L. V., Greenberg, R. J., and Argus II Study Group. (2012) Interim results from the international trial of Second Sight's visual prosthesis. Ophthalmology 119 (4): 779-788
2. da, Cruz L., Coley, B. F., Dorn, J., Merlini, F., Filley, E., Christopher, P., Chen, F. K., Wuyyuru, V., Sahel, J., Stanga, P., Humayun, M., Greenberg, R. J., Dagnelie, G., and Argus II Study Group. (2013) The Argus II epiretinal prosthesis system allows letter and word reading and long-term function in patients with profound vision loss. British Journal of Ophthalmology 97 (5): 632-636
3. Dorn, J. D., Ahuja, A. K., Caspi, A., da, Cruz L., Dagnelie, G., Sahel, J. A., Greenberg, R. J., McMahon, M. J., and gus II Study Group. (2013) The Detection of Motion by Blind Subjects With the Epiretinal 60-Electrode (Argus II) Retinal Prosthesis. JAMA Ophthalmology 131 (2): 183-189
4. Ahuja, A. K., Dorn, J. D., Caspi, A., McMahon, M. J., Dagnelie, G., Dacruz, L., Stanga, P., Humayun, M. S., Greenberg, R. J., and Argus II Study Group. (2011) Blind subjects implanted with the Argus II retinal prosthesis are able to improve performance in a spatial-motor task. British Journal of Ophthalmology 95 (4) 539-543
5. Barry MP, Dagnelie G, et al. (2012) Use of the Argus II retinal prosthesis to improve visual guidance of fine hand movements. Investigative Ophthalmology & Visual Science 53 (9) 5095-5101
6. Kotecha, A., Zhong, J., Stewart, D., and da, Cruz L.(2014) The Argus II prosthesis facilitates reaching and grasping tasks: a case series. BMC Ophthalmology 14: 71
7. Rizzo, S., Belting, C., Cinelli, L., Allegrini, L., Genovesi-Ebert, F., Barca, F., and di, Bartolo E. (2014) The Argus II Retinal Prosthesis: 12-month outcomes from a single-study center. American Journal of Ophthalmology 157 (6): 1282-1290.

Appendix A: Additional papers on insertion of an epiretinal prosthesis 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
Klauke S, Goertz M, Rein S, et al. (2011) Stimulation with a wireless intraocular epiretinal implant elicits visual percepts in blind humans. Investigative Ophthalmology & Visual Science 52 (1) 449-455.	Case series n=6 Follow-up: not reported	All patients reported visual percepts as a result of electrical stimulation by the implant: no head mounted camera was used. Thresholds for eliciting visual percepts varied between them but were below the safety limits of electrical stimulation.	The study was a feasibility study that assessed action potentials and stimulus thresholds.
Stronks HC, Barry MP, Dagnelie G. (2013) Electrically elicited visual evoked potentials in Argus II retinal implant wearers. Investigative Ophthalmology & Visual Science 54 (6) 3891-3901	Case series n=4 Follow-up: 4.5 years	Visual percepts were reported after various electrodes on the microarray were switched on: no head mounted camera was used. The size of phosphenes increased with increasing electrical stimulation	The study was a feasibility study that assessed action potentials and stimulus thresholds.
Sabbah N, Authié CN, Sanda N et al. (2014) Importance of Eye Position on Spatial Localization in Blind Subjects Wearing an Argus II Retinal Prosthesis. Investigative Ophthalmology & Visual Science. 55(12):8259-66. doi: 10.1167/iovs.14-15392.	Case series n=3 Follow-up: 4 years	Eye and head movements were recorded as patients tried to localise a visual target. Subsequently, coordinates were recorded as patients directed their gaze toward predetermined directions, and pointed to corresponding perceived spot locations on a touch screen. Head and gaze misalignment was reported in 2 out of 3 patients during 'head-free visual searching'. The perceptual location of the visual target was affected by gaze position and, consequently, the conflict between head (i.e., camera) and gaze information affected visuomotor coordination. Adaptive strategies were	The study did not report sufficient information on the safety or efficacy of the procedure.

		developed to partly overcome the misalignment. Authors did not report additional information on the clinical utility of the procedure.	
Caspi A, Dorn JD, McClure KH, et al. (2009) Feasibility study of a retinal prosthesis: spatial vision with a 16-electrode implant. Archives of Ophthalmology 127 (4) 398-401.2009.	Case report n=1 Follow-up: not reported	The study demonstrated that the 'brain could identify spatial forms that were determined by retinotopic organisation of electrical stimulation of electrodes in the stimulation array. Significant improvements in the patient's visual acuity were reported when the epiretinal prosthesis was turned on'	Larger studies that reported similar outcome measures were included in table 2. Furthermore, the study displayed results graphically and no adverse events were reported.
Lauritzen, TZ, Harris J, Mohand-Said S, et al. (2012) Reading visual braille with a retinal prosthesis. Frontiers in Neuroscience 6 168	Case report n=1 Follow-up: 4.5 years	Groups of electrodes were directly stimulated (no head mounted camera used) to create percepts of visual brail. The patient correctly identified 89% of single letters, 80% of 2-letter, 60% of 3-letter, and 70% of 4-letter words	The study was a feasibility study that assessed action potentials and stimulus thresholds.
Humayun, MS, Weiland, JD, Fujii GY, et al. (2003) Visual perception in a blind subject with a chronic microelectronic retinal prosthesis. Vision Research 43 (24) 2573-2581	Case report n=1 Follow-up: 2.5 months	Visual percepts were reported after various electrodes on the microarray were switched on: no head mounted camera was used. The size of phosphenes increased with increasing electrical stimulation	The study was a feasibility study that assessed action potentials and stimulus thresholds.

Appendix B: Related NICE guidance for insertion of an epiretinal prosthesis for retinitis pigmentosa

There is currently no NICE guidance related to this procedure.

Appendix C: Literature search for insertion of an epiretinal prosthesis for retinitis pigmentosa

Databases	Date searched	Version/files	No. retrieved
Cochrane Database of Systematic Reviews – CDSR (Cochrane Library)	30/12/2014	Issue 12 of 12, December 2014	40
Database of Abstracts of Reviews of Effects – DARE (Cochrane Library)	30/12/2014	Issue 4 of 4, October 2014	1
HTA database (Cochrane Library)	30/12/2014	Issue 4 of 4, October 2014	3
Cochrane Central Database of Controlled Trials – CENTRAL (Cochrane Library)	30/12/2014	Issue 11 of 12, November 2014	33
MEDLINE (Ovid)	31/12/2014	1946 to November Week 3 2014	11
MEDLINE In-Process (Ovid)	31/12/2014	December 30, 2014	45
EMBASE (Ovid)	31/12/2014	1974 to 2014 Week 52	32
PubMed	30/12/2014	n/a	159
JournalTOCS	30/12/2014	n/a	1

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	((Epiretin* or retin* or visual* or vision* or eye*) adj4 (prosth* 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	Argus II.tw.
26	Second Sight.tw.
27	Retinal Implant AG.tw.
28	or/24-27
29	animals/ not humans/
30	28 not 29