

Technology Assessment



Retinal Prostheses in the Medicare Population



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Retinal Prostheses in the Medicare Population

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ECRI Institute – Penn Medicine Evidence-based Practice Center

Joann Fontanarosa, Ph.D.

Jonathan R. Treadwell, Ph.D.

David J. Samson, M.S.

Brian L. VanderBeek, M.D., M.P.H., M.S.C.E.

Karen Schoelles, M.D., S.M.

Preface

The Agency for Healthcare Research and Quality (AHRQ), through its Evidence-based Practice Centers (EPCs), sponsors the development of systematic reviews to assist public- and private-sector organizations in their efforts to improve the quality of health care in the United States. The Centers for Medicare & Medicaid Services requested this report from the Evidence-based Practice Center (EPC) Program at the Agency for Healthcare Research and Quality (AHRQ). AHRQ assigned this report to the following EPC: (ECRI Institute-Penn Medicine) Evidence-based Practice Center (Contract Number: HHS-290-2015-00005-I).

The reports and assessments provide organizations with comprehensive, evidence-based information on common medical conditions and new health care technologies and strategies. They also identify research gaps in the selected scientific area, identify methodological and scientific weaknesses, suggest research needs, and move the field forward through an unbiased, evidence-based assessment of the available literature. The EPCs systematically review the relevant scientific literature on topics assigned to them by AHRQ and conduct additional analyses when appropriate prior to developing their reports and assessments.

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Andrew Bindman, M.D.
Director
Agency for Healthcare Research and Quality

Arlene Bierman, M.D., M.S.
Director
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

Stephanie Chang, M.D., M.P.H.
Director
Evidence-based Practice Center Program
Agency for Healthcare Research and Quality

Elise Berliner, Ph.D.
Task Order Officer
Director, Technology Assessment Program
Center for Evidence and Practice Improvement
Agency for Healthcare Research and Quality

This report is based on research conducted by the (ECRI Institute-Penn Medicine EPC) under contract to AHRQ, Rockville, MD (Contract No. HHS-290-2015-00005-I). The findings and conclusions in this document are those of the authors, who are responsible for its contents. The findings and conclusions do not necessarily represent the views of AHRQ. Therefore, no statement in this report should be construed as an official position of AHRQ or of the U.S. Department of Health and Human Services.

None of the investigators has any affiliations or financial involvement related to the material presented in this report.

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Key Informants

In designing the study questions, the Evidence-based Practice Center (EPC) consulted a panel of Key Informants who represent subject experts and end-users of research. Key Informant input can inform key issues related to the topic of the technical brief. Key Informants are not involved in the analysis of the evidence or the writing of the report. Therefore, in the end, study questions, design, methodological approaches, and/or conclusions do not necessarily represent the views of individual Key Informants.

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 role as end-users, individuals with potential conflicts may be retained. The Task Order Officer and the EPC work to balance, manage, or mitigate any conflicts of interest.

The list of Key Informants who provided input to this report follows:

Key Informants

Ava K. Bittner, O.D., Ph.D., FAAO (Dipl.)*
Associate Professor
Nova Southeastern University College of Optometry
Ft. Lauderdale, FL

Denice Brown, M.Ed.
President, Greater Philadelphia Chapter
National Federation of the Blind
National Trustee
Foundation Fighting Blindness
Philadelphia, PA

Duane R. Geruschat, Ph.D.*
Research Associate, Department of Ophthalmology
Specialist in low vision and blindness rehabilitation research
Wilmer Eye Institute
Johns Hopkins University
Baltimore, MD

Robert J. Greenberg, M.D., Ph.D.
Chairman
Second Sight Medical Products, Inc.
Sylmar, CA

Denise Hampton, Ph.D.*
Chief, Contact Lenses and Retinal Devices Branch
Division of Ophthalmic and Ear, Nose and Throat Devices
Office of Device Evaluation
Center for Devices and Radiological Health
U.S. Food and Drug Administration
Silver Spring, MD

Anil Lewis, M.P.A.
Executive Director
Jernigan Institute
National Federation of the Blind
Baltimore, MD

Aleksandra Rachitskaya, M.D.*
Assistant Professor of Ophthalmology
Lerner College of Medicine of Case Western Reserve University
Cole Eye Institute, Cleveland Clinic
Cleveland, OH

Sherie Smalley, M.D.*
Senior Medical Director, Medical Policy
UPMC Health Plan
Pittsburgh, PA

*This Key Informant (KI) also provided comments on the draft report.

Peer Reviewers

Before publication of the final evidence report, EPCs sought input from independent Peer Reviewers without financial conflicts of interest. However, the conclusions and synthesis of the scientific literature presented in this report do not necessarily represent the views of individual reviewers.

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The list of Peer Reviewers appears below:

Cagri G. Besirli, M.D., Ph.D.
Assistant Professor, Ophthalmology and Visual Sciences
Kellogg Eye Center
University of Michigan
Ann Arbor, MI

Emily Y. Chew, M.D.
Deputy Director, Division of Epidemiology and Clinical Applications
Deputy Clinical Director
National Eye Institute
Bethesda, MD

Ninel Z. Gregori, M.D.
Associate Professor of Clinical Ophthalmology
Bascom Palmer Eye Institute
Chief, Ophthalmology Section
Miami Veterans Affairs Medical Center
Miami, FL

Flora Lum, M.D.
Vice President, Quality and Data Science
American Academy of Ophthalmology
San Francisco, CA

Retinal Prostheses in the Medicare Population

Structured Abstract

Objectives. To determine the safety, efficacy, and evidence for halting disease progression for retinal prosthesis systems (RPSs) and the outcomes that are and could be assessed in future studies of these devices.

Data sources. We searched Medline, EMBASE, Cumulative Index to Nursing and Allied Health (CINAHL), the Cochrane Library, PubMed (unprocessed records only), and gray literature sources, including conference proceedings from specialty societies, for studies of RPS devices published from January 1, 2000, through April 25, 2016.

Review methods. We performed redundant title and abstract screening with one reviewer's selection required for full-text article retrieval. Dual independent review was performed on all full-text articles, with disagreements resolved by consensus. Data extraction was performed by a single reviewer and was fully verified by a second reviewer. Extracted data included study design, psychometric properties assessment methods based on the COSMIN checklist, 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. We assessed risk of bias of individual studies for the outcomes of interest, and graded the overall strength of evidence using Evidence-based Practice Centers guidance.

Results. Eleven studies of RPS effectiveness were included. Although some patients clearly improve on tests of visual function, visual acuity, visual field, color vision, laboratory-based function, and day-to-day function from an RPS, the evidence was insufficient to estimate the proportion of patients who would benefit. Intraoperative adverse events were typically mild but some serious adverse events were reported, including intraocular pressure increase, hypotony, and presumed endophthalmitis. Three studies pointed to the possibility that RPSs may provide neuroprotection. Of the 74 outcomes reported in the 11 included studies, only 4 (Early Treatment of Diabetic Retinopathy Study visual acuity test [ETDRS], Grating Acuity Test [GAT], Chow Color Test [CCT], and Functional Low-Vision Observer Rated Assessment [FLORA]) had evidence of validity and/or reliability. Measures with evidence of validity and reliability that could be used in future RPS studies include full-field flash test, Grating Contrast Sensitivity (GCS), FAST instrument (Functional Assessment of Self-Reliance on Tasks), Very Low Vision Instrumental Activities of Daily Living (IADL-VLV), Modified National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) plus supplement, and the Modified Impact of Vision Impairment (IVI).

Conclusions. Some patients clearly benefit from RPSs. Future studies of retinal prosthesis should make an effort to report valid and reliable measures of day-to-day function and quality of life.

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Executive Summary

Background

Retinitis Pigmentosa

Retinitis pigmentosa (RP) is a collection of genotypically and phenotypically diverse eye disorders, all of which attack the rods and cones within the retina. This inherited disease is often identified by its main clinical features, which typically include symptoms of poor night vision, visual field loss, and 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 40.¹ Loss of central vision occurs in very advanced RP or in atypical RP. Upon ophthalmic examination, a triad of clinical findings is typically noted: 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.

Age-related Macular Degeneration

The RP population, particularly those with vision poor enough to qualify for a retinal prosthesis system (RPS), is rather small. A paper by Grover and colleagues (1999) examined the visual abilities of 982 patients with RP, of whom 25 percent had visual acuity of 20/200 or worse in both eyes.² Many of these patients had more vision than light perception, so they would not meet the U.S. Food and Drug Administration (FDA) indication for the approved Argus II RPS device (which requires light perception only, or worse). Thus, the broader goal for most of the companies developing retinal prostheses 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. AMD is the leading cause of irreversible visual loss in industrialized countries,³ and in the United States, it accounts for about half of severe sight loss. However, the number of patients with advanced AMD who could possibly benefit from an RPS is much smaller. Although the etiology is incompletely understood, AMD develops as a result of deposition of cellular debris—including lipids, amyloid, complement factors, and other components—in Bruch’s membrane.^{4,5}

Retinal Prosthesis Systems

Multiple types of ocular prosthetic devices are under development.⁶⁻¹⁰ The devices have focused on stimulating different parts of the visual pathway, including the visual cortex,⁸ the optic nerve,⁹ and the retina when placed in the suprachoroidal,¹⁰ epiretinal,⁷ and subretinal⁶ spaces. Of the seven RPS devices for which there was at least one published article describing a study in humans, 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 Silicon 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 EPIRET3 device. The IRIS device (also epiretinal) began development in Germany but is now produced by the French manufacturer Pixium Vision (Paris, France). The suprachoroidal Bionic Eye RPS comes from Bionic Vision in Parkville, Victoria, Australia. Nidek Co., Ltd. (Gamagori, Japan), produces the Suprachoroidal Transretinal Stimulation (STS) Artificial Vision System. These devices are discussed in detail in the body of this report.

We also identified three additional devices subjected to preclinical tests. 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.¹¹ Another American device, the Photovoltaic Retinal Prosthesis (Stanford University Palanker Laboratory) has a subretinal array of thousands of photodiodes that convert light pulses to bi-phasic pulses of electric current.¹² From Japan, the Okayama University-Type Retinal Prosthesis uses a unique approach with photoelectric dye molecules coupled to polyethylene film.¹³

Alternative Treatments for Retinitis Pigmentosa and Age-Related Macular Degeneration

For RP, the current state of care is generally 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. Some pharmacologic agents approved for other conditions may potentially maximize visual acuity in RP patients. (For example, the topical carbonic anhydrase inhibitor dorzolamide, used in open-angle glaucoma or ocular hypertension, may have an ancillary benefit of reducing cystoid macular edema in RP patients who have this feature of the disease).¹⁴ The absence of RP-specific FDA-approved medications is not for lack of effort, with most of the past focus being on nutritional supplements. Supportive care is offered to patients with nonexudative AMD. For those patients who smoke, they are advised to quit. Those with intermediate or advanced disease may be advised to take antioxidant vitamins and minerals to reduce the risk of progression. For the nonexudative patients who have progressed to exudative AMD, the main treatment is vascular endothelial growth factor (VEGF) inhibitor therapy.

Scope and Key Questions

The scope of this review is defined in Table A according to the PICOTS framework (population, intervention, comparators, outcomes, timing, and setting; see Table A). Key questions (KQs) appear below. Figure A presents an analytic framework that depicts KQs, populations, treatments, patient-centered outcome measures, and associated psychometric properties.

Table A. PICOTS framework

PICOTS component	Description
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 RPSs?

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 an RPS compared with baseline (or device OFF or untreated eye) and compared with alternative treatments?

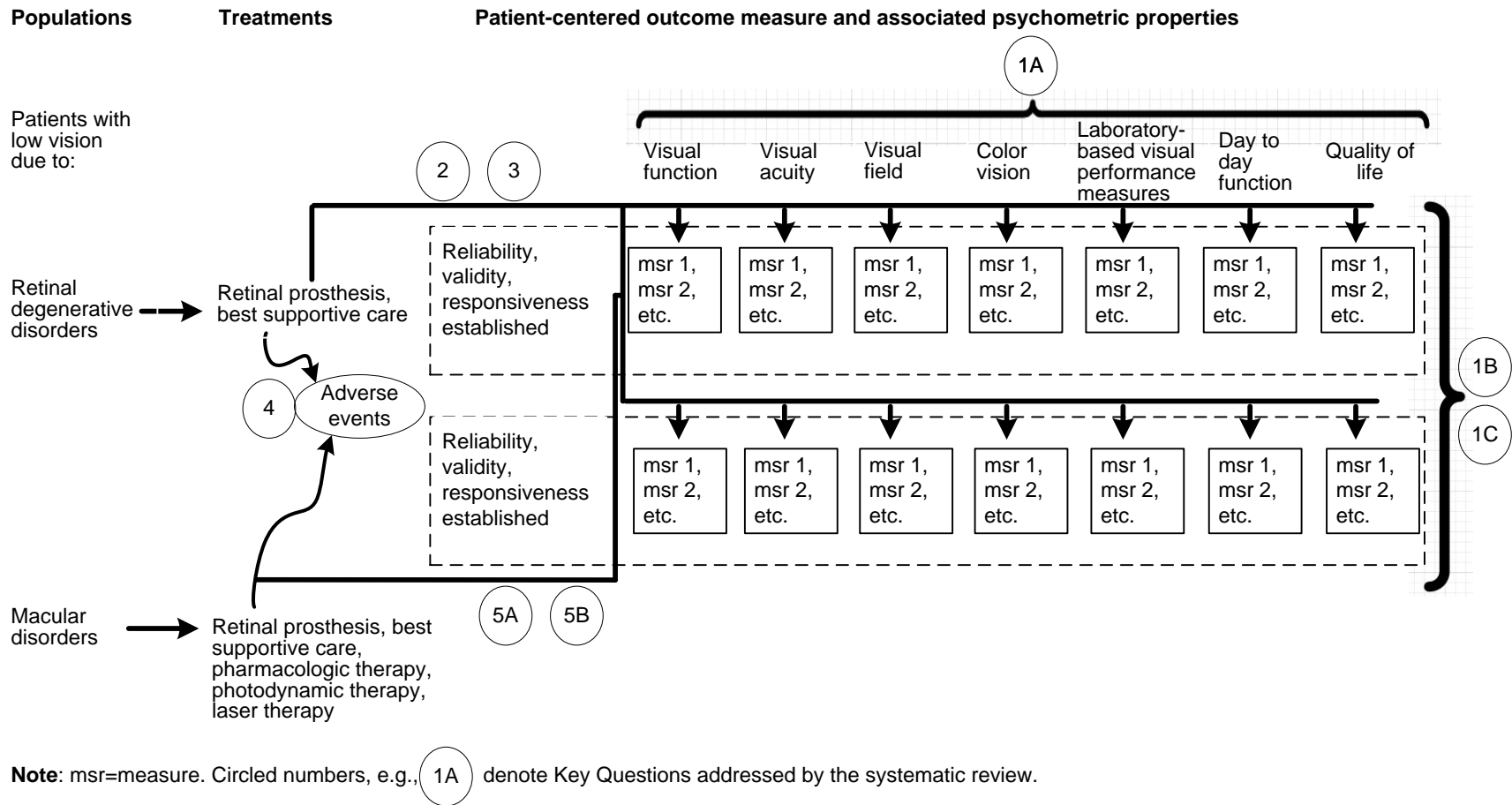
KQ3: What is the evidence that the use of RPS arrests the progression of RP?

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 other uses suggested for RPS?

Figure A. Analytic framework



Methods

Literature Search Strategy

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 April 25, 2016.

We included RPS device articles that met the following criteria: reported use of an RPS device 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. We excluded studies of the IRIS system because the current version began studies only in late 2015. For psychometric properties (KQ1B and KQ1C), we required that articles be published in English; be primarily designed to evaluate reliability, validity, and/or responsiveness of relevant outcome measures; and have at least two-thirds of patients with very low vision (as defined by logarithm of the minimum angle of resolution [$\log\text{MAR}$] ≥ 1.0 and/or visual field ≤ 20 degrees) due to retinal conditions. Correlations between different outcome categories (e.g., visual acuity and quality of life) were not considered validity studies because they measure fundamentally different traits.

We performed dual independent review of abstract and full articles using the Distiller SR tool (Evidence Partners, Ottawa, Ontario, Canada). Extracted data were stored in Microsoft Word and Microsoft Excel files. Please refer to the review protocol (<http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/retinal-prosthesis-protocol.pdf>) for more details about the methods.

Risk-of-Bias Assessment of Individual Studies

Because we did not identify any randomized controlled trials, risk-of-bias assessment of RPS device studies focused on single-group designs (case series: pretest-posttest, posttest only, device ON/OFF, fellow eye). We selected seven pertinent risk-of-bias items from the Agency for Healthcare Research and Quality (AHRQ) Methods Guide¹⁵ (i.e., control for confounding, concurrent interventions, fidelity to protocol, low attrition, outcome assessor blinding, outcome definition/implementation, and prespecified outcomes). Each study was categorized as Low, Moderate, or High risk of bias. For studies addressing psychometric properties of outcomes, we based risk-of-bias assessments on the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) checklist.¹⁶ This instrument contains recommended items for internal consistency reliability, test-retest reliability, face validity, construct validity, and responsiveness.

Data Synthesis

Due to the designs of the studies (i.e., single-group designs), this review was limited to qualitative synthesis. To permit a clear synthesis, we placed each reported outcome into one of seven categories: visual function, visual acuity, visual field, color vision, laboratory-based visual

performance measures (e.g., functioning during a test such as finding a door), day-to-day function, and quality of life.

Strength of the Body of Evidence

We used the strength-of-evidence grading approach described in the AHRQ Methods Guide.¹⁵ Domains addressed included the following: study limitations, directness, consistency, precision, and reporting bias. If relevant, we also considered a dose-response association (e.g., whether more electrodes yielded greater effects) and magnitude of effect. We did not use the domain involving plausible confounders reducing an observed effect, because studies did not have separate control groups. Based on the domains, we assigned a grade of High, Moderate, Low, or Insufficient, according to definitions stated below. See Table B for more information.

Table B. Evidence grade definitions

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.

Thus, when the evidence did not permit a conclusion (that RPS either improves or does not improve an outcome), we rated the evidence as Insufficient. A lack of statistical significance was not assumed to imply the lack of an effect, since nonsignificance may simply mean low statistical power. We rated the strength of evidence only for KQ2 and the following outcomes because of their relative importance: visual function and visual acuity, visual field, laboratory-based visual performance measures, day-to-day function, and quality of life. We did not rate the strength of evidence for other outcomes or other KQs.

Results

Results of Literature Searches

We recorded our process of reducing our initial list of 6,022 potentially relevant publications to a final included set of 40 publications. We excluded 2,647 publications at the title level (they were not relevant to the topic), and another 2,771 at the abstract level. The most common reasons for exclusion at the abstract level were wrong population (1,112 exclusions) and a lack of psychometric property data in studies being considered for KQ1B or KQ1C (890 exclusions). We examined 603 articles in full, and excluded 565 of these for various reasons, the most common being wrong or unclear population (225 exclusions) and no psychometric data (120 exclusions). A complete list of articles excluded at the full-text level appears in Appendix B.

Two included articles had been identified by peer reviewers. The 40 included publications described 21 unique studies.

Key Question 1A. Outcome Measures Used in RPS Studies

- For KQ1A we included 30 publications of 11 RPS studies.
- The 30 publications reported 74 different outcomes. Most outcomes involved either visual function (31 percent), visual acuity (26 percent), or laboratory-based visual performance measures (30 percent). Four studies measured day-to-day visual function, and one study measured vision-specific quality of life 3 weeks after implantation and at 5 months and 2 years after planned explantation.
- Only three outcomes were reported by three or more studies: the percentage of patients who passed the light localization task of the Basic Assessment of Light and Motion (BaLM), the percentage of patients whose square localization results were significantly better with system ON than system OFF, and the percentage of patients whose Grating Visual Acuity test results were significantly better with the system ON versus OFF. Seven other outcomes were reported by two studies each. Little consensus exists among authors of RPS studies about which specific measures are important.

Key Question 1B. Psychometric Properties of Outcome Measures Used in RPS Studies

- The Early Treatment Diabetic Retinopathy Study (ETDRS), a measure of visual acuity, has acceptable test-retest reliability, but no included studies measured its validity or responsiveness.
- The Grating Acuity Test (GAT) and the Chow Color Test (CCT) have acceptable test-retest reliability and construct validity, but no included studies measured their responsiveness.
- The Functional Low-Vision Observer Rated Assessment (FLORA) has acceptable face validity, but no included studies measured its reliability or responsiveness.

Key Question 1C. Psychometric Properties of Other Possible Outcome Measures

- For measuring light sensitivity, the full-field flash test (also known as the full field stimulus test) has better psychometric properties than either dark adaptometry with SST-1 or dark-adapted Humphrey perimetry. For the latter two tests, many patients with RP do not provide measurable or reliable results. The full-field flash test has acceptable test-retest reliability and construct validity.
- For measuring contrast sensitivity, the Grating Contrast Sensitivity (GCS) has better test-retest reliability than the Pelli-Robson test. The Pelli-Robson test may not produce meaningful results in some patients with RP, because of their limited vision.
- The FAST instrument (Functional Assessment of Self-Reliance on Tasks) has acceptable reliability, validity, and responsiveness. Further, its psychometric properties are better than those of the Veterans Health Administration-13 (VA-13). Both clinician-completed and patient-completed versions of the FAST instrument have reliability and responsiveness, but they yield somewhat different answers.

- The Very Low Vision Instrumental Activities of Daily Living (IADL-VLV) and the Modified National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) plus supplement have acceptable reliability, validity, and responsiveness.
- The Modified Impact of Vision Impairment (IVI) has acceptable reliability and validity, but no included studies measured its responsiveness.

Key Question 2. Effect of RPS on Health-related Quality of Life, Activities of Daily Living, Visual Function, and Other Outcomes

- Some patients clearly benefit from RPS, but evidence is insufficient to estimate the proportion of patients who would benefit. Some patients improved on visual function, visual acuity, visual field, color vision, laboratory-based function, and day-to-day function but not quality of life.
- Visual function was improved in 40 percent to 100 percent of patients with an implanted device.
- Visual acuity was improved in 0 percent to 100 percent of patients with an implanted device.
- Visual fields were improved in 17 percent to 100 percent of patients with an implanted device.
- One study assessed color vision and found one of six patients improved.
- Laboratory-based visual performance measures were varied and patients improved on some tasks but not others.
- Day-to-day function measures were varied, and patients improved on some tasks but not on others. Results from FLORA, the only validated measure used to assess day-to-day function, found patients improved on most tasks assessed with these exceptions: travel within the home independently, identify bottom steps, negotiate stairs, chop food, heat/reheat food, and maintain safety from falls.
- Quality of life was assessed in one study using the NEI-VFQ-25-German version, which the authors note has not been validated in an RP population. They found no significant change in six patients 3 weeks after implantation or after planned explantation (at 5-month and at 2-year followup).

Key Question 3. RPS to Arrest the Progression of Retinitis Pigmentosa

- Limited evidence has been interpreted as possibly indicating that implanted RPS devices may stop the progression of RP. Patients implanted with the Argus II for 12 months experienced improved visual fields even when the system was in OFF mode.
- Evidence from animal studies has suggested a possible neuroprotective effect from electrical stimulation of the retina, mediated through induction of certain growth factors.
 - Electroretinographic waveforms in rat eyes with an active implant experienced temporary preservation compared with unoperated rat eyes through 6–7 weeks of followup.
 - Electroretinographic b-waves were significantly larger in rat eyes with active implants versus rat eyes without active implants at the 4- to 6-week followup.

- Rat eyes with and without active implants had similar results for electroretinographic a-waves.
- Rat eyes with active implants had four to six rows of photoreceptors, compared with a single sparse layer of photoreceptor cells in unoperated eyes 8 weeks after implantation.
- Photoreceptor preservation occurred in all rat eyes that received an implant, even if it was an inactive implant.
- Expression of fibroblast growth factor 2 (Fgf2) was significantly higher in rat eyes with active implants by postoperative day 9 compared with eyes with minimally active implants, eyes that underwent sham surgery, and unoperated eyes, and a dose-response relationship was evident.
- Rat eyes with active implants and those without an active implant were similar on growth factor expression of fibroblast growth factor 1 (Fgf1), ciliary neurotrophic factor (Cntrf), insulin-like growth factor (Igf), glial cell line–derived neurotrophic factor (Gdnf), and brain-derived neurotrophic factor (Bdnf).

Key Question 4. Adverse Events of RPS

- Intraoperative adverse events occurred in more than half of studies reporting this outcome, with injury to the optic nerve being the most serious.
- Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure increase, eye scratchiness, and eye-movement restrictions.
- Intraoperative explantation adverse events were reported in two-thirds of the studies reporting this outcome, the most serious being a central retinal defect caused by removal of loose tacks.
- Post-explantation adverse events were reported by two-thirds of the studies reporting this outcome, with the most serious events including a decrease in visual acuity and a retinal detachment.
- Serious adverse events were reported by just under half of the studies reporting this outcome and included intraocular pressure increase, hypotony, and presumed endophthalmitis.
- Device-related adverse events were reported by more than one-third of studies reporting this outcome and included device failure and need for retacking.
- Adverse events at the long-term followup were reported by just over half of studies reporting this outcome and were varied.

Key Question 5A. Off-label Use of RPS

- One clinical trial of Argus II in patients with advanced dry AMD with central geographic atrophy who are legally blind is under way and due to be completed by June 2019.

Key Question 5B. Other Uses of RPS

- We did not identify any studies of RPS devices being used for nonvisual purposes, although this technology is being used to create cortical implants.

Discussion

Key Findings and Strength of Evidence

The RPS studies assessed in this review reported 74 different outcomes, mostly dealing with visual function (31 percent), visual acuity (26 percent), or laboratory-based visual performance measures (30 percent). Day-to-day visual function and quality of life were rarely measured. Little consensus exists among authors of RPS studies about which specific measures are important.

There is some evidence for the validity and/or reliability of the ETDRS visual acuity, GAT, CCT, and FLORA. No included evidence on patients with very low vision addressed the validity or reliability of other outcomes reported in the RPS studies.

Future RPS studies should consider measuring the following outcomes because some evidence shows that they are valid and/or reliable measures: full-field flash test (tested in RP patients but most had much better vision than RPS recipients), GCS (tested in legally blind patients), the patient and clinician version of the FAST instrument (tested in populations with better eye mean logMAR 1.3 and 1.09, which is much better vision than RPS recipients' vision), IADL-VLV (tested in patients with mean 2.3 logMAR (CF) which is slightly better than RPS recipients' vision)) NEI-VFQ-25 plus supplement (tested in patients with mean logMAR 1.00, much better than RPS patients), and IVI (tested in a majority of patients with CF to LP vision including 14% with worse than LP, so very applicable to RPS recipients). Until better evidence is available, it appears that these tests hold the most promise.

During our interviews with Key Informants, particularly patient/advocate Key Informants, we learned that patients vary in their expectations of a treatment such as RPS implantation. Some patients hope to have their sight restored to “normal” vision. Others would be satisfied with more modest gains, such as the ability to color coordinate their clothing, use a color-contrast cutting board, or, for those patients with comorbid insulin-dependent diabetes, give themselves insulin injections.

One patient who had a good experience with the Argus II device and who was not a Key Informant but commented on our draft report, described his/her experience (the person's sex was not identified), which may reflect a more realistic expectation of RPS implantation. The patient reported that his/her eye had healed sufficiently after just a few weeks and vision improved instantaneously. This patient reported the following improvements:

- Identified the window where the light was coming from
- Located various items hanging on office walls
- Spotted the left and right sides of a doorway
- In conversation, looked a person squarely in the face (rather than trying to aim his/her eyes toward the voice)
- Saw a fireworks display for the first time in 25 years
- Walked with confidence with a white cane on city streets, avoiding the tables and chairs at sidewalk cafes
- Saw his/her two grandchildren standing before him/her and identified them without needing to hear their voices.¹⁷

Retinal surgeons performing RPS implantation need to accurately present the full range of likely visual acuity gains—which at this point do not include “normal” vision, color vision, or a level of sight sufficient to allow a diabetic to safely self-administer insulin. Surgeons also need to

advise patients of the possibility that they may not benefit from an implant and could lose residual light perception after implantation.

When choosing outcomes to include in future RPS studies, investigators should routinely measure quality of life (QoL) and ADLs in addition to traditional visual acuity measures because these measures are interrelated. QoL and ADLs should be measured with the IVI and IADL-VLV and FLORA, respectively, because these are the measures with the most evidence of being valid in patients with vision similar to that seen in a RPS population. The Modified NEI-VFQ-25 plus supplement and FAST also measure QoL and function, respectively, but were tested in patients with much better vision than is typical of RPS recipients. Small gains in any vision measure (acuity, visual field, contrast sensitivity, color vision) has the potential to bring about clinically meaningful changes in QoL and ADLs from the patient’s perspective.

Although some patients clearly experienced improved visual acuity, visual field, and visual function, the percentages varied greatly among studies of Moderate to High risk of bias. Thus, evidence is insufficient to estimate the proportion of patients who will benefit from an RPS.

There is some suggestion, based on both animal and human studies, that RPSs may have a neuroprotective effect that causes at least a temporary increase in vision in areas far away from the implantation site.

See Table C for strength of evidence grades for the evidence on beneficial outcomes.

Table C. Strength of evidence for effectiveness

Strength-of-Evidence Domain	Visual function	Visual Acuity	Visual Field	Laboratory-based Visual Performance Measures	Day-to-Day Function	Quality of Life^a
Study limitations	High	High	Moderate	Moderate	High	Moderate
Directness	Direct	Direct	Direct	Direct	Direct	Direct
Consistency	Inconsistent	Inconsistent	Inconsistent	Inconsistent	Inconsistent	Inconsistent
Precision	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise
Reporting bias	Undetected	Undetected	Undetected	Undetected	Undetected	Undetected
Strength of evidence	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

^aQuality of life measurement in the single study measuring it was used to detect adverse consequences following device explantation.

Intraoperative adverse events were reported in more than half of all included studies, the most serious of which included injury to the optic nerve and central retinal defect. Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure increase, eye scratchiness, and eye-movement restrictions. Serious adverse events were reported by just under half of the studies reporting this outcome and included intraocular pressure increase, hypotony, and presumed endophthalmitis. Device explantation occurred in 3 out of 47 patients implanted with the Argus II device. Devices were explanted at 14 months, 3.5 years and 4.3 years, respectively. Reasons for explantation included recurrent conjunctival erosion (2 patients) and chronic hypotony and ptosis (1 patient).

Applicability

The patients enrolled in the 11 included RPS publications had RP, choroideremia, rod-cone dystrophy, or Bardet-Biedl syndrome and very low vision (counting fingers to no light perception) and are representative of patients who will receive RPS devices in the future. Because there are no other treatments for patients with late-stage disease, the comparators used in these studies (pre- vs. post-implantation, system ON vs. OFF) were appropriate.

The maximum duration of study followup was 10 years for one patient with the ASR device. In the Argus II study, 24 of 30 patients still had functioning devices at a mean of 6.2 years followup. Because patients as young as 25 years of age may receive this device, longer-term followup is needed. One single-patient cadaver study suggested that the Artificial Silicon Retina device had a functional life expectancy of about 20 years.

Outcomes reported in these studies were varied, making study-to-study comparisons difficult. They were often not measured with tools that have been shown to be valid and/or reliable in very low-vision populations.

Only a limited number of sites are permitted to perform Argus II surgery, but that number will increase over time. As the procedure diffuses more widely, outcomes may vary from those at the clinical trial sites, which have received significant training and other resources for surgeons and other personnel involved in caring for the participating patients.

Evidence Gaps/Future Research Recommendations

The first identified gap is the paucity of direct information about how RPS affects quality of life. Only one of the 11 included RPS studies reported data on a quality-of-life instrument (NEI-VFQ-25-German Version). Authors reported no statistically significant change in QoL at 3 weeks after implantation or during the 2-year study period after planned explantation of the device. This does not mean there was no change, because the study was too small (only 6 patients enrolled, and only 5 at final follow up) to rule out the possibility of a difference, and the instrument, albeit tested in a low-vision population, may not have been sensitive enough to measure change in this ultra-low vision population. We recognize that the other reported outcomes (visual acuity, laboratory-based measures of function, day-to-day function) may be surrogates for QoL (on the premise that improved acuity will translate into improved quality of life). However, these outcomes are less patient-oriented than QoL itself.

The second identified gap is the inability to estimate the proportion of patients who would improve after RPS implantation. Because studies used different devices, different comparators, and different outcomes (see previous section), there can be no single estimate of the proportion, because all of these aspects will likely affect improvement rates. Even controlling for the type of RPS, there was too much outcome heterogeneity to permit an estimate.

A third gap is our inability to predict which patients will benefit from these devices. Arevalo and colleagues^{18,19} and Chow and colleagues^{20,21} report that younger patients have better outcomes following surgery and both sets of authors speculate that this is a result of younger patients having healthier retinas than older patients. However, both studies enrolled fewer than 10 patients each so more studies are needed to replicate this finding.

A fourth gap involved psychometric testing of outcome measures in patients with very low vision (K1A and KQ1B). The studies we found used relatively advanced methods for testing psychometric properties (i.e., Rasch-based analysis, separation of item difficulty from person ability). Several of these studies had devised new instruments specifically for people with very

low vision. The 11 included RPS studies, however, generally did not use these tests (an exception was the studies of the Artificial Silicon Retina by Chow et al. and Geruschat et al.,²⁰⁻²² which also provided psychometric properties of certain tests). We encourage greater use of tested instruments in future studies of RPS. With greater consistency of outcome measures, future evidence reviews might be able to estimate the likelihood of improvement after RPS implantation.

Although this is not necessarily a gap, we note that we found limited information on potential other uses or off-label use of RPS devices. RPS technology is being used as the basis for creating cortical implants. One review article described that the Argus II device is being modified for use as a cortical implant, Orion I (Second Sight, Sylmar, CA, USA), with human trials planned to commence in 2017. There is also one ongoing clinical trial examining use of the Argus II in severely sight-impaired patients with advanced dry AMD.

Conclusion

Some patients clearly benefit from implantation with an RPS, but determining who those patients are is still a challenge. Future studies of retinal prostheses devices should make an effort to report valid and reliable measures of important outcomes, especially day-to-day function and QoL.

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Introduction

Recent advances in technology have permitted the first attempts to “restore” sight 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. With this technology, patients do not regain their lost vision, but instead learn how to interpret novel visual stimuli (artificial vision) for the purpose of improving their activities of daily living. 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 such system in patients with retinitis pigmentosa (RP), the Agency for Healthcare Research and Quality (AHRQ) commissioned an Evidence-based Practice Center to prepare this Technology Assessment to provide an overview of retinal prosthesis systems (RPSs). This assessment summarizes the current state of RPS technology as well as the existing evidence addressing the clinical utility of RPSs and potential future directions for research in areas in which information is limited.

Background

Retinitis Pigmentosa

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, including rods and cones. These cells act as the “ignition switch” that starts the 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 RPSs because the rest of the native pathway remains intact.

RP is one such disease. It is a collection of genotypically and phenotypically diverse eye disorders, all of which attack the rods and cones within the retina. This inherited disease is often identified by its main clinical features, which typically include symptoms of poor night vision, visual field loss, and 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 40.¹ Upon ophthalmic examination, a triad of clinical findings is typically noted: 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 of every 4,000 people and affects nearly 1 million people worldwide.²⁻⁵ More than 100 different genes have been implicated as causing the various forms of RP, representing all possible modes of genetic inheritance—autosomal dominant, autosomal recessive, X-linked, and mitochondrial.⁴ Despite the numerous genes associated with RP, only 60 percent of the cases can be associated with a known mutation.⁴ 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.^{4,6}

Common to many inherited diseases, age of onset is typically early in life, with patients who have autosomal recessive inheritance first exhibiting symptoms at about age 10 and those with autosomal dominant inheritance around age 23.⁷ 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. Because of these population age differences, blindness from RP has much higher direct medical and societal costs than other common causes of vision loss.^{8,9}

Age-Related Macular Degeneration

The RP population, particularly those with vision poor enough to qualify for an RPS, is rather small. The broader goal for most of the companies developing retinal prosthesis technology would be for implementation in more common disease states. The most logical of these is late-stage nonexudative 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.¹⁰ AMD is the leading cause of irreversible visual loss in industrialized countries,¹¹ and in the United States, it accounts for about half of severe sight loss. However, the number of patients with advanced AMD who could possibly benefit from RPS is much smaller.

Diagnosis of AMD does not depend on the presence of visual symptoms¹² but can include metamorphopsia (distorted wavy vision), loss in visual acuity, blurred vision, scotoma (partially diminished area in the visual field), impaired color perception, and loss in contrast sensitivity. The American Academy of Ophthalmology AMD guideline adopts a disease classification system developed for the Age-Related Eye Disease Study (AREDS) and described in 2013 by Ferris et al.¹³ Early AMD is defined as a combination of multiple small drusen, few intermediate drusen, and mild retinal pigment epithelium (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 nonexudative/nonneovascular ("dry") and exudative/neovascular ("wet") subtypes. Dry AMD is more common, accounting for about 90 percent of cases. Advanced dry AMD is characterized by GA. Wet AMD can feature CNV or pigment epithelial detachment and progresses more rapidly than dry AMD.¹¹

Retinal Prosthesis Systems

Multiple types of ocular prosthetic devices are under development.¹⁴⁻¹⁷ The devices stimulate different parts of the visual pathway, including the visual cortex,¹⁶ the optic nerve,¹⁷ and the retina when placed in the suprachoroidal,¹⁸ epiretinal,¹⁵ and subretinal¹⁴ spaces. A

literature search identified seven RPS devices for which there was 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.

In March 2013, the U.S. Food and Drug Administration provided guidance to industry with respect to pre-clinical and clinical testing of retinal prosthesis systems.¹⁹ For clinical testing, the document recommended (among other things) that studies identify a primary safety endpoint, that studies use effectiveness outcomes appropriate for the specific device (e.g., low-level visual acuity, grating acuity, spatial mapping of simulated visual phosphine fields, form vision assessment, orientation and mobility testing, activities of daily living, and self-reported patient outcomes), and that patients be followed for three years or longer.¹⁹

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 Silicon 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 EPIRET3 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 use in the United States for patients with RP.¹⁵ This system has three parts: an implantable 60-electrode 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.²⁰ 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 EPIRET3 uses video camera input with radiofrequency telemetric transmission from the eyeglass to a posterior chamber receiver. From the receiver, data are 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 EPIRET3 devices because rather than providing data to the electrode array via a video camera, it uses incident light projected through the recipient’s native lens.²¹ The subretinal microchip implant contains 1,500 pixels of photodiode-amplifier-electrode units that 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.²² The self-contained ASR 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.¹⁸ 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's 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.²³ 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 searches found published reports of human recipients, we identified five additional devices subjected to preclinical tests. 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.²⁴ Another American device, the Photovoltaic Retinal Prosthesis (Stanford University Palanker Laboratory) has a subretinal array of thousands of photodiodes that convert light pulses to biphasic pulses of electric current.²⁵ 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 of photoelectric dye molecules coupled to polyethylene film.²⁶ 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.

We identified a press release describing the Bio-Retina for use in patients with AMD. The device was created by an Israeli company, Nano-Retina, which was expected to start clinical trials in 2013, but our searches did not identify any completed human trials.²⁷ Finally, our searches identified a patent for Iridium Medical Technology Co., Ltd., for a flexible artificial retina device. The company describes the technology as an implant comprised of photosensors, microelectrodes, and circuitry. The photosensors receive incoming light, and microelectrodes stimulate retinal neurons. The flexible nature of the apparatus allows it to conform to the shape of the eye so that the microelectrodes align with the retinal neurons.²⁸ See Table 1 for more information.

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 that convert light into electrical pulses, delivered locally to overlying retinal neurons via microelectrodes; power supplied through subretinal polyimide foil that exits the 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 radiofrequency 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 Silicon Retina (Optobionics, United States)	Light projected through recipient's native lens	None	Subretinal	Microchip containing about 5,000 microscopic solar cells called microphotodiodes, 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
EPIRET3 (Fraunhofer IMS Biohybrid Systems, Germany)	Eyeglass-mounted camera in extraocular component with radiofrequency 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 radiofrequency telemetry, no cables connecting extraocular and intraocular components

Table 1. Retinal prosthesis system devices with published human studies (continued)

Device	Input Source	Signal Processor	Implant Placement	Electrode/ Stimulation Array	Power Source
IRIS (Pixium Vision, France)	Eyeglass-mounted camera in extraocular component with induction transmitter that sends data telemetrically	Eyeglass-mounted signal processor 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 send data to controller	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

Regulatory Aspects of RPS

The Argus II (Second Sight Medical), a second-generation unit, has been through multiple completed clinical trials.^{29,30} 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.³¹

Second Sight Medical provides resources for implanting and operating the Argus II device. Surgeons receive instructions in screening patients for eligibility, along with a recommended clinical followup schedule. A video surgeon manual describes the surgical procedure for implanting the device. Additionally, a previously trained Argus II surgeon must be 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 17 sites across the United States and Canada are certified for implanting the Argus II (<http://www.secondsight.com/stutus-us-launch-en.html>). 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. A visual rehabilitation guide is available for low vision therapists, along with hands-on training.

The hands on-training includes a “face-to-face continuing education program.”³² “An experienced therapist must attend the first rehabilitation session.”³²

Device recipients receive a patient manual describing use of extraocular components. After initial therapy in the clinic, patients are referred for local blind rehabilitation integration training with the Argus II. “The challenge for these patients is to learn to integrate the newly restored vision in the context of their blindness skills.”³²

Alternative Treatments for Retinitis Pigmentosa and Age-Related Macular Degeneration

Retinitis Pigmentosa

No FDA-approved medications exist to reverse or slow the progression of RP. The current state of care is generally 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),^{33,34} lutein,³⁵ vitamins A and E,³⁶ and various combinations of these agents.^{37,38} Unfortunately, none of these studies showed a definitive benefit to patients with RP, with a possible small exception being vitamin A supplementation.³⁶ 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.³⁹⁻⁴³ Transcorneal electrical stimulation is being studied for treating RP.⁴⁴

Pharmacologic Therapies

In RP, pharmacologic attempts have been made at neuroprotection through neurotrophic factors, with trials ongoing, but those that have reported have yet to show any efficacy.^{45,46} Although successful pharmacologic interventions have been developed for exudative AMD (e.g., intravitreal injection of a vascular endothelial growth factor [VEGF] inhibitor, such as aflibercept, bevacizumab, or ranibizumab, or photodynamic therapy with verteporfin), nonexudative AMD is still managed supportively.

Gene-based Therapies

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.⁴⁷⁻⁵⁰ Additionally, more recent gene therapy trials in patients with choroideremia⁵¹ and *RPE65*-mediated inherited retinal dystrophy.^{52,53} similarly found improved visual outcomes and retinal sensitivity. However, excitement for this modality has been tempered because a followup study conducted in patients with a recessive early-onset form (Leber congenital amaurosis) showed continued disease progression despite stable visual improvements over 3 years.⁵⁴

Some cases of RP are due to mutations in the genes *RPE65* and/or *LRAT*, and a 2014 study by Koenekoop⁵⁵ administered a 7-day course of oral QLT091001, a synthetic retinoid replacement, to 14 enrolled patients with either mutation. After 2 years, three of 14 had sustained improvements in visual fields, and two of 14 had sustained improvements in visual acuity.

Although gene therapy is promising, two hurdles make its application 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 percent of the RP cases.⁵⁶ Second, gene therapy appears to work best at rescuing failing tissue and does not appear to 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.

Stem Cell Therapy

Because dysfunction of the retinal pigment epithelium (RPE) occurs in both RP and AMD, RPE replacement strategies are being investigated. Some researchers are using pluripotent stem cells, which have been shown to preserve vision in animal studies. In 2011, an FDA multicenter trial of patients with dry AMD or Stargardt's disease was undertaken. Patients received subretinal injections of RPE cells produced from human stem cells. Some patients demonstrated improved visual acuity, improved color vision, and improved contrast/dark adaptation.⁵⁷

Other investigators are testing whether transplanting an entire layer of RPE, as opposed to a cell suspension, is a viable approach, with animal trials underway. Other approaches include using patient-matched cell transplantation, which may eliminate or reduce the need for immunosuppression, brain tissue from fetuses, or umbilical cord stem cells. Clinical trials of each of these methods were initiated in 2013, 2012, and 2010, respectively.⁵⁷

Finally, multiple studies are testing the use of bone marrow stem cells. Siqueira and colleagues have reported results for 20 patients with RP who received intravitreal injections of bone-marrow-derived stem cells. Vision-related quality of life improved at 3 months following the procedure, but was not significantly different from baseline at 12 months.⁵⁸

Low-Vision Aids and Rehabilitation

Low-vision rehabilitation is a multidisciplinary effort to maximize a patient's quality of life despite limited vision.⁵⁹ Ophthalmologists and optometrists make assessments and write prescriptions for any of a variety of low-vision aids that use magnification, enhanced lighting, and/or voice-recognition technologies. Optometrists or low-vision therapists dispense the devices, and occupational therapists and other health care professionals provide training. Some Veterans Health Administration hospitals offer specific programs for low-vision rehabilitation.

Blind Rehabilitation

For patients with ultra-low vision, such as light perception, blind rehabilitation skills are taught, with the aim of maintaining the patient's independence. Training includes instruction in using a long cane or a guide dog for walking, Braille or computer software that reads documents aloud, tactile markings on appliances, techniques for folding money to identify its value, and many smart phone apps.⁶⁰

Scope and Key Questions

Scope of the Review

Key Questions

The first of two key objectives to be pursued in this report 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 the future. The second key objective 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 scope of this review is defined below according to the population, intervention, comparators, outcomes, timing, and setting (PICOTS) framework (Table 2). Key questions (KQs) appear below.

Table 2. PICOTS framework

PICOTS component	Description
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

Key Question 1A: What outcome measures have been used in studies of RPSs?

Key Question 1B: 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?

Key Question 1C: 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?

Key Question 2: What is the evidence that HRQoL, ability to perform ADLs and IADLs, visual function, and other outcomes are improved in patients who use an RPS compared with baseline (or device off or untreated eye) and compared with alternative treatments?

Key Question 3: What is the evidence that the use of an RPS arrests the progression of RP?

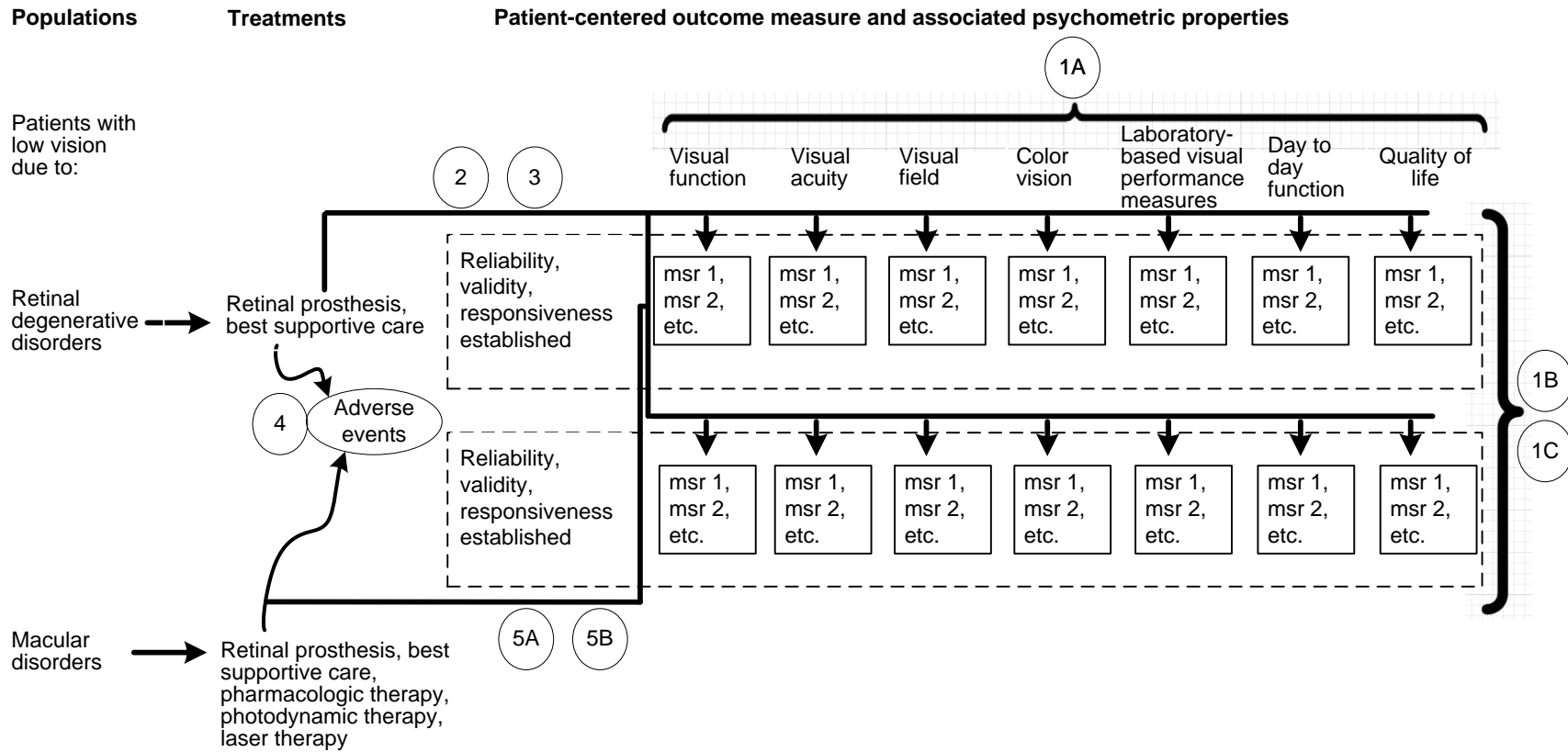
Key Question 4: What is the evidence on adverse events associated with the use of RPSs?

Key Question 5A: What is the evidence on off-label use of RPSs?

Key Question 5B: From a narrative review of the literature, are other uses suggested for RPSs?

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

Figure 1. Analytic framework



Note: msr=measure. Circled numbers, e.g., 1A denote Key Questions addressed by the systematic review.

Organization of This Report

The remainder of this report is structured as follows:

- Methods, in which we detail our processes in performing the review
- Results, in which we summarize the evidence, separately for each KQ
- Discussion, in which we highlight our key findings, provide context, discuss limitations, and summarize evidence gaps
- References
- List of abbreviations and acronyms
- Appendix A of search strategies
- Appendix B of excluded studies
- Appendix C containing all evidence tables
- References for evidence tables

Methods

The methods for this systematic review follow the Agency for Healthcare Research and Quality (AHRQ) Methods Guide for Effectiveness and Comparative Effectiveness Reviews (available at <http://www.effectivehealthcare.ahrq.gov/methodsguide.cfm>) and the PRISMA checklist. See the review protocol (<http://www.ahrq.gov/sites/default/files/wysiwyg/research/findings/ta/topicrefinement/retinal-prosthesis-protocol.pdf>) for full details.

Topic Refinement and Review Protocol

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

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

All KIs were asked which outcome measures could potentially be improved by RPS devices, in the following categories: vision, activities of daily living (ADLs), instrumental activities of daily living (IADLs), health-related quality of life (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 were based on evidence and if so, what evidence sources they considered. At the Evidence-based Practice Center (EPC), 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 KIs to the Task Order Officer.

Literature Search Strategy

Search Strategy

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 April 25, 2016. 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 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 April 25, 2016. Literature searches were updated after the draft report was posted to the AHRQ Technology Assessment Web site. Search strategies appear in Appendix A.

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, the Association for Research in Vision and Ophthalmology, the American Society of Retina Specialists, and the Retina Society. We also searched the trial registry National Clinical Trials (ClinicalTrials.gov).

Web sites and databases associated with the following institutions and organizations were searched using text words: U.S. Food and Drug Administration (FDA), CMS, U.S. Centers for Disease Control and Prevention, Healthcare Common Procedure Coding System, National Guideline Clearinghouse, the UK's National Institute for Health and Care Excellence, Trip database, Healthcare Standards database, Medline Plus, Medscape, and MediRegs. ECRI Institute resources that we searched included reports produced for ECRI's 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.

Study Selection

We included RPS device articles that met the following criteria: it reported use of an RPS device 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. We excluded studies of the IRIS system because the current version began studies only in late 2015. For psychometric properties (Key Question [KQ]1B and KQ1C), we required that articles be published in English; be primarily designed to evaluate reliability, validity, and/or responsiveness of relevant outcome measures; and have at least two-thirds of patients with very low vision (as defined by logarithm of the minimum angle of resolution $[\log\text{MAR}] \geq 1.0$ and/or visual field ≤ 20 degrees) due to retinal conditions. Correlations between different outcome categories (e.g., visual acuity and quality of life) were not taken as validity studies because they measure fundamentally different traits.

Data Extraction

We performed redundant title and abstract screening using the Distiller SR tool (Evidence Partners, Ottawa, Ontario, Canada). All articles that were excluded by one reviewer in title and abstract screening were submitted to duplicate review. Only one reviewer's selection was required for full-text article retrieval. Dual independent review was performed on all full-text

articles. Resolution of full-text article review disagreements was achieved by consensus. A PRISMA diagram was produced (see “Results of Literature Searches”).

Data extraction was performed by a single reviewer and was fully verified by a second reviewer. Extracted data are stored in Microsoft Word and Microsoft Excel files. Information extracted included the following: study design, psychometric properties assessment methods (from CONsensus-based Standards for the selection of health Measurement INSTRUMENTS [COSMIN] checklist items),⁶¹ 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.

Risk-of-Bias Assessment of Individual Studies

Because we did not expect to identify randomized controlled trials, our risk-of-bias assessment of RPS device studies focused on single-group designs (case series: pretest-posttest, posttest only, device ON/OFF, fellow eye). These risk-of-bias items have been selected from the AHRQ Methods Guide⁶²:

- 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?

Risk-of-bias assessment of studies addressing the effectiveness of RPS was based on seven predetermined items. To receive a rating of Low, studies needed to have a Yes response for the first five risk-of-bias items (confounder controlling, concurrent intervention controlling, intervention protocol fidelity, attrition handled appropriately, and outcome assessor blinding). For a rating of Moderate, studies needed at least three Yes responses on risk-of-bias items 1 through 5 and a Not Reported or Yes on items 6 and 7 (outcomes assessed using valid and reliable measures and outcomes prespecified by investigators). All other studies were rated High risk of bias.

Risk-of-bias assessment of studies addressing outcome-measures psychometric properties was based on the COSMIN checklist.⁶¹ This instrument was developed using rigorous methods including Delphi procedures. Items addressed the following domains: internal consistency, reliability, measurement error, content validity, structural validity, hypothesis testing, cross-cultural validity, criterion validity, and responsiveness.

Data Synthesis

Because of the designs of the studies (i.e., single-group designs), this review was limited to qualitative synthesis. To permit a clear synthesis, we placed each reported outcome into one of seven categories:

- Visual function
- Visual acuity
- Visual field
- Color vision
- Laboratory-based visual performance measures
- Day-to-day function
- Vision-related quality of life

Strength of the Body of Evidence

We used the strength-of-evidence grading approach described in the AHRQ Methods Guide.⁶² Domains addressed were study limitations, directness, consistency, precision, and reporting bias. If relevant, we also considered a dose-response association (e.g., whether more electrodes yielded greater effects) and magnitude of effect. We did not use the domain involving plausible confounders reducing an observed effect, because studies did not have separate control groups. We assigned a grade of High, Moderate, Low, or Insufficient, according to definitions stated below, in Table 3.

Table 3. Evidence grade definitions

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.

Thus, when the evidence did not permit a conclusion (e.g., RPS either improves or does not improve an outcome), we graded the evidence as Insufficient. A lack of statistical significance was not assumed to imply the lack of an effect, since nonsignificance may simply mean low statistical power. We graded the strength of evidence only for KQ2 and the following outcomes because of their relative importance: visual acuity, visual field, laboratory-based visual performance measures, day-to-day function, and quality of life. We did not grade the strength of evidence for other outcomes or other KQs.

Applicability

Factors of interest in assessing applicability focused on the framework defined by population, intervention, comparators, outcomes, timing, and setting (PICOTS). More specifically, applicability was determined mainly by patient-selection methods, patient-sample characteristics, intervention characteristics, and magnitude of effects on outcomes.

Peer Review and Public Commentary

The full draft report was posted for public and peer review after review by the AHRQ EPC Task Order Officer and Associate Editor. Peer reviewers, chosen by methods similar to KI selection, were 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 were 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.

Results

Results of Literature Searches

Figure 2 shows the process of reducing our initial list of 6,022 potentially relevant publications to a final included set of 40 publications. We excluded 2,647 publications at the title level (as not relevant to the topic), and another 2,771 at the abstract level. The most common reasons for exclusion at the abstract level were wrong population (1,112 exclusions) and a lack of psychometric property data in studies being considered for Key Question [KQ]1B or KQ1C (890 exclusions). We examined 603 articles in full, and excluded 565 of these for various reasons, the most common being wrong or unclear population (225 exclusions) and no psychometric data (120 exclusions). A complete list of articles excluded at the full-text level appears in Appendix B. Two included articles were identified by peer reviewers.

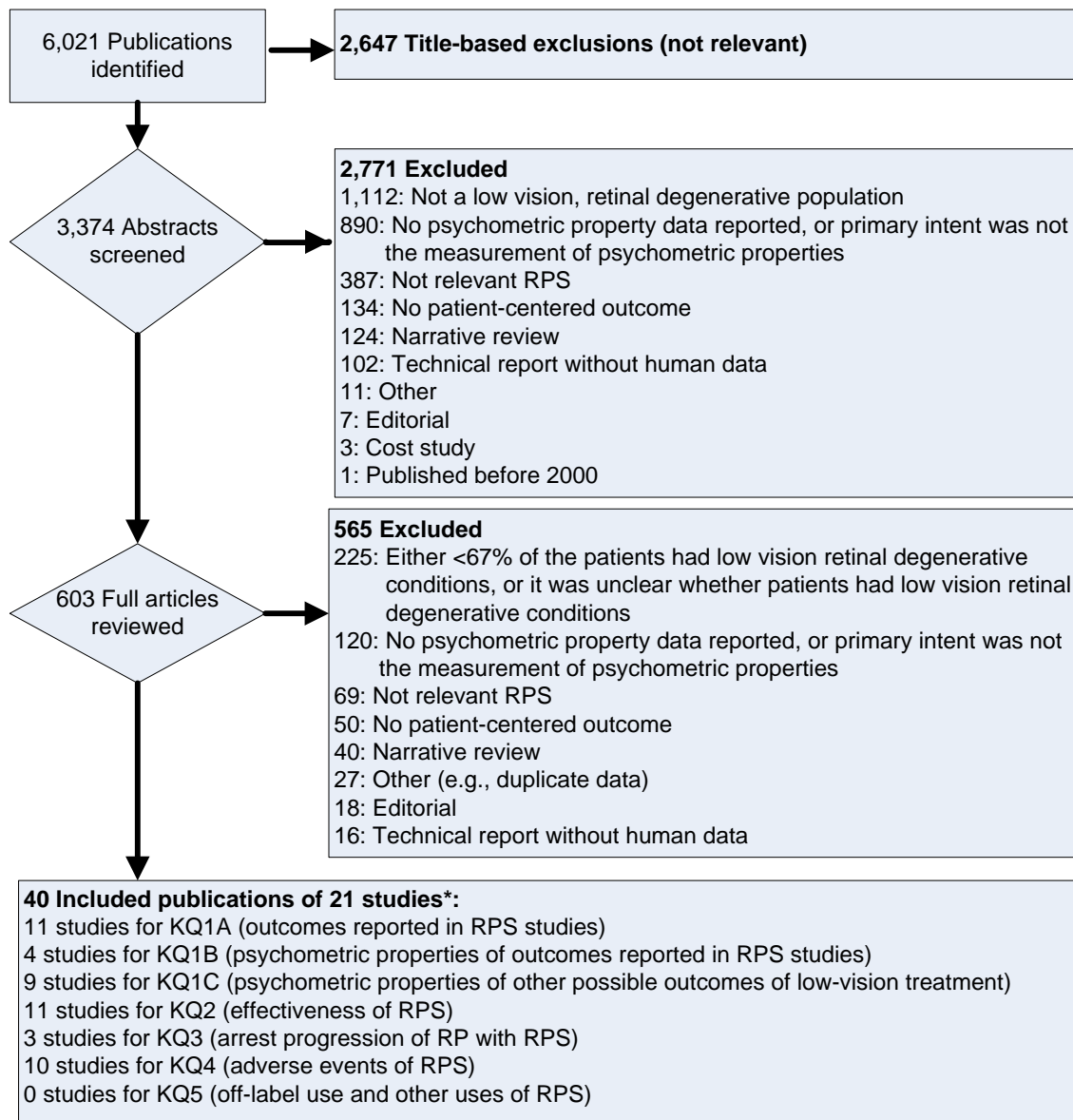
The 40 included publications described 21 unique studies. Per KQ, we included:

- Eleven studies included for KQ1A (outcomes reported in retinal prosthesis system [RPS] studies)
- Four studies included for KQ1B (psychometric properties of outcomes reported in RPS studies)
- Nine studies included for KQ1C (psychometric properties of other possible outcomes of low-vision treatment)
- Eleven studies included for KQ2 (effectiveness of RPS)
- Three studies included for KQ3 (arrest progression of retinitis pigmentosa [RP] with RPS)
- Ten studies included for KQ4 (adverse events of RPS)
- No studies included for KQ5 (off-label use and other uses of RPS)

(These numbers do not add to 21 because some studies contributed data to multiple KQs.)

The remainder of the Results section summarizes the evidence separately for each of the KQs.

Figure 2. Study attrition diagram



* The numbers do not add to 21 because some studies contributed to multiple KQs

** The number of full length studies reviewed does not include the 2 studies identified by peer reviewers

KQ=key question, RP=retinitis pigmentosa, RPS=retinal prosthesis system

Key Question 1A. Outcome Measures Used in RPS Studies

Description of Included Studies

For KQ1A we included 30 publications of 11 RPS studies:

- Alpha IMS study by Stingl et al., reported in 2013 and 2015^{63,64}
- Alpha IMS study by Zrenner et al. 2011¹⁴
- Argus II study by Arevalo et al. 2015^{65,66}
- Argus II study by Ho et al. 2015, also reported by other authors^{15,30,67-76}
- Argus II study by Seider and Hahn 2015⁷⁷
- Argus II study by Rizzo et al. 2014⁷⁸
- Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Khan et al. 2015^{22,79}
- Artificial Silicon Retina (ASR) extension study by Chow et al. 2010, also reported by Geruschat et al. 2012^{80,81}
- Bionic Vision study by Ayton et al. 2014¹⁸
- EPIRET3 study by Klauke et al. 2011 and also reported by other authors⁸²⁻⁸⁶
- Suprachoroidal Transretinal Stimulation (STS) study by Fujikado et al. 2011²³

Both Alpha IMS studies were conducted in Germany; the four Argus II studies were conducted in the United States, Europe, and Saudi Arabia; the two ASR studies were conducted in the United States; the Bionic Vision study was conducted in Australia; the EPIRET3 study was conducted in Germany; and the STS study was conducted in Japan.

The studies were all small, with enrollments ranging from 1 to 30 patients (the median was 6 patients per study). Study durations ranged from 7 weeks to 10 years. Mean patient age at implantation ranged from 40.7 to 69.5 years, and more than half of the patients were male (median 67 percent among the 10 studies reporting the sex distribution). For more information, including other patient characteristics, intervention details, comparators, and outcome data, see tables in Appendix C. This KQ focuses on types of outcome metrics used in these 11 studies.

Key Points

- The 30 publications reported 74 different outcomes. Most outcomes involved either visual function (31 percent), visual acuity (26 percent), or laboratory-based visual performance measures (30 percent). Four studies measured day-to-day visual function, and one study measured vision-specific quality of life.
- Only three outcomes were reported by three or more studies: the percentage of patients who passed the light localization task of the Basic Assessment of Light and Motion (BaLM), the percentage of patients whose square localization results were significantly better with system ON than system OFF, and the percentage of patients whose Grating Visual Acuity results were significantly better with system ON than system OFF. Seven other outcomes were reported by two studies each. Little consensus exists among authors of RPS studies about which specific measures are important.

Detailed Synthesis

Table 4 below shows the 74 types of outcomes reported by the 11 studies. We categorized outcomes as follows:

- Visual function: 23 outcomes, reported by 9 studies
- Visual acuity: 19 outcomes, reported by 9 studies
- Visual field: 4 outcomes, reported by 2 studies
- Color vision: 1 outcome, reported by a single study
- Laboratory-based visual performance measures: 22 outcomes, reported by 6 studies
- Day-to-day function: 4 outcomes, reported by 4 studies
- Quality of life: 1 outcome reported by a single study

Only 3 outcomes were reported by 3 or more of the 11 studies: the percentage of patients who passed the light localization task of BaLM, the percentage of patients whose square localization results were significantly better with system ON than system OFF, and the percentage of patients whose Grating Visual Acuity results were significantly better with system ON than system OFF. Seven other outcomes were reported by two studies each: (1) BaLM, light perception subtask, percentage passing the test; (2) BaLM, movement subtask, percentage passing the test; (3) Direction of motion test, percentage who performed better with the device ON than OFF; (4) Direction of motion test, number of correct responses; (5) Landolt C, percent passing the test; and (6) Clock task, percentage passing the test; and (7) Gray levels test: percentage passing the test. Thus, there is little consensus among authors of RPS studies about which specific measures are important. Once released, the Harmonization of Outcomes and Vision Endpoints in Vision Restoration (HOVER) Trials Taskforce recommendations may rectify this situation. The committee's goal is to guide the conduct of research and standardize outcome reporting in trials of patients with visual prosthetic devices.^{87,88}

Table 4. Outcomes reported in included retinal prosthesis system studies

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67,75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{22,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Geruschat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ^{82,86}	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Visual function	Ability to differentiate spatiotemporal patterns										✓	
Visual function	Ability to perceive 2 distinct phosphenes better than chance when stimuli were delivered through 2 channels											✓
Visual function	Ability to perceive phosphenes at all											✓
Visual function	Ability to see any light	✓										
Visual function	BaLM, light localization, % passing the test	✓	✓							✓		
Visual function	BaLM, light perception, % passing the test	✓	✓									
Visual function	BaLM, movement,% passing the test	✓	✓									
Visual function	Direction of motion test, number of correct responses				✓	✓						
Visual function	Direction of motion test, % of subjects whose system ON results were better than system OFF			✓			✓					

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Geruschat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ⁸²⁻⁸⁶	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Visual function	False-positive responses to stimulation										✓	
Visual function	Grid detection, % passing the test		✓									
Visual function	Motion direction test, better than chance											✓
Visual function	Object detection with head scanning better than chance											✓
Visual function	Object discrimination with head scanning better than chance											✓
Visual function	Pattern U in 4 directions, % passing the test		✓									
Visual function	Positive response to first stimulation pulses										✓	
Visual function	Reliable phosphene precepts									✓		
Visual function	Seeing visual percepts at all										✓	
Visual function	Seeing visual percepts in all sessions										✓	
Visual function	Single pulse oblique line, % passing the test		✓									

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Gerschhat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ⁸²⁻⁸⁶	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Visual function	Single pulse, row of 4 electrodes, % passing the test		✓									
Visual function	Square localization, mean distance from target center					✓						
Visual function	Square localization: % of subjects whose system ON results were significantly better than system OFF			✓	✓		✓					
Visual acuity	ETDRS, logMAR average								✓			
Visual acuity	ETDRS, logMAR, % who improved								✓			
Visual acuity	ETDRS: number of letters seen by each eye							✓				
Visual acuity	GAT, logMAR, average								✓			
Visual acuity	GAT, logMAR. % who improved								✓			
Visual acuity	GAT, % of subjects whose system ON results were better than system OFF	✓			✓	✓	✓					
Visual acuity	Grating visual acuity: % of subjects who scored between 2.9 and 1.6 logMAR with the system ON			✓								

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Geruschat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ⁸²⁻⁸⁶	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Visual acuity	Landolt C rings, LogMAR									✓		
Visual acuity	Landolt C rings, % passing the test	✓	✓									
Visual acuity	Letter recognition, mean seconds for correctly identified letters			✓								
Visual acuity	Letter recognition, % correct			✓								
Visual acuity	Letter size reduction test, total number of letters identified correctly			✓								
Visual acuity	Multiple letters, % passing the test		✓									
Visual acuity	Reading letters, % passing the test	✓										
Visual acuity	Seeing optotypes at all									✓		
Visual acuity	Single letter detection, % passing the test		✓									
Visual acuity	Word recognition, number of 4-letter words identified			✓								
Visual acuity	Word recognition, number of 3-letter words identified			✓								

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Gerschhat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ⁸²⁻⁸⁶	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Visual acuity	Word recognition, number of 2-letter words identified			✓								
Visual field	Central Humphrey visual field test, % who consistently positively responded							✓				
Visual field	Goldmann visual field test, % who improved					✓						
Visual field	Subjective visual field, % of patients who indicated perception of light sensation to infrared light in the projected visual field							✓				
Visual field	Visual field light threshold testing, % of patients who improved							✓				
Color vision	Pseudoisochromatic color plate test, % who improved							✓				
Laboratory-based visual performance measures	Clock task, % of patients passing the test	✓	✓									
Laboratory-based visual performance measures	Controlled mobility course, % who successfully completed the course								✓			

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Geruschat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ⁸²⁻⁸⁶	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Laboratory-based visual performance measures	Dining objects identification, mean score out of 4 (4 being best)	✓										
Laboratory-based visual performance measures	Dining objects localization, mean score out of 4 (4 being best)	✓										
Laboratory-based visual performance measures	Dining objects localization, % of patients passing		✓									
Laboratory-based visual performance measures	Dining objects number, mean score out of 4 (4 being best)	✓										
Laboratory-based visual performance measures	Finding the door, % of patients successful			✓								
Laboratory-based visual performance measures	Following the line, % of patients successful			✓								
Laboratory-based visual performance measures	Geometric shape identification, mean score out of 4 (4 being best)	✓										

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Geruschat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ⁸²⁻⁸⁶	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Laboratory-based visual performance measures	Geometric shape identification, % of patients passing		✓									
Laboratory-based visual performance measures	Geometric shape location, mean score out of 4 (4 being best)	✓										
Laboratory-based visual performance measures	Geometric shapes number, mean score out of 4 (4 being best)	✓										
Laboratory-based visual performance measures	Grasping objects, % of patients who were better than chance											✓
Laboratory-based visual performance measures	Gray levels test: % of patients passing the test	✓	✓									
Laboratory-based visual performance measures	Meander Maze Tracing, whether tracing errors reduced			✓								
Laboratory-based visual performance measures	Meander Maze Tracing, whether tracing time improved			✓								

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Geruschat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ⁸²⁻⁸⁶	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Laboratory-based visual performance measures	Mobility test, % of patients successful					✓						
Laboratory-based visual performance measures	Object prehension (locate, reach and grasp), % of patients successful			✓								
Laboratory-based visual performance measures	Reading Braille, whether single-letter recognition was better than chance			✓								
Laboratory-based visual performance measures	Touch panel test, % of patients who were better with system ON than OFF											✓
Laboratory-based visual performance measures	Path reproduction			✓								
Laboratory-based visual performance measures	Triangle path			✓								
Day-to-day function	FLORA			✓								

Table 4. Outcomes reported in included retinal prosthesis system studies (continued)

Category	Outcome	Alpha IMS study by Stingl et al. 2013 and 2015 ^{63,64}	Alpha IMS study by Zrenner et al. 2011 ¹⁴	Argus II study by Ho et al. 2015 and other authors ^{15,30,67-75}	Argus II study by Seider and Hahn 2015 ⁷⁷	Argus II study by Rizzo et al. 2014 ⁷⁸	Argus II study by Arevalo et al. 2015 ^{65,66}	Artificial Silicon Retina (ASR) study by Chow et al. 2004 and Kahn et al. 2015 ^{52,79}	Artificial Silicon Retina (ASR) extension study by Chow et al. 2010 and Geruschat et al. 2012 ^{80,81}	Bionic Vision study by Ayton et al. 2014 ¹⁸	EPIRET3 study by Klauke et al. 2011 and other authors ^{82,86}	Suprachoroidal transretinal stimulation (STS) study by Fujikado et al. 2011 ²³
Day-to-day function	Patients' impression of their visual experiences in home and daily life, % reporting improvement	✓										
Day-to-day function	Patients' impression of vision improvement for specific activities (e.g., watching son play basketball), % who reported improvement								✓			
Day-to-day function	Patients' impression of visual perceptions for 7 aspects of visual function (brightness, contrast, color, shape, resolution, movement, and visual field size), % who reported improvement							✓				
Quality of life	NEI-VFQ-25 visual-specific quality of life questionnaire										✓	

BaLM=Basic Assessment of Light and Motion test; ETDRS=Early Treatment of Diabetic Retinopathy Study; FLORA=Functional Low-Vision Observer Rated Assessment; GAT=Grating Acuity Test; logMAR=logarithm of the minimum angle of resolution; NEI-VFQ-25=National Eye Institute Visual Function Questionnaire 25-item

Key Question 1B. Psychometric Properties of Outcome Measures Used in RPS Studies

Description of Included Studies

We included four studies of psychometric properties of the outcome metrics used in studies of RPS. The four studies investigated four metrics: Early Treatment of Diabetic Retinopathy Study (ETDRS), the Chow GAT, the Chow Color test (CCT), and the Functional Low-Vision Observer Rated Assessment (FLORA). For general information about the studies, patient characteristics, interventions, comparators, and outcome data, see Table C-4 of Appendix C. In this section as well as Key Question 1C, when we refer to the “responsiveness” of a measure, we mean whether the measure has demonstrated improvements after a treatment with *known efficacy*. Since the efficacy of RPS is not known (and indeed is the focus of Key Question 2), we address pre-post changes after RPS in Key Question 2.

Key Points

- The ETDRS has acceptable test-retest reliability, but no included studies measured its validity or responsiveness.
- The GAT and the CCT have acceptable test-retest reliability and construct validity, but no included studies measured their responsiveness.
- The FLORA has acceptable face validity, but no included studies measured its reliability or responsiveness.

Detailed Synthesis

We included evidence on the psychometric properties of four outcome measurements that have been used in RPS studies: ETDRS, FLORA, the Chow GAT, and the CCT. The psychometric properties were reported in a total of four studies.^{31,80,89,90} Evidence tables in Appendix C provide the following: general information about the studies (Table C-1), patient characteristics (Table C-2), details about the measurements (Table C-3), psychometric data (Table C-4), and risk-of-bias assessments (Table C-5). Below, we discuss the outcome measurements in separate sections.

Visual Acuity: Early Treatment of Diabetic Retinopathy Study (ETDRS)

The Snellen visual acuity chart is the standard chart most people associate with an eye exam and was first created in the 19th century. Despite its wide spread use even today, the visual acuity fractions are not amenable to statistical comparisons. To address this shortcoming, the ETDRS chart was developed. With standard spacing between lines and letters and with letters of equal discrimination difficulty, the chart is considered a standard measure of visual acuity for clinical trials. Results of Snellen acuity in clinical studies are typically reported on the scale of logarithm of the minimum angle of resolution (logMAR) to attempt to correct for the lack of statistical basis between different acuity lines. Normal vision is a logMAR of 0, meaning the ability to see details as small as one minute of visual acute angle (i.e., $\log_{10}(1)=0$). Legal blindness is defined as a patient with a logMAR of 1.0 or higher, and/or less than 20 degrees of

visual field. A logMAR of 1.0 corresponds to 20/200 vision as measured by the classic Snellen chart.

We included two studies of the test-retest reliability of the ETDRS.^{89,90} Bittner et al.⁸⁹ performed ETDRS under regular illumination, and we judged it at Low risk of bias. Kiser et al.⁹⁰ performed it under both regular and dim illumination, and we judged it at Low risk of bias. Both studies reported data in terms of the coefficient of repeatability ($CR_{.95}$). This is on the scale of logMAR, and is interpreted as how much variation can be expected from an initial value (e.g., if a patient's logMAR is 1.2 at one visit, and the test has a $CR_{.95}$ of 0.15, then one would expect with 95 percent confidence that the next visit's logMAR will be within 0.15 of the first visit, i.e., between 1.05 and 1.35).

Bittner et al.⁸⁹ reported median $CR_{.95}$ values of 0.10 for patients with RP and 0.16 for patients with other retinopathies. These values are relatively low, indicating good test-retest reliability. By contrast, Kiser et al.⁹⁰ reported somewhat higher $CR_{.95}$ values, ranging from 0.13 to 0.26 for patients with RP, 0.21 to 0.27 for patients with macular degeneration, 0.18 for those with diabetic retinopathy, and 0.20 for those with other retinopathies. These medians are all for regular illumination; under dim illumination, the investigators⁹⁰ generally found similar $CR_{.95}$ values to those under regular illumination. Neither study reported additional psychometric properties of the ETDRS.

Visual acuity: Chow Grating Acuity Test (GAT)

The GAT was developed to be more sensitive than the ETDRS for patients with very low vision. Patients are shown a series of lines in one of four orientations: vertical, horizontal, diagonal left-right, or diagonal right-left, and asked to choose which orientation they are viewing. Results are provided on the logMAR scale for easy comparison with ETDRS results. The two studies that we included^{80,89} were each at Moderate risk of bias for both test-retest reliability and construct validity.

Results for test-retest reliability were good, with $CR_{.95}$ values around 0.16 for patients with RP in both studies, and even better (0.11) for patients with other retinopathies in one of the studies.⁸⁹ Both studies tested construct validity by determining the correspondence between GAT and ETDRS, and both found strong associations (e.g., a correlation of 0.92 in Chow et al. 2010),⁸⁰ with regression slopes near 1.0. These data provide evidence that GAT has good test-retest reliability and construct validity. One caveat is that both studies found that the construct validity of GAT was restricted to patients who had RP. For patients with other retinopathies, when GAT and ETDRS were compared, authors only found a weak correspondence, as GAT appeared to overestimate patients' visual acuity.

Color Vision: Chow Color Test (CCT)

The CCT was developed to be more sensitive for patients with low vision than the standard low color vision testing, the Farnsworth PV-16. The CCT is composed of both high saturation and low saturation discs, and the best possible score is 40. One Moderate risk-of-bias study⁸⁰ has tested its test-retest reliability as well as its construct validity (by comparing CCT results to the PV-16).

For test-retest reliability, authors reported a mean $CR_{.95}$ values of 5.8. However, this mean included all patients in the study. When results were given specifically for patients with RP, $CR_{.95}$ was slightly better at 4.8. Thus, for an average patient with RP, if his or her color vision tested at 13 of 40 at one visit (13 was the RP average), then the next visit would be expected

(with 95 percent confidence) to be between 8 and 18 of 40. The median CR_{.95} value for patients with macular degeneration was even lower (3.9), and they had better color vision than patients with RP (mean 30 of 40).

Regarding construct validity, because higher scores on the CCT mean better color vision but higher scores on the PV-16 mean worse color vision, good construct validity would be indicated by a large negative correlation. The study found a strong negative correlation of $r=-0.77$, suggesting good construct validity. Authors felt that the PV-16 was less sensitive to differences among patients, because the PV-16 scores appeared to cluster in the middle of the range, whereas for patients receiving CCT, scores were more evenly dispersed across its range.

Day-to-Day Function: Functional Low-Vision Observer Rated Assessment (FLORA)

FLORA was developed specifically for patients with very low vision and has three components: (1) patient self-report, which includes 14 open-ended questions (e.g., “What would you like me to know about how the system has affected you?”), and any of the 14 can be skipped if the assessor so decides; (2) observation of performance in 26 activities, in which the assessor observes the patient performing common activities of daily living, and any can be skipped if the assessor so decides; and (3) the case summary, which is a narrative case report summarizing the assessor’s findings.

One low risk-of-bias study³¹ reported the face validity of FLORA. A team of experts in blind and low-vision rehabilitation met to draft a first assessment. During multiple rounds of revision, the team reviewed commonly accepted instruments and tailored FLORA to the challenges of this population. For the self-report questions, the assessor chose to address all 14 questions for 22 of 26 patients. For the 26 activities, assessors asked patients to perform an average of 20. Based on these methods, FLORA appears to have acceptable face validity. The study reported no other psychometric properties of FLORA.

Key Question 1C. Psychometric Properties of Other Possible Outcome Measures

Description of Included Studies

We included nine studies of the psychometric properties of other instruments that could be used to measure the effects of RPS. These studies investigated 10 outcome measures: dark adaptometry, dark-adapted Humphrey perimetry, the full-field flash test (also known as the full field stimulus test), the Pelli-Robson contrast sensitivity test, the Grating Contrast Sensitivity (GCS) test, the Veterans Health Administration-13 (VA-13; formerly the Blind Rehabilitation Service Follow-up Outcomes Survey), the Functional Assessment of Self-Reliance on Tasks (FAST), the Very Low Vision Instrumental Activities of Daily Living (IADL-VLV), the Modified National Eye Institute Visual Function 25 Item (NEI-VFQ-25) plus supplement, and the Modified Impact of Vision Impairment (IVI) questionnaire. For general information about the studies, patient characteristics, interventions, comparators, and outcome data, see tables C-6 through C-10 of Appendix C.

Key Points

- For measuring vision in relative darkness, the full-field flash test (also known as the full field stimulus test) has better psychometric properties than either dark adaptometry with SST-1 or dark-adapted Humphrey perimetry. For the latter two tests, many patients with RP do not provide measurable or reliable results. The full-field flash test has acceptable test-retest reliability and construct validity.
- For measuring contrast sensitivity, the GCS has better test-retest reliability than the Pelli-Robson test. The Pelli-Robson test may not produce meaningful results in some patients with RP, due to their limited vision.
- The FAST instrument has acceptable reliability, validity, and responsiveness. Further, its psychometric properties are better than those of the VA-13. Both clinician-completed and patient-completed versions of the FAST instrument have reliability and responsiveness, but they yield somewhat different answers.
- The IADL-VLV and Modified NEI-VFQ-25 plus supplement have acceptable reliability, validity, and responsiveness.
- The IVI has acceptable reliability and validity; no included studies measured its responsiveness.

Detailed Synthesis

We included evidence on the psychometric properties of 10 outcome measurements that have not been used in RPS studies. Their psychometric properties were reported in eight studies.⁸⁹⁻⁹⁶ Evidence tables in Appendix C provide the following: general information about the studies (Table C-6), patient characteristics (Table C-7), details about the measurements (Table C-8), psychometric data (Table C-9), and risk-of-bias assessments (Table C-10). Below, we discuss the outcome measurements in separate sections.

Light Sensitivity Tests: Dark Adaptometry, Dark-Adapted Humphrey Perimetry, and Full-Field Flash Test

We discuss the psychometric properties of dark adaptometry with SST-1, dark-adapted Humphrey perimetry, and full-field flash test together, because they were directly compared in the same study.⁹¹ All three tests were used in patients with very low vision as an attempt to assess their visual abilities in the dark (see test details in Table C-8 of Appendix C). The study reported test-retest reliability for all three measures and also measured construct validity as the correlation between the measures. We graded the risk of bias as Low for test-retest reliability, and Moderate for construct validity.

Two of the three tests—dark adaptometry with SST-1 and dark-adapted Humphrey perimetry—had the problem that only about half of the patients with RP could both complete the tests and provide measurable or reliable results. By contrast, 75 of 77 patients (97 percent) could sensibly complete the full-field flash test.⁹¹ Below, we first discuss each test's test-retest reliability, and then we turn to inter-test correlations.

For dark adaptometry with SST-1, researchers determined each person's threshold for detecting faint light (with lower decibel [dB] thresholds indicating greater sensitivity), as well as the amount of time it took to determine the person's threshold (shorter time indicates greater sensitivity). They measured test-retest reliability using the coefficient of variation (CoV), which

is the standard deviation (SD) of the time required to reach the person's light perception threshold divided by the average time the person needed to reach the threshold. CoV is on a percentage scale, and lower numbers indicate greater test-retest reliability. The various patient groups in the study averaged about 10 percent to 20 percent, which is generally good. The authors did not report results specifically for patients with RP (although, as noted above, only 16 of 33 of these patients could actually complete this test).⁹¹

For dark-adapted Humphrey perimetry, patients focused on a red light-emitting diode (LED) in the middle of a 4- by 4-inch square after being dark-adapted. Researchers determined each person's threshold for detecting faint light over the visual field. Data were on the dB scale, with higher dB indicating greater sensitivity. The authors measured test-retest reliability using the CR.₉₅ (discussed earlier), which is also expressed as dB. The authors reported CR.₉₅ values separately for (1) rod-based sensitivity, (2) cone-based sensitivity, and (3) rod-cone sensitivity ratios. Further, they reported CR.₉₅ values separately for several different groups of patients (see Table C-9 in Appendix C). The three RP groups had means ranging from about 1 dB to 18 dB; mean CR.₉₅ values ranged from 1 dB to 10 dB. Variability within a given patient visit was less than variability across patient visits. For this report, the most pertinent finding is that only 15 of 33 patients with RP could provide measurable or reliable results.⁹¹

After dark adaptation for 45 minutes, patients underwent the full-field flash test (also known as the full field stimulus test). Two studies provided psychometric data on the full-field flash test: Kiser et al.⁹¹ and Roman et al.⁹⁷ In Kiser et al.,⁹¹ two white-light flashes appeared (one at maximum attenuation, the other at a level to determine the patient's threshold for detecting faint light), and each patient's threshold was determined. Higher dB thresholds indicate greater sensitivity. Test completion was not problematic, as 75 of 77 patients provided measurable and reliable results. The authors measured test-retest reliability using the CR.₉₅. Mean values for the full-field flash thresholds for the four RP groups (grouped by varying levels of visual acuity) ranged from 20 to 43 dB, with CR.₉₅ values ranging from 6 to 12 dB. For example, a typical RP-I patient (vision 20/40 or worse but with limited visual field) had a threshold of 43 dB, and one would expect with 95 percent probability that a retest would be between 37 dB and 49 dB. This appears to be reasonably good test-retest reliability.⁹¹

For construct validity, the authors measured two types of associations: (1) between dark adaptometry and full-field flash tests and (2) between Humphrey perimetry and full-field flash tests. The first correlation was weak ($r=0.37$) and the authors theorized that the adequacy of adaptometry had device concerns ("limited response range of the SST" [scotopic sensitivity test instrument]). The second correlation was stronger ($r=0.60$); authors noted that macular disease (MD)-I patients were outliers, and after removing them, the correlation became even stronger ($r=0.80$). Overall, among the three methods, the data suggest that the full-field flash test is the best for assessing dark-adapted vision in patients with very low vision.⁹¹

Roman et al.⁹⁷ compared two versions of the full-field flash test after 45 minutes of dark adaptation: FST1 and FST2. They confirmed construct validity of the FST2 by showing its high correlation with FST1 ($r=0.98$) as well as demonstrating poorer light sensitivity among patients than among people with normal vision. Further, they found good test-retest reliability of FST2 (SD of only 1.41 dB from an approximate patient median of 17 dB). We rated the Roman et al. 2007⁹⁷ study as risk of bias as Low for test-retest reliability, and Moderate for construct validity.

Contrast Sensitivity: Pelli-Robson Contrast Sensitivity Test

The Pelli-Robson test is a standard contrast-sensitivity test using letter charts, and two studies^{89,90} have reported its test-retest reliability in patients with very low vision. The authors reported CR.₉₅ and median values, and results are on the logMAR scale. The low risk-of-bias Bittner et al.⁸⁹ study reported a median CR.₉₅ value of 0.14 for patients with RP and 0.24 for patients with other retinopathies. The low risk-of-bias Kiser et al.⁹⁰ study reported poorer test-retest reliability, with median CR.₉₅ values ranging from 0.39 to 0.49 for various RP groups. Kiser et al.⁹⁰ also reported the test-retest reliability of the Pelli-Robson test under two alternate illumination conditions: dim and glare. For dim illumination, median CR.₉₅ values ranged from 0.22 to 0.50 for various RP groups, whereas for glare illumination, they were 0.25 for the best-vision RP group, 0.68 for the next-best-vision RP group, and only 0.10 for the poorest-vision patients with RP.

Contrast Sensitivity: Grating Contrast Sensitivity (GCS) Test

Bittner et al.⁸⁹ described the GCS test as an alternative to the Pelli-Robson test. Gratings are presented in varying shades of gray, and each patient's threshold is determined. This low risk-of-bias study reported test-retest reliability using CR.₉₅ values (logMAR scale). For patients with RP, results were generally good, with median CR.₉₅ values of 0.13 for within-visit testing and 0.15 for between-visit testing. For patients with other retinopathies, within-visit data were similarly good; however, between-visit reliability was poor (medians of 0.34 and 0.41 for the two pertinent subgroups).⁸⁹

The authors also measured construct validity by determining the correlation between the GCS and the Pelli-Robson contrast sensitivity test. The correlation was low, which may indicate that the two tests measure different abilities.⁸⁹

Day-to-day Function: VA-13 and Functional Assessment of Self-Reliance on Tasks (FAST)

We discuss VA-13 and FAST together because the two pertinent studies on these instruments were published by the same authors from a single Veterans Health Administration (VA) hospital in Tucson, AZ,^{92,93} and they were the only included studies of these instruments. All patients in both studies had undergone a low-vision rehabilitation program at the Tucson VA hospital. The first study⁹³ compared the clinician-completed FAST (both before and after the program) to the patient-completed VA-13 (after the program), whereas the second study⁹² compared the clinician-completed FAST to a patient-completed FAST (both were administered before and after the program).

Regarding reliability, only the first study reported pertinent data (Low risk of bias), and the authors measured it in three ways: (1) separation reliability, which is how well the instrument classified respondents into different levels of the trait; (2) internal consistency reliability for persons, which is whether the items are measuring the same underlying construct of patient ability; and (3) internal consistency reliability for items, which is whether the items are measuring the same underlying construct of item difficulty. They used *a priori* thresholds for acceptable levels of these metrics. For VA-13, only the second of the three had acceptable reliability, but FAST met criteria for all three.⁹³

The first study also discussed face validity of each item, based on whether the distribution of pretreatment item difficulty (assessed using a Rasch-based analysis) was “the same order of difficulty that is observed in clinical practice at admission or in pre-test self-reports.”⁹³ For

VA-13, 11 of 13 items achieved the expected ordering, and for FAST it was achieved for all 13 items. Furthermore, the VA-13 at discharge requires patients to remember their pretreatment levels of vision functionality, and therefore has less face validity.⁹³

Both studies reported data on construct validity and both were at Low risk of bias. Babcock-Parziale et al. theorized that the estimated item difficulties should not change before and after vision rehabilitation because the items do not change, and they found this to be true for both the VA-13 and the clinician-completed FAST.⁹³ Both instruments also met their criteria for response category thresholds (whether participants could discriminate between items). McKnight and Babcock-Parziale⁹² assumed that item difficulty should not change depending on whether patients or clinicians complete the FAST instrument. They found a near-linear relationship between the two types of administrations (i.e., Rasch statistical analysis generally found that if an item was relatively difficult based on clinician-completed forms, it was also relatively difficult based on patient-completed forms). However, McKnight and Babcock-Parziale⁹² found real differences based on the respondent, because only 55 percent of the variance in patient scores was explained by clinician scores. They performed a multiple regression to investigate this further, and found that the timing of administration (at admission or at discharge) was the primary explanatory factor.

For responsiveness (Moderate risk of bias for both studies), both versions of the FAST were acceptably responsive to changes in patient abilities after the program. The VA-13, however, was judged by Babcock-Parziale et al.⁹³ to be insufficiently responsive, based on their opinion that amount of improvement as measured by the VA-13 was considerably less than what is typically observed in the field.

Overall, these data suggest that for veterans with low vision in Arizona, FAST is a better instrument than VA-13, and that for the FAST, patients and clinicians give different answers.

Day-to-day Function: Very Low Vision Instrumental Activities of Daily Living (IADL-VLV)

A small study by Finger et al.⁹⁴ in Australia (n=40) tested the IADL-VLV instrument for its reliability and validity. Patients were observed attempting up to 53 different tasks (e.g., searching a shelf for a can of tomato soup), and they were scored on successful completion and the number of attempts needed. We rated the study's data on face validity as Low risk of bias, and its data on reliability and validity as Moderate risk of bias (because of the small enrollment).⁹⁴

For reliability, authors measured both separation reliability (how well the instrument classified respondents into different levels of the trait) and internal consistency reliability of persons (whether the items are measuring the same underlying construct of patient ability). Both metrics met the authors' predefined criteria for acceptability.⁹⁴

For face validity, the authors began with 296 items from existing activities of living (ADLs) tools. These were reduced to 25 general activities based on importance rankings with 62 participants with severe low vision. A panel of low vision experts then reduced the 25 activities to 11, which were comprised of 53 specific tasks.⁹⁴

The 53 tasks were then subjected to construct validity testing based on task observance in 40 legally blind patients. Authors tested the construct validity of the 28-item instrument in 4 ways: (1) response category thresholds (whether participants could discriminate between items); (2) a test of unidimensionality based on the residuals of the first factor in principal components analyses; (3) another test of unidimensionality based on the first contrast of residuals; and (4) whether responses were associated with non-vision-related aspects of health, such as age and

sex. For the first three metrics, all three acceptability thresholds were met. For targeting (whether the items adequately target the ability of respondents), authors noted that the questionnaire was “slightly suboptimal,” but “still well within acceptable levels.” Various analyses reduced the initial 28 items into a final list of 23 items. This final list satisfied the first two metrics for construct validity. The third was not satisfied because the analyses indicated various separate domains of tasks related to table search, recognition of symbols, clock reading, signature placement, clothes sorting, and recognition of hand gestures. For the fourth metric, authors found no associations with age and sex after controlling for both cognitive impairment and depression. Thus, patients’ abilities to perform the activities are associated with both cognitive impairment and depression.⁹⁴

Quality of Life: Modified NEI-VFQ-25 Plus Supplement

The NEI-VFQ-25 is a standard instrument for assessing visual function. Stelmack et al.⁹⁵ modified it to improve the assessment of veterans with very low vision such as legal blindness. Authors started with the 25 items from the NEI-VFQ-25 and 14 supplemental items. Directions were modified to add consideration of low-vision devices, directions were repeated if necessary because the patients frequently forgot the instructions, the driving-related items were removed (because few of the patients were driving), and the general vision/health questions were removed (items A1 and A2 in the supplement). The final instrument contained 34 items.

Data on construct validity (Low risk of bias) involved a Rasch analysis and an assessment of whether item difficulty and/or person ability fit statistics changed before and after the low-vision rehabilitation. Neither did, indicating construct validity.

For responsiveness (Moderate risk of bias), authors found that 7 of the 34 items became statistically significantly easier after treatment (see a list of the 7 items in Table C-9 in Appendix C). Furthermore, 69 of 77 patients had a higher estimate of visual ability after treatment than before treatment. The typical degree of improvement corresponded to a four-line improvement in visual acuity. These data suggest acceptable responsiveness of the modified instrument.

Quality of Life: Modified Impact of Vision Impairment (IVI) Questionnaire

The IVI questionnaire was tested in Australia by Finger et al. in a single moderate-quality study.⁹⁶ It differs from the IADL-VLV mentioned earlier in that the IADL-VLV asks patients to perform tasks, whereas the IVI is a self-administered questionnaire to measure patients’ assessments of their general abilities and difficulties. The IVI was modified by the authors in an effort to measure the functional limitations of people with severe vision loss. It contains 28 items in two domains (activities of daily living mobility and safety [ADLMS] and emotional well-being [EWB]; higher scores indicate higher functionality). An example item is “In the PAST MONTH, how much has YOUR EYESIGHT INTERFERED with...handling money” (to which the patient answers “Not at all/A Little/Sometimes/A lot/Don’t do this for other reasons”).

Authors reported three types of reliability: (1) separation reliability, which is how well the instrument classified respondents into different levels of the trait; (2) internal consistency reliability for persons, which is whether the items are measuring the same underlying construct of patient ability; and (3) internal consistency reliability for items, which is whether the items are measuring the same underlying construct of item difficulty. They used *a priori* thresholds for the

acceptability of these metrics, and the final version of the questionnaire met all three reliability criteria.

The face validity of their modifications of the standard IVI was established through focus-group discussions and telephone interviews with vision-impaired patients, healthy controls, and professionals. The item pool was reduced from an initial 76 items to 52, and then further reduced to 28 based on telephone interviews with 198 legally blind people.

Authors tested the construct validity of the 28-item instrument in seven ways: (1) response category thresholds, which is whether participants could discriminate between items; (2) a test of unidimensionality based on the residuals of the first factor in principal components analyses; (3) another test of unidimensionality based on the first contrast of residuals; (4) targeting, which is whether the items adequately target the ability of respondents; (5) differential item functioning, which is whether sample subgroups with similar underlying ability (e.g., of different age or sex) have similar scores on the instrument; (6) whether responses were associated with patients' eye conditions; and (7) whether responses were associated with other aspects of health. For the first three metrics, all three acceptability thresholds were met. For targeting, authors noted that the questionnaire was "slightly suboptimal," but "still well within acceptable levels."

For differential item functioning, authors tested six demographic patient characteristics that (theoretically) should not be associated with visual function scores, and none were statistically significantly associated for either domain. Thus, the questionnaire appears to specifically measure visual function and vision-related quality of life. In the sixth test, authors found that ADLMS scores were associated with the type of eye condition: patients with RP had relatively high scores, whereas those with age-related macular degeneration (AMD) and glaucoma had relatively low scores. EWB scores, however, showed no relationship with the eye condition. For the seventh and final test of construct validity, authors found that both ADLMS and EWB subscores correlated with four other measures of health (general health, other health problems, do other health problems interfere, and anxiety/depression). As expected, higher ADLMS and EWB subscores predicted better health responses to these questions.

Overall, these data indicate good reliability and validity of the modified IVI for patients with very low vision.

Key Question 2. Effect of RPS on Health-related Quality of Life, Activities of Daily Living, Visual Function, and Other Outcomes

Description of Included Studies

We included the same 11 studies that were included for KQ 1A. See Appendix C (Table C-11 through Table C-18) for more details.

Key Points

- Some patients clearly improve on measures of visual function, visual acuity, visual field, color vision, laboratory-based function, and day-to-day function from RPS, but evidence is insufficient to estimate the proportion of patients who would benefit.
- Visual function was improved in 40 percent to 100 percent of patients with an implanted device.

- Visual acuity was improved in 0 percent to 100 percent of patients with an implanted device.
- Visual field was improved in 17 percent to 100 percent of patients with an implanted device.
- One study assessed color vision and found improvement in one patient out of six.
- Laboratory-based function measures were varied, and patients improved on some tasks but not on others.
- Day-to-day function measures were varied, and patients improved on some tasks but not on others. Results from FLORA, the only validated measure used to assess day-to-day function, found patients improved on most tasks assessed with these exceptions: travel within the home independently, identify bottom steps, negotiate stairs, chop food, heat/reheat food, and maintain safety from falls.
- Quality of life was assessed in one study using the NEI-VFQ-25-German version, which has not been validated in a RP population. The authors found no significant change in six patients 3 weeks after implantation or after planned explantation of the device (at 5-month and at 2-year followup).

Detailed Synthesis

Below, we discuss the effectiveness evidence in seven categories: visual function, visual acuity, visual field, color vision, laboratory-based visual performance measures, day-to-day function, and quality of life. Then we provide our strength-of-evidence assessments for six of them (we did not assess the strength of evidence for color vision because of its lesser importance).

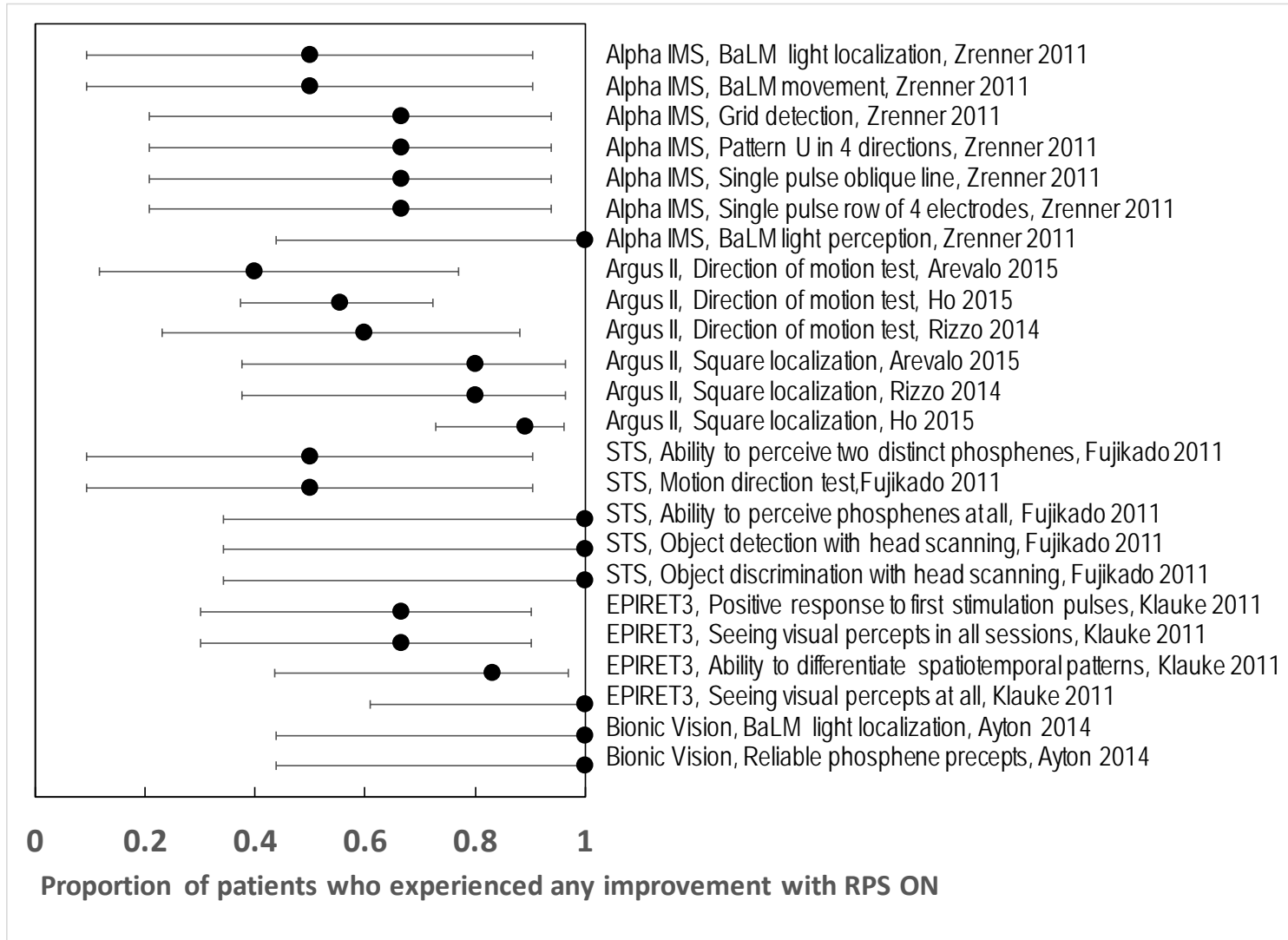
Visual Function

At least one measure of visual function was reported by nine studies. Seven studies reported direction of motion.^{14,15,23,30,63-74,77,78} The percentage of patients passing or with improved performance on this test ranged from a low of 21 percent in the Stingl et al. study of the Alpha IMS to a high of 100 percent in the case report by Seider and Hahn of Argus II. Four studies reported the ability to detect percepts (light).^{14,18,23,82-86} In all studies, 100 percent of patients could detect percepts. Four studies, all testing Argus II, reported square localization.^{15,30,65-74,77,78} The percentage of patients who performed better with the system ON versus OFF or who improved on this test ranged from a low of 80 percent in the Arevalo et al. study to a high of 100 percent in the case report by Seider and Hahn. Three studies reported light localization.^{14,18,63,64} The percentage of patients passing this test or performing better with the system in the ON versus OFF mode ranged from a low of 33 percent in the Zrenner et al. study of the Alpha IMS device to a high of 100 percent in the Ayton et al. study of a suprachoroidal retinal prosthesis. Two studies, both testing the Alpha IMS device, reported light detection.^{14,63,64} The percentage of patients who did better when the system was in the ON versus OFF mode ranged from 86 percent in the Stingl et al. study to 100 percent in the Zrenner et al. study.

Examining only the four Argus II studies results, square localization was improved in 80 percent to 100 percent of subjects in all four studies and direction of motion was improved in 40 percent (Arevalo et al.), 56 percent (Ho et al.), 60 percent (Rizzo et al.) and 100 percent (Seider and Hahn) of Argus II patients.

See Figure 3 for a plot of the data on the proportion of patients whose visual function improved when comparing ON to OFF or comparing before-implantation to after-implantation. Additional details are provided in Table C-13 of Appendix C.

Figure 3. Visual function: proportion of patients improved



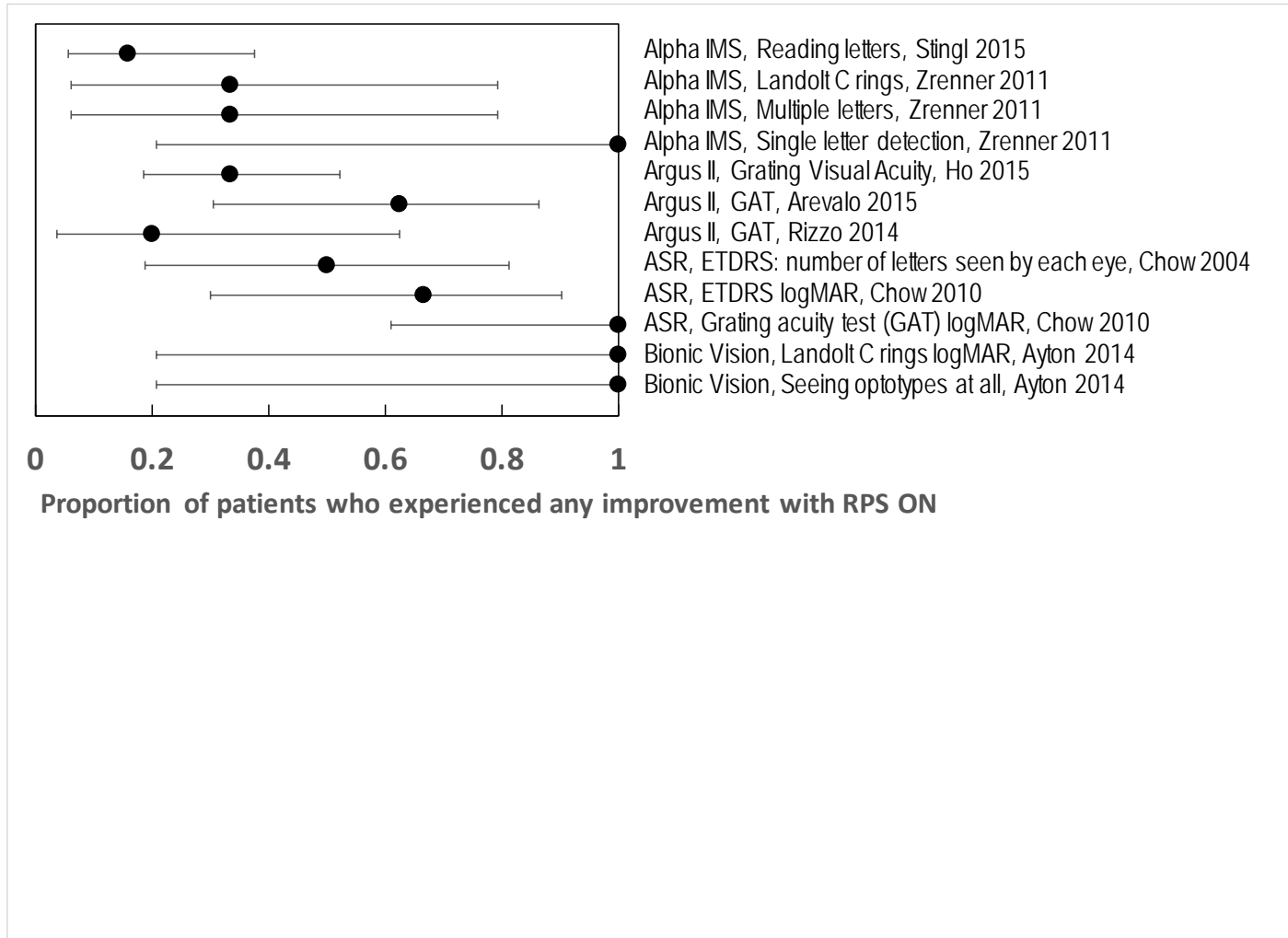
Note: Each filled circle shows the proportion of patients who experienced any improvement with RPS ON, and the horizontal bar shows the 95% confidence interval around the proportion. BaLM=Basic Assessment of Light and Motion; RPS=retinal prosthesis system; STS=Supra-choroidal Transretinal Stimulation

Visual Acuity

Nine studies reported at least one measure of visual acuity. Six studies reported some measure of grating visual acuity.^{15,30,63-74,77,78,80,81} The percentage of patients experiencing an improvement ranged from a low of 0 percent in the case report by Seider and Hahn of Argus II to a high of 100 percent in the Chow et al. extension study of the ASR device. Two studies reported Freiburg Acuity and Contrast Test (FrACT) visual acuity.^{14,18} One study administered the test to one out of three patients enrolled and found that that patient did significantly better with the system ON than OFF.¹⁸ The other study administered this test to all three patients enrolled and one out of three passed with the system in ON mode. That patient then went on to take the test with the system in OFF mode and failed.¹⁴

Examining only the four Argus II studies results, grating acuity was improved by 0/1 patients (Seider and Hahn), 17 percent of patients (Rizzo et al.), 33 percent (Ho et al.), and an unspecified majority percent (Arevalo et al.). See Figure 4 for a plot of the data on the proportion of patients whose visual acuity improved when comparing ON to OFF or comparing before-implantation to after-implantation. Additional details are provided in Table C-13 in Appendix C.

Figure 4. Visual acuity: proportion of patients improved



Note: Each filled circle shows the proportion of patients who experienced any improvement with RPS ON, and the horizontal bar shows the 95% confidence interval around the proportion. ETDRS=Early Treatment of Diabetic Retinopathy Study test; logMAR=logarithm of the minimum angle of resolution; RPS=retinal prosthesis system

To determine if visual acuity gains were maintained over time, we chose one visual acuity measure from each study that reported a measure of visual acuity. We chose measures that were commonly reported and for which the most timepoints were presented. A majority of studies reported only one timepoint. For the Ho and colleagues Argus II trial, visual acuity results were better in Year 1 and 2 than Year 3 and 5 but approximately 40% of patients were still showing gains at the final followup visit. Alpha IMS gains, as reported by Stingl, declined over the one year followup period. Both Chow ASR studies found that the two patients who had the biggest gains by the Month 1 postoperative visit (patients 5 and 6) experienced a decrease in those gains over the course of the study. Seven patients did not improve over time and one patient (patient 7) experienced steadily improved over time but had a sharp decline at the final followup visit. See the table below for more details.

Table 5. Visual Acuity Results Over Time

Study	Outcomes	Comparator	<1 year	1 to 3 Years	3 to 5 Years	≥5 Years	Change
Arevalo et al. 2015 ^{65,66} Argus II	GAT	Pre-implantation: 1 L projection, 7 LP	NA	Post-implantation: 4 HM, 2 L projection, 2 LP.	NA	NA	A majority of patients improved. Study did not report how many improved.
Ho et al. 2015 and other authors ^{15,30,67-76} Argus II	GAT: percentage of subjects who scored between 2.9 and 1.6 logMAR with the system ON. None of the subjects scored with the system OFF	Stimulator OFF/Fellow eye: No subject could score on the scale at baseline.	NR	Stimulator ON Year 1 (n=29 patients): 48.2% did significantly better than with the stimulator OFF Stimulator ON Year 2 (n=29 patients): 49% did significantly better than with the stimulator OFF	Year 3 (n=27): 33.3% did significantly better than with the stimulator OFF Year 4 (n=22): 28% did significantly better than with the stimulator OFF	Year 5 (n=21) 38.1% of patients did significantly better with the stimulator ON than with the stimulator OFF	Proportion of subjects with significantly better system ON than OFF results was not significantly different between 1 and 3 years for this test. Performance has remained better with the System ON than OFF on all visual tests, with these results sustained out beyond 5 years of chronic use.
Seider and Hahn 2015 ⁷⁷ Argus II	Grating visual acuity	System OFF: NR	NA	Year 1 System ON: NR	NA	NA	Patient did not benefit from the System being ON

Table 5. Visual Acuity Results Over Time (continued)

Study	Outcomes	Comparator	<1 year	1 to 3 Years	3 to 5 Years	≥5 Years	Change
Stingl et al. 2015, 2013 ^{63,64} Alpha IMS	Grating acuity and VA with standardized Landolt C-rings in contrast reversal	Stimulator OFF Grating acuity, percentage of patients passing test	<p>Month 1 (n=22) 50%</p> <p>Month 3 (n=17) 46%</p> <p>Month 6 (n=15) 20%</p> <p>Month 9 (n=10) 30%</p> <p>For grating acuity, only comparisons at months 1–3 were statistically significant.</p> <p>Landolt C-rings, percentage of patients passing test</p> <p>Month 1(13) 0%</p> <p>Month 3 (n=9) 0%</p> <p>Month 6 (n=4) 0%</p> <p>Month 9 (n=4) 0%</p> <p>Month 12 (n=1) 0%</p> <p>No time points showed statistically significant comparison for Landolt C rings.</p>	<p>Month 12 (n=6) 18%</p> <p>Landolt-C rings</p> <p>Month 12 (n=1) 0%</p> <p>No time points showed statistically significant comparisons</p>	NA	NA	<p>Significantly better for implant ON versus OFF for visits months 1–3.</p> <p>Grating acuity resolutions with the implant ON ranged from 0.1 to 3.3 cycles per degree.</p> <p>5 patients passed the grating acuity test with the implant OFF but all 5 patients had higher percentage of correct responses with the implant ON.</p> <p>4 patients completed standardized VA testing with contrast reversal Landolt C-rings with VA of v20/2000, 20/2000, 20/606, and v320/546 with the implant ON.</p>

Table 5. Visual Acuity Results Over Time (continued)

Study	Outcomes	Comparator	<1 year	1 to 3 Years	3 to 5 Years	≥5 Years	Change
Ayton et al. 2014 ¹⁸ Bionic Vision	Visual acuity was assessed with the Landolt C optotype recognition subtest from FrACT, presented in a darkened room. Floor effect (unable to estimate VA lower than 3.24 logMAR).	Device OFF no optotypes were seen (n=1)	NA	Year 1 Device ON: 2.62 mean logMAR, Rng 2.35–3.02 across 19 sessions (n=1)	NA	NA	Significant difference in favor of the device ON condition, n=1 patient (who was enrolled in the trial the longest)
Rizzo et al. 2014 ⁷⁸	Grating acuity was tested only in implanted eye with the device ON	Pre-implantation: 0 patients could identify gratings	NA	12 months Post-implantation: 1 patient was able to identify gratings, grating VA 2.2 logMAR in the operative eye with stimulator ON	NA	NA	1 patient improved
Zrenner et al. 2011 ¹⁴ Alpha IMS	Standardized FrACT test with Landolt C optotypes and an up and down staircase procedure. If Landolt C was passed, single letters were used subsequently.	Stimulator OFF Only presented to patient who passed with the stimulator ON: patient failed	4 month followup: 1/3 could see the Landolt C rings and discern letters with VA logMAR 1.69, 2 patients failed (but one of these patients reported seeing the Landolt ring gap clearly).	NA	NA	NA	1/3 passed test. Authors note that patient performance improved over the course of the 4 month study.

Table 5. Visual Acuity Results Over Time (continued)

Study	Outcomes	Comparator	<1 year	1 to 3 Years	3 to 5 Years	≥5 Years	Change
Chow et al. 2010 and Geruschat et al. ^{80,81} Extension study ASR	ETDRS acuity	Implanted eyes baseline	Implanted Eye Patient 5: Month 1: 42 letters Month 6: 38 letters Patient 6: Month 1: 26 letters Month 6: 27 letters Patient 7: Month 1: 0 letters Month 6: 2.5 letters Patient 8: Month 1: 0 letters Month 6: 0 letters Patient 9: Month 1: 0 letters Month 6: 1.7 letters Patient 10: Month 1: 0.5 letters Month 6: 3.7 letters	Implanted Eye Patient 5: Year 1: 30.5 letters Year 2: 25 letters Patient 6: Year 1: 24 letters Year 2: 15 letters Patient 7: Year 1: 2.7 letters Year 2: 4.7 letters Patient 8: Year 1: 0.3 letters Year 2: 0.7 letters Patient 9: Year 1: 0.7 letters Year 2: 1 letters Patient 10: Year 1: 2 letters Year 2: 0.7 letters	Implanted Eye Patient 5: Year 4: 25 letters Patient 6: Year 4: 17.3 letters Patient 7: Year 3.5 to 4.5: 12.3 to 10 letters Patient 8: Year 4: 0.3 letters Patient 9: Through 3.5 years: 0 to 1.5 letters Patient 10: Years 2 to 6: 0.3 to 0.7 letters	Implanted Eye Patient 5: Year 8: 22.7 letters Patient 6: Year 8: 5 letters Patient 7: Year 7.5: 1 letter Patient 8: Year 6.5: 0.7 letters Patient 9: NR Patient 10: Years 2 to 6: 0.3 to 0.7 letters	4/6 patients improved from pre- to post-operative period.
Chow et al. 2004 ^{22,79} ASR	Letter recognition	ETDRS VA Patients 1–4: 0 letters Patient 5: 16–25 letters OD, 24–28 letters OS Patient 6: 0 letters OD, 0 to 3 letters OS	ETDRS Patient 5 at 6-month followup: 35–41 letters OD, 21–28 letters OS Patient 6 at 6-month followup: 25–29 letters OD, 0 letters OS	ETDRS Patients 1 through 4: 0 letters (3 patients), able to see some of the largest letters OD only (20/1280 to 20/1600) at 12–18 month followup (1 patient)	NA	NA	3/6 patients experienced some improvement

ETDRS=Early Treatment of Diabetic Retinopathy Study test; FrACT=Freiburg Acuity and Contrast Test; GAT=grating acuity test; logMAR=logarithm of the minimum angle of resolution; NA=not applicable; NR=not reported; OD=ocular dextrus; OS=ocular sinister; VA=visual acuity

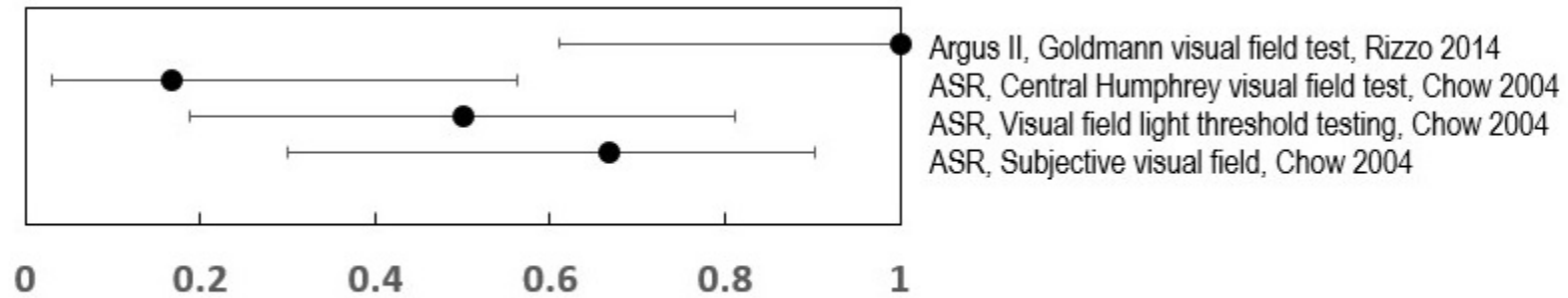
Visual Field

Two studies out of 11 reported visual field outcome data but the studies reported different measures of visual field. The Chow et al.²² study of the ASR device reported Humphrey visual field test results, Nine Sector Test results, and patient subjective impression of their visual field, while the Rizzo et al.⁷⁸ study of Argus II reported Goldmann visual field results. Compared with the unoperated eye or their subjective impression of their visual field before implantation, patients reported their visual field improved in the following proportions: one of the six subjects tested with Humphrey visual field, three of six patients tested with the Nine Sector test, and four of six patients reporting subjective impressions of their visual field.²²

The single Argus II study to examine this outcome tested the Goldmann visual field and found all of the patients improved with the system in OFF mode at the 12-month followup compared to pre-implantation.⁷⁸

See Figure 5 for a plot of the data on the proportion of patients whose visual field testing improved when comparing ON to OFF or comparing before-implantation to after-implantation. Additional details are provided in Table C-14 in Appendix C.

Figure 5. Visual field: proportion of patients improved



Proportion of patients who experienced any improvement with RPS ON

Note: Each filled circle shows the proportion of patients who experienced any improvement with RPS ON, and the horizontal bar shows the 95% confidence interval around the proportion. ASR=Artificial Silicon Retina; RPS=retinal prosthesis system

Color Vision

One of the 11 studies reported color vision. Chow et al. reported that one of the six patients who received the ASR implant device improved on the pseudoisochromatic test plates. The improved patient could correctly identify blue and orange dots on the control isochromatic plate and red and green dots on the test plate in the operated eye. This same patient reported that he gained the ability to detect colors in the environment (e.g., red and white of stop signs, green and white of street signs) after implantation. When the unoperated eye was tested, no patient could perceive or discriminate color.²² Additional details are provided in Table C-15 in Appendix C.

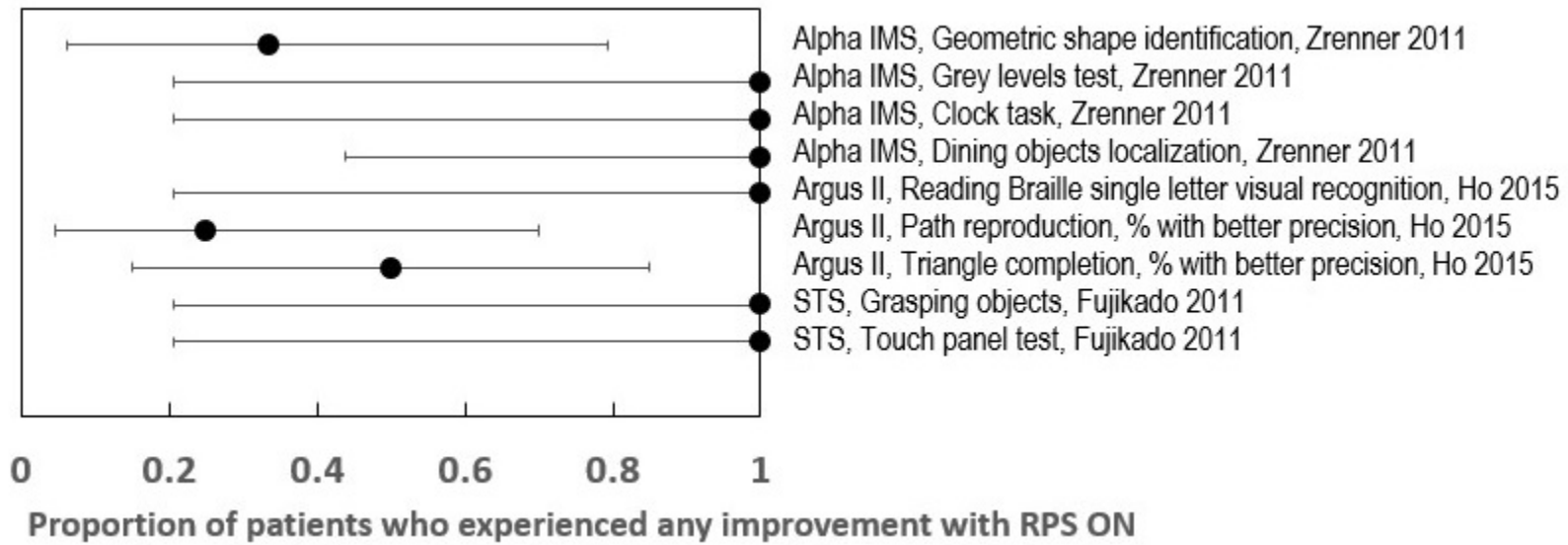
Laboratory-based Visual Performance Measures

Six of the 11 studies reported some measure of laboratory-based visual performance measures. The ability to grasp an object was measured by two studies.^{15,23,30,67-75} Only one patient in the Fujikado et al. study of the Suprachoroidal Transretinal Stimulation (STS) device performed this test and outperformed chance with the system in ON mode but failed when the system was in OFF mode. Subjects in the Ho et al. study of Argus II also performed significantly better when the device was in ON mode versus OFF mode. Multiple authors reporting on three studies reported patient performance on a mobility course.^{15,30,67-75,78,80,81} The Chow et al. extension study of the ASR device found no differences in patient performance of this task in the pre- versus post-implantation period. The Ho et al. study of Argus II found patients performed the Meandering Maze Test significantly better with the device in the ON mode, but results were mixed for other similar tests, including the Triangle Path and Path Reproduction Test. The Rizzo et al. study, also of the Argus II device, found all patients able to perform the task in the postoperative period. Two studies, both testing the Alpha IMS device, reported patients' abilities to recognize shades of gray.^{14,63,64} Only one patient in the Zrenner et al. study completed this test and that person passed with the system in ON mode but failed when it was turned to OFF. Stingl et al. also found patients performed significantly better with the system ON than OFF. Two studies, both reporting on the Alpha IMS device, reported the ability of patients to read a clock.^{14,63,64} Stingl et al. found no significant benefit to having the device in ON versus OFF mode, while the one patient tested in the Zrenner et al. study passed when the system was ON but failed when it was turned OFF. These same two studies of Alpha IMS also reported the ability of patients to recognize geometric shapes and flatware.^{14,63,64} Again, patients passed the test with the system in ON mode but failed when it was turned to OFF. They also did significantly better when the system was ON versus OFF in the Stingl et al. study but only for the first few months, after which no statistically significant difference was noted. All other laboratory-based visual performance measures were either reported by a single study or the tests performed did not seem to have been conducted in the same way across studies.

Examining the Argus II studies separately, Ho et al. found subjects performed significantly better when the device was in ON mode versus OFF mode. For mobility course tests, the Ho et al. study found patients performed the Meandering Maze Test significantly better with the device in the ON mode, but results were mixed for other similar tests, including the Triangle Path and Path Reproduction Test. The Rizzo et al. study found all patients able to perform the task in the postoperative period.

See Figure 6 for a plot of the data on the proportion of patients whose laboratory-based function improved when comparing ON to OFF or comparing before-implantation to after-implantation. See also Table C-16 of Appendix C for more detailed outcomes data.

Figure 6. Laboratory-based visual performance measures: proportion of patients improved



Note: Each filled circle shows the proportion of patients who experienced any improvement with RPS ON, and the horizontal bar shows the 95% confidence interval around the proportion. RPS=retinal prosthesis system; STS=Suprachoroidal Transretinal Stimulation

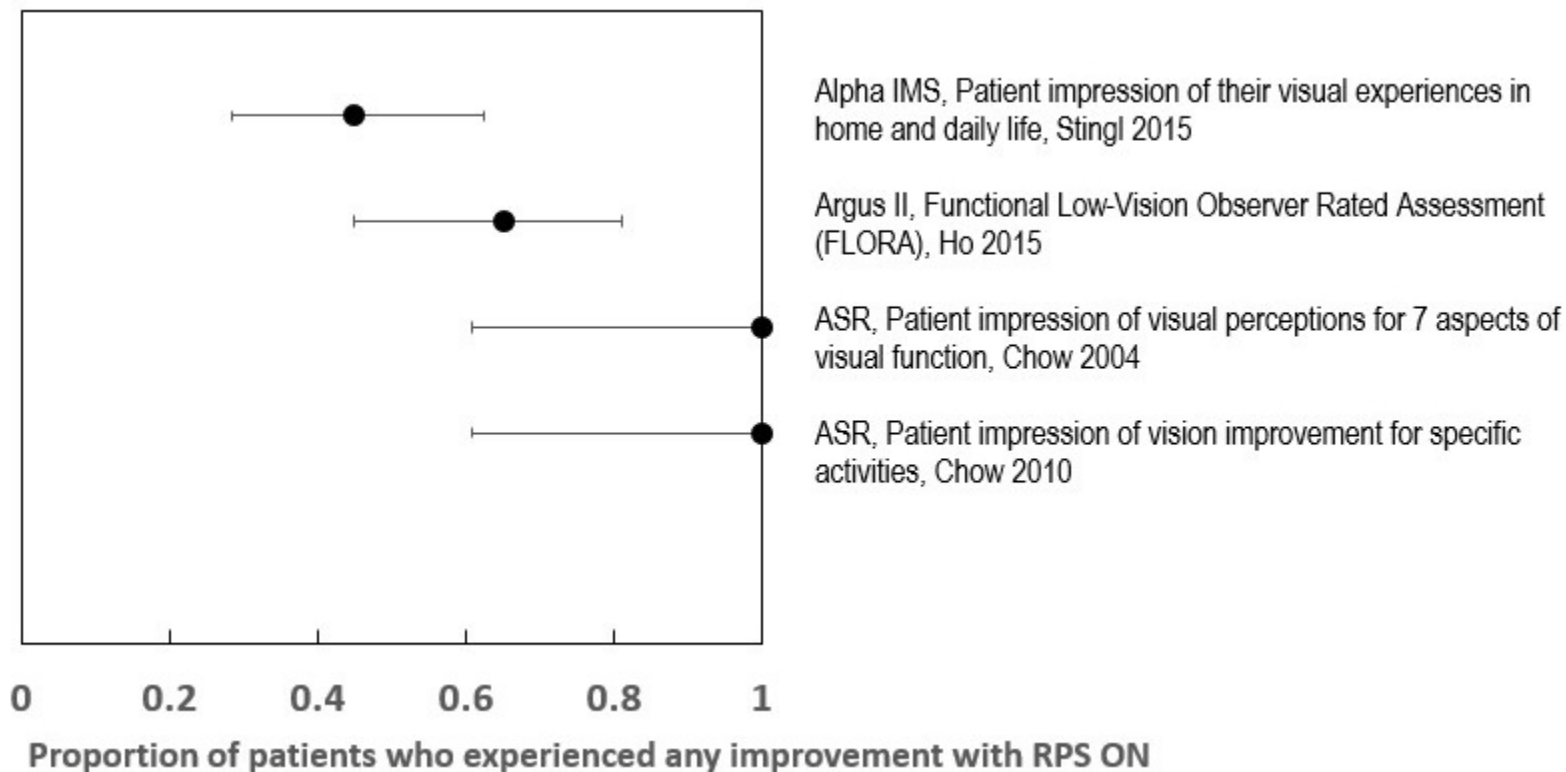
Day-to-Day Function

Four studies out of 11 reported on measures of day-to-day function. Chow et al. asked patients to rate their subjective impression of their visual acuity by comparing their eye implanted with the ASR device to the nonimplanted eye and reported that all six patients reported better vision in the implanted eye.²² The Chow et al. extension study also had patients subjectively rate their visual acuity in the implanted eye, but the comparator was to their memory of preimplantation visual acuity. This study also found that all six patients improved.^{80,81} Stingl et al. asked patients in whom Alpha IMS device was implanted if it was useful, a little useful, or not useful in their daily life. Of the 29 patients enrolled, 13 described the device as useful, and 8 patients each described it as a little useful or not useful.^{63,64}

The final study to report day-to-day function was by Ho et al. and was the only study of Argus II to report this outcome. Ho et al. reported day-to-day function with the FLORA test, which was administered at 1 and 3 years after implantation.^{15,30,67-72,74,75} Low vision specialists interviewed subjects using FLORA about their functional vision performance on day-to-day tasks compared with how they remembered their functioning before implantation. Low vision specialists also observed subjects functioning and rated the effect of the Argus II System on their lives. At the 1-year followup, 80 percent were rated as having received a positive or mild positive benefit, 20 percent experienced a neutral effect or self-reported functional benefits in the past that could not be demonstrated at the time of observation, and none were judged as having received a negative effect. A similar pattern emerged at the 3-year followup visit, but with only 65 percent of patients rated as having received a positive or mild positive effect from the system. Additionally, all patients did significantly better with the System ON in the day-to-day function subcategories of visual orientation, mobility, and interactions with others. For most tasks in the daily life subcategory, patients did better with the System ON, but for a few tasks, they performed better with the System OFF.

See Figure 7 for a plot of the data on the proportion of patients whose daily function improved when comparing ON to OFF or comparing before-implantation to after-implantation. See also Table C-17 in Appendix C for more detailed outcomes data.

Figure 7. Day-to-day function: proportion of patients improved



Note: Each filled circle shows the proportion of patients who experienced any improvement with RPS ON, and the horizontal bar shows the 95% confidence interval around the proportion. ASR=Artificial Silicon Retina; RPS=retinal prosthesis system

Quality of Life

One study out of 11 included data on quality of life. Klauke et al. administered the German version of the NEI-VFQ-25 to six patients who had received the EPIRET3, before implantation and at the 3-week, 6-month, and 27- to 29-month after-implantation visits. Patients underwent planned device explantation after 1 month. Klauke et al. and other authors found no statistically significant difference in quality of life for the six patients at 3 weeks after implantation of the EPIRET3 compared to baseline. Repeat measurements at 5 months and at 26 to 28 months after explanation also showed no significant change.⁸²⁻⁸⁶

Strength of Evidence

Table 6 below shows our ratings of the strength of evidence and each domain that contributed to it.

We rated the strength of evidence for visual field, laboratory-based visual performance measures, and quality of life as Moderate and visual function, visual acuity and day-to-day function as High. In cases in which half of the studies received a study-limitation rating of Moderate and the other half a rating of High, we rated that domain as Moderate. For individual study ratings, to receive a rating of Low, studies needed to have a “Yes” response for the first five risk-of-bias items (confounder controlling, concurrent intervention controlling, intervention protocol fidelity, attrition handled appropriately, and outcome assessor blinding). For a rating of Moderate, studies needed at least three “Yes” responses on risk-of-bias items 1 through 5 and a “Not Reported” or “Yes” on items 6 and 7. All other studies were rated High risk of bias. See Appendix C, Table C-20 through Table C-25 for our assessment on each item for each study.

We considered all outcomes reported to be Direct because the patients enrolled in these studies had diagnoses (e.g., RP, choroideremia) and visual acuities (e.g., light perception, hand motion) that met the U.S. Food and Drug Administration (FDA) requirements or European requirements for implantation with an RPS and because the comparators evaluated (e.g., system ON vs. OFF) are appropriate choices, given that no other treatments are available for this patient population.

We rated all outcomes as Inconsistent and Imprecise because although some patients clearly benefit from these devices, the percentage who benefit is highly variable across studies for any given outcome and the number of patients enrolled was small (≤ 30 patients).

We did not detect any evidence of reporting bias for any outcome. We made this determination by looking for studies reported at the National Clinical Trials ([ClinicalTrials.gov](https://clinicaltrials.gov)) registry that should have been completed and published but for which we could not find a publication. No instances of that were found. See Appendix C, Table C-27 through Table C-34.

Overall, for all outcomes assessed, the evidence bases were found to be insufficient to estimate the proportion of patients who would benefit from RPS.

Table 6. Strength of evidence for effectiveness of retinal prosthesis systems for retinitis pigmentosa for each outcome

Strength of Evidence Domain	Visual function	Visual Acuity	Visual Field	Laboratory-based Visual Performance Measures	Day-to-day Function	Quality of Life ^a
Study limitations	High	High	Moderate	Moderate	High	Moderate
Directness	Direct	Direct	Direct	Direct	Direct	Direct

Table 6. Strength of evidence for effectiveness of retinal prosthesis systems for retinitis pigmentosa for each outcome (continued)

Strength of Evidence Domain	Visual function	Visual Acuity	Visual Field	Laboratory-based Visual Performance Measures	Day-to-day Function	Quality of Life ^a
Consistency	Inconsistent	Inconsistent	Inconsistent	Inconsistent	Inconsistent	Inconsistent
Precision	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise	Imprecise
Reporting bias	Undetected	Undetected	Undetected	Undetected	Undetected	Undetected
Strength-of-evidence rating	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient	Insufficient

^aQuality of life measurement in the single study measuring it was used to detect adverse consequences following device explantation.

Key Question 3. RPSs to Arrest the Progression of Retinitis Pigmentosa

Description of Included Studies

Of the 11 included studies of RPS devices for KQ1A and KQ2, the two Chow et al. studies^{22,80} of the ASR and the Rizzo et al. study of Argus II reported the neuroprotective effects of device implantation. “It should be noted that the focus of RPS devices is to provide some degree of visual perception to patients whose severe RP indications otherwise render them functionally blind. No rigorous scientific clinical studies on humans with RPS have investigated operational aspects attendant to halting disease progression.”⁹⁸ For details about these studies, see tables in Appendix C.

Key Points

- Limited evidence has been interpreted as possibly indicating that implanted RPS devices may arrest RP progression. Patients in whom the Argus II was implanted for 12 months experienced improved visual fields even when the system was in OFF mode.
- Evidence from animal studies has suggested a possible neuroprotective effect from electrical stimulation of the retina, mediated through induction of certain growth factors.
 - Electroretinographic waveforms in rat eyes with an active implant experienced temporary preservation compared with unoperated rat eyes through 6–7 weeks of followup.
 - Electroretinographic b-waves were significantly larger in rat eyes with active implants versus rat eyes without active implants at the 4- to 6-week followup.
 - Rat eyes with and without active implants were similar on electroretinographic a-waves.
 - Rat eyes with active implants had four to six rows of photoreceptors compared with a single sparse layer of photoreceptor cells in unoperated eyes 8 weeks after implantation.
 - Photoreceptor preservation occurred in all rat eyes that received an implant, even if it was an inactive implant.
 - Growth factor expression of fibroblast growth factor 2 (Fgf2) was significantly higher in rat eyes with active implants by postoperative day 9 compared with eyes with

- minimally active implants, eyes that underwent sham surgery, and unoperated eyes, and a dose-response relationship was evident.
- Rat eyes with active implants and those without an active implant were similar on growth factor expression of fibroblast growth factor 1 (Fgf1), ciliary neurotrophic factor (Cntf), insulin-like growth factor (Igf), glial cell line-derived neurotrophic factor (Gdnf), and brain-derived neurotrophic factor (Bdnf).

Detailed Synthesis

Of the 11 included studies of RPS devices for KQ1A and KQ2, the two Chow et al. studies^{22,80} of the ASR device and the Rizzo et al. study of Argus II⁷⁸ reported apparent neuroprotective effects of device implantation. In the Chow et al. extension study,⁸⁰ investigators completed two studies on Royal College of Surgeons (RCS) rats with a genetic mutation that causes photoreceptor loss starting at 12 days of age and ending by 77 days of age. They also conducted a cadaver study on one human patient with RP who had been implanted with the ASR device for 5 years before dying of natural causes.

The ASR device containing 5,000 microelectrode-tipped microphotodiodes was implanted in the superior to superior temporal retina, stimulating a small portion of the retina. Chow et al.²² noted that visual fields distant from the implant, including the macular region and far peripheral field regions, were improved from about 1 week to 2 months after implantation, and these improvements were maintained at 6–12 months postoperatively. They theorize that patients' experiences of complex visual capabilities including improved contrast, color, resolution, movement, and visual field size are the result of low-level electrical stimulation inducing up-regulation of protective neurotrophic factors. This up-regulation, in turn, improves the functioning of remaining photoreceptors. To support this hypothesis, they note that patients' improvements were not immediate after implantation but took weeks to 2 months to take effect. They also note that patients with better baseline vision, or more viable retinas, experienced greater gains from the implant than those with worse preoperative vision.²²

In the Chow et al. extension study,⁸⁰ RCS rats were implanted subretinally at postnatal age 3 weeks with either active or inactive ASR chips, or underwent sham surgery or no surgery. Fifteen rats were studied. Thirteen were implanted with active devices in the right eye and the left eye was either implanted with an inactive implant, had sham surgery, or had no surgery. Two of the 15 rats served as unoperated controls. Cage luminance was controlled. Implants used in this study were similar to those used in humans but modified for use in animals. Electroretinographic (ERG) recordings were performed weekly for 8 weeks after surgery, and then the animals were sacrificed.

ERG waveforms on unoperated rats demonstrated a rapid drop over the 8-week followup period while rats with an active implant experienced a temporary preservation of ERG waveforms, most notable at 4–7 weeks after implantation. At the 6-week followup, ERG amplitudes were four times greater in the rats with an active implant than in those without; however, this difference was no longer significant by the final followup at week 8. ERG b-wave responses were similar across groups at the 2-week followup, with the exception of the inactive implant group, whose b-waves were significantly smaller. By weeks 4 and 6, rats with the active implant had significantly larger b-waves than the other three groups, but this difference disappeared at week 8.⁸⁰

Histologic examination of the rats' eyes showed a single sparse layer of photoreceptor cells in unoperated eyes compared to four to six rows of photoreceptor cells in active implant eyes.

However, in rats with an active implant in one eye and an inactive implant in the other eye, photoreceptor preservation occurred over both implants. The two eyes were indistinguishable in terms of morphologic preservation, but this did not result in functional preservation as measured by ERG. Only the superior region of the retina near the implant experienced this morphologic preservation.⁸⁰

The second of the Chow et al. extension studies was designed to measure growth factor expression of Fgf2 and was composed of the same four arms as the first study, with the exception that inactive implants are referred to as “minimally electrically active implants.” By week 4, the active implant group demonstrated significantly larger dark-adapted and light-adapted ERG b-waves than the control and minimally active implant groups. No group differences were noted in a-wave amplitudes.⁸⁰

At day 9, Fgf2 expression was significantly elevated in the active implant eyes compared with all other eyes, and there appeared to be a dose-response relationship (i.e., higher to lower Fgf2 expression in the active, minimally active, sham, and unoperated groups). At 30 days after implantation, the active implant eyes still had significantly greater expression of Fgf2 than the other three treatment arms, but Fgf2 expression was slightly lower than at postoperative day 9. This finding suggests that subretinal electrical stimulation from an implant confers benefit over and above the presence of nonactive chip placement or the surgical procedure alone. No between-group differences were observed in Fgf1, Cntf, Igf, Gdnf, or Bdnf.⁸⁰

Before his death, the RP patient in the cadaver study reported subjective improvements after ASR implantation, but these subjective impressions did not correlate with objective tests. Chow et al. attributed this lack of correlation to insensitivity of the objective tests. Upon death, the man’s eyes were enucleated within 10 minutes and examined. Both retinas appeared to be in late stages of photoreceptor degeneration, with massive reorganization and remodeling. However, in the area over and in close proximity to the implant, the retina maintained some inner nuclear layer cells and inner plexiform layer structure. This pattern was not observed in the man’s unimplanted eye. Compared with other retinal regions, both eyes showed a thicker fibrous glial cell layer on the inner side of the retina and around the implant, indicating substantial remodeling.⁸⁰

Rizzo et al. found that compared to preimplantation, all six patients in whom the Argus II was implanted for 12 months experienced an improvement in their visual field when tested with the Goldmann visual field test. The authors did not present visual field test results with the System in ON mode.⁷⁸

Key Question 4. Adverse Events of RPSs

Description of Included Studies

Of the 11 studies included for KQ2, 10 reported adverse events (the only exception was Chow et al. 2010 and Geruschat et al. 2013 reports on the extension study).^{80,81} The reported adverse event data appear in Table C-26 of Appendix C.

Key Points

- Intraoperative adverse events occurred in more than half of studies reporting this outcome, with trauma to the optic nerve being the most serious.

- Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure (IOP) increase, eye scratchiness, and eye-movement restrictions.
- Intraoperative explantation adverse events were reported in two-thirds of the studies reporting this outcome, the most serious being a central retinal defect caused by removal of loose tacks.
- Post-explantation adverse events were reported by two-thirds of the studies reporting this outcome, with the most serious events including a decrease in visual acuity and a retinal detachment.
- Serious adverse events were reported by just under half of the studies reporting this outcome and included IOP increase, hypotony, and presumed endophthalmitis.
- Device-related adverse events were reported by more than a third of studies reporting this outcome and included device failure and need for retacking.
- Adverse events at the long-term followup were reported by just over half of studies reporting this outcome and were varied.

Detailed Synthesis

Device implantation intraoperative adverse events were reported by six studies.^{14,18,63,64,75,77,78,82-86} Two studies indicated no intraoperative events.^{18,82-86} One study each reported subretinal bleeding with complete reabsorption by day 10 in one patient,¹⁴ device malfunction associated with optic disc swelling due to trauma to the optic nerve in one patient,^{63,64} and touching and pulling of the ciliary body in one patient.⁷⁸

Five studies reported the occurrence of adverse events in the post-implantation period. Klauke et al. and other authors found a mild inflammatory response in two patients, a significant inflammatory response with a painless hypopyon without chemosis in one patient, and hypotony with a flat anterior chamber, inflammation, and epiretinal proliferation at the central tack in one patient.⁸²⁻⁸⁶ All three patients in the study conducted by Ayton et al. experienced a subretinal hemorrhage, pain, and mild inflammation while one patient each experienced eye-movement limitations and a staphylococcus infection.¹⁸ Both patients in the study conducted by Fujikado et al. also experienced eye-movement restriction.²³ Chow et al. reported that several patients experienced eye scratchiness, three patients had elevated IOP, and one patient each had aniseikonia (image in one eye differs in size and shape from the image seen by the other eye) and syneresis (floaters).²² Rizzo et al. also found elevated IOP in one patient and a choroidal detachment in one patient.⁷⁸

Intraoperative explantation adverse events were reported in three studies. Klauke et al. and other authors reported two patients with loose tacks requiring removal, which led to a central retinal defect in one of these patients;⁸²⁻⁸⁶ Zrenner et al. reported one patient with a mild skin infection of the retroauricular cable exit;¹⁴ and Fujikado et al.²³ found no intraoperative adverse events during explantation surgery.

Post-explantation adverse events were reported in three studies. Klauke et al. and other authors found mild epiretinal gliosis formation at the tack fixation site in four patients and a temporary decrease in visual acuity in one patient through the 6-month followup visit.⁸²⁻⁸⁶ Stingl et al. reported a retinal detachment immediately after explantation, which was treated surgically and resolved with local retinal fibrotic changes in one patient.^{63,64} Fujikado et al.²³ reported no post-explantation adverse events.

Five investigators categorized adverse events as serious or nonserious and did not tie those events to a specific followup time. Arevalo et al.,^{65,66} Zrenner et al.,¹⁴ and Rizzo et al.⁷⁸ reported that no serious adverse events occurred throughout the study period. Stingl et al.^{63,64} reported IOP elevation to 46 mm Hg in one patient, which was treated without sequel. Ho et al. and other authors^{15,30,67-74} reported subconjunctival erosion and hypotony in four patients, conjunctival dehiscence and presumed endophthalmitis in three patients, and corneal opacity, rhegmatogenous retinal detachment, tractional and serous retinal detachment, retinal tear, uveitis, infective uveitis, and corneal melt in one patient each. Ho et al. reported that most serious adverse events occurred within the first 6 months after implantation and those that occurred more than 1 year after implantation were “part of a cascade of events that had begun earlier.”

Seven investigators reported the incidence of device-related adverse events. Arevalo et al.,^{65,66} Ayton et al.,¹⁸ Chow et al.,²² and Rizzo et al.⁷⁸ reported that no device-related events occurred throughout the study followup period. Stingl et al.^{63,64} reported that an unspecified number of patients experienced infraorbital cable-part breaks due to stress from eye movements and one patient each experienced a device technical failure, retinal perfusion overlying the device, and retinal edema leading to device failure. Ho et al. and other authors^{15,30,67-75} reported that seven patients elected to have revision surgery, two patients required retacking, and one patient experienced fibrosis around the tack, but no device failures occurred. Through an average of 6.2 years of followup, 24 patients still had functioning devices. Seider and Hahn reported that one patient experienced tack malrotation and speculated that the patient’s previously unrecognized posterior staphyloma made this adverse event more likely.⁷⁷

The occurrence of adverse events over the course of long-term followup (>6 months) was reported by five investigators. Klauke et al. and other authors⁸²⁻⁸⁶ reported nonprogressive gliosis in four patients, slightly reduced visual acuity (in one case in association with retinal tack removal) in two patients, conjunctivitis in one patient, and an inflammatory reaction due to corneal sutures in one patient. Arevalo et al.^{65,66} reported edema in two patients, and elevated IOP, pain, suture irritation, and conjunctival erosion in one patient each over the approximate 1.5-year followup period. Ho et al. and other authors reported a long list of nonserious adverse events through the 3-year followup, with most occurring within the first year after implantation.^{15,30,67-74} The most common events included epiretinal membrane in 11 patients, conjunctival congestion in 10 patients, ocular pain in 9 patients, hypotony in 7 patients, suture irritation and choroidal detachment in 6 patients, and uveitis and macular edema in 5 patients. Additionally, both patients who received the Argus II implant and subsequently had a magnetic resonance imaging (MRI) scan experienced local moderate paramagnetic artifacts approximately 50×50 mm that precluded clear visualization of the intraorbital space near the implant. Chow et al.^{22,79} and Rizzo et al.⁷⁸ found no adverse events at their studies’ final followup visits, which occurred 6–18 months after implantation for 5 patients and 10 years for 1 patient for Chow and at 12 months for Rizzo.

Studies using the subretinal approach (ASR^{22,79} and Alpha IMS^{14,63,64} implanted in 38 patients total) reported the following adverse events: elevated IOP (3), aniseikonia (1), mild skin infection (1), subretinal bleeding that resolved quickly (1), syneresis of images seen in the implanted eye (1), and scratchiness (NR). The epiretinal approach (Argus II^{15,30,67-76} and EPIRET⁸²⁻⁸⁶ implanted in 53 patients total) reported a larger variety of adverse events, including a large number of events classified as serious, including a central retinal defect, hypotony, presumed endophthalmitis, conjunctival erosion and dehiscence, corneal opacity, retinal detachment and tear, corneal melt, uveitis, and enucleation.

Key Question 5A. Off-label use of RPSs

Description of Included Studies

We identified a single ongoing clinical trial of Argus II in severely sight-impaired patients with advanced dry AMD that is due to be completed in June 2019. We also identified two relevant press releases.

Key Points

- One clinical trial of Argus II in patients with advanced dry AMD is ongoing.

Detailed Synthesis

For the Argus II, the FDA indication is “for use in patients with severe to profound retinitis pigmentosa who meet the following criteria:

- Adults, age 25 years or older.
- Bare light or no light perception in both eyes. (If the patient has no residual light perception, then evidence of intact inner layer retina function must be confirmed.)
- Previous history of useful form vision.
- Aphakic or pseudophakic. (If the patient is phakic prior to implant, the natural lens will be removed during the implant procedure.)
- Patients who are willing and able to receive the recommended post-implant clinical followup, device fitting, and visual rehabilitation.”

In Europe, the device is approved for use in patients with slightly better, hand motion vision,⁹⁹ and can be used in patients 18 years of age or older, based on patient recruitment at sites outside the United States.

Numerous reviews have suggested that patients with advanced AMD may be candidates for retinal prostheses and, outside of investigational studies, this would be an off-label use, according to FDA criteria. No completed studies in AMD have been identified, but one clinical trial is under way. See Table C-27.

One news release from November 2015 indicated that both Pixium Vision and Second Sight are developing next-generation products to target AMD.¹⁰⁰ A 2015 press release of the American Society of Retina Specialists quotes one Argus II investigator suggesting that the company may explore the use of Argus II or another similar RPS in patients with a retinal detachment, whose retina has been reattached but whose vision has not been restored to an acceptable level.⁹⁹

Key Question 5B. Other Uses of RPSs

We did not identify any information to address the use of RPSs for nonvisual uses. As noted above, one trial is ongoing, testing the Argus II device in patients diagnosed with dry AMD which, outside of an investigational trial, would be an off-label use ([NCT02227498](#)).

Other visual uses of RPSs include modifying the Argus II device for use as a cortical implant, Orion I (Second Sight, Sylmar, CA, USA), with human trials planned to commence in 2017.¹⁰¹

Discussion

Key Findings and Strength of Evidence

The retinal prosthesis system (RPS) studies assessed in this review reported 74 different outcomes, mostly dealing with visual function (31 percent), visual acuity (26 percent), or laboratory-based visual performance measures (30 percent). Day-to-day visual function and quality of life were rarely measured. Little consensus exists among authors of RPS studies about which specific measures are important.

There is some evidence for the validity and/or reliability of the Early Treatment of Diabetic Retinopathy Study (ETDRS), Grating Acuity Test (GAT), Chow Color Test (CCT), and Functional Low-Vision Observer Rated Assessment (FLORA). No included evidence on patients with very low vision addressed the validity or reliability of other outcomes reported in the RPS studies.

Future RPS studies should consider measuring the following outcomes because some evidence shows that they are valid and/or reliable measures in patients with visual acuity 20/200 or worse: full-field flash test (also known as the full field stimulus test), Grating Contrast Sensitivity (GCS), the patient and clinician version of the Functional Assessment of Self-Reliance on Tasks (FAST) instrument, the Very Low Vision Instrumental Activities of Daily Living (IADL-VLV), the Modified National Eye Institute Visual Function Questionnaire 25-item (NEI-VFQ-25) plus supplement, and the Modified Impact of Vision Impairment (IVI).

The table below provides a detailed comparison of the visual acuities of patients assessed in the validation studies compared with the patients enrolled in RPS studies. Three measures in particular have been tested in patients with ultra-low vision. FLORA was tested in a majority of patients enrolled in the Argus II multicenter trial so its applicability to patients implanted with an RPS has been established. The Modified Impact of Vision Impairment Questionnaire and Very Low Vision Instrumental Activities of Daily Living were both tested in patients with Count Finger vision so they are also applicable to this population. The other measures were tested in patients with low but better vision than the typical RPS recipient. However, they represent the best instruments available at this time for measuring other outcomes important to patients receiving an RPS.

Table 7. Baseline vision in the validation studies by baseline vision in the RPS studies

Validation Study Baseline Visual Acuity Instrument(s) Tested	RPS Study and Baseline Visual Acuity
Geruschat et al. 2015 ³¹ Enrolled a majority (26/30) of Argus II subjects from the multicenter trial so vision was similar to that reported by Ho and colleagues 29 Bare LP in both eyes, 1 No LP FLORA	Arevalo et al. 2015 ^{65,66} Argus II 7 LP, 1 L projection
Bittner et al. 2011 ⁸⁹ 32 of 40 eyes met the criteria for legal blindness, best corrected visual acuity 20/200 or worse in the better eye, and/or visual field diameter 20 degrees or less. Grating Acuity Test, ETDRS Visual Acuity, Grating Contrast Sensitivity	Ho et al. 2015 and other authors ^{15,30,67-76} Argus II 29 Bare LP in both eyes, 1 No LP

Table 7. Baseline vision in the validation studies by baseline vision in the RPS studies (continued)

Validation Study Baseline Visual Acuity Instrument(s) Tested	RPS Study and Baseline Visual Acuity
Chow et al. 2010 ⁸⁰ 17 Mean 1.29 logMAR (range 0.32 to 2.0) Grating Acuity Test and Chow Color Test	Seider and Hahn 2015 ⁷⁷ Argus II 1 Bare LP
Kiser et al. 2005 ⁹⁰ 78 subjects in total. Patients with RP were divided into 3 groups of visual acuity (RP-I had VA better than 20/40 [4 patients]; RP-II had VA between 20/40 and 20/199 [12 patients]; RP-III had VA between 20/200 and 20/1000 [10 patients]). Patients with MD were divided into 2 groups of visual acuity (MD-I had VA between 20/200 and 20/500 [8 patients], and MD-II had VA worse than 20/500 [8 patients]). The other 3 patient groups (ON, OR, DR) all had VA worse than 20/200. 18 had normal vision 20/25 or better (control group) ETDRS Visual Acuity	Stingl et al. 2015, 2013 ^{63,64} Alpha IMS 20 LP without projection, 9 No LP
Finger et al. 2014 ⁹⁶ 201 patients total. 22% had between 20/200 and counting fingers; 63% had between counting fingers and light perception; 14% had worse than light perception. Modified Impact of Vision Impairment (IVI) questionnaire	Aytton et al. 2014 ¹⁸ Bionic Vision 3 LP
Finger et al. 2014 ⁹⁴ 40 patients total. Mean 2.3 logMAR (SD 1.0) Very Low Vision Instrumental Activities of Daily Living (IADL-VLV)	Rizzo et al. 2014 ⁷⁸ Argus II 6 Monocular logMAR acuity that was immeasurable and worse than 2.9
McKnight and Babcock-Parziale 2007 ⁹² 81 patients total. Better eye mean logMAR 1.09 FAST (Functional Assessment of Self-Reliance on Tasks), patient-completed and clinician-completed	Fujikado et al. 2011 ²³ STS 2 Bare LP
Roman et al. 2007 ⁹⁷ 61 patients total. "severely blind"; acuity NR Light Perception test: Full Field Flash Test	Klauke et al. 2011 and other authors ⁸²⁻⁸⁶ EPIRET3 4 LP, 1 No LP, 1 HM
Kiser et al. 2006 ⁹¹ 77 patients total. RP patients were divided into 4 groups of visual acuity (RP-I had VA better than 20/40 (8 patients); RP-II had VA between 20/40 and 20/199 (8 patients); RP-III had VA between 20/200 and 20/1000 (12 patients); RP-IV had VA worse than 20/1000 (5 patients)). MD patients were divided into 2 groups of visual acuity (MD-I had VA between 20/200 and 20/500 [12 patients], and MD-II had VA worse than 20/500 [2 patients]). The other 3 patient groups (ON, OR, DR) all had VA worse than 20/200. Light Perception: Full-field flash test	Zrenner et al. 2011 ¹⁴ Alpha IMS 3 Blind (bright light stimulation mediated some limited LP without any recognition of shapes)
Babcock-Parziale et al. 2005 ⁹³ 190 patients total. Better eye mean logMAR 1.3 FAST (Functional Assessment of Self-Reliance on Tasks), clinician-completed	Chow et al. 2010, Geruschat et al. ^{80,81} Extension study ASR 1 CF at 1–2 feet, 1 HM at 4–5 feet, 1 HM at 2–3 feet, 1 HM at 1–2 feet, 1 HM at 5–6 feet, 1 HM at 5 feet
Stelmack et al. 2002 ⁹⁵ 77 patients. Mean 1.00 logMAR Modified NEI-VFQ-25 plus supplement	Chow et al. 2004 ²² ASR At 0.5 m 1 patient (0 letters OD, 0–3 letters OS), 2 patients no letters, 1 patient Bare to No LP, 1 patient HM at 1 foot, 1 patient CF at 1–2 feet

Table 7. Baseline vision in the validation studies by baseline vision in the RPS studies (continued)

CF=counting fingers; DR=diabetic retinopathy; ETDRS=Early Treatment of Diabetic Retinopathy Study test; FLORA=Functional Low-Vision Observer Rated Assessment; HM=hand motion; logMAR=logarithm of the minimum angle of resolution; L=light; LP=light perception; MD=macular degeneration; NR=not reported; OD=*oculus dexter*, right eye; ON=optic neuropathy; OR=other retinal disease; OS=*oculus sinister*, left eye; RP=retinitis pigmentosa; VA= visual acuity

During our interviews with key informants (KIs), particularly patient/advocate KIs, we learned that patients vary in what they expect from a treatment like RPS implantation. Some patients hope to have their sight restored to “normal” vision. Other patients would be satisfied with more modest gains, such as the ability to color coordinate their clothing, use a color-contrast cutting board, or, for those patients with comorbid insulin-dependent diabetes, give themselves insulin injections. With the current state of the technology, both of these expectations may be too high.

One patient who was not a KI but who had a good experience with the Argus II device and commented on our draft report, described his/her experience (the person’s sex was not identified), which may reflect a more realistic expectation of RPS implantation. The patient reported that his/her eye had healed sufficiently after just a few weeks and vision improved instantaneously. This patient reported the following improvements:

- Identified the window where the light was coming from
- Located various items hanging on office walls
- Spotted the left and right sides of a doorway
- In conversation, looked a person squarely in the face (rather than trying to aim his/her eyes toward the voice)
- Saw a fireworks display for the first time in 25 years
- Walked with confidence with a white cane on city streets, avoiding the tables and chairs at sidewalk cafes
- Saw his/her two grandchildren standing before him/her and identified them without needing to hear their voices.¹⁰²

Retinal surgeons performing RPS implantation need to accurately present the full range of likely visual acuity gains—which at this point do not include “normal” vision, color vision, or a level of vision sufficient to allow a diabetic to safely self-administer insulin. Surgeons also need to advise patients of the possibility that they may not benefit from an implant and could possibly lose residual light perception following implantation.

When choosing outcomes to include in future RPS studies, investigators should routinely measure quality of life (QoL) and ability to perform activities of daily living (ADLs) in addition to traditional visual acuity measures because these measures are interrelated. Small gains in any vision measure (acuity, visual field, contrast sensitivity, color vision) has the potential to bring about clinically meaningful changes in patients’ QoL and ability to perform ADLs.

Although some patients clearly experienced improved visual acuity, visual field, and visual function, the percentages varied greatly among studies of Moderate to High risk of bias. Thus, evidence is insufficient to estimate the proportion of patients who will benefit from an RPS.

There is some suggestion, based on both animal and human studies, that RPSs may have a neuroprotective effect that causes at least a temporary increase in vision in areas far away from the implantation site.

Intraoperative adverse events were reported in more than half of all included studies, the most serious of which included injury to the optic nerve and central retinal defect.

Postimplantation adverse events were common and typically mild, including inflammation, temporary intraocular pressure increase, eye scratchiness, and eye-movement restrictions.

Serious adverse events were reported by just under half of the studies reporting this outcome and included intraocular pressure increase, hypotony, and presumed endophthalmitis.

Findings in Relationship to What is Already Known

To assess what is already known about the effectiveness and safety of retinal prostheses for retinitis pigmentosa (RP), we searched for pertinent systematic reviews and cost-effectiveness analyses. We identified one systematic review¹⁰³ and one cost-effectiveness analysis.¹⁰⁴ The cost-effectiveness analysis¹⁰⁴ did not offer an independent analysis of effectiveness or safety, since authors simply used the data from the Argus II study by Ho et al. and by other authors.^{15,30,67-75} The systematic review was conducted by the National Institute for Health and Care Excellence (NICE) in the United Kingdom;¹⁰³ its last search date was December 31, 2014. The review included seven publications, and authors acknowledged that some of the publications may have had overlapping patient populations (they did not attempt to identify a set of unique studies). Regarding efficacy, the authors made no overarching statements about efficacy, but rather made five efficacy statements:

- In a case series of 30 patients implanted with an epiretinal prosthesis, improvements in visual acuity were reported in 23 percent (7 of 30 of patients at follow-up of up to 2.7 years). Visual acuity improved from worse than 2.9 logarithm of the minimum angle of resolution (logMAR) to between 2.9 and 1.6 logMAR (p value not reported).¹⁰³
- In the case series of 30 patients, patients were asked to locate a white square that randomly appeared on a black liquid crystal display (LCD) touchscreen. Significantly better square localization test results were reported in 96 percent (27 of 28) of patients when their prosthesis systems were switched on. No further details were provided.¹⁰³
- 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 percent (16 of 28) of patients when their prosthesis systems were switched on. No further details were provided.¹⁰³
- In the case series of 30 patients, patients were asked to stand in the center of a room, or offset left of center by 3 feet, or offset right of center 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 percent when the prostheses were switched on compared against 5 percent when the prostheses were switched off, at 24- month followup.¹⁰³
- In a case series of 6 patients, the mean percentage of successful grasps of a white cube placed on a black surface was 69 percent when prostheses were switched on compared against 0 percent 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.”¹⁰³

All five statements were about the 30-patient Argus II study by Ho et al., also reported by other authors^{15,30,67-75} (the 6-patient case series was a subset). The above statements merely reiterate the data, with no general synthesis of multiple studies. Similarly, regarding safety, the NICE review¹⁰³ simply reiterated data from the studies. Our review includes all the studies included by the NICE review, and several more. In the absence of other evidence syntheses, and given the recent introduction of this technology, we do not comment further on how our findings compare to what is already known.

Applicability

The patients enrolled in the 11 included RPS publications had RP, choroideremia, rod-cone dystrophy, or Bardet-Biedl syndrome and very low vision (counting fingers to no light perception) and are therefore representative of patients who will receive RPS devices in the future. Because there are no other treatments for patients with late-stage disease, the comparators used in these studies (pre- vs. post-implantation, system ON vs. OFF) were appropriate. One study specified that patients continued to use guide dogs throughout the study and typically underwent cataract removal in conjunction with the implantation procedure.

The maximum duration of study followup was 10 years for one patient with the Artificial Silicon Retina (ASR) device. In the Argus II study, 24 of 30 patients still had functioning devices at a mean of 6.2 years followup. Because patients as young as 25 years of age may receive this device, longer term followup is needed. One single-patient cadaver study suggested that the ASR device had a functional life expectancy of about 20 years.

Outcomes reported in these studies were varied, making cross-study comparisons difficult. Additionally, outcomes were often not measured with valid and/or reliable instruments.

Only a limited number of sites are currently permitted to perform Argus II surgery, but that number will increase over time. As the procedure diffuses more widely outcomes may vary from those at the clinical trial sites, which have received significant training and other resources for surgeons and other personnel involved in caring for the participating patients.

Implications for Clinical and Policy Decisionmaking

Due to inconsistencies in the evidence, this report makes no conclusions about the likelihood of patient benefit from RPS. Clearly, however, some patients do benefit. The magnitude of that benefit is unknown because of a paucity of evidence on QoL and day-to-day function. However, for these patients, no other intervention exists to address their vision problems, so even small gains may be considered important for clinical and policy decisionmaking.

Limitations of the Systematic Review Process

The first set of challenges we faced involved literature searching. Even the best search strategies may fail to identify certain records; however, the chance of missing relevant studies is greatly reduced when searches are conducted, as they were for this report, across multiple resources using a combination of controlled vocabulary and keywords. Also, our information specialists searched the Web sites of selected medical association meetings for abstracts and presentation on retinal prosthetic devices.

Key Question 1C presented a particular search challenge, in that the scope of this question was extremely broad. To focus the search, the search strategies for this question (see Appendix A) included some additional limiting options, such as searching for controlled terms that had been indexed as a major focus of the article, and using additional terminology to identify studies that reported reliability, reproducibility, validity, and responsiveness. An additional bibliographic database, PsycINFO, was also introduced to ensure that relevant studies published in the psychological literature were captured.

Limitations of the Evidence Base

Two key limitations of the evidence base concern heterogeneity of interventions and comparators. First, the 11 studies used six different types of RPSs, and they are in different

phases of development and testing. This means that the tested systems may differ in important ways from future versions. We excluded any systems that are known to be obsolete, in an effort to focus on our efforts on current systems. The only RPS that is cleared for marketing in the United States is the Argus II; therefore, this device's outcomes are likely more relevant to U.S. decisionmakers. Second, different studies used different comparators. Some compared patients' pre-implant performance to their post-implant performance. Others compared post-implant ON performance to post-implant OFF performance. Still others compared an implanted eye to an unimplanted eye (presuming that the patients' two eyes had similar acuity and function before implant, which is often not the case). And still others compared post-implant ON performance to a predefined level of chance performance. The variety of comparators clouded whatever true RPS benefits exist.

Another set of problems concerned the outcomes. We noted large variability in the types of outcomes used by authors in an effort to measure the impact of RPS. For visual acuity alone, 19 different outcomes were found in just 9 studies. Part of the reason for this is that visual acuity is a multifaceted concept. Even for a given acuity test, however, authors often reported data in different ways. The most common method was to report the proportion of patients who improved as compared to pre-implantation. Another method of reporting was to compare the proportion of patients who passed a test before versus after implantation (which differs subtly from the proportion improved, since some patients could pass a test both before and after, and yet still have improved). Other studies reported mean results of tests such as logMAR, the number of seconds to identify letters on a screen, or the total number of letters identified correctly. Furthermore, only four of the reported tests have been tested for psychometric properties (see Key Question 1B). Other tests are available (see Key Question 1C) that have been specifically developed for people with very low vision, and future authors of RPS studies should consider them.

A fourth limitation was the small size of the typical study of RPS. The median study enrollment was six patients. Furthermore, some enrolled patients did not receive all of the post-implantation tests, so the actual number of patients per study with data on certain outcomes was sometimes only one or two. These low counts are reflected in the wide confidence intervals around proportion estimates in figures for Key Question 2, as well as our ratings of imprecision during strength-of-evidence assessment. Granted, RPS is rare, and large studies are impractical. However, large imprecision results in little confidence in any estimate of the proportion of patients who would improve after RPS implantation.

Evidence Gaps

We used Evidence-based Practice Center guidance by Robinson et al.¹⁰⁵ to delineate reasons for the evidence gaps: A. Insufficient or imprecise information; B. Biased information; C. Inconsistency or unknown consistency; D. Not the right information.

The first identified gap is the paucity of direct information about how RPS affects quality of life. Only one of the 11 included RPS studies reported data on a quality-of-life instrument (NEI-VFQ-25-German Version). Authors reported no statistically significant change in QoL at 3 weeks after implantation or during the 2-year study period after planned explantation of the device. This does not mean there was no change, because the study was too small (only 6 patients enrolled, and only 5 at final follow up) to rule out the possibility of a difference, and the instrument, albeit tested in a low-vision population, may not have been sensitive enough to measure change in this ultra-low vision population. We recognize that the other reported

outcomes (visual acuity, laboratory-based measures of function, day-to-day function) may be surrogates for QoL (on the premise that improved acuity will translate into improved quality of life). However, these outcomes are less patient-oriented than QoL itself. The reason for this gap is A: Insufficient or imprecise information.

The second identified gap is the inability to estimate the proportion of patients who improve after RPS implantation. Because studies used different devices, different comparators, and different outcomes (see previous section), there can be no single estimate of the proportion, because all of these aspects will likely affect improvement rates. Even controlling for type of RPS, there was too much outcome heterogeneity to permit an estimate. The reason for this gap is C: Inconsistency.

A fourth gap involved psychometric testing of outcome measures in patients with very low vision (Key Questions 1A and 1B). The studies we found used relatively advanced methods for testing psychometric properties (i.e., Rasch-based analysis, and separation of item difficulty from person ability). Several of these studies had devised new instruments specifically for people with very low vision. The 11 included RPS studies, however, generally did not use these tests (an exception was the Chow et al. studies of the Artificial Silicon Retina,^{22,80,81} which also provided psychometric properties of certain tests). The reason for this gap is D: Not the right information. We encourage greater use of tested instruments in future studies of RPS. With greater consistency of outcome measures, future evidence reviews might be able to estimate the likelihood of improvement after RPS implantation.

A fifth “gap” involves Key Question 5 (off-label uses and other uses of RPS), for which we found one ongoing trial of the Argus II device in patients diagnosed with dry age-related macular degeneration (AMD; NCT02227498). We summarized narrative reviews, and mention a few possible alternate uses. The reason for this gap is A: Insufficient or imprecise information.

Conclusion

Future studies of RPS devices should make an effort to report valid and reliable measures of important outcomes, especially day-to-day function and quality of life using the FLORA, IADL-VLV, and IVI.

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Abbreviations and Acronyms

ADL:	activities of daily living	HRQoL:	health-related quality of life
ADLMS:	activities of daily living mobility and safety	IADL-VLV:	very low vision instrumental activities of daily living
AE:	adverse event	IOP:	intraocular pressure
AFC:	alternative forced choice	IVI:	Modified Impact of Vision Impairment
AHRQ:	Agency for Healthcare Research and Quality	KI:	Key Informant
AMD:	age-related macular degeneration	KQ:	Key Question
ANOVA:	analysis of variance	LCD:	liquid crystal display
AREDS:	Age-Related Eye Disease Study	LED:	light-emitting diode
ARVO:	Association for Research in Vision and Ophthalmology	logMAR:	logarithm of the minimum angle of resolution
ASR:	Artificial Silicon Retina	LP:	light perception
BaLM:	Basic Assessment of Light and Motion (BaLM) test	mm Hg:	millimeters of mercury
CCT:	Chow Color Test	MRI:	magnetic resonance imaging
CF:	counting fingers	NA:	not applicable
CINAHL:	Cumulative Index to Nursing and Allied Health	NEI-VFQ-25:	National Eye Institute Visual Function Questionnaire 25-item
cm:	centimeter	NICE:	National Institute for Health and Care Excellence
CMS:	U.S. Centers for Medicare and Medicaid	NR:	not reported
CNV:	choroidal neovascularization	OD:	<i>oculus dexter</i> ; right eye
COI:	conflict of interest	OS:	<i>oculus sinister</i> ; left eye
COSMIN:	COnsensus-based Standards for the selection of health Measurement Instruments	OUReP:	Okayama University-Type Retinal Prosthesis
CoV:	coefficient of variation	PICOTS:	population, intervention, comparators, outcomes, timing, and setting
CR _{.95} :	coefficient of repeatability	QoL:	quality of life
dB:	decibel	RCS:	Royal College of Surgeons
EPC:	Evidence-based Practice Center	Rng:	range
ERG:	electroretinographic	RP:	retinitis pigmentosa
ETDRS:	Early Treatment of Diabetic Retinopathy Study test	RPE:	retinal pigment epithelium
EWB:	emotional well-being	RPS:	retinal prosthesis system
FAST:	Functional Assessment of Self-Reliance on Tasks	SAE:	serious adverse event
FDA:	U.S. Food and Drug Administration	SD:	standard deviation
FLORA:	Functional Low-Vision Observer Rated Assessment	STS:	Suprachoroidal Transretinal Stimulation
FrACT:	Freiburg Acuity and Contrast Test	UK:	United Kingdom
GA:	geographic atrophy	VA:	Veterans Health Administration
GAT:	Grating Acuity Test	VEGF:	vascular endothelial growth factor
GCS:	Grading Contrast Sensitivity test	VF:	visual field
HM:	hand motion		

