Evidence-based Practice Center

Technology Assessment Protocol

Project Title: Retinal Prostheses in the Medicare Population

Project ID: EYET1215

March 10, 2016

I. Introduction

Recent advances in technology have permitted the first attempts at sight restoration by combining a patient's native intrinsic visual pathway with advanced light sensing, signal processing, and stimulation components in the form of an ocular prosthesis. Because of the novelty that this technology represents and the recent approval by the U.S. Food and Drug Administration (FDA) for use of one system in patients with retinitis pigmentosa (RP), the Agency for Healthcare Research and Quality (AHRQ) commissioned the ECRI Institute–Penn Medicine Evidence-based Practice Center to prepare this Technology Assessment to provide an overview of retinal prosthesis systems (RPSs). This assessment will summarize the current state of RPSs as well as the existing evidence addressing their clinical utility and the potential future directions for research in areas in which information is limited.

Retinal Prosthesis Systems (RPS)

Multiple types of ocular prosthetic devices are under development.[1-4] The devices have focused on stimulating different parts of the visual pathway, including the visual cortex,[3] the optic nerve,[4] and the suprachoroidal,[5] epiretinal,[2] and subretinal[1] spaces. A preliminary literature search has identified seven RPS devices for which there is at least one published article describing human recipients of the technology. Regarding placement of intraocular electrode arrays/stimulation components, three implants are inserted on the retinal surface (epiretinal), two are placed in a subretinal space, and two are implanted suprachoroidally.

Of the seven RPS devices, the only one to date to receive FDA approval is the Argus II epiretinal RPS (Second Sight Medical Products, Inc., Sylmar, CA). Another device originating in the United States is the subretinal Artificial Silicone Retina (ASR), developed by Optobionics (Glen Ellyn, IL). The subretinal Alpha-IMS was created by Retina Implant AG (Reutlingen, Germany). Another German manufacturer is Fraunhofer IMS Biohybrid Systems (Duisburg, Germany) which developed the epiretinal Epi-Ret 3 device. The IRIS device began development in Germany but is now produced by the French manufacturer Pixium Vision (Paris, France). The suprachoroidal Bionic Eye RPS comes from BionicVision in Parkville, Victoria, Australia. Nidek Co., Ltd. (Gamagori, Japan), produces the Suprachoroidal Transretinal Stimulation (STS) Artificial Vision System.

In 2011, the Argus II retinal prosthesis system was approved for use in Europe, which was followed by FDA approval in 2013 for U.S. use in patients with RP.[2] This system has three parts,

including an implantable 60-electrode stimulating microelectrode array, a pair of glasses with a video camera attached, and a video-processing unit worn typically on the belt of the user. The video camera captures surrounding visual images, which are processed by the wearable unit and transmitted wirelessly to the implanted array. The array then stimulates the inner retina with electrical impulses, which follow the "typical" visual processing pathway. The Argus II RPS is a second-generation unit with the most notable difference from the first generation being an increase in the electrode-array size, from 16 to 60 electrodes.

The French manufacturer of the epiretinal IRIS device, Pixium Vision, uses extraocular and intraocular components similar to the Argus II, but the electrode array contains 150 electrodes.[6] This company is also developing the PRIMA device, not yet implanted in humans, that uses similar extraocular components, including video camera input, but introduces subretinal microchips in modules of up to several thousand electrodes. The Argus II and IRIS devices use induction for energy and data transmission, and the German Epi-Ret 3 uses video camera input with radiofrequency telemetric transmission from the eyeglass to a posterior chamber receiver. From the receiver, data is relayed via micro-cable to an epiretinal array containing 25 electrodes.

The German Alpha-IMS device may be distinguished from the Argus II, IRIS, and Epi-Ret 3 devices by use of incident light projected through the recipient's native lens, as opposed to providing data to the electrode array via a video camera.[7] The subretinal microchip implant contains 1,500 pixels of photodiode-amplifier-electrode units which convert light into electrical pulses, delivered locally to overlying retinal neurons. A cable exits the sclera and orbit, leading to a periauricular subdermal coil that is coupled by transdermal magnetic induction with an external primary coil. A portable signal processor has knobs for adjusting contrast sensitivity and brightness.

The American Optobionics ASR device, like the Alpha-IMS device, uses incident light instead of video camera data as the input source for the prosthesis.[8] The self-contained ARS is a disc-shaped microchip containing about 5,000 microphotodiodes, each with its own stimulating electrode. Fully powered by light, this is the only device used in humans so far that has no external power source.

An article on the Australian Bionic Eye has described the device in prototype form. This report detailed a suprachoroidal array with 33 stimulating electrodes.[5] The prototype had a helical lead wire extended from the implant to a periauricular percutaneous connector. A head-mounted video camera provided data input to the implant. The manufacturer Web site states that other prototypes have used 25 and 44 electrodes. Next-generation models will use an eyeglass-mounted video camera, an external vision processing unit that will connect to the camera, and arrays with 98 and 256 electrodes.

The Japanese STS Artificial Vision System (Nidek) is a suprachoroidal device connected to periauricular components fixed to the skull.[9] An eyeglass-mounted video camera sends data to a controller which relays it to a periauricular external coil coupled by induction with a secondary coil/decoder. A micro-cable extends to the array containing 49 electrodes.

Besides the seven devices for which our preliminary search found published reports of human recipients, three additional devices subjected to preclinical tests have been identified. The Boston Retinal Implant Prosthesis (Visus Technology, Inc., Boston, MA) uses a subretinal array of 16 electrodes that receives energy and data from an eyeglass-mounted video camera and radiofrequency coil, with assistance from a controller that performs image signal processing.[10]

Another American device, the Photovoltaic Retinal Prosthesis (Stanford University Palanker Lab) has a subretinal array of thousands of photodiodes that convert light pulses to bi-phasic pulses of electric current.[11] The device's light source comes from an eyeglass-mounted LCD (liquid crystal display) microdisplay that receives images from a video camera. From Japan, the Okayama University-Type Retinal Prosthesis (OUReP) uses a unique approach with photoelectric dye molecules coupled to polyethylene film.[12] The dye absorbs light and converts it into electric potentials. Thus the film, implanted in a subretinal space, acts as both the image receiver from incident light and neuron stimulator, with no external power source.

Table 1. Retinal Prosthesis System devices with published human studies

Device	Input Source	Signal Processor	Implant Placement	Electrode/ Stimulation Array	Power Source
Alpha-IMS (Retina Implant AG, Germany)	Light projected through recipient's native lens	Part of external power supply; 2 knobs allow recipient to adjust contrast sensitivity and brightness	Subretinal	Microchip containing 1,500 pixels of photodiode-amplifier-electrode units which convert light into electrical pulses, delivered locally to overlying retinal neurons via microelectrodes; power supplied through subretinal polyimide foil that exits eye through choroid and sclera through equator	Cable exits the orbit, leads to subdermal coil fixed onto skull behind the ear; external power supply and controller attaches by transdermal magnetic induction at external primary coil.
Argus II (Second Sight Medical Products, Inc., United States)	Eyeglass-mounted video camera	Video processing unit (computer), mounted on belt or shoulder strap, attached by cable to camera and to eyeglass-mounted RF transmitter coil	Epiretinal	Electronics case fixed to sclera, secured by encircling scleral buckle containing an antenna/receiver; sclera-penetrating ribbon cable leads to the 60-electrode array	Part of video processing unit
Artificial Silicone Retina (Optobionics, United States)	Light projected through recipient's native lens	None	Subretinal	Microchip containing about 5,000 microscopic solar cells called microphoto-diodes, each with its own stimulating electrode; self-contained, no cable	Microchip is powered by incident light
Bionic Eye (BionicVision, Australia)	Next-generation model will use eyeglass-mounted video camera	External vision processing unit will connect to camera	Supra-choroidal	33 stimulating electrodes	Prototype helical lead wire extends to percutaneous connector

Device	Input Source	Signal Processor	Implant Placement	Electrode/ Stimulation Array	Power Source
Epi-Ret 3 (Fraunhofer IMS Biohybrid Systems, Germany)	Eyeglass-mounted camera in extraocular component with radiofrequency (RF) transmitter; sends data and energy telemetrically	Digital signal processor, in extraocular eyeglass component, calculates a stimulation pattern	Epiretinal	After lens removal, intraocular receiver unit placed in posterior chamber receives energy and data, sends pulses along micro-cable to 25 stimulation electrodes	Part of extraocular component, energy sent with RF telemetry, no cables connecting extraocular and intraocular components
IRIS (Pixium Vision, France)	Eyeglass-mounted camera in extraocular component with induction transmitter that sends data telemetrically	Eyeglass-mounted signal processer connected to pocket computer with tunable software, sends signals to induction transmitter	Epiretinal	Electronics case fixed to sclera sends ribbon cable through sclera to 150-electrode array	Unclear
Supra-choroidal Transretinal Stimulation (STS)/Nidek Artificial Vision System (Nidek Co., Ltd., Japan)	Eyeglass-mounted video camera and processor sends data controller processor	Controller sends data to external coil, coupled by induction to implanted secondary coil, which sends data to implanted decoder, which generates biphasic pulses across internal micro-cable to individual electrodes	Supra-choroidal	Electrode array has 49 electrodes, associated intravitreal return electrode	Battery attached to controller

Clinical Context

The retina is the light-sensitive layer of tissue within the eye and is responsible for converting light into electrical impulses. These impulses are delivered through the visual pathway and interpreted in the visual centers of the brain, leading to sight. Central to this functioning is the outermost layer of the retina, the photoreceptors, comprised of rods and cones. These cells act as the "ignition switch" that starts the entire process of sight by initiating the visual pathway. Diseases that preferentially affect the photoreceptors (or their support cells, the retinal pigment epithelium) are ideally suited for sight restoration by RPS because the rest of the native pathway remains intact.

RP is one such disease. RP is a collection of genotypically and phenotypically diverse eye disorders, all of which specifically attack the rods and cones within the retina or their support cells adjacent to the photoreceptors. This inherited disease is often identified by its main clinical

features, which typically include symptoms of poor night vision, visual field loss, and/or peripheral flickering lights. As the disease progresses and more photoreceptors are lost, patients experience an indolent, progressive constriction of their visual field until legal and functional blindness occurs, typically by age 40.[13] On ophthalmic examination, a triad of clinical findings is typically noted, including attenuation of retinal blood vessels, "bone spicule" clumping and mottling of the retinal pigment epithelium (a single layer of pigmented cells that nourishes the retina photoreceptors), and optic nerve head pallor. All of these findings are a direct result of the main pathophysiologic action of RP, atrophy of the photoreceptor layer.

RP is thought to occur in 1 out of every 4,000 people and affects nearly 1 million people worldwide.[14-17] More than 100 different genes have been implicated in causing the various forms of RP, representing all possible modes of genetic inheritance, including autosomal dominant, recessive, X-linked, and mitochondrial.[16] Despite the numerous genes found to be associated with RP, only 60% of the cases can be associated with a known mutation.[16] Clinical and family histories are of extreme importance in the diagnosis of RP, because the time course of disease and prognosis are well correlated to the pattern of inheritance, with X-linked disease being the most severe and autosomal dominant RP having later onset and milder symptoms.[16,18] Common to many inherited diseases, age of onset is typically early in life with autosomal recessive patients first noticing symptoms around age 10 and autosomal dominant patients around age 23.[19] This age of onset is in contrast to other, more familiar vision-threatening maladies including cataracts, glaucoma, and age-related macular degeneration (AMD), all of which most commonly occur in elderly populations. These population age differences lead to blindness from RP having much higher direct medical and societal costs than other common etiologies of vision loss.[20,21]

An ongoing clinical trial is testing RPS in AMD. AMD is the leading cause of irreversible visual loss in industrialized countries.[22] In the United States, it accounts for about half of severe sight loss. Risk factors for AMD include smoking, hypertension, cardiovascular disease, low levels of systemic antioxidants, low dietary intake of omega-3 long-chain polyunsaturated fatty acids, high dietary intake of saturated fats and cholesterol, high body mass index, regular use of aspirin, and genetic factors.[22]

Although the etiology is incompletely understood, it develops as a result of deposition of cellular debris in Bruch's membrane, including lipids, amyloid, complement factors, and other components.[23,24] As this process progresses, clinicians may detect the appearance of drusen, whitish yellow excrescences, between the retinal pigment epithelium (RPE) and Bruch's membrane. Drusen may be found on optical coherence tomography (OCT) or fluorescein angiography. The American Academy of Ophthalmology (AAO)[25] guideline on AMD describes three size categories for drusen: small (<63 μm in diameter), intermediate (between 63 and 125 μm), and large (≥125 μm). Reticular pseudodrusen appear as a yellow interlacing network.

Diagnosis of AMD does not depend on the presence of visual symptoms,[25] but can include metamorphopsia (distorted wavy vision), loss in visual acuity, blurred vision, scotomas, impaired color perception, and loss in contrast sensitivity. The AAO AMD guideline adopts a disease classification system developed for the Age-Related Eye Disease Study (AREDS) and described in 2013 by Ferris and colleagues.[26] Early AMD is defined as a combination of multiple small drusen, few intermediate drusen or mild RPE abnormalities (e.g., hyper- or hypopigmentation). Intermediate AMD can include numerous intermediate drusen, at least one large druse, or geographic atrophy (GA, defined as a sharply demarcated, usually round or oval area of atrophy

of the RPE not involving the center of the fovea). Advanced AMD can involve one or more of the following features:

- GA of the RPE within the foveal center
- Choroidal neovascularization (CNV, choroidal angiogenesis extending through a defect in Bruch's membrane)
- Serous and/or hemorrhagic detachment of the neurosensory retina or RPE
- Retinal hard exudates
- Subretinal and sub-RPE fibrovascular proliferation
- Disciform scar

AMD is often separated into dry and wet subtypes. Dry AMD is more common, accounting for about 90% of cases, defined as nonexudative or nonneovascular. Advanced dry AMD is characterized by GA. Wet AMD (exudative, neovascular) can feature CNV or pigment epithelial detachment (PED) and progresses more rapidly than dry AMD.[22]

Pharmacologic Treatments for Retinitis Pigmentosa and Age-Related Macular Degeneration

No FDA-approved medications exist to reverse or slow the progression of RP. The current state of care for patients with RP mostly can be considered supportive in nature, focusing on maximizing the visual acuity of a patient (i.e., performing cataract surgery) and offering training with low-vision aids and services helping patients to function within their limited visual capacity. The absence of a therapy is not for lack of effort, with most of the past focus being on nutritional supplements. Randomized clinical trials have been performed on potential treatments, including docosahexaenoic acid (DHA),[27,28] lutein,[29] vitamins A and E,[30] and various combinations of these agents.[31,32] Unfortunately none of these studies showed a definitive benefit to patients with RP, with a possible small exception being vitamin A supplementation.[30] These findings however, are not without controversy, because the benefit of vitamin A was seen only in electrophysiological testing and not in any psychophysical visual parameters perceivable by patients, despite 4 years of treatment. This is particularly important in light of the expansive literature of the potential harmful effects of excessive vitamin A supplementation.[33-37] Lastly, pharmacologic attempts have been made at neuroprotection through neurotrophic factors, with trials ongoing, but those that have reported have yet to show any efficacy.[38,39]

Effective treatment intended to slow the progression of AMD has not been found for early disease.[25] The AREDS (2001)[40] and AREDS2 (2013)[41] studies support use of antioxidant vitamins and minerals among patients with intermediate AMD and advanced AMD in one eye. Current AAO recommendations include vitamin C (500 mg), vitamin E (400 IU), lutein (10 mg), zeaxanthin (2 mg), zinc oxide (25 mg) and cupric (copper) oxide (2 mg). Recommended first-line treatment for AMD with CNV (wet) is intravitreal injection of a VEGF inhibitor such as aflibercept, bevacizumab, or ranibizumab. Less commonly used, but still recommended nonpharmacologic treatments for CNV include photodynamic therapy with verteporfin and laser photocoagulation surgery.

Gene Therapy for Retinitis Pigmentosa

Recent landmark clinical trials of *RPE65* gene therapy for *RPE65*-related early onset retinal dystrophy, a form of RP, successfully rescued visual function and improved full-field sensitivity and pupillary light reflex in a small group of pediatric patients.[42-45] Additionally, a more recent

gene therapy trial replaced the *REP1* gene for another genetic eye disorder, choroideremia, and similarly found improved visual acuity and retinal sensitivity.[46] However, excitement for this modality has been moderately tempered since a follow-up study showed continued disease progression despite stable visual improvements over 3 years.[47]

Although gene therapy is promising, two major hurdles make the application of gene therapy to RP difficult. The first is the large number of genes that converge into the phenotype of RP. For each of the 100 genes that have been associated with RP, a new therapy would need to be developed, and even then it might not resolve all RP cases because the currently known genes do not represent 100% of the RP cases.[48] Second, gene therapy appears to work best at rescuing failing tissue and does not appear be as effective once all function is lost. This would leave those who are currently blind without help and make early diagnosis and treatment imperative, a goal not always easily accomplished.

The RP population, particularly those with vision poor enough to qualify for an RPS, is rather small. The bigger-picture goal for most of the companies developing this technology would be for implementation in more common disease states. The most logical of these is late-stage age-related macular degeneration (AMD), because many of the pathologic aspects of RP for RPS can also be found in AMD, namely physiologic damage limited to the outer retina. This work has already begun with a clinical trial under way in patients with end-stage AMD and poor vision.[49]

Regulatory Aspects of RPS

The Argus II (Second Sight Medical Products, Inc., Sylmar, CA), a second-generation unit, has been through multiple completed clinical trials.[50,51] The FDA approval for the Argus II specifies that only patients with RP and the most severe loss of vision (light perception only or worse) in both eyes are eligible for device implantation. New quality-of-vision scales designed to better assess the changes and improvements in eyesight for patients with such severe vision loss are an active area of study.[52]

Second Sight Medical provides resources for implanting and operating the Argus II device. A video Surgeon Manual describes the surgical procedure for implanting the device. Surgeons receive instructions in screening patients for eligibility to receive the device along with a recommended clinical followup schedule. An additional requirement is having a previously trained Argus II surgeon present during the first surgical implantation at any new institution. Because of these requirements, as well as the high cost and limited patient pool outlined by FDA, only 16 sites across the United States are certified for implanting the Argus II. Second Sight Medical gives clinical centers a Device Fitting Manual with instructions on how to use all device components and requires training and qualification of personnel involved in fitting the Argus II RPS. Device recipients receive a Patient Manual describing use of extraocular components. A Visual Rehabilitation Guide is available for low vision therapists, along with hands-on training.

Scope of Review and Key Questions

The first of two key objectives to be pursued in this report is review of the evidence reported on the effects of RPS devices on patient-centered outcomes among patients with retinal degenerative disorders or macular disorders. The second key objective is to examine the psychometric properties (validity, reliability, and responsiveness) of outcome measures that have been reported in RPS device studies or may be used in future RPS studies. The scope of this

review is defined below according to the population, intervention, comparators, outcomes, timing, and setting (PICOTS) framework. Key questions (KQs) appear below.

Patients	Individuals in the Medicare population with low vision and retinal degenerative disorders or macular disorders
Intervention	Retinal prosthesis system devices
Comparators	Best supportive care (both retinal degenerative disorders and macular disorders); pharmacologic therapy, photodynamic therapy, laser therapy (macular disorders)
Outcomes	Health-related quality of life, activities of daily living, instrumental activities of daily living, visual function, visual acuity, changes in concurrent treatments/supportive care
Timing	Any
Setting	Any

KQ1A: What outcome measures have been used in studies of RPS?

KQ1B: What are the psychometric properties of the health-related quality of life (HRQoL), ability to perform activities of daily living (ADLs), and instrumental activities of daily living (IADLs), visual function, and other measures used in the studies?

KQ1C: What other reliable and valid measures could be used in future studies of RPSs to demonstrate improvement in HRQoL, ability to perform ADLs and IADLs, visual function, and other functions?

KQ2:   What is the evidence that HRQoL, ability to perform ADLs and IADLs, visual function, and other outcomes are improved in patients who use RPS compared to baseline (or device off or untreated eye) and compared to alternative treatments?

KQ3:   What is the evidence that the use of RPS arrests the progression of RP?
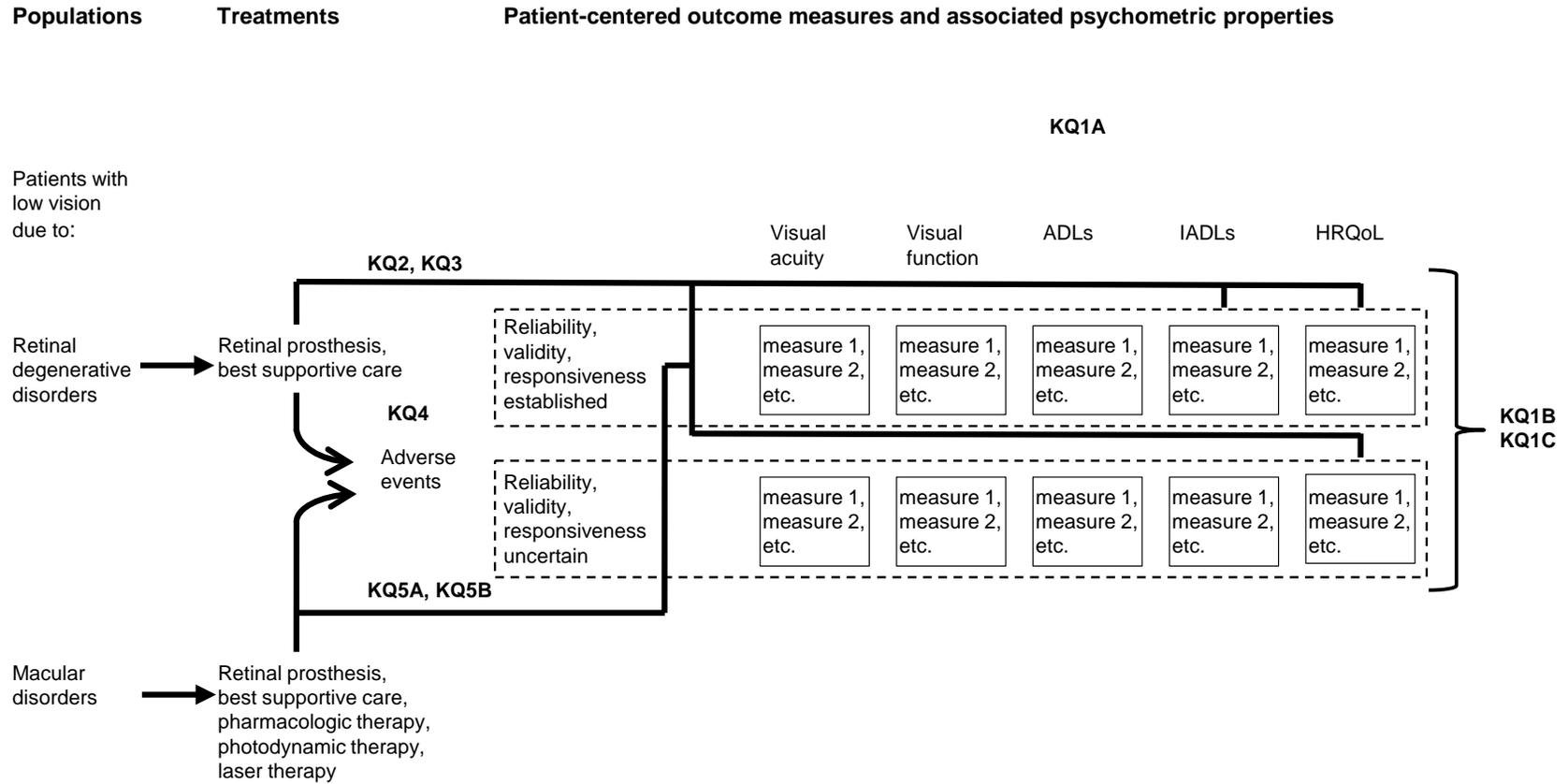
KQ4:   What is the evidence on adverse events associated with the use of RPS?

KQ5A: What is the evidence on off-label use of RPS?

KQ5B: From a narrative review of the literature, are there other uses that have been suggested for RPS?

Figure 1 presents an analytic framework that depicts KQs, populations, treatments, patient-centered outcome measures, and associated psychometric properties.

Figure 1: Analytic framework

Populations   **Treatments**   **Patient-centered outcome measures and associated psychometric properties**

KQ1A

Patients with
low vision
due to:

| | | | | Visual acuity | Visual function | ADLs | IADLs | HRQoL |

KQ2, KQ3

| Retinal degenerative disorders | → | Retinal prosthesis, best supportive care | Reliability, validity, responsiveness established | measure 1, measure 2, etc. | measure 1, measure 2, etc. | measure 1, measure 2, etc. | measure 1, measure 2, etc. | measure 1, measure 2, etc. |

KQ4

Adverse events

| | | | Reliability, validity, responsiveness uncertain | measure 1, measure 2, etc. | measure 1, measure 2, etc. | measure 1, measure 2, etc. | measure 1, measure 2, etc. | measure 1, measure 2, etc. |

KQ1B
KQ1C

KQ5A, KQ5B

Macular disorders → Retinal prosthesis, best supportive care, pharmacologic therapy, photodynamic therapy, laser therapy

Note: Examples of outcome measures for which psychometric properties have been established or are uncertain could include visual acuity measures such as the Basic Grating Acuity Test and the Freiburg Acuity and Contrast Test. Examples of visual function measures may include the Basic Assessment of Liight and Motion and the Functional Low-vision Observer Rated Assessment.

Abbreviations: ADLs = activities of daily living; HRQoL = health-related quality of life; KQ = Key Question; IADLs = instrumental activities of daily living;

II. Methods

Key Informant Input

With input from the Task Order Officer (TOO), we recruited Key Informants. As partners, the Centers for Medicare and Medicaid Services (CMS) representatives were included among our Key Informants. We selected additional key informants (KIs) with expertise in each of the following areas: clinical and research ophthalmology, patient advocacy, healthcare insurance administration, psychometrics, and industry. KIs were interviewed in groups of two to four.

Each KI must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Perspectives of KIs with potential COI were balanced by perspectives of other neutral participants. We asked ophthalmologists about RPS candidate selection criteria, specifically about diagnoses, vision characteristics, age, and comorbidities. We also asked which management strategies RPS devices should be compared with, and what comprises optimal care for RPS candidates.

All KIs were asked which specific outcome measures could potentially be improved by RPS devices, in the following categories: vision, ADLs, IADLs, HRQoL, and others. All were asked about which outcome measures have empirically established favorable psychometric properties such as validity, reliability, and responsiveness. KIs were asked to what extent their statements are based on evidence and if so, evidence sources. We used KI input to refine the literature search concerning the psychometric properties of outcome measures and to enhance our understanding of the strengths and limitations of available outcome measures. The EPC followed the requirements of the Office of Management and Budget in limiting the number of KIs asked the same questions to no more than nine participants. We submitted summaries of the discussion with the Key Informants to the TOO.

Gray Literature Search

Gray literature includes reports, articles, abstracts, and presentations produced by government agencies, private organizations, educational institutions, consulting firms, and corporations that typically do not appear in peer-reviewed journal literature. For this report, we searched gray literature sources to identify RPS manufacturers, obtain descriptions of RPS devices, and identify unpublished studies.

Among sources we consulted were conference proceedings over the past 3 years for the following organizations: the American Academy of Ophthalmology (AAO), the Association for Research in Vision and Ophthalmology (ARVO), the American Society of Retina Specialists (ASRS), and the Retina Society. We also searched the trial registry ClinicalTrials.gov.

Web sites and databases associated with the following institutions and organizations were searched using text words: U.S. Centers for Disease Control and Prevention (CDC), U.S. Food and Drug Administration (FDA), U.S. Centers for Medicare & Medicaid Services (CMS), Healthcare Common Procedure Coding System (HCPCS), National Guideline Clearinghouse (NGC), the UK's National Institute for Health and Care Excellence (NICE), Trip database, Healthcare Standards database, Medline Plus, Medscape, and MediRegs. ECRI Institute resources that we searched include our internal library, reports produced for our subscribers, and the periodical Health Devices. We also searched manufacturer and health care insurer Web sites. We requested that manufacturers and other stakeholders submit scientific information packets and other relevant information to the AHRQ Scientific Resource Center.

Literature searches will be updated when the draft report is posted to the AHRQ website.

Published Literature Searches

Medical librarians performed systematic literature searches following established systematic review protocols. In seeking references for RPS devices, we searched the following databases using controlled vocabulary and text words: MEDLINE, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL), the Cochrane Library, and PubMed (unprocessed records only). The search concerning RPS devices covered the literature published from January 1, 2000, through September 17, 2015. This time frame was chosen because preliminary searches did not find relevant references before 2002, and early devices have either been abandoned or replaced by technologically improved versions that are either in development or commercially available in some market. The literature search on psychometric properties of outcome measures covered the same databases as the device search but also included PsycINFO. Search limits spanned January 1, 1990, through December 14, 2015. These searches will be updated when the draft report is posted to the AHRQ website.

Study Selection

We will perform redundant title and abstract screening using the Distiller SR tool (Evidence Partners, Ottawa, Ontario, Canada). All articles that are excluded by one reviewer in title and abstract screening will be submitted to duplicate review. Only one reviewer's selection will be required for full text article retrieval. Dual independent review will be performed on all full text articles. Resolution of full text article review disagreements will be achieved by consensus. A PRISMA diagram will be produced.

We will include RPS device articles that meet these criteria: it reported use of a RPS device still in development or on the market, reported at least one patient-centered outcome, included any number of human participants with any retinal degeneration disorder or macular disorder diagnosis, described any study design, and was published in any language. An article describing outcome measures psychometric properties will be included if it is published in English and is designed to evaluate the validity, reliability, or responsiveness of relevant outcome measures used in patient populations of interest.

Data Extraction

Data extraction will be performed by a single reviewer and will be fully verified by a second reviewer. Extracted data will be stored in Microsoft Word and Microsoft Excel files. Information to be extracted will include: study design, psychometric properties assessment methods (from COSMIN checklist items);[53] patient blinding to experimental condition, outcome assessor blinding to experimental condition, experimental condition randomly presented, number of outcome assessors, country/site, number of patients enrolled, patient inclusion criteria, patient exclusion criteria, RPS treatment details, prior treatment, concurrent treatment, study duration, diagnosis, age at diagnosis, age at implantation, eye implanted, time from implantation to study participation, sex, race, visual acuity at time of implantation, outcomes, and outcome definitions.

Assessing Study Quality

Study quality assessment of RPS device studies will focus on single-group designs (case series: pretest-posttest, posttest only, device on/off, fellow eye) because we do not expect to identify randomized controlled trials. These risk-of-bias items have been selected from the AHRQ Methods Guide[54]:

- Does the design or analysis control or account for important confounding and modifying variables through matching, stratification, multivariable analysis, or other approaches?

- Did researchers rule out any impact from a concurrent intervention or an unintended exposure that might bias results?

- Did the study maintain fidelity to the intervention protocol?

- If attrition (overall or differential nonresponse, dropout, loss to followup, or exclusion of participants) was a concern, were missing data handled appropriately (e.g., intention-to-treat analysis and imputation)?

- Were the outcome assessors blinded to the intervention or exposure status of participants?

- Were outcomes assessed/defined using valid and reliable measures and implemented consistently across all study participants?

- Were the potential outcomes prespecified by the researchers? Are all prespecified outcomes reported?

Study quality assessment of studies addressing outcome measures psychometric properties will be conducted according to the COSMIN checklist.[53] This instrument was developed using rigorous methods including Delphi procedures. Items address the following domains: internal consistency, reliability, measurement error, content validity, structural validity, hypothesis testing, cross-cultural validity, criterion validity, and responsiveness.

Assessing Applicability

Factors of interest in assessing applicability in general focus on the framework defined by population, intervention, comparators, outcomes, timing, and setting. More specifically, applicability will be determined mainly by patient selection methods, patient sample characteristics, intervention characteristics, and magnitude of effects on outcomes. Summary applicability tables will be produced.

Evidence Synthesis and Grading Strength of Evidence

Evidence synthesis will be qualitative because we expect meta-analysis will not be feasible. We will use the strength-of-evidence grading approach described in the AHRQ Methods Guide.[54] Domains that will be addressed include: study limitations, directness, consistency, precision, reporting bias, and strength of association (magnitude of effect). We will assign a grade of high, moderate, low, or insufficient, according to definitions stated below.

Grade	Definition
High	We are very confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has few or no deficiencies. We believe that the findings are stable, i.e., another study would not change the conclusions.
Moderate	We are moderately confident that the estimate of effect lies close to the true effect for this outcome. The body of evidence has some deficiencies. We believe that the findings are likely to be stable, but some doubt remains.
Low	We have limited confidence that the estimate of effect lies close to the true effect for this outcome. The body of evidence has major or numerous deficiencies (or both). We believe that additional evidence is needed before concluding either that the findings are stable or that the estimate of effect is close to the true effect.
Insufficient	We have no evidence, we are unable to estimate an effect, or we have no confidence in the estimate of effect for this outcome. No evidence is available or the body of evidence has unacceptable deficiencies, precluding reaching a conclusion.

<u>Peer Review and Public Commentary</u>

The full draft report will be posted for public and peer review after review by the Task Order Officer and Associate Editor. Peer reviewers, chosen by methods similar to KI selection, will be invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report will be considered by the EPC in preparation of the final report. The dispositions of the peer review comments will be documented and posted on the AHRQ Technology Assessment Program Web site.

III. References

1. Zrenner E, Bartz-Schmidt KU, Benav H, et al. Subretinal electronic chips allow blind patients to read letters and combine them to words. Proc Biol Sci. 2011 May 22;278(1711):1489-97. Epub 2010 Nov 3. PMID: 21047851.

2. Humayun MS, Dorn JD, da Cruz L, et al. Interim results from the international trial of Second Sight's visual prosthesis. Ophthalmology. 2012 Apr;119(4):779-88. PMID: 22244176.

3. Dobelle WH, Quest DO, Antunes JL, et al. Artificial vision for the blind by electrical stimulation of the visual cortex. Neurosurgery. 1979 Oct;5(4):521-7. PMID: 534058.

4. Veraart C, Raftopoulos C, Mortimer JT, et al. Visual sensations produced by optic nerve stimulation using an implanted self-sizing spiral cuff electrode. Brain Res. 1998 Nov 30;813(1):181-6. PMID: 9824694.

5. Ayton LN, Blamey PJ, Guymer RH, et al. First-in-human trial of a novel suprachoroidal retinal prosthesis. PLoS ONE. 2014;9(12):e115239. PMID: 25521292.

6. Keseru M, Feucht M, Bornfeld N, et al. Acute electrical stimulation of the human retina with an epiretinal electrode array. Acta Ophthalmol. 2012 Feb;90(1):e1-8. PMID: 22067614.

7. Stingl K, Bartz-Schmidt KU, Gekeler F, et al. Functional outcome in subretinal electronic implants depends on foveal eccentricity. Invest Ophthalmol Vis Sci. 2013 Nov;54(12):7658-65. PMID: 24150759.

8. Chow AY, Chow VY, Packo KH, et al. The artificial silicon retina microchip for the treatment of vision loss from retinitis pigmentosa. Arch Ophthalmol. 2004;122(4):460-9. PMID: 15078662.

9. Fujikado T, Kamei M, Sakaguchi H, et al. Testing of semichronically implanted retinal prosthesis by suprachoroidal-transretinal stimulation in patients with retinitis pigmentosa. Invest Ophthalmol Vis Sci. 2011 Jun;52(7):4726-33. PMID: 21436271.

10. Rizzo JF, Shire DB, Kelly SK, et al. Overview of the Boston retinal prosthesis: challenges and opportunities to restore useful vision to the blind. Conf Proc IEEE Eng Med Biol Soc. 2011;2011:7492-5. PMID: 22256071.

11. Mandel Y, Goetz G, Lavinsky D, et al. Cortical responses elicited by photovoltaic subretinal prostheses exhibit similarities to visually evoked potentials. Nat Commun. 2013;4:1980. PMID: 23778557.

12. Alamusi, Matsuo T, Hosoya O, et al. Vision maintenance and retinal apoptosis reduction in RCS rats with Okayama University-type retinal prosthesis (OUReP^{TM}) implantation. J Artif Organs. 2015 Sep;18(3):264-71. Epub 2015 Mar 3. PMID: 25732059.

13. Heckenlively JR. Retinitis pigmentosa. Philadelphia (PA): Lippincott; 1988. 269 p.

14. Bunker CH, Berson EL, Bromley WC, et al. Prevalence of retinitis pigmentosa in Maine. Am J Ophthalmol. 1984 Mar;97(3):357-65. PMID: 6702974.

15. Grondahl J. Estimation of prognosis and prevalence of retinitis pigmentosa and Usher syndrome in Norway. Clin Genet. 1987 Apr;31(4):255-64. PMID: 3594933.

16. Hartong DT, Berson EL, Dryja TP. Retinitis pigmentosa. Lancet. 2006 Nov 18;368(9549):1795-809. PMID: 17113430.

17. Haim M. Epidemiology of retinitis pigmentosa in Denmark. Acta Ophthalmol Scand Suppl. 2002;(233):1-34. PMID: 11921605.

18. Guadagni V, Novelli E, Piano I, et al. Pharmacological approaches to retinitis pigmentosa: a laboratory perspective. Prog Retin Eye Res. 2015 Sep;48:62-81. PMID: 26113212.

19. Tanino T, Ohba N. Studies on pigmentary retinal dystrophy. II. Recordability of electroretinogram and the mode of inheritance. Jpn J Ophthalmol. 1976;20:482-6.

20. Taylor HR. LXIII Edward Jackson Memorial Lecture: eye care: dollars and sense. Am J Ophthalmol. 2007 Jan;143(1):1-8. Epub 2006 Nov 13. PMID: 17188039.

21. Hahm BJ, Shin YW, Shim EJ, et al. Depression and the vision-related quality of life in patients with retinitis pigmentosa. Br J Ophthalmol. 2008 May;92(5):650-4. PMID: 18356260.

22. Bowling B. Acquired macular disorders. In: Kanski's clinical ophthalmology: a systematic approach. 8th ed. Philadelphia (PA): Elsevier; 2016. p. 579-639.

23. Nunes RP, Rosenfeld PJ, de Amorim Garcia Filho CA, et al. Age-related macular degeneration. In: Ophthalmology. 4th ed. Saunders; 2014. p. 580-99.e3.

24. Bressler SB, Ryan, SJ, Bressler NM. Age-related macular degeneration: non-neovascular early AMD, intermediate AMD, and geographic atrophy. In: Ryan SJ, editor(s). Retina. Vol. 2.Medical retina. Elsevier Saunders; 2013. p. 1150-82.

25. American Academy of Ophthalmology Retina/Vitreous Panel. Preferred practice pattern guidelines. Age-related macular degeneration. San Francisco (CA): American Academy of Ophthalmology (AAO); 2015 Jan. 52 p. Available: http://www.aao.org/ppp.

26. Ferris FL, Wilkinson CP, Bird A, et al. Clinical classification of age-related macular degeneration. Ophthalmology. 2013 Apr;120(4):844-51. PMID: 23332590.

27. Hoffman DR, Locke KG, Wheaton DH, et al. A randomized, placebo-controlled clinical trial of docosahexaenoic acid supplementation for X-linked retinitis pigmentosa. Am J Ophthalmol. 2004 Apr;137(4):704-18. PMID: 15059710.

28. Wheaton DH, Hoffman DR, Locke KG, et al. Biological safety assessment of docosahexaenoic acid supplementation in a randomized clinical trial for X-linked retinitis pigmentosa. Arch Ophthalmol. 2003 Sep;121(9):1269-78. Also available: http://dx.doi.org/10.1001/archopht.121.9.1269. PMID: 12963609.

29. Aleman TS, Duncan JL, Bieber ML, et al. Macular pigment and lutein supplementation in retinitis pigmentosa and Usher syndrome. Invest Ophthalmol Vis Sci. 2001 Jul;42(8):1873-81. PMID: 11431456.

30. Berson EL, Rosner B, Sandberg MA, et al. A randomized trial of vitamin A and vitamin E supplementation for retinitis pigmentosa. Arch Ophthalmol. 1993 Jun;111(6):761-72. PMID: 8512476.

31. Berson EL, Rosner B, Sandberg MA, et al. Further evaluation of docosahexaenoic acid in patients with retinitis pigmentosa receiving vitamin A treatment: subgroup analyses. Arch Ophthalmol. 2004 Sep;122(9):1306-14. PMID: 15364709.

32. Berson EL, Rosner B, Sandberg MA, et al. Clinical trial of lutein in patients with retinitis pigmentosa receiving vitamin A. Arch Ophthalmol. 2010 Apr;128(4):403-11. PMID: 20385935.

33. Bendich A, Langseth L. Safety of vitamin A. Am J Clin Nutr. 1989 Feb;49(2):358-71. PMID: 2492745.

34. Evans K, HickeyDwyer MU. Cleft anterior segment with maternal hypervitaminosis A. Br J Ophthalmol. 1991 Nov;75(11):691-2. PMID: 1751468.

35. Rothman KJ, Moore LL, Singer MR, et al. Teratogenicity of high vitamin A intake. New Eng J Med. 1995 Nov 23;333(21):1369-73. PMID: 7477116.

36. Melhus H, Michaelsson K, Kindmark A, et al. Excessive dietary intake of vitamin A is associated with reduced bone mineral density and increased risk for hip fracture. Ann Intern Med. 1998 Nov 15;129(10):770-8. PMID: 9841582.

37. Feskanich D, Singh V, Willett WC, et al. Vitamin A intake and hip fractures among postmenopausal women. JAMA. 2002 Jan 2;287(1):47-54. PMID: 11754708.

38. Birch DG, Weleber RG, Duncan JL, et al. Randomized trial of ciliary neurotrophic factor delivered by encapsulated cell intraocular implants for retinitis pigmentosa. Am J Ophthalmol. 2013 Aug;156(2):283-292.e1. PMID: 23668681.

39. Ferrari MP, Mantelli F, Sacchetti M, et al. Safety and pharmacokinetics of escalating doses of human recombinant nerve growth factor eye drops in a double-masked, randomized clinical trial. Biodrugs. 2014 Jun;28(3):275-83. PMID: 24327173.

40. Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E, beta carotene, and zinc for age-related macular degeneration and vision loss: AREDS report no. 8. Arch Ophthalmol. 2001 Oct;119(10):1417-36. PMID: 11594942.

41. Age-Related Eye Disease Study 2 Research Group. Lutein + zeaxanthin and omega-3 fatty acids for age-related macular degeneration: the Age-Related Eye Disease Study 2 (AREDS2) randomized clinical trial.[Erratum appears in JAMA. 2013 Jul 10;310(2):208. JAMA. 2013 May 15;309(19):2005-15. PMID: 23644932.

42. Maguire AM, High KA, Auricchio A, et al. Age-dependent effects of RPE65 gene therapy for Leber's congenital amaurosis: a phase 1 dose-escalation trial. Lancet. 2009 Nov 7;374(9701):1597-605. PMID: 19854499.

43. Maguire AM, Simonelli F, Pierce EA, et al. Safety and efficacy of gene transfer for Leber's congenital amaurosis. N Engl J Med. 2008 May 22;358(21):2240-8. PMID: 18441370.

44. Hauswirth WW, Aleman TS, Kaushal S, et al. Treatment of leber congenital amaurosis due to RPE65 mutations by ocular subretinal injection of adeno-associated virus gene vector: short-term results of a phase I trial. Hum Gene Ther. 2008 Oct;19(10):979-90. PMID: 18774912.

45. Bainbridge JW, Smith AJ, Barker SS, et al. Effect of gene therapy on visual function in Leber's congenital amaurosis. N Engl J Med. 2008 May 22;358(21):2231-9. PMID: 18441371.

46. MacLaren RE, Groppe M, Barnard AR, et al. Retinal gene therapy in patients with choroideremia: initial findings from a phase 1/2 clinical trial. Lancet. 2014 Mar 29;383(9923):1129-37. PMID: 24439297.

47. Cideciyan AV, Jacobson SG, Beltran WA, et al. Human retinal gene therapy for Leber congenital amaurosis shows advancing retinal degeneration despite enduring visual improvement. Proc Natl Acad Sci U S A. 2013 Feb 5;110(6):E517-25. PMID: 23341635.

48. Zheng A, Li Y, Tsang SH. Personalized therapeutic strategies for patients with retinitis pigmentosa. Expert Opin Biol Ther. 2015 Mar;15(3):391-402. PMID: 25613576.

49. Second Sight Medical Products. Argus II Retinal Prosthesis System dry AMD feasibility study protocol. In: ClinicalTrials.gov [database online]. Bethesda (MD): National Library of Medicine (U.S.); 2000- [accessed 2015 Jul 02]. [4 p]. Available: https://clinicaltrials.gov/ct2/show/NCT02227498 NLM Identifier: NCT02227498.

50. Yue L, Falabella P, Christopher P, et al. Ten-year follow-up of a blind patient chronically implanted with epiretinal prosthesis Argus I. Ophthalmology. 2015 Sep 16. [Epub ahead of print]. PMID: 26386850.

51. Ho AC, Humayun MS, Dorn JD, et al. Long-term results from an epiretinal prosthesis to restore sight to the blind. Ophthalmology. 2015 Aug;122(8):1547-54. PMID: 26162233.

52. Geruschat DR, Flax M, Tanna N, et al. FLORA: Phase I development of a functional vision assessment for prosthetic vision users. Clin Exp Optom. 2015 Jul;98(4):342-7. Also available: http://dx.doi.org/10.1111/cxo.12242. PMID: 25675964.

53. Mokkink LB, Terwee CB, Patrick DL, et al. The COSMIN checklist for assessing the methodological quality of studies on measurement properties of health status measurement instruments: an international Delphi study. Quality of life research : an international journal of quality of life aspects of treatment, care and rehabilitation. 2010 May;19(4):539-49. PMID: 20169472.

54. Methods guide for effectiveness and comparative effectiveness reviews, AHRQ Publication No. 10(14)-EHC063-EF. Rockville (MD): Agency for Healthcare Research and Quality (AHRQ); 2014 Jan. Available: http://www.effectivehealthcare.ahrq.gov.

IV. Definition of Terms

Not applicable.

V. Summary of Protocol Amendments

No amendments have been filed.

VI. Key Informants

Within the Technical Brief process, Key Informants serve as a resource to offer insight into the clinical context of the technology/intervention, how it works, how it is currently used or might be used, and which features may be important from a patient or policy standpoint. They may include clinical experts, patients, manufacturers, researchers, payers, or other perspectives, depending on the technology/intervention in question. Differing viewpoints are expected, and all statements are crosschecked against available literature and statements from other Key Informants. Information gained from Key Informant interviews is identified as such in the report. Key Informants do not do analysis of any kind or contribute to the writing of the report and have not reviewed the report, except as given the opportunity to do so through the public review mechanism

Key Informants must disclose any financial conflicts of interest greater than $10,000 and any other relevant business or professional conflicts of interest. Because of their unique clinical or content expertise, individuals are invited to serve as Key Informants and those who present with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any potential conflicts of interest identified.

VII. Peer Reviewers

Peer reviewers are invited to provide written comments on the draft report based on their clinical, content, or methodologic expertise. Peer review comments on the preliminary draft of the report are considered by the EPC in preparation of the final draft of the report. Peer reviewers do not participate in writing or editing of the final report or other products. The synthesis of the scientific literature presented in the final report does not necessarily represent the views of individual reviewers. The dispositions of the peer review comments are documented and will be published 3 months after the publication of the Evidence report.

VIII. EPC Team Disclosures

EPC core team members must disclose any financial conflicts of interest greater than $1,000 and any other relevant business or professional conflicts of interest. Related financial conflicts of interest that cumulatively total greater than $1,000 will usually disqualify EPC core team investigators.

IV. Role of the Funder

This project was funded under Contract No. 290-2015-00005-I from the Agency for Healthcare Research and Quality, U.S. Department of Health and Human Services. The Task Order Officer reviewed contract deliverables for adherence to contract requirements and quality. The authors of this report are responsible for its content. Statements in the report should not be construed as

endorsement by the Agency for Healthcare Research and Quality or the U.S. Department of Health and Human Services.