Research Review Disposition of Comments Report

Research Review Title: Retinal Prostheses in the Medicare Population

Draft review available for public comment from May 26, 2016 to June 17, 2016.

Research Review Citation: Fontanarosa J, Treadwell J, Samson, D, VanderBeek BL, Schoelles K. Retinal Prostheses in the Medicare Population No. xx. (Prepared by the ECRI Institute – Penn Medicine Evidence-based Practice Center under Contract No. 290-2015-00005-I). AHRQ Publication No. XX-EHCXXX-EF. Rockville, MD: Agency for Healthcare Research and Quality. Month Year. www.effectivehealthcare.ahrq.gov/reports/final.cfm.

Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #5	Executive Summary	Page 6 line 9: 'halting disease progression' is not typically a goal of RPSs and therefore, it is confusing why it is the objective for this review. I would suggest that the goal of RPSs is to attempt to improve visual functioning. Same comment applies to page 16 (KQ3).	Thank you for this comment. The nominator of this topic requested that we address the ability to halt disease progression (or lack thereof).
KI reviewer #5	Executive Summary	Page 6 line 33: it would be helpful to quantify and report here the prevalence of serious adverse events (same comment for this section at the top of page 17 and page 69, line 11)	Unfortunately, we cannot quantify the SAE as some authors reported events as serious and non-serious and others did not. As many events can be classified as serious or non-serious, we do not believe we have enough detail to classify these events ourselves into these groups.
KI reviewer #5	Executive Summary	Page 6 line 36: Please add/clarify that the Early Treatment of Diabetic Retinopathy Study test is for visual acuity	We made this change as suggested.
KI reviewer #5	Executive Summary	Page 6 line 42: The modified NEI-VFQ-25 plus supplement does not necessarily capture visual function in the appropriate range of patients with very low vision and the Stelmack et al. IOVS 2002 paper showed that only a very few items were responsive to change following rehabilitation, plus none had RP; therefore, I would not advocate for its use in future RPS trials. And for this reason, it is not surprising that the one RPS trial that used it did not find a change (page 19 lines 11-12 and page 76, line 3) and this comment should be added to the text, rather than a potential issue with small sample size. The same is true for modified impact of vision impairment, which was validated by Lamoureux et al. IOVS 2006 in a majority of patients with VA 20/40-20/200, which is not the same population that would be candidates for RPS. Recent conference proceedings will reveal that Dagnelie et al. have validated a PLoVR Ultra low vision questionnaire that was developed for the RPS population with VA worse than 20/500. (same comment applies for page 17 lines 49-51) (also relevant to page 51, line 21 and page 72, lines 24-25)	We understand that the reviewer believes that neither the NEI-VFQ-25 nor the Modified Impact of Vision Impairment (IVI) should be used in future RPS trials. KQ1c addresses "possible" outcome measures, and since we found evidence pertaining to their psychometric properties in patients with very low vision, we still mentioned it. It is true that the pertinent studies did not primarily enroll patients with retinitis pigmentosa. For example, the appendix tables state that the Stelmack study enrolled patients who were "Legally blind, in the BRC program, best corrected visual acuity 20/200 or worse in the better eye, and/or visual field diameter 20 degrees or less as measured by Goldmann perimetry," and about 2/3rd of them had macular degeneration. We look forward to full publication of validation data for the PLoVR Ultra-low vision questionnaire.
KI reviewer #5	Executive Summary	Page 9 line 16: 'peripheral flickering lights' is not entirely correct since RP patients in more advanced stages will experience the flickering lights or photopsia in more central locations (see Bittner et al. IOVS 2011); please correct	We removed the word "peripheral" to acknowledge that the flickering could be either peripheral or central.
KI reviewer #5	Executive Summary	Page 9 line 19: Please add a sentence here to indicate there is a loss of central visual function that occurs in either atypical RP or later stages of RP disease progression	Thank you. We have added this information.

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KI reviewer #5	Executive Summary	Page 9 line 30: please attempt to quantify an estimate for 'rather small' when describing the potentially eligible RP population (may be helpful to use a paper by Grover S et al. Ophthalmology 1999 to determine the proportion of RP patients with very low vision who would be potential RPS candidates)	We added "A paper by Grover in 1999 examined the visual abilities of 982 patients with RP, and about 25% had visual acuity of 20/200 or worse in both eyes.{847093} Many of these patients have more vision than light perception, so they would not meet the FDA indication for the Argus II device (which requires light perception only, or worse)."
KI reviewer #5	Executive Summary	Page 9 line 54: it would be helpful to add the location for the IRIS device (i.e., epiretinal) so that the information provided matches that given for the other RPS devices	We specified that the IRIS device is epiretinal.
KI reviewer #5	Executive Summary	Page 10 line 21: please add that pharmacologic agents such as Cosopt may be used to attempt to maximize visual acuity loss due to cystoid macular edema in RP (in addition to cataract surgery)	We added a sentence "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)."
KI reviewer #5	Executive Summary	Page 12: would it make more sense to use the same 6 domains as in those identified in the data synthesis section instead of the 5 domains identified for KQ1A in figure A; as it is confusing that these do not match	There is a new analytic framework that contains a new list of 7 categories of outcomes. We took reviewers' advice to split "visual acuity" into two categories: "visual function" and "visual acuity"
KI reviewer #5	Executive Summary	Page 12 and page 13 line 56: For the domains in KQ1A and the data sysnthesis section, it would be helpful to clarify if you are including performance measures and/or patient-reported outcomes for the domains of 'day-to-day function', ADLs, IADLs, and visual function.	We added a new category called "laboratory-based visual performance measures," which should clarify this.
KI reviewer #5	Executive Summary	Page 12 note: The Functional Low-vision Observer Rated Assessment is a measure of performed ADLs	In later analyses, we categorized FLORA as a measure of day-to-day function.

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KI reviewer #1	Introduction	Page 6 lines 38 – 47. Surgeons and rehab providers have equivalent programs that support their work. Providers of rehabilitation complete a face to face continuing education program and an experienced therapist attends the first rehabilitation session. And as described an instructional curriculum has been developed. After the 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.	On page 6 of the main document, we modified the paragraph to read as follows: 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]

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KI reviewer #1	Introduction	Page 7 discussed Low Vision Aids and Rehabilitation but not Blind Rehabilitation. When considering alternative treatments, it's important to understand that low vision aids and rehabilitation are only part of the story. The recipients of RPS have been blind for over a decade on average. They utilize blindness skills to accomplish functional tasks rather than low-vision aids such as magnifiers. They walk with a long cane or a guide dog and they read braille or computer software that reads document aloud. Therefore I suggest adding language acknowledging that alternative treatments include blind rehabilitation as part of the process of rehabilitation.	On page 7 of the main document, under Alternative Therapies, we added a short description of Blind Rehabilitation. Thank you for this important piece of information.
KI reviewer #1	Introduction	Page 12 lines 18 – 20. I was a KI and would classify myself as a specialist in low vision and blindness rehabilitation research. I suggest adding this language to the list.	Thank you. We have added your expertise to the list of KI areas of expertise.
KI reviewer #2	Introduction	ES 1, Line 12: The majority of "adjacent support cells" (such as bipolar, horizontal, amacrine, and ganglion cells) are usually not affected. Retinal pigment epithelium cells are affected.	We made the correction. Thank you.
KI reviewer #2	Introduction	ES 1, Line 36: "In the United States, it [AMD] accounts for about half of severe sight loss". However, the number of patients with advanced AMD who could possibly benefit from RPS is small.	Thank you. We made the correction.
KI reviewer #2	Introduction	ES1, line 45-46 and page 2, line 55-57: "Stimulating different parts of the visual pathway, including the visual cortex,7 the optic nerve,8 and the suprachoroidal,9 epiretinal,6 and subretinal5 spaces." The suprachoroidal, epiretinal, and subretinal spaces are not stimulated, it is retina that is stimulated by placing the prosthesis placed in suprachoroidal, epiretinal, and subretinal space.	We modified the sentence. Thank you.
KI reviewer #3	Introduction	Introduction is very good. For specific comments, see attached notes.	Thank you.
KI reviewer #5	Introduction	Page 27: Please add transcorneal electrical stimulation (Schatz et al. IOVS 2011) as a potential therapy for RP currently under further study, which may work similarly to RPS by upregulating neurotrophic factors to improve or maintain visual function	We added "Transcorneal electrical simulation is currently being studied for the treatment of RP."
KI reviewer #5	Introduction	Page 27 line 27: Under gene based therapies, please add info on the Koenekoop et al. Lancet 2015 paper on an oral synthetic retinoid treatment for RPE65 or LRAT mutations that lead to RP (inherited retinal degeneration)	We added "Some cases of RP are due to mutations in the genes RPE65 and/or LRAT, and a 2014 study by Koenekoop administered a seven-day course of oral QLT091001 to 14 enrolled patients with either mutation. After two years, three of 14 had sustained improvements in visual field, and two of 14 had sustained improvements in visual acuity."
KI reviewer #5	Introduction	Page 27 line 54: it is usually not opticians that dispense the low vision devices, but rather the optometrists themselves or low vision therapists	We changed "opticians" to "optometrists or low vision therapists."

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Peer reviewer #1	Introduction	The purpose of undertaking this activity and the significance at the current time for patients and clinicians and policymakers could be expanded upon. The existence of clinical trials for stem cell therapy for RP doesn't seem to have been included as an alternative treatment: https://www.centerwatch.com/clinical-trials/listings/condition/787/retinitis-pigmentosa	We added a section on stem cell therapy and some ongoing clinical trials on this treatment. Thank you.
Peer reviewer #2	Introduction	Introduction outlines background information appropriately. It presents details about RP and AMD as well as the various RPS under development worldwide.	Thank you.
Peer reviewer #3	Introduction	The introduction nicely describes the different retinal prostheses either completed or in development. The two main ocular diseases that have been studied to receive the retinal prostheses for therapy include retinitis pigmentosa and very advanced age-related macular degeneration (AMD). The background information also provided excellent information regarding the current standard of care which was really very limited.	Thank you.
Peer reviewer #4	Introduction	Introduction is well organized and provides a concise background of the target diseases. A large portion of the introduction is dedicated to RPS devices and a table included nicely summarizes the current RPS devices that are clinically relevant. Brief information on each device is included in the table, allowing the reader to quickly learn about the existing technology, compare different methods, and use the table as a convenient reference.	Thank you.

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Public reviewer #5 (Tammy Smith at Spark Therapeutics)	Introduction	To reflect recent developments in the field of gene therapy, Spark Therapeutics recommends revising the ?Gene-based Therapies? discussion to read as follows: Recent landmark clinical trials of investigational RPE65 gene therapy for RPE65-related early onset retinal dystrophy, a form of RP, successfully rescued visual and retinal function in a small group of pediatric and adult patients.42-45 Another (2014) gene therapy trial replaced the CHM gene in a different genetic eye disorder, choroideremia, and similarly found improved visual acuity and retinal sensitivity.46 Positive results were announced in 2015 from the first randomized, controlled Phase 3 gene therapy trial for the treatment of RPE65-mediated inherited retinal dystrophy. The trial demonstrated improvement of functional vision, as measured by the change in bilateral mobility testing between baseline and one year, with no product-related serious adverse events.R1,R2 Data from this same group have also been presented on the durability of effect after three years as measured by mobility testing and full-field light sensitivity threshold testing in a cohort of subjects who participated in a Phase 1 follow-on study.R1,R3 However, a study conducted by another group with a different investigational product in patients with RPE65-related early onset retinal dystrophy showed continued disease progression despite stable visual improvements over 3 years.	We revised the report as follows: Recent landmark clinical trials of RPE65 gene therapy for RPE65-related early onset retinal dystrophy, a form of RP, successfully rescued visual function and improved full-field sensitivity and pupillary light reflex in a small group of pediatric patients.[42-45] Additionally, more recent gene therapy trials in patients with choroideremia[46] and RPE65-mediated inherited retinal dystrophy.[50,51] 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.[47] 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.[48] Second, gene therapy appears to work best at rescuing failing tissue and does not appear be as effective once all function is lost. This would leave those who are currently blind without help and make early diagnosis and treatment imperative, a goal not always easily accomplished.

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Public reviewer #5 (Tammy Smith at Spark Therapeutics)	Introduction	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 RP cases.48 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 only accomplished through broader adoption of genetic testing.	We revised the report as follows: Recent landmark clinical trials of RPE65 gene therapy for RPE65-related early onset retinal dystrophy, a form of RP, successfully rescued visual function and improved full-field sensitivity and pupillary light reflex in a small group of pediatric patients.[42-45] Additionally, more recent gene therapy trials in patients with choroideremia[46] and RPE65-mediated inherited retinal dystrophy.[50,51] 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.[47] 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.[48] Second, gene therapy appears to work best at rescuing failing tissue and does not appear be as effective once all function is lost. This would leave those who are currently blind without help and make early diagnosis and treatment imperative, a goal not always easily accomplished. Thank you for your comment.

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Public reviewer #5 (Tammy Smith at Spark Therapeutics)	Introduction	Added References: (R1): Russell SR, Bennett J, High KA, Chung DC, Wellman JA, Maguire AM. ?Phase 3 Trial of AAV2- hRPE65v2 (SPK-RPE65) to Treat RPE65-Mediated Inherited Retinal Dystrophies (IRDs): Top-line Safety and Efficacy Results?. Abstract presented at The Retina Society Annual Meeting; 10 October 2015, Paris, France. (R2) Maguire AM, Russell SR, Bennett J, Chung DC, Wellman JA, Yu Z, Wittes J, High KA. ?Phase 3 Trial of AAV2-hRPE65v2 (SPK-RPE65) to Treat RPE65-Mediated Inherited Retinal Degenerations?. Abstract presented at the American Academy of Ophthalmology Annual Meeting; 15 November 2015, Las Vegas, NV. (R3) Bennett J, et al. Contralateral-eye administration of AAV2 gene therapy in patients with childhoodonset blindness caused by RPE65 mutations: a follow-on phase 1 trial. 2016 Lancet, in press.	We revised the report as follows: Recent landmark clinical trials of RPE65 gene therapy for RPE65-related early onset retinal dystrophy, a form of RP, successfully rescued visual function and improved full-field sensitivity and pupillary light reflex in a small group of pediatric patients.[42-45] Additionally, more recent gene therapy trials in patients with choroideremia[46] and RPE65-mediated inherited retinal dystrophy.[50,51] 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.[47] 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.[48] Second, gene therapy appears to work best at rescuing failing tissue and does not appear be as effective once all function is lost. This would leave those who are currently blind without help and make early diagnosis and treatment imperative, a goal not always easily accomplished. Thank you. We have added these references.

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KI reviewer #1	Methods	The review period concluded on September 17, 2015 with indications that the literature will be updated prior to final publication. This is important as there is additional literature that will contribute to addressing the key questions. Specifically, in January 2016, Clinical and Experimental Optometry published a manuscript titled: An Analysis of Observer-Rated Functional Vision in Patients Implanted with the Argus II Retinal Prosthesis System at Three Years". This paper is extends the work reported in the paper reviewed in the Technology Assessment (citation #28, a methods paper that demonstrated face validity of the Functional Low-vision Observer Rated Assessment, or FLORA). The new paper reports data that complement the FLORA results reported in citation #27.	We included this publication when the literature search was updated. Thank you for your comment.
KI reviewer #1	Methods	Page 13 describes the process for identifying Gray Literature; however, it does not appear all relevant abstracts and posters from the Association for Research in Vision and Ophthalmology (ARVO), the European Society of Retina Specialists conference (EURETINA) and other similar conferences were included. Perhaps the authors wish to include only peer reviewed papers?	Searches were conducted in EMBASE, which catalogs some conference information. In addition, conference websites for each of the societies mentioned in the protocol (conference proceedings over the past 3 years for the following organizations: the American Academy of Ophthalmology (AAO), the Association for Research in Vision and Ophthalmology (ARVO), the American Society of Retina Specialists (ASRS), and the Retina Society) were also searched. Conference abstracts were used as ancillary information.
KI reviewer #3	Methods	The inclusion and exclusion criteria are appropriate, however, I noted that since the device may help slow the progression of retinal degeneration, it may be worthwhile performing a separate analysis of publications which evaluate patients with less advanced degeneration in their vision. Preserving vision that allows ADLs and IADLs seems it would have greater clinical utility than preserving vision that is almost completely gone.	Thank you for your suggestion. Unfortunately, only three of the included studies reported that the devices may halt disease progression so a separate analysis is not possible given the limited and speculative nature of that data.
Peer reviewer #1	Methods	As noted above, the exclusion of studies that evaluate visual acuity but don't include the psychometric properties could have a difference in the conclusions of the report. Although there was a large number of outcome measures, there didn't seem to be an overall summary of the improvement of patients on these measures, either visual acuity or laboratory function, although there was an acknowledgement that some patients experienced improved visual acuity, visual field and visual function but this varied greatly among studies of moderate to high risk of bias.	Studies were not excluded from KQ1a or KQ2 -4 based on a lack of psychometric property data. Only KQ1b dealt with psychometric properties and required that information to address KQ1b. Based on this and other comments we attempted to separate out the Argus II studies from the other studies in the efficacy evaluation (KQ2).
Peer reviewer #2	Methods	Search strategies are explicitly stated and logical, study evaluation logic is clearly outlined.	Thank you.

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Peer reviewer #3	Methods	The methodology was also well described for these analyses. The inclusion and exclusion of the papers included in these analyses were justified. Although there was such a large number of potential papers for evaluation, only a very select and small number of manuscripts were truly eligible. The statistical analyses were not really applied to these studies. It was not a meta-analyses but clearly just a description of each of the studies. I believe it would be difficult to combine or do meta-analysis because it is really comparing oranges and apples for this subject. Only individual statistics from each of the studies were presented.	We did not feel a meta-analysis was justified in this report for the reasons you cite.
Peer reviewer #4	Methods	Literature search methods and databases chosen for search are outlined in great detail in the report and should capture all relevant papers on the subject of RPS devices. Inclusion of gray literature increases the strength of the analysis. Inclusion and exclusion criteria are well designed and applied to all identified papers. Data synthesis and the categories chosen permit clear analysis of the included manuscripts.	Thank you.
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	Methods	The outcomes mentioned in Key Question (KQ) 1B are designed for patients utilizing native vision and not artificial vision. Although these are validated tests for the visually impaired, they may not be validated for those with artificial vision where a "floor" effect may be observed (Bittner et al).	The purpose of both KQ1b and KQ1c is to determine the extent to which various outcomes have been tested in studies of retinal prostheses and/or in studies of patients with similarly low vision as those with retinitis pigmentosa. Our goal is to identify other measures for use in future RPS research. Whether those outcomes were originally designed to assess artificial or natural vision would not affect our approach to KQ1b or KQ1c.
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	Methods	KQ 1C refers to other possible outcomes measures. However, many of these measures require better vision than light perception. Currently, the only approved RPS in the U.S. requires patients have light perception or worse vision. These outcome measures would not be appropriate and would not reliably measure improvements afforded by artificial vision (ie: Grating Contrast Sensitivity, NEI-VGQ-25, and Functional Assessment of Self-Reliance on Tasks/Veteran's Administration-13). These tests require higher levels of visual function.	We understand the commenter believes that the considered outcomes are invalid for measuring artificial vision. The question is intended to document the data on this issue.
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	Methods	Low vision includes patients with vision up to 20/200 or patients with even better central vision but with constricted visual fields (<20 degrees). Many of the RPS candidates have vision much worse than 20/200. Grouping these patients together functionally would not be accurate. Different tests may be needed depending on the baseline vision.	The goal of this Key Question was to identify possible outcome measures for use in future RPS studies, so we wanted to be more, rather than less, inclusive. Also, the technology may ultimately be modified and used in patients with AMD and their vision may be better than the RP population that currently receive RPS.

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KI reviewer #1	Results	Page 45. I was struck by the analysis of Table 5 on page 45. As a provider of rehabilitation services and as one of the developers of the FLORA, I appreciate that Table 5 scored day-to-day Strength of Evidence so well by comparison to all of the other categories. However the summary table may be painting with too broad a brush and would benefit from some refinement, specifically for laboratory function. My first introduction to the Argus II was observing data collection at Johns Hopkins Wilmer Eye Institute. I personally thought the Second Sight testing was well conceived, carefully administered, and provided high quality data. Experts can argue over which items to measure and how to measure, but WHAT was measured and HOW it was measured by Second Sight is the highest quality of work you will find. Future researchers may be misled upon reading peer reviewed manuscripts on methodology and thinking the conclusions of Table 5 are true for all studies. I don't think that is accurate and would do a dis-service to future researchers. I would recommend some ranking, weighting, or separation of well-designed laboratory measures.	Thank you for your comment. The strength of evidence assessment reflects the body of evidence for RPS effectiveness as measured by the outcome categories.

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KI reviewer #1	Results	Assessments of day-to-day function and quality of life The report concludes that measures of QofL and ADL have not demonstrated “statistical changes in quality of life”. The authors suggest one reason as small sample size. Another reason is a mismatch between the currently available questionnaires and anticipated benefits of the RPS. Basically the questionnaires require a higher level of visual ability than the RPS are capable of providing. For example, the FAST, described on page 33: The major limitation of the FAST is that it is a poor match for this population. As described in the report, it was designed for patients in a low vision clinic.	We recognize that some of the measures identified in this report as being reliable and/or valid were tested in patients with better vision than is typical of candidates for a RPS. However, we wanted to err on the side of being more inclusive, rather than less, in identifying potential measures to be used in future studies of patients with RPS so we set our inclusion criteria as 20/200 or worse visual acuity. We modified page 56 of the main document, Evidence Gaps, to read as follows: " 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."
KI reviewer #1	Results	Key Question 3 discussed RPS to arrest progression of retinitis pigmentosa. The evidence is limited with the leading explanations being primarily physiologic/neurologic. Since the authors are speculating/theorizing I will offer the best explanation from the point of view of rehabilitation may be psychological/experiential. Keep in mind the average years of functional blindness for the Argus II study pt was 15 years, but many still have some perception of light. However these patients have not tried to use/attend to/nor be aware of their minimal visual input for over a decade. Suddenly they receive an implant, participate in extensive and repeated visual testing over a long period of time and re-engage what it means to “see” whether that is with a retinal implant or some remaining native vision. I think this attentional aspect along with continued practice using limited vision is the most likely explanation of what has occurred.	Thank you for this comment.

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KI reviewer #1	Results	Page 43, lines 16-25: the report indicates that in the FLORA, the patients themselves rated the effect of the Argus II System on their daily lives. This is not correct. Expert observers interviewed the patients, assessed their performance on tasks, and then synthesized their findings in a case narrative. An observer then made the ratings based on the case narratives.	We corrected the text to read as follows on page 43 of the main document: "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."
KI reviewer #2	Results	ES9, 54-57: "Some patients hope to have their sight restored to "normal" vision." No patient would ever be promised "normal" vision, as it is not possible. Extensive pre-operative consultations are held with the patient and the family. Also, at least with the current version of RPS, patients could not "give themselves insulin injections." It might be possible in the future, but not with the current technology. I would refrain from using these examples as it might mislead the public of what the RPS is able to provide for the patients.	We included these examples as they came up in the KI-patient interviews. However, we did discuss at length that these results are not possible with the current technology.
KI reviewer #2	Results	ES7, line 19: I found this confusing. It states that "no included studies measured grating visual acuity responsiveness". However, later (page 20, line 13) mentions GAT as one of the visual acuity outcomes used. The following study examined GAT. Please see Ho AC, Humayun MS, Dorn JD, da Cruz L, Dagnelie G, Handa J, Barale PO, Sahel JA, Stanga PE, Hafezi F, Safran AB. Long-term results from an epiretinal prosthesis to restore sight to the blind. Ophthalmology. 2015 Aug 31;122(8):1547-54.	Thank you. "Responsiveness" in this sentence refers to one of the psychometric properties of a test.
KI reviewer #2	Results	ES7, line 22: In regards to FLORA, it states that "no included studies measured its reliability or responsiveness". FLORA was assessed in Argus II RPS. Please see Geruschat, D.R., Richards, T.P., Arditi, A., Cruz, L., Dagnelie, G., Dorn, J.D., Duncan, J.L., Ho, A.C., Olmos de Koo, L.C., Sahel, J.A. and Stanga, P.E., 2016. An analysis of observer-rated functional vision in patients implanted with the Argus II Retinal Prosthesis System at three years. Clinical and Experimental Optometry. 2016 May;99(3):227-32	The face validity, but not reliability or responsiveness, of FLORA was tested, as we reported in the Draft.
KI reviewer #2	Results	ES8- S10: for adverse events, it might be beneficial to add the number of patients who suffered them. For example, a single injury to the optic nerve would have different implications than multiple instances of optic nerve injury.	Adverse events are reported in a variety of ways and the same adverse events are not reported consistently by the included studies. Numbers of patients experiencing each event are reported in the Appendices.
KI reviewer #2	Results	Page 1, line 26: "the photoreceptors, comprising rods and cones" Rods and cones are subtypes of photoreceptors.	We changed this to the photoreceptors, including rods and cones.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #2	Results	Page 3, line 22: "60- electrode stimulating microelectrode array" should be changed to "60- electrode array"	Thank you, We made the change.
KI reviewer #2	Results	Page 6, line 42: United States and Canada	Thank you. We made the correction.
KI reviewer #2	Results	Page 6, regulatory aspects of RPS: Second Sight expert is present at all surgeries and critical post-operative visits.	Thank you. We added that information.
KI reviewer #3	Results	The detail is appropriate, however I found it challenging to review all the tables at the end of the document due to the density of the information contained within.	Thank you for your comment. We try to be thorough in extracting all relevant information.
KI reviewer #4	Results	KQ1A: What outcome measures have been used in studies of RPS? The report does not provide a thorough outcome measure list or evaluate the outcome measures that have been used in retinal prosthesis studies. The report contains the following in a footnote to the figure: "Examples of outcome measures for which psychometric properties have been established or are uncertain could include visual acuity measures such as the Basic Grating Acuity Test and the Freiburg Acuity and Contrast Test. Examples of visual function measures may include the Basic Assessment of Light and Motion and the Functional Low-Vision Observer Rated Assessment" and a list of outcomes (pages 21 – 27). However, many of the tests listed as a visual acuity test are actually light sensitivity, motion, or other tests that do not assess visual acuity. In addition, the cited examples do not adequately describe the field's use or acceptance of different kinds of outcome measures for retinal prosthesis studies. For example, no retinal prosthetic has the technical ability to provide color vision. Finally, there are several working groups that are discussing and evaluating potential outcome measures that should be used in retinal prosthesis studies (e.g., HOVER; Harmonization of Outcomes and Vision Endpoints in Vision Restoration) and it would have been beneficial to interview members of these working groups.	KQ1a lists all outcomes that have been reported in RPS studies, regardless of whether there is evidence for the psychometric properties for that outcome. Table 4, starting on page 21 of the Main document, lists every outcome reported in every included study. KQ1b lists every outcome reported by any RPS study that had psychometric property data. As for color vision, the current technology may not have the ability to give patients color vision but the manufacturers are working to improve upon current devices and we are trying to be proactive in anticipating what may come down the line. Finally, based on your comment as well as others who reviewed the draft, we have subdivided the visual acuity category into two categories. Finally, we added a statement about HOVER recommendations.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #4	Results	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? The report lists only four outcome measures (ETDRS Chart, GAT, CCT, and FLORA) as measures that have psychometric properties, but no critical assessment for the evidence of these psychometric properties (and again, the CCT tests the color vision which is not relevant to retinal prosthesis technology). The report does not provide psychometric properties of the Patient Reported Outcome (PRO) measures, Clinician Reported Outcome (ClinRo) measures, Observer Reported Outcome (ObsRO) measures or other instruments (IADLs) that evaluated the performance of activities of daily living in retinal prosthesis studies (although some of these types of tests are listed in the next section, KQ1C).	We used the COSMIN checklist to evaluate the quality of the psychometric property studies. Color vision was tested in our population of interest (vision less than 20/200) and therefore is reported here. RPS are being modified with the goal of providing better vision to future patients so we are trying to capture outcomes that may be relevant in the future with technological advances.
KI reviewer #4	Results	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? The report discusses light sensitivity tests (dark adaptometry and dark adapted visual fields) and contrast tests (Pelli-Robson and GCS) but incorrectly refers to them as visual acuity tests.	We corrected that terminology throughout the document (ES-7, page 34-36) of the Main document). Thank you for the comment.
KI reviewer #4	Results	KQ2: What is the evidence that HRQoL, ability to perform ADLs and IADLs, visual function, and other outcomes are improved in patients who use RPS compared to baseline (or device off or untreated eye) and compared to alternative treatments? a. The report states (page 45) “We considered all outcomes reported to be Direct because the patients....had diagnoses...and visual acuities...that met the US Food and Drug Administration (FDA) requirements...for implantation with an RPS...” It is unclear to which requirements the report refers. b. The evidence presented from the published studies that documents the results of clinical research studies investigating retinal prostheses or alternative rehabilitative interventions does not appear to distinguish between statistically significant differences in outcomes and clinically significant differences in outcomes. Therefore, it is not clear what evidence bases are referred to in the concluding statement (“Overall, for all outcomes assessed, the evidence bases were found to be insufficient to estimate the proportion of patients who would benefit from RPS”).	We were referring to the FDA requirements for RPS implantation in relation to the Argus II device. We did not attempt to determine clinical significance for this report and no meta-analysis was performed.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #4	Results	KQ3: What is the evidence that the use of RPS arrests the progression of RP? A retinal prosthesis is not a medical treatment for any disease including RP. Retinal prosthesis devices are a rehabilitation intervention to compensate for the effect of the disease on visual function in hope to return, as much as possible, functional performance in everyday life activities. This document cites many rat studies that show neuroprotective effects from electrical stimulation, changes in electrophysiology measures (b-waves) and changes in growth factors. The ASR device is not a retinal prosthesis but a device that generates low level electrical energy to stimulate nerve growth factors in the neural tissue of the retina for neuroprotection. Besides the case studies for the ASR and other devices that provide external applications of electrical stimulation, there are no controlled investigational studies showing the same effects found in the animal studies.	This report is a Technical Brief. Our task was to identify any evidence that these devices may halt disease progression. For this particular KQ we included the only three studies of patients with RPS that mentioned the possibility that these devices had neuroprotective effects.
KI reviewer #4	Results	KQ4: What is the evidence on adverse events associated with the use of RPS? The discussion of the adverse events may want to distinguish between adverse events for epi-retinal and sub-retinal prostheses. As the surgical procedures and locations of the retinal prosthesis are significantly different for these two different types of devices, a discussion of whether the reported adverse events are different would provide beneficial additional information.	Thank you. We added on page 54-55 of the Main document a statement which reads: "The subretinal approach (ASR and Alpha IMS implanted in 38 patients total) reported the following adverse events: syneresis of images seen in the implanted eye (1), aniseikonia (1), scratchiness (NR), elevated IOP (3), mild skin infection (1), and subretinal bleeding that resolved quickly (1). The epiretinal approach (Argus II and Epi-Ret3 implanted in 53 patients total) reported a larger variety of adverse events, including a large number of events classified as serious, including, but not limited to, a central retinal defect, hypotony, presumed endophthalmitis, conjunctival erosion and dehiscence, corneal opacity, retinal detachment and tear, corneal melt, uveitis, and enucleation."
KI reviewer #4	Results	KQ5A: What is the evidence on off-label use of RPS? The report states (page 51) that "...patients with advanced AMD may be candidates for retinal prostheses, and this would be an off-label use according to FDA criteria." It is unclear from where these criteria were obtained. Investigational studies for the rehabilitation of the vision loss due to a different ocular disease than RP is not an offlabel use of a retinal prosthesis.	We rephrased the following to read (page 55 Main document): "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."

Commentator & Affiliation	Section	Comment	Response
KI reviewer #4	Results	KQ5B: From a narrative review of the literature, are there other uses that have been suggested for RPS? The authors do not mention that some companies are investigating adapting the retinal prosthesis technology for use as a cortical prosthesis.	Thank you for this comment. We amended KQ5b (page 56 Main document) to reflect the technology being adapted for cortical use as follows: “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.”
KI reviewer #5	Results	Page 15 line 11: I believe that the lack of consensus is also to due lack of agreement on outcome measures that are most reliable and valid for assessment of RPSs (in addition to importance)(same comment for page 17 line 37)	We agree there is little consensus on this point, and we wanted to report thoroughly the measures that have been used.
KI reviewer #5	Results	Page 15 line 16: you refer to the ETDRS severity scale, but I believe this is actually referring to ETDRS visual acuity. Its responsiveness was assessed during the study of the Artificial Silicon Retina. The issue with the ETDRS visual acuity measure is that most patients who have received a RPS do not have sufficient vision to complete this test pre-operatively and possibly also after receiving the RPS.	We removed the phrase "ETDRS severity scale" and clarified that it measures visual acuity. We understand that many RP patients will not have sufficient vision to produce meaningful ETDRS results. Our intent in KQ1b is to document psychometric properties of outcome measures used in RPS studies. Regarding "responsiveness," the data to which you refer are covered in Key Question 2.
KI reviewer #5	Results	Page 15 line 19: Is there a published reference to support the acceptable test-retest reliability for the Chow Color Test? The responsiveness for this test and the GAT was assessed during the study of the Artificial Silicon Retina.	Yes, the Chow 2010 paper provided test-retest reliability data. Regarding "responsiveness," the data to which you refer are covered in Key Question 2.
KI reviewer #5	Results	Page 15 line 24: Wasn’t the responsiveness of the FLORA assessed during the Argus-II trial? Perhaps you are referring to responsiveness to natural disease progression/functional loss, rather than response to RPS, or something else? If so, please clarify that.	The FLORA data for Argus II are covered in Key Question 2. We have added clarification to the report that by "Responsiveness" of a measure, we mean that scores on the measure improve after an intervention of known efficacy.
KI reviewer #5	Results	Page 15 line 31: please clarify that dark-adaptometry is with the SST-1 (also relevant to page 51 line 51). Also, sometimes in the literature, the full-field flash test is referred to as the full-field stimulus test (FST).	We have added this, and we have also added the device names from this study to the corresponding appendix table. Also we added in parentheses that the full field flash test is also referred to as full field stimulus.
KI reviewer #5	Results	Page 15 line 32: ‘sensible’ would be better replaced by ‘measurable and highly reliable’ (also relevant to page 51, line 8 and page 51, line 47)	We made this change, but used "measurable or reliable," given the context of the sentence

Commentator & Affiliation	Section	Comment	Response
KI reviewer #5	Results	Page 15 line 36: The GCS may overestimate contrast relative to the Pelli-Robson, but that does not necessarily question its validity. It just means that it is easier for subjects to determine the orientation of striped lines displayed on an entire monitor screen than it is to detect a single letter or determine if a letter is an O versus a C. (also relevant to page 51, line 12 and page 53, line 14)	We removed the sentence "However, the validity of the GCS can be questioned, as it appears to overestimate patients' contrast sensitivity." We also changed the pertinent sentence in the main body and the appendices.
KI reviewer #5	Results	Page 51, line 34: 'Visual Acuity' in the subheading does not belong there and should be replaced by 'Scotopic Sensitivity' or 'Visual Function'	We changed it to "Light Sensitivity."
KI reviewer #5	Results	Page 51, line 39: There is another study that published on the reliability and validity of the full-field flash test (FST) in RP by Roman A et al. (from Samuel Jacobson's lab).	Thank you; the update includes the Roman study of the full field flash test.
KI reviewer #5	Results	Page 52, line 21: It is important to add that the full field flash test was obtained after dark-adapting for 45 minutes and that the stimulus was a white light.	We changed the text to read "After dark adaptation for 45 minutes, patients underwent the full-field flash test (also known as the full field stimulus test). 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."
KI reviewer #5	Results	Page 52, line 44: 'Visual Acuity' in the subheading does not belong there (not appropriate) and could be replaced by 'Visual Function'	We changed it to "Contrast Sensitivity."
KI reviewer #5	Results	Page 53, line 3: 'Visual Acuity' in the subheading does not belong there (not appropriate) and could be replaced by 'Visual Function'	We changed it to "Contrast Sensitivity."
KI reviewer #5	Results	Page 57, line 7 and page 58, figure 3: The subheading of "visual acuity' is not appropriate here since some of the referenced tests in this section are not measures of acuity, but other aspects of vision (e.g., detecting percepts, light localization). I would suggest to rename this section as 'Visual function'	Some of the previously-labelled "visual acuity" outcomes are now categorized as visual function, and we have created two separate figures for those two outcome categories.
KI reviewer #5	Results	Page 57, line 38 and page 58, figure 3: Please indicate the definition of 'improvement' that was used to generate this figure? Just using any level of small, positive improvement may not be appropriate (may overestimate effects) since small magnitude improvements may be within typical test-retest variability and not a 'real' or significant change, but rather just due to the usual visual fluctuations experienced by RP patients.	It was any amount of improvement. We change to axis label to read "any improvement" in order to clarify this.
KI reviewer #5	Results	Page 61, line 16: The subheading of 'Laboratory function' is not descriptive or meaningful, and I would suggest to replace with 'Laboratory-based Visual Performance Measures"	Thank you. We made that change throughout the report.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #5	Results	Page 63, line 4: In the subheading for this section, I would add/clarify that day-to-day function is "Patient-reported vision or activities of daily living" for lines 6-16 and lines 17-25, then create another subheading for lines 16-17 with the subheading of "Performance Measures of Activities of Daily Living" for the FLORA (since patient reported outcomes should be reported separately than those that were observed by a study team member)	We felt that these could both be considered day-to-day function, so we did not change the section header. An earlier section has clarified that FLORA is completed by observers.
KI reviewer #5	Results	Page 65, line 4: The NEI-VFQ is not really a measure of Quality of Life since it predominantly focuses on vision. It would make sense to group this outcome with the 'Day-to-Day Function' section on page 63, which I would suggest to reclassify as "Patient-reported vision or activities of daily living"	We decided to include this as a QoL measure because the questionnaire also asks about the respondents' overall health.
Peer reviewer #1	Results	The amount of detail, study characteristics, key messages, figures, tables and appendices all seem to be adequately described and appropriate. The inclusion and exclusion of studies is dependent upon the key questions, and because the focus of the key questions are psychometric properties of quality of life measures, the studies that contained visual acuity outcomes don't seem to have been described as much.	Psychometric property data was not a requirement for inclusion for KQ1a or KQ2-4. All studies were described with the same amount of detail.
Peer reviewer #2	Results	The amount of detail presented and the tables are appropriate, applicable, and adequate. Table 1 and Table 4 are especially helpful. Figures are well done and appropriate.	Thank you.
Peer reviewer #3	Results	The results were well described and a number of tables showed the details of each of the studies evaluated. Because these were not similar in many aspects, graphs showing the commonalities were especially helpful. Different outcomes were used in many of the different studies, making it difficult to compare across the studies. When there were exceptions to the eligible patients, these were also noted. Unfortunately, each of the studies have relatively small number of patients with not very long follow-up.	Thank you.
Peer reviewer #4	Results	The results are presented in a clear fashion with sufficient information. Each section is organized clearly based on the key questions chosen by the authors to assess RPS devices. Tables and figures are used where needed to summarize the collected information and make comparisons. Included studies are well described by the authors. Additional details are provided in the appendices and the reader is directed to these sections for further information to avoid making the results section unnecessarily long. The studies included in the report are appropriate and investigators did not overlook any other relevant studies.	Thank you.
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	The Functional low-Vision Observer Rated Assessment (FLORA) has demonstrated its value as a valid and responsive measurement of day-to-day functionalvision and overall benefit and well being in RPS users	Yes, FLORA was one of the outcome measurements that we assessed and it was found to be a valid and/or reliable instrument in this population.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	The Detailed Synthesis for Key Question lA (lines 16 and 17 of draft report page 40) states that "...there is little consensus among authors of RPS studies about which specific measures are important." We disagree. There is consensus regarding the importance of specific measures, but there is little consensus about the available instruments capable of accurately assessing these measures in a blind patient population, resulting in several RPS manufacturer-developed instruments. We support the report's recommendation for future efforts to establish consensus outcome instruments for use in RPS studies (Key Question lA). We acknowledge that effective assessment of blind patients with severe RP is a complicated task, but one that can be supported by additional clinical evidence. To this end, we encourage cooperation among researchers,developers,and regulatory agencies in an effort to develop specific,validated measures for patients who may potentially benefit from RPS devices. Our ongoing work in establishing and validating the FLORA, an observer-rated tool which was developed in concert with the FDA and an international group of clinical experts, indicates the potential for successful partnerships towards this aim.[3, 4] FLORA is widely used across the country, and is now being implemented in other countries as part of the outcomes data collection requirements under national reimbursement programs,such as with the HAS in France.	We respectfully disagree that there is consensus on which specific measures are important in RPS studies. While a majority of studies did report some measure of visual acuity (7 studies), visual function (9 studies), and laboratory based visual performance (6 studies), day-to-day function and QoL were only measured by 4 studies and 1 study each, respectively.
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Regarding KQ1B. In a recent study employing FLORA,the use of Argus II implants allowed patients with severe RP to perform practical everyday tasks in uncontrolled, real-world environments. In 35 tasks across four domains -visual orientation,activities of daily living,mobility,and socialinteractions- trained low vision specialist evaluators observed that when the Argus II implant was turned on, patients demonstrated statistically significant improvements on 24 (69%) tasks;patients only performed 2 tasks more easily with Argus II implants turned off.[3] These and other study data also support the face validity,internal responsiveness,and inter-observer reliability of FLORA, addressing a primary concern raised in Key Question 1B.[3-5] The FLORA has demonstrated its usefulness as a valid and responsive measurement of day-to-day functional vision and overall benefit and well-being. Second Sight continues to use the FLORA In post-market studies of the Argus II prosthesis and has made this tool available to other RPS researchers for use in their evidence development.	Yes, we included the 2015 report by Geruschat in our review (the commenter's reference #3). We have updated the report to include the 2016 report by Geruschat that you mentioned.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Key Question IC: This technology assessment also attempts to identify alternative outcome instruments that can inform the impact of RPS systems on patients' quality of life,ability to perform activities of daily living,and other functional domains {Key Question 1C). Specifically, assessment authors reference the potential utility of reliable, validated visual functioning-specific instruments, while also citing a lack of relevant studies employing these tools. We wanted to note a publication relevant to this Key Question, in press at Clinical and Experimental Optometry. This paper reports the use of the validated,vision-specific Vision and Quality of life Index (VisQoL) to measure treatment-related quality of life changes among patients with Argus It implants. Across measurements up to 36 months post-implant,VisQoL scores were associated with a significant and persistent improvement among patients whose blindness affected their quality of life in three of the six dimensions probed by the VisQoL: Injury,Life,and Roles	In our literature review update, we identified the referenced paper. It is included in the final version of the document.
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Other published and in-review studies found that Argus II implant use was associated with improvements on four tasks representative of activities of daily living:letter and word reading[7];sock sorting- an experimentaltask mimicking discrimination of light and dark laundry items;pavement tracking-a correlate of visually following a path outdoors;and walking direction discrimination- a visual motion identification task applicable to normalenvironments.[8] In aggregate,this data offers additional evidence of Argus II implant-related benefits on realworld functionality measures,and warrants consideration in updates I revisions and in this technology assessment.	The report already included the da Cruz 2013 article (the commenter's reference 7). Regarding the under-review article (the commenter's reference 8), perhaps it can be included once published.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Key Question 2: In the "Day-to-Day Function" subsection of the Detailed Synthesis for Key Question 2 (lines 16 to 19 of draft report page 63), it should be noted that the low vision specialist observer conducting the FLORA discusses the impact of the Argus II on the patient's functional vision and quality of life in their case study narrative. Part of this is informed by an interview with the subject,during which the subject is asked how the Argus II System has affected them. The final rating, however, is given by a low vision specialist who evaluates the case study,not by the patients themselves. Therefore, we suggest rephrasing these lines,for example: "Low vision specialists interviewed subjects and observed their functional vision performance on day-to-day tasks;a final rating was given to summarize the effect of the Argus II System on their lives. At 1-year follow-up,80 percent were rated as having received a positive or mild positive benefit from the System,20 percent experienced a neutral effect,and none were judged as having received a negative effect.A similar pattern emerged at the 3-year follow-up,but with 65 percent of patients rated as having received a positive or mild positive effect from the System."	We made the suggested change on p. 43 of the document: 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 follow-up, 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 follow-up visit, but with only 65 percent of patients rated as having received a positive or mild positive effect from the System.
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Regarding long-term visual function results of Argus II System, at 3 year post-implantation, the visual performance showed a clear measurable benefit for most patients when the system was activated. At 3 years post-implantation,89.3% of subjects successfully achieved localization tasks (i.e.,performance was significantly better with the System ON than OFF), 55.6% successfully achieved motion discrimination tasks,and 33.5% achieved a repeatable acuity score with a grating visual acuity test. This demonstrates that, on average, patients with the Argus II RPS activated had an improved visual acuity from Bare Light Perception to at least Hand Motion detection, and possibly Counting Fingers, when the RPS was active. At baseline, or when the system was inactive,their visual acuity did not exceed Bare Light Perception. This Is an important outcome since It Is the first example of an FDA-approved deviceor any therapy-that has demonstrated improved visualfunction in the extremely low-vision range (No Light Perception to Hand Motion detection) in this patient population.	Thank you for your comment. The data you cite appears in Table C-13 in the Appendices.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	The significant improvements in visual function also corresponded to similar achievements in orientation and mobility, which was one measure of clinical utility. Consistent with how patients scored on the battery of low-vision tests, the "door" and "line" tests confirmed that patients were significantly better (p<O.OS) at touching a door or walking on a white line when the System was ON versus when it was OFF. These data correctly correlated improvements In visual function with "real world" activities. This again was a significant achievement for patients who were bare light perception before implantation.	Thank you for your comment. The data you cite appears in Table C-16 in the Appendices.
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Key Question 3: To our knowledge,the focus of RPS devices, including the Argus II, is to provide some degree of visual perception to patients whose severe RP indications otherwise render them functionally blind. Consequently, we assert that no rigorous scientific clinical studies of RPS have investigated operational aspects attendant to halting disease progression, and caution against unsupported interpretation of any findings beyond the intended use and approved scopes of these devices (Key Question 3).	Thank you for your comment. We kept our original text for this Key Question but added the following text in the KQ3 section on page 51: "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."
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Key Question 5: Similarly in response to Key Question 5, we are not aware of any RPS devices being used for any non-RP indications in the United States. Specific to Argus II, Second Sight Medical Products and trained vitreoretinal surgeons who implant the Argus II ensure that patients meet all FDA indications (including an RP diagnosis) before receiving the Argus 11.1	Thank you for your comment.
Public reviewer #3 (Robert Greenberg, SecondSight)	Results	Results from all primary endpoints from Argus II feasibility study indicate that visual function -the ability to locate objects, determine the direction of a moving object, and visual acuity-are improved for RP patients when using the Argus II system compared to only using their residual vision. These results are consistent and sustained to at least 5 years post-implant demonstrating the long-term durability of Argus II System. Eight years on,as of January 2016, the Argus II system is still implanted and functionalin 24 out of 30 clinical trial patients.	Thank you for the comment. We have included data from the 5-year follow-up on Argus II subjects after updating the searches.
KI reviewer #3	Discussion	The implications and limitations are clear. I appreciate the clarity of direction in the future research section.	Thank you.
KI reviewer #5	Discussion	Page 17 line 40: please add that the ETDRS is VA	We did this here as well as on ES-7.
KI reviewer #5	Discussion	Page 19 line 43-44 and page 74, line 11: As the development of RPS progresses and improves, it is likely that future trials of RPS would expand to include patients with slightly better vision than count fingers, so the trials to date may not be representative of all future patients	Thank you.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #5	Discussion	Page 72, line 9: I believe the 59% estimate of visual acuity measures is not correct since the authors included other aspects of vision (light localization) that do not measure acuity.	Yes, we agree, we have re-categorized many of those as "visual function."
KI reviewer #5	Discussion	Page 74, line 20-21: There is also a published case report on the 10 year follow up in a patient with the ASR by Julia Haller et al. 2015.	We have included that article in the update.
KI reviewer #5	Discussion	The discussion should mention that candidates for RPS are not only the Medicare population, but could also include younger patients with private insurance or Medicaid.	We have noted that younger patients may be candidates for the device.
Peer reviewer #1	Discussion	The implications of the major findings are clearly stated and the limitations of the review are described adequately. The authors raise the issue of the small size of the typical study and also the impracticality of large studies. However, this doesn't help to resolve the issue of precision if large studies are unattainable.	Thank you for your comment.
Peer reviewer #2	Discussion	While little consensus exists among authors of RPS studies about which specific measures are important, each study was designed to evaluate visual and laboratory outcomes thought to be important for patients' daily functions. Because of lack of uniformity in the reported outcomes measures among the different studies, study-to-study comparison was difficult. Not all tools have been shown valid or reliable in the very-low-vision populations. However, no other interventions exist for these ultra-low vision patients, and any improvement in vision or independence, despite lack of uniformly accepted outcome measures, may be considered important. Thus insurance agencies should be encouraged to pay for RPS in order to drive the improvement of quality of health care for these patient populations.	EPC reports do not make clinical recommendations or recommendations related to reimbursement or coverage policies. Our goal is to summarize and present the available evidence, which is then used to inform clinical and coverage decisionmaking by patients, providers and policymakers.
Peer reviewer #2	Discussion	While showing the effect of RPS on daily function and quality of life is important, physicians would also like to know the acuity levels achieved by patients. The authors state that Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale has acceptable rest-retest reliability, but published studies do not measure its validity or responsiveness in patients with RPS. Thus, I would also recommend testing validity or responsiveness of ETDRS chart in patients with RPS, possibly in electronic format on a computer screen, making it possible to compare visual outcomes in different patients and across devices and studies. Certainly, suggesting that the centers developing and conducting research should devise visual outcome measures that would be used uniformly, is important.	Thank you.
Peer reviewer #2	Discussion	Despite these gaps, it is important to acknowledge that there is evidence that many patients are able to perform better in orientation and mobility tasks with the device on. I agree that it is difficult to know a priori which patient is going to benefit from RPS, however choosing patients with positive personality and strong work ethics, who would be expected to put in hard work into mastering the device is important. Discussing personality traits with providers who know the patient well, perhaps the occupational therapist or low vision provider, is one of the best ways for character screening.	Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	Discussion	I agree that the screening ophthalmologist should give a realistic representation of all possible visual acuity gains and the possibility that the patient may not benefit from an implant and perhaps will lose residual light perception in the eye after implantation.	Thank you. We added that the patient may lose residual light perception post-implantation.
Peer reviewer #2	Discussion	I agree with the statement that investigators should routinely measure QOL and ADLs in addition to traditional visual acuity measures, as these measures are interrelated. Making the patient more independent and connected to other RPS users, most likely increases QOL and needs to be measured as suggested. Newer tools for QOL assessment need to be devised and validated in the future studies.	Thank you.
Peer reviewer #2	Discussion	I agree that more evidence and newer validated tests should be developed to evaluate benefit provided to the patient by the implanted device. These tests should be agreed upon and accepted as gold standards across RPS developers and researchers. However, even before these future research goals are met, RPS devices should be funded for appropriate patients as there is evidence that many patients benefit from RPS in one or more of the ways reported in the studies.	Thank you. EPC reports do not make clinical recommendations or recommendations related to reimbursement or coverage policies. Our goal is to summarize and present the available evidence, which is then used to inform clinical and coverage decisionmaking by patients, providers and policymakers.
Peer reviewer #2	Discussion	I agree with the statement that studies with longer follow-up are needed, and the research community should be encouraged to conduct them.	Thank you for this comment.
Peer reviewer #2	Discussion	I agree with the assessment that because of standardized training Argus II maker provides, the quality of outcomes is expected to be the same at the new sites as in the sites involved in the approval study.	Thank you.
Peer reviewer #2	Discussion	I agree with the conclusion and implication for clinical and policy decision-making statements	Thank you.
Peer reviewer #3	Discussion	There are indications as to where the next step should be, including the more patient reported quality of life. I would agree that this would be crucial for the next step. I believe the synthesis was excellent. We still have some ways to go to thoroughly the benefits of this technology. More important, we need to understand the needs of the patients who would indeed benefit from this treatment.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #4	Discussion	The discussion summarizes the key findings of this technology assessment clearly. Applicability to medical practice and how this information may affect policy making are discussed. Since the evidence is mostly lacking, the authors make no recommendations on the use of RPS devices as they currently stand. The limitations of their review process and the limitations of the evidence gathered from the studies included in the assessment are discussed. All relevant literature is included in the report and the authors compare their study to what is already present in the literature. This comparison clearly highlights the strength in evidence gathering and the robust methodology used in this technology assessment. Conclusion section is short and could be expanded. The authors make recommendations on how the future studies should be designed but a separate section on future research may allow the readers to translate the findings of this report to their study design. In particular, the authors make recommendations on which tests may be best applicable to assess the clinical efficacy RPS devices and how these tests may be administered during future investigations to collect valid data that can be compared across multiple different trials. A separate subsection with more detailed recommendations for investigators designing future research on RPS devices would improve the discussion. The authors may also consider discussing the extensive amount of post-surgical training the patients have to participate in for some of the RPS devices and how this may affect the patient selection process.	Thank you. EPC reports do not make clinical recommendations or recommendations related to reimbursement or coverage policies. Our goal is to summarize and present the available evidence, which is then used to inform clinical and coverage decisionmaking by patients, providers and policymakers.
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	Discussion	A key knowledge gap is the validity of visual function test in patients with artificial vision. Studies will need to address this in the future.	We agree, and that was a key purpose of KQ1b.
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	Discussion	Continued monitoring of adverse events associated with RPS is important.	We agree, and surely such monitoring will occur.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	Discussion	The ability to see “normal” vision, color vision, or patients safely giving themselves insulin injections is not possible with the current RPS. Thus, we recommend the report temper any patient expectations of being able to perform such tasks with artificial vision (p.ES-9).	We modified ES page 9 and 10 to read as follows "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, and the possibility that any individual patient may not benefit from an implant.”
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	Discussion	The recommendations made in this report are broad and may not apply to all RPS. Due to the large variability in patient population, design of each RPS, length of study, and outcomes measured for each of the RPS evaluated, it is difficult to come to a consensus on the best methods to evaluate the efficacy of these systems. We recommend focusing recommendations on the Argus II, which is currently the only approved device for use in the United States.	EPC reports do not make clinical recommendations or recommendations related to reimbursement or coverage policies. Our goal is to summarize and present the available evidence, which is then used to inform clinical and coverage decisionmaking by patients, providers and policymakers. Second, regarding variability in patients/devices/outcomes, the funder for this report is interested in any general statements that can be made about the evidence on the technology for patients with retinitis pigmentosa. This requires a willingness to group patients, devices and/or outcomes that may be somewhat different.
KI reviewer #1	General comments	The purpose of the report “Retinal Prostheses in the Medicare Population” is to present the findings of a comprehensive review of evidence-based literature. This is achieved via a panel of Key Informants who are subject matter experts followed by a comprehensive review and analysis of the literature that address 5 themes known as Key Questions (KQ).	Yes, thank you. Key informants also included patients with RP.
KI reviewer #1	General comments	This reviewer was a key Informant, specializing in rehabilitation of the visually impaired. My comments will be directly related to the content that is within my experience as a subject matter expert. I have structured these comments by topic rather than following the paging of the Technology Review; however, page and line numbers are given for reference.	Thank you.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #1	General comments	These patients have very low vision and haven't been seen by lv clinics for decades. They function blind. Even with the RPS they still have difficulty engaging the items of the FAST using vision only. The same is true of other assessments identified in the report as standardized or validated: they are either unlikely to be appropriate for this very-low vision population (e.g., the NEI-VFQ-25) or are not useful in determining function with a visual prosthesis (e.g., full-field flash test and Grating Contrast Sensitivity).	We recognize that some of the measures identified in this report as being reliable and/or valid were tested in patients with better vision than is typical of candidates for a RPS. However, we wanted to err on the side of being more inclusive, rather than less, in identifying potential measures to be used in future studies of patients with RPS so we set our inclusion criteria as 20/200 or worse visual acuity. We modified page 56 of the main document, Evidence Gaps, to read as follows: "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."
KI reviewer #1	General comments	This is why so many groups are trying to develop assessments that address the functional vision abilities of the recipient of RPS. The same thing is true for the assessments of ADL and Quality of Life. Thus the development of the FLORA, and the work of the group in Australia in developing the IADL-VLV. These instruments are designed to be valid measures of functional vision and quality of life (in the case of the FLORA) for very-low vision patients and visual prosthesis recipients.	We recognize that some of the measures identified in this report as being reliable and/or valid were tested in patients with better vision than is typical of candidates for a RPS. However, we wanted to err on the side of being more inclusive, rather than less, in identifying potential measures to be used in future studies of patients with RPS so we set our inclusion criteria as 20/200 or worse visual acuity. We agree that developing reliable and valid measures for use in the very low-vision population is important work.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #1	General comments	The manuscript lists in a variety of places the companies/institutions that are working on retinal implants. You did not list Nano Retina (www.nanoretina.com). I'm not sure of the inclusion/exclusion criteria but I know they are planning on going to a phase III clinical trial in 2017.	Our searches only identified a press release on this device indicating that clinical trials were due to start in 2013. However, we did not identify any human trials. We added a sentence about the device on page 4 of the Introduction in the Main Report.
KI reviewer #1	General comments	A small item: on page 185, table C 11 should be Geruschat, not Beruschat	We fixed that error. Thank you.
KI reviewer #2	General comments	I enjoyed reading this comprehensive report. There are several big-picture issues that I would like to comment on regarding this report. Some of these issues are mentioned in the limitations part of the discussion. However, in my opinion, they affect the impact of this important report and I would recommend the authors address them. The field of RPS includes a variety of devices and approaches. However, reporting on all devices and their outcomes together can be misleading and confusing and basically translates into comparing "apples and oranges". The devices studied, the characteristics of the recipients, the outcomes, and the follow-up are too heterogeneous for all the data to be combined together. Although most studies focus on patients with profound vision loss of hand motion or less, some included patients with vision as good as 20/800 (e.g. Artificial Silicone Retina (Optobionics, US)). Most devices are implanted in the macular area, but some are secured outside of the macula. A few of the studies have only early preliminary data. It would be erroneous to compare results of the studies when "study durations ranged from 7 weeks to 7 years." (page 19, line 30) Although it is important to mention all the investigational RPS devices, it might be more pertinent to focus on Argus II RPS. The Argus II device has been studied most extensively, has the largest number of subjects for the longest period of time and has been approved by the FDA.	For KQ2, efficacy, we discussed all devices together and then did a separate qualitative analysis for Argus II only.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #2	General comments	The authors also focus extensively on tests to assess visual acuity. It is important to have validated and standardized outcomes. The larger problem in the field of low vision, I believe, is that prior to the RPS and other new interventions for patients with extremely low vision, there was no need to have standardized measures, as no interventions were available. Establishing these outcomes should be an active area of research. Some of the tests mentioned in the current report are simply not applicable to the population of patients who are candidates for RPS. For instance, ETDRS is mentioned several times. None of the patients who are currently approved for Argus II RPS can see the ETDRS chart. Their vision is light perception or worse in US and hand motions in Europe. They are also not expected to be able to read an ETDRS chart after the surgery as RPS is not capable of providing that level of vision at this point in time. The authors mention studies by Bittner et. al. and Kiser et. al. that assess the validity of ETDRS testing in retinitis pigmentosa. However, these studies were conducted in patients who had vision much better than RPS candidates. Low vision represents a spectrum and there is a significant difference between different levels of "low vision", since 20/500 and bare light perception have dramatically different implications on patients' function. Additionally, color vision is mentioned as one of the outcomes. Once again, Argus II RPS surgical candidates do not have any color vision. The study referenced focused on a totally different patient population with better pre-operative vision and an implant that was placed outside the macula. Including color vision as an outcome for all RPS devices is not only misleading but incorrect. Thus, I would not agree with the statement that "There is some evidence for the validity and/or reliability of the Early Treatment of Diabetic Retinopathy Study (ETDRS)" and "Chow Color Test (CCT)" (page 52, line 13-14).	We included psychometric studies that enrolled patients with vision up to 20/200. We did this because, although the current state of technology is not designed to allow for vision good enough to be tested by ETDRS, for example, the manufacturers are working toward improving these devices. In future versions of these devices ETDRS vision may be a possibility.
KI reviewer #2	General comments	Please see specific comments below. The comments addressing the issues in the executive summary also apply to the full report.	Thank you.
KI reviewer #3	General comments	The authors did an incredible job on this evidence review. The technology and different measures of vision are quite esoteric. The report is meaningful, however it sometimes becomes unclear whether the studies were limited to only RP, or whether they also included AMD. It is clear that RP is a smaller population, and the AMD population is larger. I made notes as I read the report, which are in a document i will attach. I had some difficulty understanding parts of the report, and I noted the areas. The key questions are appropriate and clearly stated. The key questions highlight the limitations of the included studies.	Thank you for this thoughtful comment. None of the patients evaluated for KQ1a,b or KQ2-4 had AMD. Only patients enrolled in studies which addressed KQ1c could have AMD.
KI reviewer #3	General comments	As stated in the attached notes, I think the section, "Implications for Clinical and Policy Decision Making", should be included in the exec summary.	Thank you. We hope that readers will read that section in the main document.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #4	General comments	The objective of this guidance document (Retinal Prostheses in the Medicare Population) is inconsistent with the intended use and technology of currently available and developing technologies for the RP population with respect to the objective of halting disease progression. Medicare aged RP patients would typically be end stage RP and the use of retinal implants is not for halting the disease progression, but rather for improving the functional abilities of the end stage RP patient and not halting the disease progression. Technologies that would halt the progression of RP would have to be implemented in much younger patients and much earlier in the disease process. Prostheses are not disease treatment devices. They are surgically implanted devices that provide some functional performance elements to assist the visually impaired person. There have been no retinal prostheses implanted in the United States for Age Related Macular Degeneration or any other macular degenerations. Gene therapy studies for Liebers Congenital Amaurosis, as well as other disease entities, are currently underway and have not been given appropriate address with respect to actual disease reversal or halting of progression.	Thank you. We were asked to address the Key Questions that appear in the report in relation to RPSs only. Addressing the ability, or lack thereof, of Gene Therapy to halt disease progression is outside the scope of work for this particular report.
KI reviewer #4	General comments	The recommendations made in this document are consistent and reflective of FDA's Retinal Prostheses Guidance Document not only in clinical objective measures but also regarding functional vision assessment, QOL and ADLs in additional to traditional visual acuity measures. However, although guidance from the UK was cited, the FDA guidance document (Investigational Device Exemption (IDE) Guidance for Retinal Prostheses Guidance for Industry and Food and Drug Administration Staff Document issued on: March 6, 2013; http://www.fda.gov/RegulatoryInformation/Guidances/ucm341954.htm) was not referenced.	Thank you, we cited the document.
KI reviewer #4	General comments	There is concern with the authors' methodology for the compilation of this report. The RP population intended for implantation with retinal prostheses are end stage victims of the disease. They have bare to no light perception. It is not possible to evaluate these subjects with current, developing technologies as a study sample that would represent expected outcomes. Outcomes of effectiveness are highly individualized based on many factors --- physical health, age, cognitive skill levels, adaptive skill levels, independence and selfreliance, and effectiveness goals driven by the needs of the patient/subject. These effectiveness factors are not measured by any one specific instrument or assessment tool. Therefore, this document should be presented within this context.	We understand that vision is very limited in many patients with RP who receive RPS, and that measuring effectiveness is challenging in this population. Our purpose was to summarize the outcomes that have been reported in RPS studies, as well as determine which of them have been tested for validity, reliability, and responsiveness among patients with similarly poor vision.
KI reviewer #4	General comments	The literature review did not provide an accurate or adequate listing of all the retinal prosthesis studies that have been published. The Iridium Medical Technology Company retinal prosthesis is the most notable group that is not acknowledged.	We added a description of the Iridium Group, as well as the Nano-Retina, to the Background section on page 4 of the Main document. Thank you for your comment.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #4	General comments	The patients interviewed for the technology assessment are described as: "Individuals in the Medicare population with low vision and retinal degenerative disorders or macular disorders." There is no explanation for why the authors did not interview patients who have a retinal prosthesis or those that identify as choosing to not have a retinal prosthesis. This group of patients would have a much better ability to evaluate the rehabilitation potential of a retinal prosthesis than a general individual with retinal degeneration or macular disorders. In addition, the authors could have reviewed the FDA panel meeting for retinal prosthetics public record. The public record of this panel meeting includes patient and other perspective on the risks and benefits of a retinal prosthetic device.	We interviewed patient(s) with low vision and retinal degeneration as KI(s). Part of the role of being a KI is to give feedback on the Key Questions addressed in the report. By including patients with the disease, but without the device, we were hoping to learn whether the Key Questions were the right questions that they would ask themselves in thinking about whether or not to have the device implanted. We were also concerned that if we chose to interview a patient implanted with Argus II we would have to find patients with both good and bad experiences to balance the report. Also, as this report is about all RPSs, we felt that all devices would have to be represented. We did receive comments from the Public that included patients who had been implanted with the Argus II and incorporated their comments into the final report.
KI reviewer #4	General comments	There is no specifics given as to the Key Informants that contributed to the technology assessment other than: "We selected additional key informants (KIs) with expertise in each of the following areas: clinical and research ophthalmology, patient advocacy, healthcare insurance administration, psychometrics, and industry." There is no description of how the technical Key Informants were vetted to provide confidence that the Key Informants were the appropriate technical content experts that could provide accurate and thorough knowledge for the technology assessment.	We believe we have provided sufficient information about the Key Informants. Key Informants for EPC reports are not necessarily technical content experts.

Commentator & Affiliation	Section	Comment	Response
KI reviewer #5	General comments	Page 162, table C-5 and page 178, table c-10: It is unclear why some of the questions are listed for the risk of bias consideration for the Bittner et al. 2011 study since the manuscript does indicate there were 3-4 measures obtained for each test at 3-4 separate visits (to address: At least 2 measurements available? Were administrations independent?), the paper states 'Visits were spaced by at least 6 days and not more than 50 days, with a mean ± standard deviation of 20 ± 9 days between visits.' And 'The subjects were tested during three or four visits, each of which lasted between 1 to 3 h, depending on whether one eye or both were tested.' (to address: Was time interval stated?, Was time interval appropriate?), the paper also indicates that 'Subjects who were not undergoing treatment or surgery for their eye disease and whose vision was likely to remain stable throughout a 1- to 3-mo study period were enrolled; their visual status was monitored during every visit. Any significant changes in the subjects' visual condition were detected through either the subjective medical and ocular history taken at the start of each return visit or an unanticipated shift in the results of several of the tests.' (to address: Were patients stable in the interim?), and the paper also stated 'On each visit for every subject, the same examination room and equipment were used to ensure that all test conditions were consistent.' (to address: Were test conditions similar for the 2 measurements?). Perhaps accounting for this information that is provided in the methods of the paper would improve the risk of bias from moderate to low.	Thank you for these clarifications. Based on re-reading the methods section, we have categorized that study as Low risk of bias.
KI reviewer #5	General comments	Please see above comments for suggestions to improve subheadings	Thank you.
Peer reviewer #1	General comments	In general, this seems to be a topic of fairly limited scope and clinical applicability at the present time for an intensive evaluation. The clinical relevance at this point in time seems to be uncertain. The major problem I have with the key question is that although visual acuity and visual field are acknowledged as outcomes, studies were then excluded if the psychometric properties of outcomes were not reported. For Snellen visual acuity testing, if performed in these studies, its not clear what psychometric properties are required. Visual acuity is also considered by many as a patient-centered outcome, and definitely has an impact on activities of daily living like driving, mobility, social function, working, etc.	Studies were not excluded from KQ1a or KQ2-4 based on a lack of psychometric property data, so all relevant efficacy and safety data was included in the report. Only KQ1b was limited to outcomes used in RPS studies that had psychometric property data.
Peer reviewer #1	General comments	The report is well structured and organized, and the main points are clearly presented. However, because of the limited scope of this technology, the conclusions may be limited in their relevance to policy and practice decisions. Patients start at a baseline of such limited visual function and NLP, and may have varied expectations but they may also be appreciative of any improvements achieved, as noted in the report. The new information is pointing towards specified valid and reliable quality of life measures, which is useful.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #2	General comments	The report is clinically meaningful.	Thank you.
Peer reviewer #2	General comments	The target population and audience are defined.	Thank you.
Peer reviewer #2	General comments	The Key questions are appropriate and explicitly stated.	Thank you.
Peer reviewer #2	General comments	The report is well structured and organized.	Thank you.
Peer reviewer #2	General comments	I was a bit puzzled by the repetitive nature of the summary and the rest of the report. If the summary is needed due to required format, perhaps it could be made more concise?	The report follows the required format.
Peer reviewer #3	General comments	I believe this report is clinically meaningful and has covered the questions skillfully and fully with the data available in the literature. I believe the audience, which was targeted for health care providers, purchasers, was appropriately addressed. The key questions were also very well stated and appropriately addressed. These are the questions that one would need to address to determine the clinical use of this technology of retinal prosthesis in the medicare population. The only caveat is that in some of the hereditary diseases in which the patient may be very young with for example rare hereditary retinal degenerations, and this would not be the medicare set. However, if it is geared towards the health care providers, this should be covered.	RPS are available for adults only so we limited our report to the adult populations.
Peer reviewer #3	General comments	This report was well organized and structured. It was easy to follow the train of thought. The conclusions were very reasonable given the data. They do contribute to our understand and particular to the future of this research.	Thank you.
Peer reviewer #3	General comments	Page vi: line 36 Under testing, the Early Treatment Diabetic Retinopathy Study (ETDRS) test should specify that this is the visual acuity testing, whether with a regular ETDRS chart or with the electronic version (EVA: for electronic visual acuity). The ETDRS is sometimes referred to as the classification of diabetic retinopathy severity. It is better to be specific. On page ES-7, line 17, the ETDRS is referred to as a severity scale. Is this for diabetic retinopathy? Not likely as this is not one of the intended diseases to be studied.	We modified the Executive Summary on page 7 as you suggested: The Early Treatment Diabetic Retinopathy Study (ETDRS) severity scale, a measure of visual acuity, has acceptable test-retest reliability, but no included studies measured its validity or responsiveness.

Commentator & Affiliation	Section	Comment	Response
Peer reviewer #3	General comments	Page vi: Line 42: Please spell out NEI-VFQ (National Eye Institute-Visual function questionnaire). Is the NEI-VFQ considered validated by the agency? The FDA, at least in the drugs department, has declared this to be non-validated, partly because rules for such a program had changed. Perhaps this is not considered so by AHRQ.	We spelled NEI-VFQ out as you suggested on in the Abstract (p. ix) and on ES-6. For KQ1c our goal was to identify scales with evidence of validity, reliability, or responsiveness and we found evidence for the NEI-VFQs validity and reliability, thus we reported it.
Peer reviewer #4	General comments	The authors have prepared a clinically meaningful report analyzing this novel area of vision restoration therapy. The cutting-edge nature of the RPS devices requires reviewing and analyzing complex technology and the nonuniform methods presented in the literature to assess these devices. Two specific target patient populations are defined, including patients with inherited retinal degenerations (RP as the main category) and advanced nonexudative macular degeneration. These patient populations are the initial candidates for RPS devices and next generation devices with significantly more advanced technology and efficacy will increase the number of patients who may benefit from vision restoration. The intended audience for this technology assessment is the physicians and investigators of RPS devices, payers, and policy-makers. Several key questions are outlined in the report and are well-designed to assess the RPS devices for the purposes of this report. A figure nicely presents the analytic framework of the report for quick reference.	Thank you.
Peer reviewer #4	General comments	The report is structured and organized well with several sections and subsections dedicated to the specific areas assessed by the authors. Tables allow quick access to some of the key information and allow comparisons between different data points including the studies included in the manuscript. Conclusions are valid based on the analysis presented and will assist with developing practice patterns and policy recommendations. The authors make concrete recommendations on the design of RPS device studies including methods of data collection and analysis, which will be important for future investigations as well as technology assessments.	Thank you.
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	General comments	Vision provided by current Retinal Prosthesis Systems (RPS) is not restorative. Patients do not regain their lost vision, but instead they must learn how to interpret novel visual stimuli (artificial vision). A clear distinction between the two different types of vision should be made.	In the Introduction, page 1, we added "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."
Public reviewer #1 (Elizabeth Sump, Cleveland Clinic)	General comments	Tests such as color vision, traditional ETDRS, and visual field are not applicable for the Argus II population. The device is not designed to improve these parameters. New tests need to be validated for use in patients with artificial vision.	We agree new tests need to be validated in patients who have the Argus II System. However, the technology is continually being modified and improved, so these measures may be more meaningful in patients implanted with these devices in the future.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #2 (Fran Fulton)	General comments	In July, 2014, my health insurance company approved coverage for the surgical implant of the Argus II prosthetic retinal system developed by Second Sight Biomedical Products. I would like to tell you how this action has affected my life. A few weeks after surgery, my eye had healed sufficiently and the Argus II system was calibrated specifically for me. The results were instantaneous! Electronic pixels fluttered before me as I scanned the room. Qquickly I identified the window where the light was coming from. I could tell where various items were hanging on the office walls. Most satisfying at that initial time was that I could spot the left and right sides of the door opening. This immediate awareness of my surroundings brought tears to my eyes and a pounding in my heart as I remembered the way life used to be before blindness. As the days and weeks passed, Argus II brought newe, exciting "insights" back into my life again. Sitting around a table at a business meeting, I could look directly at the person who was talking and know I was looking squarely at the person's face (not just trying to aim my eyes toward where I heard a voice.) 2015: The New Year began with a fireworks display on New Year's Eve just like the ones I could see 25 years earlier. I was told I actually jumped up from the sidewalk when the first burst of bright light appeared in the sky. You cannot possibly imagine… Today, I walk with confidence with my white cane on the city streets now avoiding (instead of hitting) the tables and chairs of sidewalk cafes and restaurants. I can even follow the white lines of crosswalks as I move from one side of the street to the other. I am thrilled each time an elevator opens and I can see the two sides of the opening and walk in without bumping my shoulder or banging my cane against the sides of the doors. Best of all, I can tell if other people are already in the elevator. I used to walk into an elevator and say "Hello." Often I got no response. Just imagine how silly I felt talking to air!! Everyday I seem to recognize something new with my Argus. As exciting as all of these experiences have been, the one I cherish the most is when I first saw my two grandchildren standing before me and I could identify them without either of them making apeep! Again, you can only imagine… This may be a cliche, but for me, it is the absolute truth: Argus II has given me a new lease on life. There is sight beyond blindness. I strongly encourage you to endorse the Argus II system for people living in the darkness of Retinitis Pigmentosa. YOU have the power to provide sight beyond blindness. Let the light in!	We are happy that you have had a good experience and we truly appreciate you sharing your experience with us.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #3 (Robert Greenberg, SecondSight)	General comments	We,the undersigned,understand the challenges associated with attempting to assess a broad slate of technologies in diverse stages of development, ranging from conceptual technologies to the Argus II Retinal Prosthesis System (Argus II)-the only commercially available retinal prosthesis system (RPS) to receive both Food and Drug Administration (FDA) approval and a CE Mark. More than 190 patients have received the Argus II worldwide. The Argus II is the only treatment that has demonstrated long-term safety and durability,with more than 207 patient-years of cumulative experience with the Argus II as of January 2016. This confound, coupled with the rarity and heterogeneity of severe RP indications within American and international patients,requires that study designs and the quality of available evidence be evaluated on a case-by-case basis, rather than relying on a one-size-fits-all approach.	We understand that the patients are heterogeneous as well as the technologies. The funder for this report is interested in any general statements that can be made about the evidence on the technology for patients with retinitis pigmentosa. This requires a willingness to group patients, devices and outcomes that may be somewhat different.
Public reviewer #3 (Robert Greenberg, SecondSight)	General comments	We believe the technology assessment may be more useful if the AHRQ publishes the information in two parts. Part I could focus on the Argus II- a technology that is approved and available to patients in the U.S.-and Part II could opine on technologies currently under investigation elsewhere in the world (since the others are not yet even in clinical trials in the US).	Even though the Argus II is the only device that has received FDA clearance, we disagree with the suggestion to separate an evidence summary of the Argus II from an evidence summary of other devices that have the same clinical purpose. Readers only interested in the Argus II can focus on the corresponding data. If other devices become FDA-cleared, this will report will have summarized their data, and some users may find that helpful.
Public reviewer #3 (Robert Greenberg, SecondSight)	General comments	Alternately, we recommend changing the title to "Retinal Prosthesis currently used in the Medicare Population and Conceptual Technologies in Early Stage Development."	The title was specified in an agreement between the Center for Medicare and Medicaid Services and AHRQ.
Public reviewer #3 (Robert Greenberg, SecondSight)	General comments	The only technology with published evidence demonstrating consistent patient benefits and Improvements in quality of life and activities of daily living is the Argus II. We respectfully provide our detailed comments and specific findings for the key questions below.	Thank you for your comments.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #3 (Robert Greenberg, SecondSight)	General comments	We believe patients with rare diseases should be afforded the opportunity to have access to treatment with the Argus II system; therefore responsible authorities should make every effort to ensure that patients are not denied this treatment due to lack of large studies that are usually not feasible to conduct for rare diseases such as retinitis pigmentosa. The challenges of developing treatments for small orphan patient populations has been well recognized by the FDA. In the U.S., the FDA approved the Humanitarian Device Exemption and designated the Argus II as a Humanitarian Use Device on February 13,2013. An HUD Is defined in 21 CFR 814.3(n) as a "medical device intended to benefit patients In the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4,000 individuals in the United States per year."	On page 55 under Limitations of the Evidence Base we noted that while the median study enrollment was six patients," RPS is rare, and large studies are impractical."
Public reviewer #3 (Robert Greenberg, SecondSight)	General comments	In summary, we recommend that AHRQ address RPS technologies with balanced consideration towards the current state of development and the progress and benefits demonstrated by the most mature devices, allowing more meaningful evaluation of products and their respective evidence bases. Our response is submitted in a collaborative spirit,and in service of patients who may benefit from RPS interventions.	Thank you for your comment. Again, our aim was to present data on all RPSs that have been tested in human trials.
Public reviewer #3 (Robert Greenberg, SecondSight)	General comments	We support the assessment's recommendation to establish consensus outcome instruments for use in RPS studies.	Thank you for your comment. EPC reports do not make clinical recommendations or recommendations related to reimbursement or coverage policies. Our goal is to summarize and present the available evidence, which is then used to inform clinical and coverage decisionmaking by patients, providers and policymakers.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #4 (Larry Hester)	General comments	Wednesday, September 10, 2014 was a monumental day in my life. On that day, I received the retinal implant, Argus II. It has forever changed my life for the good. My surgery took place at Duke Eye Center in Durham, North Carolina. Dr. Paul Hahn was my surgeon. Three weeks after my surgery, the device was activated. Words cannot express my joy as I experienced seeing light after living in darkness for over 33 years. My family gathered around me and cheered me as I saw where the door was located only minutes after turning on the Argus II. I have experienced many wonderful things in these last 21 months. I can navigate easier with the aid of my Argus. I can tell when people are moving about and which direction they are going. I have looked at the faces of my dear granddaughters and can actually see where their foreheads, noses and chins are. I have never seen them before. What a gift! I can play basketball with them with the help of a lighted basketball hoop. A candlelight dinner with my wife is more romantic because I can actually see the candles burning, too. Fireworks are dazzling to me. Lighted fountains astound me. And, on the practical side, I can find where my plate and glass are located at the dinner table. During the Christmas holidays, I enjoyed the lights on our tree and I was able to see the burning candle that I held at our church's Christmas Eve Candlelight Service. I can't begin to express how meaningful that was to me. These things might seem small and insignificant to a sighted person, but to me they are amazing. Without the Argus II I have very little light perception. With it, a whole new world has opened up for me. I didn't know before I received the Argus II how much more connected I would feel to the world around me when I am using it. I didn't know how it would enhance my relationship with my wife, loved ones and friends. My heart is full of thankfulness for this second chance at sight. It is very basic, and yet, at the same time it seems miraculous to me. It is my hope and fervent prayer that others might be able to experience this, too.	Thank you very much for sharing your story with us. We have added additional detail about patient experiences in the report to help the reader understand that even small gains are important to RPS recipients.