Health Quality Ontario

The provincial advisor on the quality of health care in Ontario

Ontario Health Technology Assessment Series

Retinal Prosthesis System for Advanced Retinitis Pigmentosa: A Health Technology Assessment

KEY MESSAGES

Retinitis pigmentosa is an eye disease people are born with, and people who have it can slowly become blind. Many drugs have been tested to try to treat retinitis pigmentosa, but none of them have worked very well. A new device called the Argus II retinal implant may help people with retinitis pigmentosa. The device is implanted inside a patient's eye during surgery. The implant, along with a tiny video camera in a set of special glasses, helps people to see again.

This review looked at how well the Argus II system works, and how safe it is for patients. It also looked at how much the Argus II system costs. It asked people what it is like to have retinitis pigmentosa, and what it is like to have the Argus II implant.

People talked about how losing their eyesight made many parts of their lives more difficult. The Argus II implant can make people's eyesight better, but the surgery may lead to complications. The Argus II implant is much more expensive than usual treatment.

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ABSTRACT

Background

Retinitis pigmentosa is a group of genetic disorders that involves the breakdown and loss of photoreceptors in the retina, resulting in progressive retinal degeneration and eventual blindness. The Argus II Retinal Prosthesis System is the only currently available surgical implantable device approved by Health Canada. It has been shown to improve visual function in patients with severe visual loss from advanced retinitis pigmentosa. The objective of this analysis was to examine the clinical effectiveness, cost-effectiveness, budget impact, and safety of the Argus II system in improving visual function, as well as exploring patient experiences with the system.

Methods

We performed a systematic search of the literature for studies examining the effects of the Argus II retinal prosthesis system in patients with advanced retinitis pigmentosa, and appraised the evidence according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria, focusing on visual function, functional outcomes, quality of life, and adverse events.

We developed a Markov decision-analytic model to assess the cost-effectiveness of the Argus II system compared with standard care over a 10-year time horizon. We also conducted a 5-year budget impact analysis.

We used a qualitative design and an interview methodology to examine patients' lived experience, and we used a modified grounded theory methodology to analyze information from interviews. Transcripts were coded, and themes were compared against one another.

Results

One multicentre international study and one single-centre study were included in the clinical review. In both studies, patients showed improved visual function with the Argus II system. However, the sight-threatening surgical complication rate was substantial.

In the base-case analysis, the Argus II system was cost-effective compared with standard care only if willingness-to-pay was more than $207,616 per quality-adjusted life-year. The 5-year budget impact of funding the Argus II system ranged from $800,404 to $837,596.

Retinitis pigmentosa significantly affects people's ability to navigate physical and virtual environments. Argus II was described as enabling the fundamental elements of sight. As such, it had a positive impact on quality of life for people with retinitis pigmentosa.

Conclusions

Based on evidence of moderate quality, patients with advanced retinitis pigmentosa who were implanted with the Argus II retinal prosthesis system showed significant improvement in visual function, real-life functional outcomes, and quality of life, but there were complications associated with the surgery that could be managed through standard ophthalmologic treatments. The costs for the technology are high.

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BACKGROUND

Health Condition

Retinitis pigmentosa is a group of hereditary outer retinal degenerative diseases that involves the progressive breakdown and loss of photoreceptors (i.e., rod cells for peripheral and night vision, cone cells for central and colour vision). It results in profound vision loss (0.5% of patients have no light perception, 25% have ≤ 20/200 vision in both eyes).[1] However, despite the degeneration of photoreceptors, the nerve fibre and inner retinal cells (e.g., bipolar, horizontal, amacrine, and ganglion cells) remain largely preserved.[2]

The prevalence of retinitis pigmentosa is 0.04%.[3] The Foundation Fighting Blindness has estimated that it affects 1 in 3,500 Canadians: approximately 10,000 people in Canada and 4,000 people in Ontario have some form of retinitis pigmentosa.[4]

Clinical Need and Target Population

The Argus II retinal prosthesis system is the only surgical implantable device currently available to restore partial functional vision in patients with bare to no light perception as a result of advanced retinitis pigmentosa.[5] The Argus II system is the only retinal prosthesis approved by Health Canada. This HTA focusses on the Argus II device.

Technology

The Argus II system consists of three components. First, a 60-electrode array (~200 µm in diameter, ~575 µm centre-to-centre spacing) is surgically implanted on the epiretinal side of the retina, covering 11° x 19° of the visual field. Second, a miniature video camera is attached to a pair of glasses with telemetry coils on the arm. Third, the patient wears a video-processing unit on a belt or a strap.

In the Argus II system, the video camera captures visual images and converts them into electrical stimulation pulses in the video-processing unit. The video-processing unit then transmits the images wirelessly to the implant using an antenna. The implant emits small pulses of electricity, bypassing the damaged photoreceptors and stimulating the inner retinal cells. The stimulated retina cells then transmit the visual information to the brain via the optic nerve, and the induced vision is perceived as light patterns in the visual cortex.[5,6]

Regulatory Information

The Argus II retinal prosthesis system (Second Sight Medical Products, Inc.) is licensed by Health Canada (licence number 94430) as a class 3 device. It is intended to provide electrical stimulation of the retina to induce visual perception in people who are blind. It is indicated for use in individuals who meet the following criteria: adult; age 25 years or older; severe to profound outer retinal degeneration; some residual light perception; and a previous history of useful form vision. If no residual light perception remains, the retina must be able to respond to electrical stimulation (personal communication, Colin Foster, Regulatory Information Officer, Device Licensing Services Division, Medical Devices Bureau, Health Canada, May 2015).

Context

The Argus II retinal prosthesis system is uninsured in Ontario, and in other Canadian provinces and territories. There is no specific fee code in the Ontario *Schedule of Benefits for Physician Services* for retinal implantation (personal communication, Dr. Jude Coutinho, medical consultant, Ontario Medical Insurance Plan, Ontario Ministry of Health and Long-Term Care, May 2015).

The University Health Network (Toronto, Ontario) is the only centre in Canada that has implanted the Argus II retinal prosthesis system. Before Health Canada approved the device in 2014, it approved a plan for the University Health Network to conduct a 10-patient observational study. Patients were eligible for the study if they met all of the following criteria:

- Blindness with severe to profound retinitis pigmentosa
- Bare light perception or no light perception in both eyes (if the patient had no residual light perception, evidence of intact inner retinal function had to be confirmed)
- Age 40 years or older
- Previous history of useful vision
- Willing and able to receive recommended post-implant clinical follow-up, device fitting and visual rehabilitation
- Consent to implantation of the Argus II system

As of August 2015, four patients had received implants, and two additional patients had been identified for upcoming surgeries (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 2015).

The Argus II system received the CE mark in Europe in 2011.[7] In 2013, it received Humanitarian Device Exemption approval from the United States Food and Drug Administration, with funding available through the Centers for Medicare and Medicaid Services.[8,9] Specifically, the Centers for Medicare and Medicaid Services approved transitional pass-through payment status to provide additional payment for outpatient procedures under the hospital outpatient prospective payment system. This pass-through payment status covers the placement of a subconjunctival retinal prosthesis receiver and pulse generator, and the implantation of intraocular retinal electrode array with vitrectomy.[8] In addition, the new technology add-on payment provides inpatient payment for the Argus II system.[9]

Research Questions

- What is the clinical effectiveness and safety of the Argus II retinal prosthesis system in treating patients with no or bare light perception vision from advanced retinitis pigmentosa?
- What is the cost-effectiveness of the Argus II retinal prosthesis system compared with standard care in treating patients with retinitis pigmentosa in the context of the Ontario Ministry of Health and Long-Term Care?
- What is the budget impact of implementing the Argus II system over the next 5 years from the perspective of the Ontario Ministry of Health and Long-Term Care?
- What is the lived experience of retinitis pigmentosa, and how does the Argus II retinal prosthesis system impact the day-to-day quality of life of individuals using it?

CLINICAL EVIDENCE REVIEW

Objective

The objective of this review was to assess the clinical effectiveness and safety of the Argus II retinal prosthesis system in treating patients with no or bare light perception vision from advanced retinitis pigmentosa.

Methods

Research questions were developed by Health Quality Ontario in consultation with experts, end users, and/or applicants in the topic area.

Sources

We performed a literature search on June 22, 2015, using Ovid MEDLINE, Ovid Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects (DARE), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database, and National Health Service (NHS) Economic Evaluation Database, for studies published from January 1, 1946, to June 22, 2015.

Search strategies were developed by medical librarians using medical subject headings (MESH). See Appendix 1 for full details, including all search terms.

Literature Screening

A single reviewer reviewed the abstracts and, for those studies meeting the eligibility criteria, we obtained full-text articles. We also examined reference lists, health technology assessment websites, and the Google Scholar Citation Index for any additional relevant studies not identified through the literature search.

Inclusion Criteria

- English-language full-text publications
- Studies published between January 1, 1946, and June 22, 2015
- Randomized controlled trials, systematic reviews, meta-analyses, health technology assessments, observational studies, and case series
- Studies that examined the effect of the Argus II retinal prosthesis system in patients with advanced retinitis pigmentosa

Exclusion Criteria

- Non-human studies
- Editorials, abstracts, non-systematic reviews

Outcomes of Interest

- Visual function (e.g., object localization, motion detection, grating visual acuity)
- Functional outcomes (e.g., orientation and mobility)
- Quality of life
- Adverse events

Data Extraction

We extracted relevant data on study characteristics—including study design, sample size, follow-up duration, reported outcomes, and outcome definition—and we summarized them in tables.

Statistical Analysis

We did not pool the results of the studies, because of the small number of studies included and the heterogeneous outcomes reported. Instead, we summarized the results in tables and described them in the text.

Quality of Evidence

The quality of the body of evidence for each outcome was examined according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) Working Group criteria.[10] The overall quality was determined to be high, moderate, low, or very low using a step-wise, structural methodology.

Expert Consultation

We consulted with experts on the use of the Argus II retinal prosthesis system between May and September 2015. Experts included clinical ophthalmologists and retinal surgeons. The role of the expert advisors was to provide advice on research questions, review methods and review results, and to contextualize the evidence on the effectiveness and safety of the Argus II retinal prosthesis system. However, the statements, conclusions, and views expressed in this report do not necessarily represent the view of the consulted experts.

Results

Literature Search

The database search yielded 684 citations published between January 1, 1946, and June 22, 2015. After removing the duplicates, we reviewed titles and abstracts to identify potentially relevant articles. We obtained the full texts of these articles for further assessment. Ten studies (one systematic review and nine observational studies) met the inclusion criteria. We hand-searched the reference lists of the included studies, along with health technology assessment websites and citation indices, and identified two additional relevant studies (both observational studies).

Figure 1 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses.
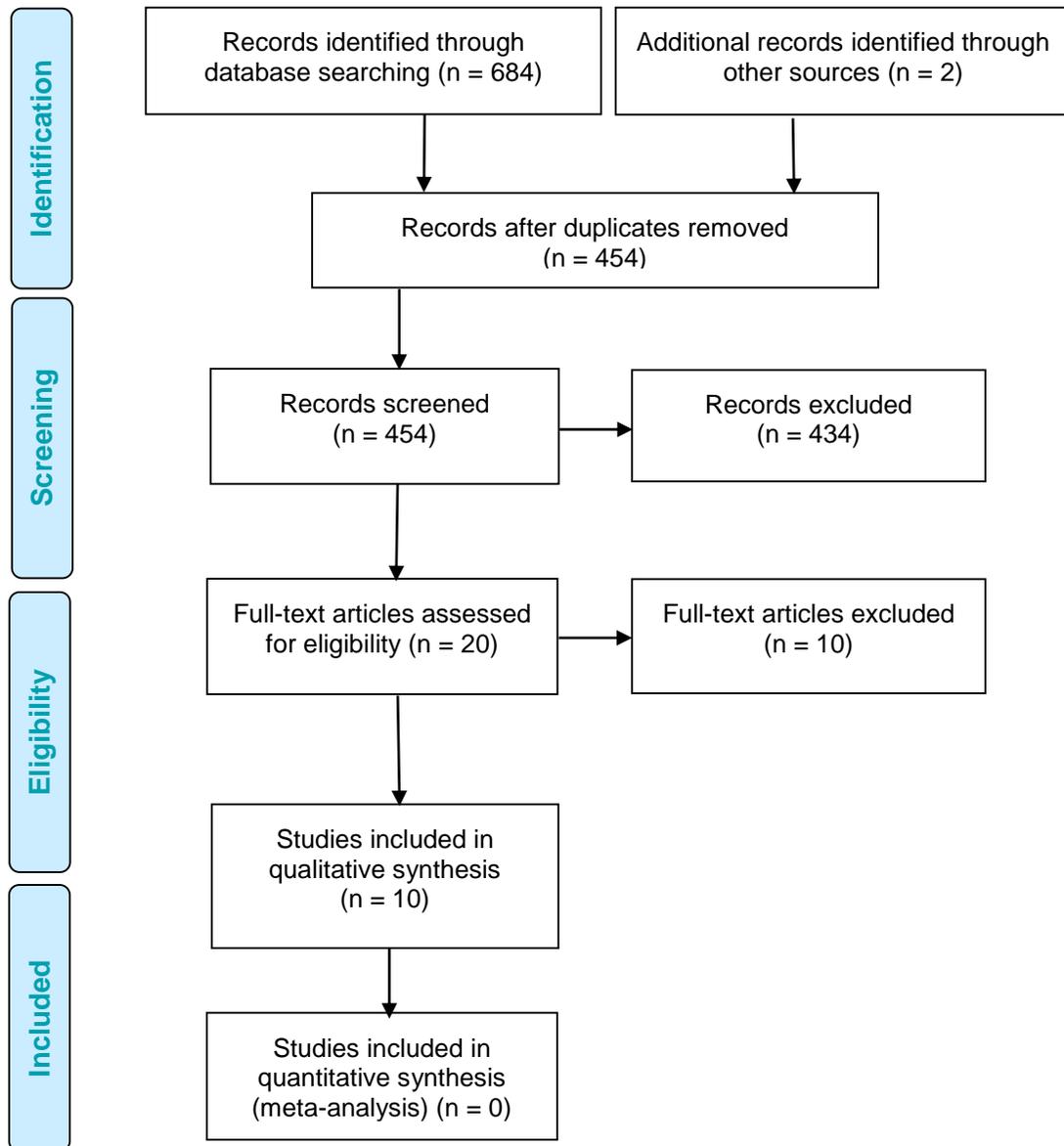
Figure 1: PRISMA Flow Diagram for the Clinical Review

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[11]

Eight of the 10 reports[12-19] published data from the Argus II International Study, an ongoing single-arm, prospective, unmasked clinical study that recruited 30 patients from 10 centres in the United States and Europe between June 6, 2007, and August 11, 2009. Patients were eligible if they had retinitis pigmentosa (United States) or outer retinal degeneration (Europe); bare or no light perception in both eyes; functional ganglion cells or optic nerve; and a history of useful form vision. The average age of patients at the time of implantation was 58 years (range 27 to 77 years), and 30% were women.

The primary outcomes of the Argus II International Study included visual acuity and safety. Secondary outcomes included activies of daily living, quality of life, orientation and mobility, spatial vision, and stability of the implant,[20] but the study protocol did not specify clinical measurements for these outcomes. Among the eight reports, two described multiple outcomes at 6 months of follow-up,[12] and at 1 and 3 years.[13] Four of the reports described a single outcome for the entire cohort,[14-17] and the remaining two reports described a single outcome for only the United Kingdom cohort.[18,19]

In addition to the large multicentre study, one smaller single-centre study of the Argus II retinal prosthesis system enrolled six patients for a follow-up period of 1 year.[21] The average age of the patients at the time of implantation was 45 years (range 30 to 59 years), and 17% were women.

The literature search also identified one systematic review on retinal implants.[22] This report evaluated the clinical availability, long-term biocompatibility, and potential for vision restoration of five retinal prostheses, including the Argus II system. The methodological quality of the studies of the Argus II system that included in the published review[12,16] were assessed seperately in this report, so the quality of the systematic review[22] was not assessed and will not be discussed further in this review.

Table 1 summarizes the characteristics of the nine included reports.

Table 1: Characteristics of Studies on the Argus II Retinal Prosthesis System

Author, Year	Sample Size, n	Follow-up Period	Outcomes
Argus II International Study[a]			
Humayun et al, 2012[12]	30	6 months	• Number, seriousness, and relatedness of adverse events • Object localization • Direction of motion • Grating visual acuity • Orientation and mobility
Ho et al, 2015[13]	30[b]	12 months 36 months	• Number, seriousness, and relatedness of adverse events • Object localization • Direction of motion • Grating visual acuity • Orientation and mobility • Activities of daily living • Quality of life
Ahuja et al, 2011[14]	27	2–28 months[c]	• Object localization
Dorn et al, 2013[15]	28	6–36 months[d]	• Direction of motion with 1:1 mapping
	11[e]		• Direction of motion with random mapping
Barry et al, 2012[16]	21	Not reported	• Eye-hand coordination
da Cruz et al, 2013[17]	21	9–35 months[c]	• Letter identification
	6[f]		• Letter-size reduction
	4[g]		• Word recognition
Kotecha et al, 2014[18]	6	Not reported	• Reach-to-grasp movement
Luo et al, 2015[19]	5	Not reported	• Reach-to-grasp movement with finger marker
Single-Centre Study			
Rizzo et al, 2014[21]	6[h]	1 week 3 months 6 months 12 months	• Number and type of adverse events • Object localization • Motion direction • Grating visual acuity • Mobility[i]

[a]Reports are organized by outcome. The first two reports described multiple outcomes for the entire cohort; the next four reports described a single outcome for the entire cohort; and the last two reports described a single outcome for only the United Kingdom cohort.
[b]One patient required explantation at 1.2 years.
[c]Based on duration of implantation.
[d]Performed during regular follow-up sessions (i.e., 3, 6, 12, 18, 24, and 36 months). Data reported were the latest available for each patient.
[e]This was a subset of patients who performed significantly better in the motion direction task with 1:1 mapping when the system was on, and who were available for the second test.
[f]This was a subset of patients who correctly identified ≥ 50% of the letters in each group within 60 seconds in the letter-identification task.
[g]This was a subset of patients who scored > 10 letters correct in the letter-size reduction task.
[h]One patient withdrew from the study a month after implantation.
[i]This outcome was measured only at 1-week follow-up.

Methodological Quality of the Included Studies

Complete results of the evidence quality assessment for included studies are presented in Appendix 2. Nine studies were deemed directly applicable or partially applicable to the research question. The quality of the evidence was moderate for object localization, direction of motion, grating visual acuity, orientation and mobility, eye-hand coordination, tasks on spatial resolution, activities of daily living, and quality of life.

Results for Visual Function

Table 2 presents the findings for visual function. With input from the low-vision research community, Second Sight Inc. (the manufacturer of the Argus II retinal prosthesis system) developed three computer-based, objective tests of basic visual skills to assess the range of low vision that could be restored by retinal implant.[13] Results were expressed as the percentage of patients who performed significantly better with the Argus II system on (versus off).

Table 2: Visual Function

Author, Year	6 Months	12 Months	36 Months
Object Localization[a]			
Humayun et al, 2012[12]	96.0% ($P < .05$)	—	—
Ho et al, 2015[13]	—	93.8% ($P < .05$)	89.3% ($P < .05$)
Ahuja et al, 2011[14]	96.0% ($P < .05$)[b]	—	—
Rizzo et al, 2014[21]	—	80.0%[c]	—
Direction of Motion[d]			
Humayan et al, 2012[12]	57.0% ($P < .05$)	—	—
Ho et al, 2015[13]	—	62.5% ($P < .05$)	55.6% ($P < .05$)
Dorn et al, 2013[15]	54.0% ($P < .05$)[e]	—	—
Rizzo et al, 2014[21]	—	60.0%[c]	—
Grating Visual Acuity[f]			
Humayun et al, 2012[12]	23.0% ($P < .05$)	—	—
Ho et al, 2015[13]	—	48.2% ($P < .05$)	33.3% ($P < .05$)
Rizzo et al, 2014[21]	—	20.0%[c]	—

[a]Patients to locate and touch a white square in random locations on a black monitor. Response error was measured by the distance (in cm) between the patient's touch and the square centre.
[b]Tests were performed from 2 to 28 months after implantation.
[c]P-value not reported.
[d]Patients to draw the path of a white line moving across a black monitor. Response error was measured by the difference (in degrees) between the response angle and the target bar angle.
[e]Tests were performed from 6 to 36 months after implantation.
[f]Patients to differentiate the orientation of black and white bars with different widths. Results indicated the percentage of patients who scored between 2.9 and 1.6 logMAR with the system on.

Comparing the Argus II system on versus off, the majority of patients performed significantly better on object localization,[12-14,21] and more than half of the patients performed significantly better on detecting direction of motion.[12,13,15,21] No patients performed significantly better when the Argus II system was off.

In addition to reporting improved accuracy in object localization (Table 3), Ahuja et al[14] also reported a significant improvement of 96% in repeatability for object localization with the system on. For the 11 patients who performed significantly better in 1:1 mapping of spatial information, 91% also performed significantly better in detecting spatial information in a scrambled setting (i.e., random scattered signal to the prosthesis).[15]

In the Argus II International Study, no patients could be scored for grating visual acuity when the system was off. Approximately one-third and one-half of the patients scored 2.9 logMAR or better with the system on at 12 months and 36 months, respectively.[13] Rizzo et al[21] reported that one patient (of five) scored 2.2 logMAR in the operative eye with the Argus II system on.

The quality of evidence for visual function was moderate (Table 3).

Table 3: GRADE Evidence Profile for Comparison of the Argus II Retinal Prosthesis System On and Off—Visual Function

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Object Localization							
4 (observational)[a]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Direction of Motion							
4 (observational)[a]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Grating Visual Acuity							
3 (observational)[c]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]Four papers published from two studies.

[b]The natural history of retinitis pigmentosa is a progressive deterioration of vision, eventually leading to blindness. The Argus II retinal prosthesis system is the only treatment option currently available to restore partial functional vision for these patients.

[c]Three papers published from two studies.

Results for Functional Outcomes

Table 4 presents findings for functional outcomes. Unless otherwise stated, results were expressed as the mean percentage of success on each task with the Argus II system on versus off.

Table 4: Functional Outcomes

Author, Year	6 Months	12 Months	36 Months
Orientation and Mobility (Find the Door)[a,b]			
Humayun et al, 2012[12]	54.0% vs. 27.0% ($P < .05$)	—	—
Ho et al, 2015[13]	—	53.0% vs. 30.8% ($P < .05$)	54.2% vs. 19.0% ($P < .05$)
Orientation and Mobility (Follow the Line)[a]			
Humayan et al, 2012[12c]	68.0% vs. 23.0% ($P < .05$)	—	—
Ho et al, 2015[13c]	—	72.8% vs. 17.1% ($P < .05$)	67.9% vs. 14.3% ($P < .05$)
Rizzo et al, 2014[21d]	100% vs. 0%[e,f]	—	—
Eye-Hand Coordination (Trace the Path)			
Barry et al, 2012[16g,h]	—	Reduced trace error by 60% ($P < .001$) Increased trace time by 211% ($P < .001$)	
Spatial Resolution (Letter and Word Reading)[a]			
da Cruz et al, 2013[17]	—	*Letter identification*[i] Group A: 72.3% vs. 17.7% ($P < .001$) Group B: 55.0% vs. 11.8% ($P < .001$) Group C: 51.7% vs. 15.3% ($P < .001$) *Letter size reduction* 6 of 6 patients were able to read letters of reduced size *Word recognition* 4 of 4 patients able to identify 2-, 3-, and 4-letter words	
Spatial Resolution (Reaching and Grasping)			
Kotecha et al, 2014[18j]	—	69.0% vs. 0%[a] ($P < .05$) 59.0% vs. 0%[k] ($P < .05$)	—
Spatial Resolution (Reaching and Grasping With Finger Marker)[a]			
Luo et al, 2015[19l]	—	77.5% vs. 0% (finger marker on) ($P < .05$) 71.3% vs. 0% (finger marker off) ($P < .05$)	

[a]Results are the mean percentage of success on each task with the Argus II system on versus off.
[b]Patients to walk across a room and find a simulated door. Success was defined as being able to touch the door.
[c]Patients to follow a white line on the floor. Success was defined as being able to end on the line at its end point.
[d]Patients to locate a bright light on the ceiling and walk along a dark line on the floor. Success was defined as being able to locate the light and walk along the line.
[e]Test was performed 1 week after implantation.
[f]P-value not reported.
[g]Patients to trace a series of paths with single-angle, mixed-angle, single-turn, and two-turn. Error measurement and trace times were recorded.
[h]No description on when the test was performed.
[i]Group A letters included those with only horizontal and vertical components (e.g., H, I, etc). Group B letters included those with oblique components involving the full height of the letter (e.g., A, M, W) or those with a minor variation on a circle (e.g., O, D, C). Group C letters included those with an oblique or curved element involving half the letter height (e.g., K, R).
[j]Patients to reach out and pick up a high-contrast cuboid object with the prosthesis in the "on," "off," or "scrambled" (i.e., random scattered signal to the prosthesis) setting. Success was defined as being able to grasp the object.
[k]Results expressed were the mean percentage of success on the task when comparing the Argus II system on the "scrambled" setting versus the "off" setting.
[l]Patients to locate, reach, and grasp a white cuboid object placed at random locations on a blacktop, with a flashing beacon as a finger marker. Success was defined as being able to grasp the object.

Patients performed significantly better in the Argus II International Study, with a higher mean percentage of success in both orientation and mobility tasks with the Argus II system on in all follow-up examinations.[12,13] The mobility task in Rizzo et al[21] was slightly different from that in the Argus II study, but all patients performed significantly better when the Argus II system was on.

For the task of tracing the path, Barry et al[16] reported that trace error was significantly lower and trace time was significantly longer in patients with the Argus II system on. Patients with the Argus II system on were able to identify significantly more letters in all groups than those with the system turned off.[17] A subgroup of high-performing patients were able to read a letter with reduced size and recognize words significantly better with the Argus II system on.[17]

Performance on the reaching and grasping tasks was significantly better with the Argus II system in the "on" or "scrambled" setting.[18] A finger marker (i.e., a flashing beacon) had no significant effect on reaching and grasping tasks when the Argus II system was on.[19]

The quality of evidence for functional outcomes was moderate (Table 5).

Table 5: GRADE Evidence Profile for Comparison of the Argus II Retinal Prosthesis System On and Off—Functional Outcomes

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Orientation and Mobility (Find the Door)							
2 (observational)[a]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Orientation and Mobility (Follow the Line)							
2 (observational)[a]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Eye-Hand Coordination (Trace the Path)							
1 (observational)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Spatial Resolution (Letter and Word Reading)							
1 (observational)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Spatial Resolution (Reaching and Grasping)							
1 (observational)	No serious limitations[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Spatial Resolution (Reaching and Grasping With Finger Marker)							
1 (observational)	No serious limitations[c]	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.
[a]Two papers published from one study.
[b]The natural history of retinitis pigmentosa is a progressive deterioration of vision, eventually leading to blindness. The Argus II retinal prosthesis system is the only treatment option currently available to restore partial functional vision for these patients.
[c]Conducted on a subset of patients only in the United Kingdom cohort. However, it is unlikely that the result would be different if the test were conducted in the entire cohort.

Results for Quality of Life

The Argus II International Study specifically developed the Functional Low-vision Observer Rated Assessment (FLORA) to evaluate the impact of the Argus II system on patients' everyday lives. Independent visual rehabilitation experts rated activities of daily living and quality of life based on patient interviews, observations of patients performing visual tasks and case study narratives from subjective judgement. The ratings were positive, mildly positive (i.e., patients' self-reported functional benefits that were not supported by assessors' observations), prior positive (i.e., patients' self-reported positive effects in the past that could not be demonstrated at the time of assessment), neutral, and negative.[23]

After 1 year of implantation, 80% of patients rated their experience as positive or mild positive, while 20% rated their experience as prior positive or neutral. After 3 years of implantation, 65.2% of patients rated their experience as positive or mild positive, while 34.8% rated it prior positive or neutral. No patients were rated their experience as negative at either follow-up point.[13]

The quality of evidence for quality of life was moderate (Table 6).

Table 6: GRADE Evidence Profile for Comparison of the Argus II Retinal Prosthesis System On and Off—Quality of Life

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Activities of Daily Living/ Quality of Life							
1 (observational)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[a]	⊕⊕⊕ Moderate

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]The natural history of retinitis pigmentosa is a progressive deterioration of vision, eventually leading to blindness. The Argus II retinal prosthesis system is the only treatment option currently available to restore partial functional vision for these patients.

Results for Adverse Events

The Argus II International Study classified adverse events as device-related, surgery-related, or patient-related, and by whether or not they met the regulatory definition of "serious." A serious adverse event required medical or surgical intervention or hospitalization to prevent permanent injury. An adverse event could be considered serious or non-serious depending on whether or how it was treated.

At 1 year after implantation of the Argus II system, the Argus II International Study reported a total of 18 serious adverse events in 10 out of 30 patients. The 10 types of serious adverse events were conjunctival erosion, hypotony, conjunctival dehiscence, presumed endophthalmitis, re-tack, corneal opacity, rhegmatogenous retinal detachment, tractional and serous retinal detachment, retinal tear, and uveitis.[13] Because of recurrent conjunctival erosions, one patient was explanted at 1.2 years.[12] The authors reported a change in the device design and surgical techniques over the course of the study, resulting in an improved safety profile. Aside from the event of explantation, 13 out of 17 serious adverse events occurred in the first 15 patients of the cohort, and the remaining 4 serious adverse events occurred in the last 15 patients.[12]

At 3 years after implantation, there were a total of 23 serious adverse events in 11 out of 29 patients. The serious events included those listed above, as well as infective keratitis and corneal melt. The majority of the serious adverse events (61%, 14 of 23) occurred within the first 6 months after implantation. Only five serious adverse events occurred after 12 months. The serious adverse events were clustered; more than one event occurred in the same patient. In the entire cohort, 19 experienced no serious adverse events. The report stated that all serious adverse events were managed by standard ophthalmic treatments.[13]

Rizzo et al[21] reported no serious adverse events that required surgical intervention or device explantation during the 12-month follow-up period. Postoperatively, one patient had elevated intraocular pressure (controlled medically), while another experienced moderate choroid detachment (resolved spontaneously).

Conclusions

Based on evidence of moderate quality, patients with severe vision loss from advanced retinitis pigmentosa showed significant improvement in visual function—including object localization, direction of motion, and grating visual acuity—with the Argus II retinal prosthesis system. These patients were also able to perform the real-life functional tasks of finding a door and following a line when the Argus II system was on. The retinal prosthesis also improved patients' quality of life. Although there were surgical and/or device-related complications in early experience of the Argus II system, it appeared that there was a trend toward an improved safety profile as the device design evolves and the surgeons refine their skills.

ECONOMIC EVIDENCE REVIEW

Objectives

The objective of this study was to review the literature on the cost-effectiveness of the Argus II retinal prosthesis system compared with standard care in patients with retinitis pigmentosa.

Methods

Sources

We performed an economic literature search on June 22, 2015, using Ovid MEDLINE (1946 to present), Ovid MEDLINE In-Process (1946 to present), Ovid Embase (1980 to 2015 week 25), Cochrane Central Register of Controlled Trials (to May 2015), Cochrane Database of Systematic Reviews, (2005 to May 2015), Database of Abstracts of Reviews of Effects (DARE) (to second quarter 2015), Centre for Reviews and Dissemination (CRD) Health Technology Assessment Database (to second quarter 2015), and National Health Service (NHS) Economic Evaluation Database (to second quarter 2015). We also reviewed reference lists of included economic literature for any additional relevant studies not identified through the systematic search.

Literature Screening

We based our search terms on those used in the clinical evidence review of this report and applied economic filters to the search results. Study eligibility criteria for the literature search are listed below. A single reviewer reviewed titles and abstracts and, for those studies meeting the inclusion/exclusion criteria, we obtained full-text articles.

Inclusion Criteria

- English-language full-text publications
- Published between January 1, 2000, and June 22, 2015
- Studies in patients with retinitis pigmentosa
- Studies reporting on the Argus II retinal prosthesis as an intervention
- Economic evaluations reporting incremental cost-effectiveness ratios (ICERs) (e.g., cost per quality-adjusted life-year (QALY)/life-year gained or cost per event avoided)

Exclusion Criteria

- Narrative reviews, letters/editorials, abstracts, posters, unpublished studies
- Studies in pediatric populations
- Foreign-language publications

Outcomes of Interest

- Full economic evaluations: cost-utility analyses, cost-effectiveness analyses, cost-benefit analyses

Data Extraction

We extracted relevant data on the following:

- Study characteristics (i.e., authors, year of publication)
- Population and comparator
- Interventions
- Outcomes (i.e., health outcomes, costs and cost-effectiveness)

Limitations

Only one reviewer screened the literature and abstracted the data.

Results

Literature Search

The database search yielded seven citations published between January 1, 2000, and June 22, 2015 (with duplicates removed). We excluded a total of five articles based on information in the title and abstract. We then obtained the full texts of two potentially relevant articles for further assessment. Figure 2 presents the flow diagram for the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA).
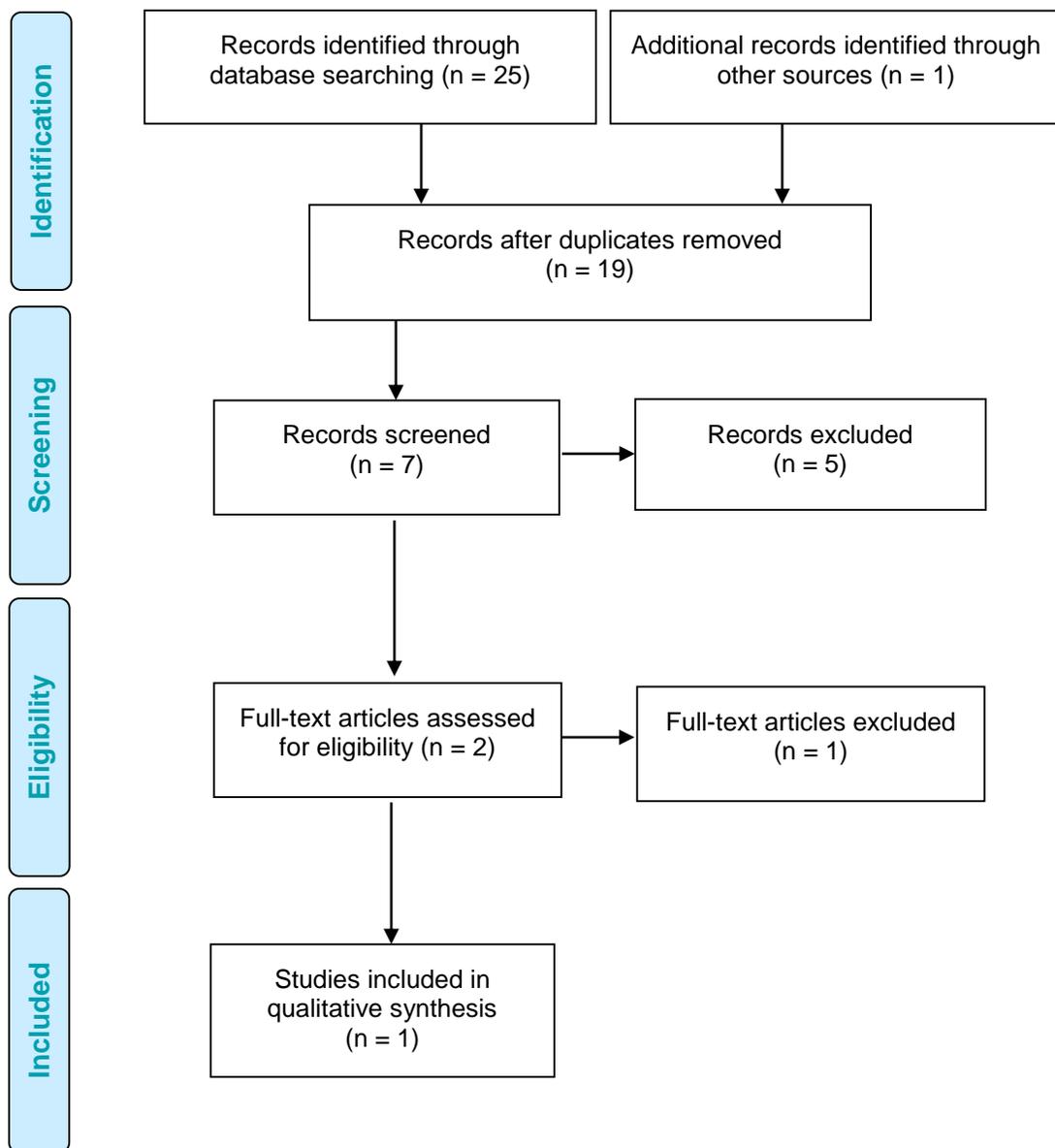
Figure 2: PRISMA Flow Diagram for the Economic Review

Abbreviation: PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses.
Source: Adapted from Moher et al.[11]

One study met the inclusion criteria. We hand-searched the reference lists of the included study to identify other relevant studies, but no additional citations were identified.

Critical Review

Vaidya et al[24] constructed a multi-state transition Markov model that compared the cost utility of the Argus II retinal prosthesis system with usual care in retinitis pigmentosa patients from the health care payer's perspective. The model followed a hypothetical cohort of patients aged 46 years and older over a lifetime horizon. Health outcomes were QALYs, costs, and ICERs.

The ICER for the Argus II was €14,603 per QALY in the base case analysis. The authors also conducted probabilistic sensitivity analyses and scenario analyses. They concluded that the Argus II was a cost-effective intervention compared to usual care.

This study had several limitations, however. The analysis was based on the results of a single non-randomized clinical trial of only 30 patients followed for 24 months, and the data were extrapolated for a lifetime. The costs and utility values applied in the model were taken from comparable patients with low vision. The authors of the study did not explain how different health states (i.e., visual acuity + with light perception, visual acuity ++ with counting fingers, and visual acuity +++ with reading letters) were defined based on functional vision. The study included an assumption that there was no decrease in visual acuity; instead, there was a progression in visual acuity of 10% annually, making the Argus II system very effective.

Table 7: Results of Economic Literature Review—Summary

Name, Year, Location	Study Design and Perspective	Population	Interventions/ Comparators	Results		
				Health Outcomes	Costs	Cost-Effectiveness

Vaidya et al, 2014,[24] United Kingdom	• Cost-effectiveness analysis (utility measured as QALYs)
	• Multi-state transition Markov model
	• Health care payer's perspective
		• N = 1,000
		• Mean age 46 years and older
		• Hypothetical cohort of patients with retinitis pigmentosa
			• Intervention: Argus II retinal prosthesis
			• Comparator: usual care
				• Expected QALYs:
				  ○ Base case analysis: Argus II, 7.34; usual care, 4.44
				  ○ Probabilistic sensitivity analysis: Argus II, 7.35; usual care, 4.44
					• 2014 Euros
					• Expected costs:
					  ○ Base case analysis: Argus II, €243,549; usual care, €201,094
					  ○ Probabilistic sensitivity analysis: Argus II, €243,511; usual care, €201,493
					• Discount rate: 3.5%
						Argus II vs. usual care (base case analysis): €14,603/QALY
						
						Argus II vs. usual care (probabilistic sensitivity analysis): €14,482/QALY

Abbreviations: QALY, quality-adjusted life-year.

Conclusions

Currently, there is no high-quality economic evaluation relevant to Ontario, Canada. As such, it was deemed important to conduct an economic evaluation specifically in the context of the province of Ontario.

PRIMARY ECONOMIC EVALUATION

The published economic evaluation identified in the literature review addressed the intervention of interest, but from a United Kingdom perspective. No published studies took a Canadian perspective. Owing to these limitations, we conducted a primary economic evaluation.

Objectives

This objective of this study was to assess the cost-effectiveness of the Argus II retinal prosthesis system compared with standard care in patients with retinitis pigmentosa within the context of the Ontario Ministry of Health and Long-Term Care.

Methods

The information presented in this report follows the reporting standards set out by the Consolidated Health Economic Evaluation Reporting Standards Statement.[25]

Type of Analysis

We conducted a cost-utility analysis to estimate the annual costs and health outcomes (i.e., QALYs) of the Argus II system.

Target Population

The study population were men and/or women aged 50 years and older presenting with retinitis pigmentosa, a hereditary genetic disease causing bilateral retinal degeneration.

Perspective

We conducted this analysis from the perspective of the Ontario Ministry of Health and Long-Term Care.

Interventions

We conducted evaluations for the Argus II retinal prosthesis system compared with standard care (i.e., rehabilitation or nursing).

Discounting and Time Horizon

We applied an annual discount rate of 5% to both costs and QALYs.[26] We used a 10-year time horizon for the base case analysis.

Model Structure/Structure of the Analysis

We developed a Markov cohort model to capture visual function—namely grating visual acuity (GVA) or no grating visual acuity (NGVA)—in retinitis pigmentosa patients fitted with the Argus II implant. The model followed a cohort for 10 years using a cycle length of 1 year (i.e., using a 1-year age structure). We compared this cohort with another that received standard care (i.e., rehabilitation or nursing care).

The Markov model included four health states:

- Patients with minimal or no light perception (retinitis pigmentosa state)
- Patients who received the Argus II implant and who had light perception but did not achieve grating visual acuity (NGVA state)
- Patients who received the Argus II implant and who had light perception and grating visual acuity (GVA state). These patients would be able to count fingers (based on communication with experts, manufacturers, and the literature)
- Death

The model began in the first stage, in which all individuals were diagnosed with retinitis pigmentosa and had bare or no light perception. After receiving the Argus II implants, patients would either enter one of two states: NGVA or GVA. After implantation, patients could return to the retinitis pigmentosa state if the Argus II device was removed due to severe adverse events or complications with the device itself. Patients in the GVA state might move to NGVA in subsequent years as a result of a decrease in visual acuity. Patients in the NGVA state would not move up to the GVA state, under the assumption that patients would achieve their best visual outcomes after the first year of implantation. We followed the Argus II implant cohort for 10 years. Death was the absorbing state for patients who died during the time horizon of the model. A schematic diagram of the Markov model is presented in Figure 3.
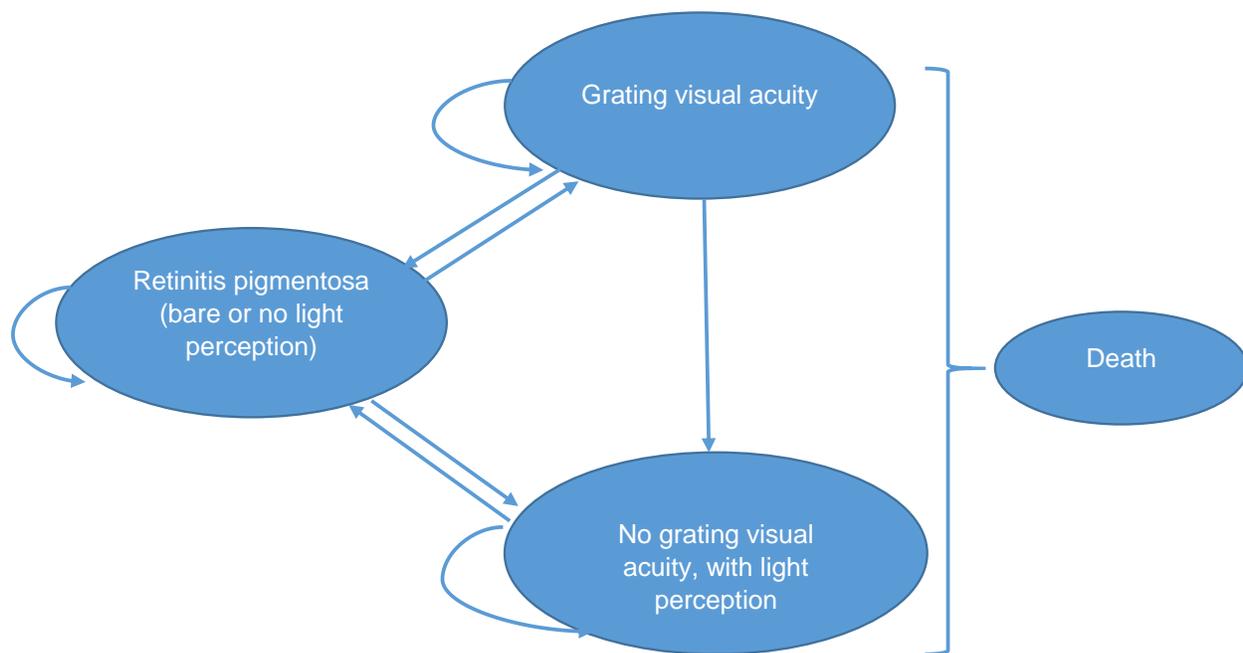
Figure 3: Markov Model for Argus II Implantation in Patients With Retinitis Pigmentosa

Definition of Grating Visual Acuity
Grating visual acuity was defined as reliably achieving a score of 2.9 and 1.6 logMAR on the scale of visual acuity with the Argus II system on.(7)

Transition Probabilities
To determine transition probabilities, we applied 3-year results from a controlled, non-randomized, prospective, multicentre study conducted in 10 sites in Europe and in the United States.[12,13]

The study reported primary outcomes for visual function, using three different visual acuity tests: square localization, direction of motion, and GVA. We selected GVA as the visual outcome for the Markov model, because we could assign utility weights for patients who did or did not achieve GVA based on expert consultation and the existing literature. We used clinical data from years 1 and 3 to calculate the yearly vision transition probability, using formulae reported elsewhere.(8) Transition probabilities are shown in Table 8. Using the available clinical data, patients fitted with the Argus II system could move from the GVA state to the NGVA state in the model, but not the reverse, based on the assumption that they would reach their best possible vision at the time of implantation. The yearly visual transition probability was assumed to be constant for the rest of the time horizon of the model.

Table 8: Model Variable Inputs Used in the Base Case Analysis

Model Parameters	Value	Range	Reference
Probability of severe adverse events resulting from Argus II implantation in the first year	0.3333	0.2499–0.4166	Humayun et al, 2012[12]
Annual probability of severe adverse events in subsequent years	0.0465	0.0349–0.0581	Ho et al, 2015, and Humayun et al, 2012, plus calculation[12,13]
Probability of patients achieving GVA after Argus II implantation in the first year	0.4820	0.3615–0.6025	Humayun et al, 2012[12]
Annual probability of patients moving from GVA to NGVA in subsequent years	0.1688	0.1266–0.2110	Ho et al, 2015, and Humayun et al, 2012, plus calculation[12,13]
Probability of Argus II explantation	0.0333	0.0249–0.0416	Humayun et al, 2012[12]

Abbreviations: GVA, grating visual acuity; NGVA, no grating visual acuity.

Argus II Explantation Probability
Data from the study described above showed that only one patient had the device removed at 1.2 years due to severe adverse events.[12,13] We assumed a one-time explantation for the 10-year time horizon of our model; once the device was extracted, the patient would return to the retinitis pigmentosa state.

Clinical Outcome and Utility Parameters

We quantified health outcomes as QALYs. The Argus II retinal prosthesis is expected to improve the quality of life of people with retinitis pigmentosa by improving their visual acuity. We applied various utility weights according to patients' visual acuity before and after Argus II implantation (Table 9). We based the utility weight for individuals with retinitis pigmentosa on the time trade-off method for people with no light perception.[27] We based the utility weight for individuals who received Argus II implants and had light perception but did not achieve GVA on the time trade-off method for people with light perception.[28] We based the utility weight for individuals who could count fingers and achieved GVA after receiving Argus II implants on the time trade-off method for people who could count fingers.[28]

Table 9: Utilities Used in the Economic Model

Health State	Utility	Range	Reference
Retinitis pigmentosa, no light perception	0.26	0.19–0.33	Brown et al, 2001[27]
NGVA, light perception	0.35	0.33–0.60	Brown et al, 1999[28]
GVA	0.52	0.36–0.68	Brown et al, 1999[28]

Abbreviations: GVA, grating visual acuity; NGVA, no grating visual acuity.

Cost Parameters

Costs included those for the device, the procedure, and maintenance. Table 10 summarizes the main cost parameters for the cost-effectiveness model. Information was provided by the University Health Network, the only centre in Canada that can perform Argus II implants at present (personal communication, Dr. Marnie Weber, University Health Network, August 2015). Appendix 3 provides a detailed breakdown of the unit costs related to the Argus II surgery.

The annual treatment cost for patients who did not receive Argus II implants was taken from a study by Frick et al.[29] Costs from Frick et al, reported in 2012 US dollars, were converted to 2015 Canadian dollars using purchasing power parity from the Bank of Canada.[30]

The Frick et al study[29] divided patients into "RP" (retinitis pigmentosa) and "non-RP" (no retinitis pigmentosa) cohorts. In our model, annual treatment costs for patients who were fitted with the Argus II system and achieved GVA were assumed to be the same as for the non-RP cohort. Annual treatment costs for patients fitted with the Argus II system who did not achieve GVA but had light perception were assumed to be the average of the annual treatment costs for the RP and non-RP cohorts. We deemed this assumption to be reasonable, and conducted sensitivity analyses for its upper and lower limits.

We calculated the costs of severe adverse events based on expert consultation (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 18, 2015). Severe adverse events associated with the Argus II implants included retinal detachment and infections. Of the patients who had infections, 90% were managed in an outpatient setting (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 18, 2015). The treatment for most infections is a single injection of vancomycin 1 mg/0.1 mL and ceftazidime 2.25 mg/0.1 mL. One or two additional office visits would be required to treat an infection.

Table 10: Costs Used in the Economic Model

Variable	Base Case Value	Range	Reference
Cost of Argus II device and implantation	$215,768	$161,826–$269,710	UHN[a]
Cost of Argus II annual device maintenance	$8,270	$6,203–$10,338	UHN[a]
Annual cost of treatment for patients who received standard care	$15,777	$13,628–$16,498	Frick et al, 2012 [29]
Annual cost of treatment for patients who did not achieve GVA after the Argus II implant	$13,133	$11,317–$13,761	Frick et al, 2012 [29] plus assumptions
Annual cost of treatment for patients who achieved GVA after the Argus II implant	$10,490	$9,007–$11,023	Frick et al, 2012 [29] plus assumptions
Annual cost of treatment for severe adverse events	$333	$250–$416	UHN[a]
Cost of Argus II device explantation	$5,042	$3,737–$6,347	UHN[a]

Abbreviations: GVA, grating visual acuity; UHN, University Health Network.
[a]Cost data were provided in the submission for the review of Argus II (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 18, 2015, and Dr. Marnie Weber, University Health Network, August 25, 2015).

Analysis

The primary outcome of the base case analysis was ICERs comparing the Argus II system with standard care. We calculated ICERs by taking the difference in expected costs between the Argus II device and standard care, divided by the difference in expected QALYs produced by these two interventions.

We assessed the variability and uncertainty of model parameters by conducting one-way and probabilistic sensitivity analyses. For the one-way sensitivity analyses, we varied model variables over plausible ranges and examined the impact on ICER values. Table 11 shows the ranges applied.

Table 11: Model Parameter Values and Ranges Varied in One-Way Sensitivity Analyses

Variable	Range	Reference
Disease Transition Probability		
Probability of severe adverse events resulting from Argus II implantation in the first year	0.2499–0.4166	Humayun et al, 2012[12]
Annual probability of severe adverse events in subsequent years	0.0349–0.0581	Ho et al, 2015, and Humayun et al, 2012, plus calculation[12,13]
Probability of patients achieving GVA after Argus II implantation in the first year	0.3615–0.6025	Humayun et al, 2012[12]
Annual probability of patients moving from GVA to NGVA in subsequent years	0.1266–0.2110	Ho et al, 2015, and Humayun et al, 2012, plus calculation[12,13]
Probability of Argus II explantation	0.0249–0.0416	Humayun et al, 2012[12]
Utility Value		
Retinitis pigmentosa, no light perception	0.19–0.33	Brown et al, 2001[27]
NGVA, light perception	0.33–0.60	Brown et al, 1999[28]
GVA	0.36–0.68	Brown et al, 1999[28]
Cost Data		
Cost of Argus II device	$151,385–$252,309	UHN[a]
Cost of Argus II implantation	$161,826–$269,710	UHN[a]
Cost of Argus II annual maintenance	$6,203–$10,338	UHN[a]
Annual cost of treatment for patients who did not receive Argus II implants	$13,628–$16,498	Frick et al, 2012[29]
Annual cost of treatment for patients who did not achieve GVA after the Argus II implant	$11,317–$13,761	Frick et al, 2012[29] and assumptions
Annual cost of treatment for patients who did achieve GVA after the Argus II implant	$9,007–$11,023	Frick et al, 2012[29] plus assumptions
Annual cost of treatment for severe adverse events	$250–$416	Expert opinion
Cost of Argus II device explantation	$3,737–$6,347	UHN[a]

Abbreviations: GVA, grating visual acuity; NGVA, non-grating visual acuity; UHN, University Health Network.
[a]Cost data were provided in the submission for the review of Argus II (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 18, 2015, and Dr. Marnie Weber, University Health Network, August 25, 2015).

To determine the impact of simultaneously varying numerous variables within the assigned distributions, we conducted a probabilistic sensitivity analysis by running 1,000 simulations of the model parameters. The distributions are presented in Table 12.

Table 12: Model Parameter Values and Distributions for Probabilistic Sensitivity Analyses

Model Parameters	Value	Distribution
Probability of severe adverse events resulting from Argus II implantation in the first year	0.3333	Beta (α = 10; β = 20)
Probability of patients achieving GVA after Argus II implantation in the first year	0.4820	Beta (α = 14; β = 15)
Probability of Argus II explantation	0.0333	Beta (α = 1; β = 29)
Utility Value		
Retinitis pigmentosa, no light perception	0.26	Beta (α = 124.8; β = 355.2)
NGVA, light perception	0.35	Beta (α = 5.18; β = 9.62)
GVA	0.52	Beta (α = 36.72; β = 31.28)
Cost Value		
Cost of Argus II device and implantation	$215,768	Gamma (α = 24.99; λ = 1.16)
Cost of Argus II annual maintenance	$8,270	Gamma (α = 25; λ = 0.003)
Annual cost of treatment for severe adverse events	$333	Gamma (α = 24.99; λ = 0.09)

Abbreviations: GVA, grating visual acuity; NGVA, non-grating visual acuity.

Generalizability

The findings of this economic analysis cannot be generalized to all patients with retinitis pigmentosa. They may, however, be used to guide decision-making about the specific patient populations addressed in the trials investigated by Health Quality Ontario.

Expert Consultation

Whenever additional evidence was needed on the disease, we conducted expert consultation.

Results

Base Case Analysis

Results of the base case analysis are shown in Table 13.

Table 13: Base Case Analysis Results

Strategy	Average Total Cost	Incremental Cost[a]	Average Total Effect	Incremental Effect[b]	ICER[c]
Standard care	$126,428	—	2.08	—	—
Argus II	$361,034	$234,606	3.21	1.13	$207,616

Abbreviations: ICER, incremental cost-effectiveness ratio.
[a]Incremental cost = average cost (Argus II) – average cost (standard care).
[b]Incremental effect = average total effect (Argus II) – average total effect (standard care).
[c]ICER = incremental cost/incremental effect.

Sensitivity Analysis

One-Way Sensitivity Analysis

The results of the one-way sensitivity analysis are presented in Figure 4. The model was most sensitive to the health-related utility of all patients; of patients who achieved GVA; of patients who did not achieve GVA but had light perception; the cost of Argus II implantation; and the cost of the Argus II device.

Figure 4: One-Way Sensitivity Analysis: Argus II Versus Standard Care[a]
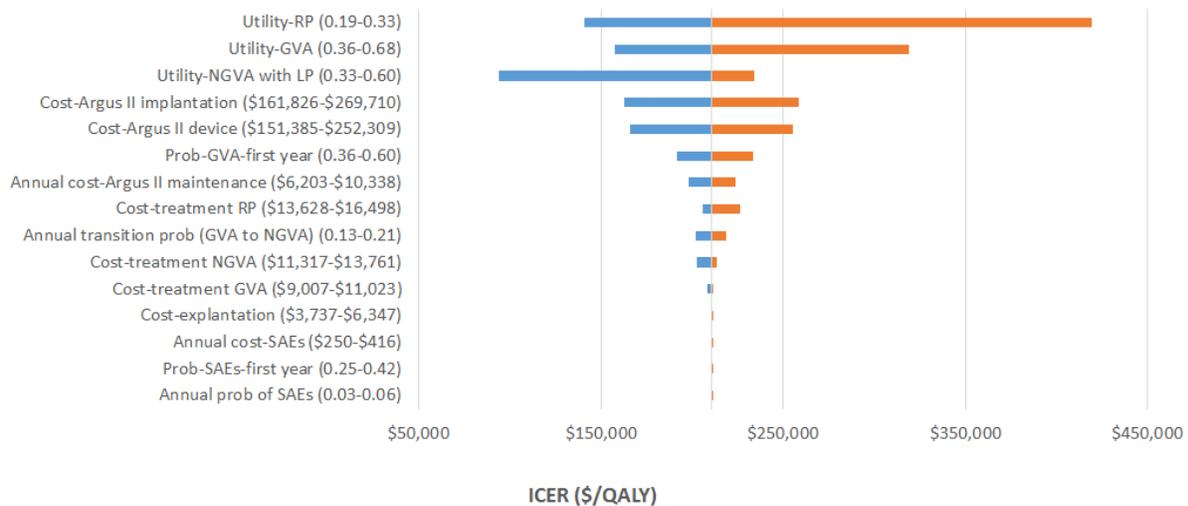
Abbreviation: GVA, grating visual acuity; ICER, incremental cost-effectiveness ratio; LP, light perception; NGVA, no grating visual acuity; QALY, quality-adjusted life-year; RP, retinitis pigmentosa; SAE, severe adverse event.

[a]X-axis represents range of ICERs when base-case values are varied (ranges shown in parentheses). Vertical line represents the ICER for the Argus II system ($207,616 per QALY gained).

Probabilistic Sensitivity Analysis

We ran a total of 1,000 simulations of the decision-analytic model comparing the Argus II system with standard care, using random draws of all model parameters within the assigned distributions. Results are presented in Figure 5. Assuming a willingness-to-pay threshold of $50,000 per QALY, there was no chance that the Argus II system would be cost-effective. At a willingness-to-pay threshold of $100,000 per QALY, there was a 21% chance that the Argus II system would be cost-effective. At a willingness-to-pay threshold of $200,000 per QALY, there was a 45% chance that the Argus II system would be cost-effective.

Figure 5: Cost-Effectiveness Acceptability Curve, Argus II Versus Standard Care
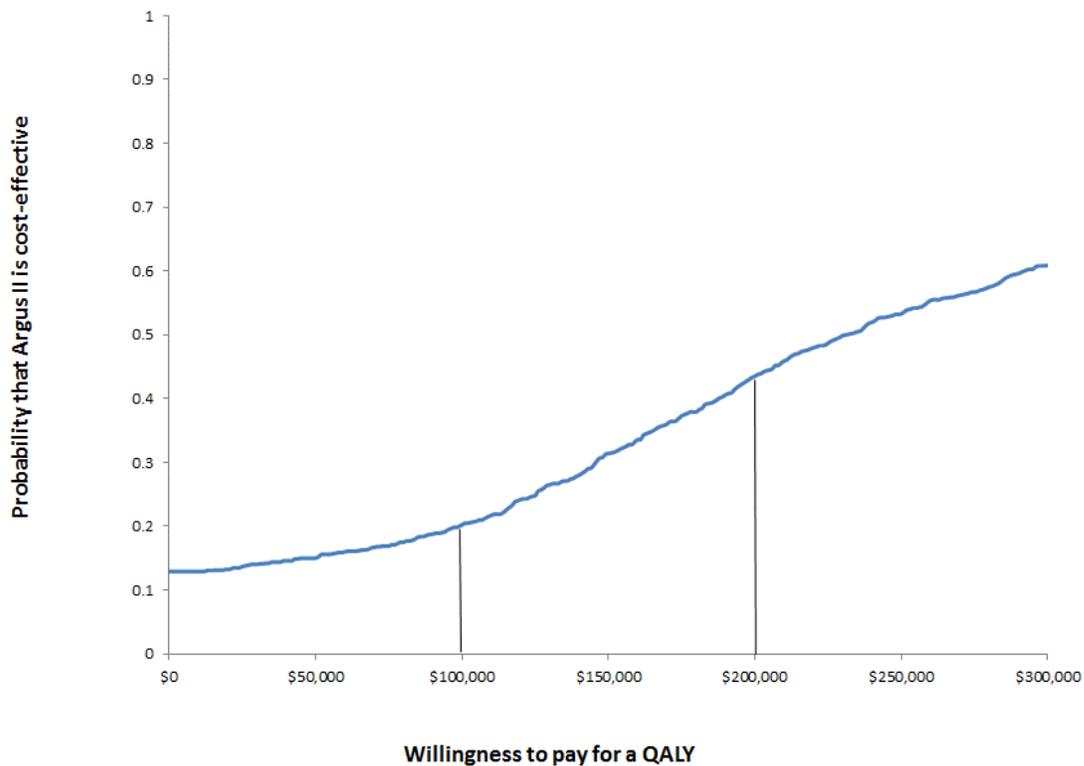
Abbreviation: QALY, quality-adjusted life-year.

Limitations

This analysis shares the general limitations of economic modelling. It was based on data from only 30 Argus II patients followed for 3 years. Data from more patients with longer follow-up would provide an opportunity to consolidate the results of our analysis.

In the absence of treatment costs from a Canadian context, we used data from the literature in a similar patient population and health care structure. No utility data were available at the time of analysis, so we used data from comparable patients with low vision function. Our model did not capture any disutility resulting from severe adverse events or Argus II explantation.

Discussion and Conclusions

Resources for health care are scarce relative to needs or wants, and an economic evaluation is intended to inform the choices that decision-makers face in these circumstances. This study investigated resource allocations and the cost-effectiveness of the Argus II system compared with standard care. Implantation of the Argus II system can improve the quality of life of retinitis pigmentosa patients who are legally blind, and no other treatment option is available for this disease. However, treatment would cost $207,616 per QALY gained. Sensitivity analyses showed that the model parameters were robust.

BUDGET IMPACT ANALYSIS

We conducted a budget impact analysis from the perspective of the Ontario Ministry of Health and Long-Term Care to determine the estimated cost burden of the Argus II system over the next 5 years. All costs are reported in 2015 Canadian dollars.

Objectives

The objective of this study was to determine the budget impact of implementing the Argus II system over the next 5 years from the perspective of the Ontario Ministry of Health and Long-Term Care.

Methods

Target Population

The target population was patients with retinitis pigmentosa who were eligible for Argus II implantation.

Resource

At present, only one centre in Ontario (University Health Network) performs Argus II implantation in patients with retinitis pigmentosa. Using a conservative approach, we assumed that there would be four implants performed each year in Ontario. We also assumed that this number of Argus II implants would remain constant over the next 5 years. (Public comment, February 4, 2016, Dr. Robert Devenyi, Ophthalmologist in Chief, University Health Network.)

Table 14: Number of Patients Expected to Receive Argus II Implants in Ontario, 2015 to 2019

Year	Patients per Year Post-implant					Total Patients, n
	Year 1	Year 2	Year 3	Year 4	Year 5	
2015	4	—	—	—	—	4
2016	4	4	—	—	—	8
2017	4	4	4	—	—	12
2018	4	4	4	4	—	16
2019	4	4	4	4	4	20

Canadian Costs

Except for treatment costs for standard care (which were assumed to be the same as those for patients who did not receive the Argus II implant in a published study[29]) all costs used in the budget impact analysis were Ontario-specific and provided by the University Health Network (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 31, 2015). All costs were expressed in 2015 Canadian dollars.

We calculated budget impact based on the estimated number of Argus II implants to be done at the University Health Network over the next 5 years (see above), using the cost of the Argus II device and surgery for each new implant, plus the annual maintenance cost. Cost details are provided in Table 15. A detailed breakdown of costs is provided in Appendix 3.

Table 15: Costs for Argus II Implantation

Resource Items	Cost	Source
Argus II device cost	$201,847	UHN[a]
Argus II implantation cost	$13,921	UHN[a]
Total cost per Argus II implant	$215,768	UHN[a]
Argus II device annual maintenance cost	$8,270	UHN[a]

Abbreviation: UHN, University Health Network.
[a]Cost data were provided in the submission for the review of Argus II (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 18, 2015, and Dr. Marnie Weber, University Health Network, August 25, 2015).

We assumed that in the year the system was implanted, only the device and surgery costs would be incurred, and that maintenance and treatment costs would be incurred in subsequent years. Costs were taken from the cost-effectiveness model (Table 10). Average costs per year per patient (Argus II implant and standard care) are presented in Table 16.

Table 16: Average Cost Per Retinitis Pigmentosa Patient Per Year

Therapy	Year Post-Implantation				
	Year 1	Year 2	Year 3	Year 4	Year 5
Argus II[a]	$215,878[c]	$19,135[d]	$18,435	$17,608	$16,843
Standard care[b]	$15,777	$15,742	$15,703	$15,662	$15,616

[a]Cost data were provided in the submission for the review of Argus II (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 18, 2015, and Dr. Marnie Weber, University Health Network, August 25, 2015). Costs decreased over time for both Argus II and standard care as a result of mortality from conditions unrelated to retinitis pigmentosa.
[b]Source: Frick et al, 2012.[29] Costs in the first year and subsequent years included treatment costs for patients with retinitis pigmentosa.
[c]Costs in the first year of Argus II implantation included the following: the Argus II device; health care labour, including rehabilitation, pre- and postoperative eye exams, Argus II system activation and fitting; surgical procedures, including instruments and supplies; and severe adverse events (if incurred). A detailed breakdown of the costs is shown in Appendix 3.
[d]Costs in the years following Argus II implantation included the following: Argus II maintenance; treatment for patients achieving NGVA; treatment for patients achieving GVA; severe adverse events (if incurred); and Argus II explanation (if incurred). Costs were calculated based on the proportion of patients who achieved NGVA and GVA after Argus II implant.

Analysis

Assuming that the price of the Argus II device would decrease in the future, we conducted sensitivity analyses varying the price of the Argus II device by 5%, 10% and 15%. Other parameters remained unchanged.

Results

Base Case Analysis

The expected budget impact of Argus II implantation for the next 5 years is presented in Table 17.

Table 17: Budget Impact of Adopting the Argus II System in Ontario, 2015 to 2019

Year	Strategy	Cost per Year Post-implantation, $					Total, $
		Year 1	Year 2	Year 3	Year 4	Year 5	
2015	Argus II	863,512	—	—	—	—	863,512
	Standard care	63,108	—	—	—	—	63,108
	Net budget impact	**800,404**	**—**	**—**	**—**	**—**	**800,404**
2016	Argus II	863,512	76,540	—	—	—	940,052
	Standard care	63,108	62,968	—	—	—	126,076
	Net budget impact	**800,404**	**13,572**	**—**	**—**	**—**	**813,976**
2017	Argus II	863,512	76,540	73,740	—	—	1,013,792
	Standard care	63,108	62,968	62,812	—	—	188,888
	Net budget impact	**800,404**	**13,572**	**10,928**	**—**	**—**	**824,904**
2018	Argus II	863,512	76,540	73,740	70,432	—	1,084,224
	Standard care	63,108	62,968	62,812	62,648	—	251,536
	Net budget impact	**800,404**	**13,572**	**10,928**	**7,784**	**—**	**832,688**
2019	Argus II	863,512	76,540	73,740	70,432	67,372	1,151,596
	Standard care	63,108	62,968	62,812	62,648	62,464	314,000
	Net budget impact	**800,404**	**13,572**	**10,928**	**7,784**	**4,908**	**837,596**

Note: numbers may appear inexact due to rounding.

Sensitivity Analysis

Table 18 presents the results of the sensitivity analysis, reflecting a decrease in price of the Argus II device.

Table 18: Budget Impact of Price Reduction for the Argus II Device

Year	Budget Impact of Argus II Price Reduction		
	5%	**10%**	**15%**
2015	757,228	714,053	670,877
2016	770,800	727,625	684,449
2017	781,728	738,553	695,377
2018	789,512	746,337	703,161
2019	794,420	751,245	708,069

Limitations

One limitation was the absence of information about treatment costs from an Ontario context. The treatment costs used in this analysis may be higher than in reality and as a result, the results of this analysis may be an overestimate.

Discussion and Conclusions

The Argus II system is a novel technology that requires surgical intervention and incurs considerable costs. If over the next 5 years, four Argus II implantations could be performed in Ontario in each year and over the next 5 years, the budget impact of funding the procedure on patients with Retinitis Pigmentosa in one Ontario centre would be $800,404, $813,976, $824,904, $832,688 and $837,956, from 2015 to 2019, respectively. Results from sensitivity analyses indicated that there would be potential savings if the price of the Argus II device were to decrease in the future.

PUBLIC AND PATIENT ENGAGEMENT ANALYSIS

Background

The primary aim of public and patient engagement in the context of health technology assessment is to "ensure that assessments and decisions are informed by the unique perspectives of those with the lived experience of a health condition and its management."[31]

Patient and caregiver input can serve as a unique source of evidence about the personal impact of a disease or condition and how technologies can make a difference in people's lives. It can also identify gaps or limitations in the published research (for example, outcome measures that do not reflect what is important to patients and/or caregivers).[32-34] Patient, caregiver and public input can also provide additional information or perspectives on the more general ethical and social-values implications of technologies and treatments.

Regaining some, if any, function of the retina is perceived as having a direct impact on the quality of life of someone with vision loss due to retinitis pigmentosa. To better understand how the Argus II retinal prosthetic system might affect a person's quality of life, we decided to speak directly with those who have experienced the condition and the intervention. Understanding and appreciating day-to-day functioning in this population helps to contextualize the potential value of the intervention.

Methods

Activity and Rationale

The engagement typology we selected for this health technology assessment was a consultation.[35] *Consultation* refers to the process of gathering information (for example, social values, experiential input) from the public, patients, and caregivers.[36] In particular, we selected a qualitative design focused on an interview methodology to examine the lived experience of people with retinitis pigmentosa and of people who have undergone implantation of the Argus II retinal prosthetic system.

The qualitative interview seeks to describe the lived reality of the subjects. In this way, the main task in qualitative interviewing is to understand the meaning of what participants say.[37] Interviews are particularly useful for getting the story behind a participant's experiences, which was the objective in this portion of the health technology assessment. The sample size and the sensitive nature of exploring quality-of-life issues also provided rationales for selecting interviews for this project.

Recruitment

We used purposive sampling[38-41] to recruit individuals with personal experience of the situation being investigated. At the outset of this health technology assessment, only four Canadians had received the Argus II system. We attempted to recruit these individuals through the University Health Network, which had an established relationship with them. Initially, Health Quality Ontario invited two individuals to participate in an interview, but only one responded.

To reach people who live with retinitis pigmentosa, we contacted the Canadian National Institute for the Blind. We reached two individuals who live with the condition at different levels of progression.

We did not pursue theoretical saturation because so few individuals with retinitis pigmentosa have undergone the intervention.[41]

Interview Questions

For the purposes of this assessment, we conducted semi-structured interviews consisting of a series of open-ended questions. Questions for the interview were based on a list developed by the Health Technology Assessment international Interest Group on Patient and Citizen Involvement in HTA to elicit lived experience specific to the impact of a health technology on lived experience and quality of life.[42]

The purpose and the broader health technology assessment evaluation process was explained to interviewees and consent was granted via a consent form. The letter of information and consent form are attached as Appendix 4. Interviews were recorded and transcribed.

Interview questions focused on how retinitis pigmentosa affects quality of life and each participant's experiences with other health interventions related to managing the condition. For the interview with the person who received the Argus II implant, additional questions focused on experiences with the procedure itself, any postoperative rehabilitation, and any perceived benefits or limitations of the technology. The interview guide is attached as Appendix 5.

Analysis

We selected a modified version of a grounded theory methodology to analyze information from the interviews, because it captured elements of the lived experience with retinitis pigmentosa and of Argus II. The inductive nature of grounded theory follows an iterative process of eliciting, documenting and analyzing responses while simultaneously collecting and analyzing data using a constant comparative approach.[43,44] In this way, we coded transcripts and compared themes. This approach allowed us to identify and interpret patterns in the interview data about the meaning and implications of the intervention for participants' quality of life.

Results

Gradual but Persistent Progression

Retinitis pigmentosa progresses gradually, typically starting in childhood and proceeding into adulthood at a varying rate. Participants described the progressive nature of retinitis pigmentosa as both positive and negative: positive because there was an opportunity to adapt over time, but negative because there was no way to slow the progression. Participants indicated that they sometimes felt stigma, especially when they were younger, because their normal appearance caused some people to accuse them of pretending to be visually impaired.

Impact of Retinitis Pigmentosa on Quality of Life

All participants described retinitis pigmentosa as having a significant impact on their quality of life. Participants were generally high-functioning and able to accomplish a variety of day-to-day tasks. Still, all participants indicated that they relied heavily on the support of family members. Participants focused on the importance of planning, organizing, and adapting to their environment to meet their accessibility needs. They also spoke about how vision loss limited their mobility, restricted their access to information (print or online), and reduced their opportunity to forge a career path. They spoke about how retinitis pigmentosa constrained their

ability to make life choices; for example, the need to live near accessible transit routes limited their choice of accommodation type and the communities where they could live.

Participants indicated how their attitude was a key determinant in overcoming challenges, being adept planners, and facing barriers. They described a strong will and determination as essential attributes:

> Any barrier or any disability is very much a matter of attitude. I don't allow my vision loss to become something that defines restrictions for me in my life.

> If you're a person who is not outgoing, resourceful, resilient, and the type of personality where you let barriers get in your way—if you're not obstinate, stubborn, and strong-willed—then vision loss is going to affect you very differently.

Accessibility Challenges

Participants described accessibility as the biggest limiting factor in their life. Individuals described how physical and virtual environments are not designed for those with vision loss. While some accessibility measures have made navigating these worlds easier, many barriers remain. For example, most Internet content is not readable or accessible for individuals with vision loss, despite the introduction of screen readers and accessible websites.

Participants noted that mobility, transport, and access to information were the biggest frustrations. As a result, participants described episodes of isolation. They also discussed the considerable expense associated with modifying their environment or obtaining supports to help them adapt to or navigate in their environments (for example, technology or a tandem bike).

Impact on Family

Participants spoke about the commitment and sacrifice of loved ones in helping them adapt, plan, and organize. They indicated that they were dependent on their loved ones, and how they perceived that as burdensome sometimes.

That said, they also talked about how loved ones can develop a sense of responsibility and independence in being given tasks to accomplish that developed skills, such as money management and organization.

> My daughter had to mature very quickly from when she was little because she had to help Mom with all these things. So she learned how to shop, how to save, how to spend and how to pay bills out of necessity, but it benefitted her when she grew up and moved out of the house. But now she has rent and bills and she understands that stuff. In exchange for that she also had a lot more freedom because she helped me with things.

Patients described everyday technology as both an enabler and a barrier: an enabler because it can assist with simple tasks (such as screen readers and apps), a barrier when it is designed without considering visual impairment (for example, devices with no buttons, such as kitchen appliances).

Process to Receive Retinal Prosthetics

The participant who received the Argus II implant described the procedure as straightforward day surgery lasting 4 hours. Surgery was followed by a pain-free 3-week recovery period. Once the glasses were introduced, the participant noticed immediate positive results.

> As soon as I put my glasses on, I was able to see the lights on in the boardroom, the doctor and my friends. I was like, "Oh my God."

The participant attended education sessions to help learn objects and shapes; this process was said to take, at minimum, several sessions.

Impact of Argus II on Quality of Life

The participant described Argus II as having a significant impact in enabling the perception of light/dark and shapes/objects. While it was not the same as restoring full sight, it provided the fundamental elements of sight, which was tremendously important in helping to navigate the physical environment and assisting with day-to-day activities such as mobility and eating. As a result, the participant noted increased confidence.

> It helps me in places like the subway, so I know where the doors are, when they open, and whether there is an empty seat instead of sitting in someone's lap. It also helps me when I eat at home or at a restaurant. Then I know I am able to find a fork or glass in the dining room.

These findings were supplemented by another individual having received Argus II, who indicated improvements and enhancements in other aspects of daily life.

> 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 had never seen them before. I can play basketball with them with the help of a lighted basketball hoop. A candlelit dinner with my wife is more romantic because now I can actually see the candle 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.

The functionality provided by Argus II was perceived to be a significant improvement over a life without vision. The participants noted that while improvements to the Argus II system would be desirable—such as providing colour or greater detail—even the perception of light was impactful in helping tell the difference between day and night and orient oneself.

Discussion

A number of important themes emerged from the interviews.

First, retinitis pigmentosa has a large impact on day-to-day functioning, especially when it comes to interacting with physical and virtual environments. Despite societal efforts to enhance accessibility, these environments can be functionally challenging for people with retinitis pigmentosa. Loss of opportunity was also described as being a barrier, preventing people with retinitis pigmentosa from making choices that were possible for others (for example, job opportunities and other career-related choices). Still, participants were generally high-functioning, primarily because they had developed a "can-do" attitude and received substantial

support from family members. They had also invested heavily in assistive devices to help them navigate these environments.

Participants also saw adaptation as a critical element of the day-to-day experience for people with retinitis pigmentosa. While there have been societal efforts to enable accessibility for people with low vision, individuals saw greater success when they adapted by further customizing their living space themselves (for example, putting markers, buttons, and Braille in certain locations, keeping all items in the same location, or purchasing items that could overcome obstacles in the physical environment, such as tandem bikes). People also adapted the virtual environment, using information technology such as screen readers. However, adaptation comes at a significant financial cost and is often only partially effective.
Finally, the Argus II retinal prosthetics system was described as being a very significant improvement for the quality of life of someone living with retinitis pigmentosa. It provides the means for someone to navigate their environment more easily and with confidence. The procedure, recovery, and rehabilitation were all described as minimally problematic.

Conclusion

Individuals with retinitis pigmentosa live full lives, but the condition has a significant impact on their quality of life, limiting opportunities and presenting accessibility challenges. The Argus II system can enable perception of light/dark and shapes/objects, providing individuals with the fundamental elements of vision. Using these informational gains, people with the Argus II implant can more easily orient themselves to their environment and avoid "living in darkness forever."

ABBREVIATIONS

FLORA	Functional Low-vision Observer Rated Assessment
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
GVA	Grating visual acuity
ICER	Incremental cost-effectiveness ratio
NGVA	Non-grating visual acuity
QALY	Quality-adjusted life-year

APPENDICES

Appendix 1: Literature Search Strategies

Search Strategy for the Clinical Review

Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Databases: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <2nd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 25>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:
----
1   exp Retinal Diseases/ (280239)
2   (retina* adj2 (disease* or degeneration)).tw. (20533)
3   exp Retinitis Pigmentosa/ (14872)
4   ((rod adj cone* adj (dystroph* or degenerat*)) or retinopath* pigment* or (tapetoretinal adj degeneration*) or ((retinitis or retinopath*) adj (pigmentosa* or pigmentary))).tw. (13569)
5   exp Vision Disorders/ (233926)
6   (micropsia* or visual impairment* or metamorphopsia* or visual disorder* or blindness or hemeralopia* macropsia* or vision disorder* or vision disabilit*or amauros?s).tw. (62153)
7   or/1-6 (509243)
8   (Argus II or (Second Sight and (visual prosthes#s or Argus or medical product*))).tw. (63)
9   Visual Prosthesis/ (1787)
10   (((visual or retinal or epiretinal) adj (prosthes#s or implant*)) or bionic eye* or epiretinal device*).tw. (1593)
11   or/8-10 (2883)
12   7 and 11 (1033)
13   exp Animals/ not (exp Animals/ and Humans/) (8184385)
14   12 not 13 (851)
15   limit 14 to english language [Limit not valid in CDSR,DARE; records were retained] (725)
16   15 use pmoz,cctr,coch,dare,clhta,cleed (289)
17   exp retina disease/ (171251)
18   (retina* adj2 (disease* or degeneration)).tw. (20533)
19   exp retinitis pigmentosa/ (14872)
20   ((rod adj cone* adj (dystroph* or degenerat*)) or retinopath* pigment* or (tapetoretinal adj degeneration*) or ((retinitis or retinopath*) adj (pigmentosa* or pigmentary))).tw. (13569)
21   exp visual impairment/ (132085)
22   (micropsia* or visual impairment* or metamorphopsia* or visual disorder* or blindness or hemeralopia* macropsia* or vision disorder* or vision disabilit* or amauros?s).tw. (66348)
23   or/17-22 (336699)
24   (Argus II or (Second Sight and (visual prosthes#s or Argus or medical product*))).tw. (63)
25   exp visual prosthesis/ (1897)

26   (((visual or retinal or epiretinal) adj (prosthes#s or implant*)) or bionic eye* or epiretinal device*).tw. (1593)
27   or/24-26 (2919)
28   23 and 27 (964)
29   (exp animal/ or nonhuman/) not exp human/ (9353137)
30   28 not 29 (782)
31   limit 30 to english language [Limit not valid in CDSR,DARE; records were retained] (663)
32   31 use emez (395)
33   16 or 32 (684)
34   remove duplicates from 33 (468)

Search Strategy for the Economic Review

Databases searched: All Ovid MEDLINE, Embase, Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, CRD Health Technology Assessment Database, Cochrane Central Register of Controlled Trials, and NHS Economic Evaluation Database

Database: EBM Reviews - Cochrane Central Register of Controlled Trials <May 2015>, EBM Reviews - Cochrane Database of Systematic Reviews <2005 to May 2015>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2015>, EBM Reviews - Health Technology Assessment <2nd Quarter 2015>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2015>, Embase <1980 to 2015 Week 25>, All Ovid MEDLINE(R) <1946 to Present>

Search Strategy:
----
1   exp Retinal Diseases/ (280239)
2   (retina* adj2 (disease* or degeneration)).tw. (20533)
3   exp Retinitis Pigmentosa/ (14872)
4   ((rod adj cone* adj (dystroph* or degenerat*)) or retinopath* pigment* or (tapetoretinal adj degeneration*) or ((retinitis or retinopath*) adj (pigmentosa* or pigmentary))).tw. (13569)
5   exp Vision Disorders/ (233926)
6   (micropsia* or visual impairment* or metamorphopsia* or visual disorder* or blindness or hemeralopia* or macropsia* or vision disorder* or vision disabilit*or amauros?s).tw. (62153)
7   or/1-6 (509243)
8   (Argus II or (Second Sight and (visual prosthes#s or Argus or medical product*))).tw. (63)
9   Visual Prosthesis/ (1787)
10   (((visual or retinal or epiretinal) adj (prosthes#s or implant*)) or bionic eye* or epiretinal device*).tw. (1593)
11   or/8-10 (2883)
12   7 and 11 (1033)
13   economics/ (245891)
14   economics, medical/ or economics, pharmaceutical/ or exp economics, hospital/ or economics, nursing/ or economics, dental/ (692510)
15   economics.fs. (362681)
16   (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or pharmacoeconomic* or pharmaco-economic*).tw. (628505)
17   exp "costs and cost analysis"/ (480603)
18   cost*.ti. (216689)
19   cost effective*.tw. (225268)
20   (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or control or sharing or instrument* or technolog*)).ab. (141108)
21   models, economic/ (125509)
22   markov chains/ or monte carlo method/ (114634)
23   (decision adj1 (tree* or analy* or model*)).tw. (30645)

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24   (markov or markow or monte carlo).tw. (90737)
25   quality-adjusted life years/ (25577)
26   (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (43760)
27   ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (86444)
28   or/13-27 (2125055)
29   12 and 28 (29)
30   limit 29 to english language [Limit not valid in CDSR,DARE; records were retained] (28)
31   30 use pmoz,cctr,coch,dare,clhta,cleed (7)
32   exp retina disease/ (171251)
33   (retina* adj2 (disease* or degeneration)).tw. (20533)
34   exp retinitis pigmentosa/ (14872)
35   ((rod adj cone* adj (dystroph* or degenerat*)) or retinopath* pigment* or (tapetoretinal adj
degeneration*) or ((retinitis or retinopath*) adj (pigmentosa* or pigmentary))).tw. (13569)
36   exp visual impairment/ (132085)
37   (micropsia* or visual impairment* or metamorphopsia* or visual disorder* or blindness or
hemeralopia* or macropsia* or vision disorder* or vision disabilit* or amauros?s).tw. (66348)
38   or/32-37 (336699)
39   (Argus II or (Second Sight and (visual prosthes#s or Argus or medical product*))).tw. (63)
40   exp visual prosthesis/ (1897)
41   (((visual or retinal or epiretinal) adj (prosthes#s or implant*)) or bionic eye* or epiretinal device*).tw.
(1593)
42   or/39-41 (2919)
43   38 and 42 (964)
44   Economics/ (245891)
45   Health Economics/ or exp Pharmacoeconomics/ (208106)
46   Economic Aspect/ or exp Economic Evaluation/ (371868)
47   (econom* or price or prices or pricing or priced or discount* or expenditure* or budget* or
pharmacoeconomic* or pharmaco-economic*).tw. (628505)
48   exp "Cost"/ (480603)
49   cost*.ti. (216689)
50   cost effective*.tw. (225268)
51   (cost* adj2 (util* or efficacy* or benefit* or minimi* or analy* or saving* or estimate* or allocation or
control or sharing or instrument* or technolog*)).ab. (141108)
52   Monte Carlo Method/ (46505)
53   (decision adj1 (tree* or analy* or model*)).tw. (30645)
54   (markov or markow or monte carlo).tw. (90737)
55   Quality-Adjusted Life Years/ (25577)
56   (QOLY or QOLYs or HRQOL or HRQOLs or QALY or QALYs or QALE or QALEs).tw. (43760)
57   ((adjusted adj (quality or life)) or (willing* adj2 pay) or sensitivity analys*s).tw. (86444)
58   or/44-57 (1740016)
59   43 and 58 (23)
60   limit 59 to english language [Limit not valid in CDSR,DARE; records were retained] (23)
61   60 use emez (18)
62   31 or 61 (25)
63   remove duplicates from 62 (19)

Appendix 2: Evidence Quality Assessment

Our first consideration was study design; we started with the assumption that randomized controlled trials are high quality, whereas observational studies are low quality. We then took into account five additional factors—risk of bias, inconsistency, indirectness, imprecision, and publication bias. Limitations in these areas resulted in downgrading the quality of evidence. Finally, we considered three main factors that may raise the quality of evidence: the large magnitude of effect, the dose-response gradient, and any residual confounding factors. [10] For more detailed information, please refer to the latest series of Grading of Recommendations Assessment, Development, and Evaluation (GRADE) articles. [10]

As stated by the GRADE Working Group, the final quality score can be interpreted using the following definitions:

High	High confidence in the effect estimate—the true effect lies close to the estimate of the effect
Moderate	Moderate confidence in the effect estimate—the true effect is likely to be close to the estimate of the effect, but may be substantially different
Low	Low confidence in the effect estimate—the true effect may be substantially different from the estimate of the effect
Very Low	Very low confidence in the effect estimate—the true effect is likely to be substantially different from the estimate of the effect

Table A1: GRADE Evidence Profile for Comparison of the Argus II Retinal Prosthesis System On and Off

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Visual Function: Object Localization							
4 (observational)[a]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Visual Function: Direction of Motion							
4 (observational)[a]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Visual Function: Grating Visual Acuity							
3 (observational)[c]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Functional Outcomes: Orientation and Mobility (Find the Door)							
2 (observational)[d]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Functional Outcomes: Orientation and Mobility (Follow the Line)							
2 (observational)[d]	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Functional Outcomes: Eye-Hand Coordination (Trace the Path)							
1 (observational)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Functional Outcomes: Spatial Resolution (Letter and Word Reading)							
1 (observational)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Functional Outcomes: Spatial Resolution (Reaching and Grasping)							
1 (observational)	No serious limitations[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate
Functional Outcomes: Spatial Resolution (Reaching and Grasping With Finger Marker)							
1 (observational)	No serious limitations[e]	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate

Number of Studies (Design)	Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Upgrade Considerations	Quality
Quality of Life: Activities of Daily Living/ Quality of Life							
1 (observational)	No serious limitations	No serious limitations	No serious limitations	No serious limitations	Undetected	Underlying trajectory of retinitis pigmentosa (+1)[b]	⊕⊕⊕ Moderate

Abbreviation: GRADE, Grading of Recommendations Assessment, Development, and Evaluation.

[a]Four papers published from two studies.

[b]The natural history of retinitis pigmentosa is a progressive deterioration of vision, eventually leading to blindness. The Argus II retinal prosthesis system is the only treatment option currently available to restore partial functional vision for these patients.

[c]Three papers published from two studies.

[d]Two papers published from one study.

[e]Conducted on a subset of patients in only the United Kingdom cohort. However, it is unlikely that the result would be different if the test was conducted in the entire cohort.

Table A2: Risk of Bias Among Observational Studies for the Argus II Retinal Prosthesis System Comparing System On and Off

Author, Year	Appropriate Eligibility Criteria	Appropriate Measurement of Exposure	Appropriate Measurement of Outcome	Adequate Control for Confounding	Complete Follow-Up
Humayun et al, 2012[12]	No limitations	No limitations	No limitations[a]	No limitations	No limitations[b]
Ho et al, 2015[13]	No limitations	No limitations	No limitations[a]	No limitations	No limitations[b]
Ahuja et al, 2011[14]	No limitations	No limitations	No limitations[a]	No limitations	No limitations
Dorn et al, 2013[15]	No limitations	No limitations	No limitations[a]	No limitations	No limitations
Barry et al, 2012[16]	No limitations	No limitations	No limitations[a]	No limitations	No limitations
da Cruz et al, 2013[17]	No limitations	No limitations	No limitations[a]	No limitations	No limitations
Kotecha et al, 2014[18]	No limitations	No limitations	No limitations[a]	No limitations	No limitations
Luo et al, 2015[19]	No limitations	No limitations	No limitations[a]	No limitations	No limitations
Rizzo et al, 2014[21]	No limitations	No limitations	No limitations	No limitations	No limitations[b]

[a]There were no predefined clinical measurements of the outcomes, and the measurements were evolved as the study progressed. However, the target population of patients with profound retinitis pigmentosa and no functional vision had not been previously studied, because there were no other treatment options available. Therefore, it was inevitable that there were no validated measurements to quantify the limited vision gained from the new Argus II retinal prosthesis system. The clinical measurements reported in the Argus II International Study were developed with input from experts in the low-vision research community.

[b]Authors provided detailed descriptions of the patients who were lost to follow-up.

Appendix 3: Detailed Breakdown of Argus II System Costs[a]

Argus II System			
1	Argus II implant	Epiretinal implant and external Argus II components (glasses and video processing unit)	$199,712
2	Surgical procedure	Operating room supplies, including standard vitrectomy surgical supplies, Argus II surgical supplies (Ekhardt tips, 3083 sleeves, camera drape), and operating room nurse staff time for the 4-hour procedure	$2,488
3	Epiretinal replacement parts	Annual replacement of Argus II epiretinal implant parts	$1,100
4	Eye exams (preoperative)	• Technician staff time (20 minutes per test) optical coherence tomography, ophthalmic angiography and fundus photography, preoperative assessment and day-surgery clinic visit (day 1) • Ward clerk staff time (10 minutes per visit) to complete administrative documentation and registration, preoperative assessment clinic visit and day surgery clinic visit (day 1)	$159
5	UHN Argus II surgical instrument replacement	Replacement of surgical instruments specifically needed to implant the Argus II epiretinal device on the patient's retina, such as retinal tack forceps, silicone tip forceps	$1,320
Low-Vision Rehabilitation			
6	Eye exams (postoperative)	Technician staff time (20 minutes per test) to perform the following postoperative assessments in an Argus II patient: • Eye exam at day 1, weeks 1 and 2, and months 1, 3, 6, and 12 • Intraocular pressure at day 1, weeks 1 and 2, and months 1, 3, 6, and 12 • Optical coherence tomography at week 1 and months 1, 3, 6, and 12 • Fundus exam at week 1 and months 1, 3, 6, and 12 • Fundus photography at week 1 and months 1, 3, 6, and 12	$995
7	Argus II system activation and fitting	Technician staff time to activate, calibrate, and fit Argus II system in a patient over 6 postoperative sessions. Continued adjustments to Argus II system during low-vision rehabilitation (30 hours annually per patient)	$2,527
8	Argus II training kits	Low-vision rehabilitation training kits for use in clinic and for patients to take home to support use of Argus II system	$2,135
9	Low vision rehabilitation specialist	Occupational therapist staff time to perform 10 low-vision rehabilitation sessions, some in the clinic and some in the patient's home or workplace, and/or public settings based on patient preference (1 hour per session)	$1,618
10	Patient coordinator	Patient coordinator staff time to coordinate scheduling of eye exam assessments, day surgery visit, and Argus II implant orders, as well as providing respective patient education and support; the coordinator also serves as a liaison between the manufacturer, the patient, and the clinical team (50 hours per patient per year)	$4,814
11	UHN Argus equipment maintenance	Annual maintenance of Argus II equipment for clinician fitting system, psychophysical test system, and communication adapter system	$7,171
Total cost to provide 1 Argus II system			$224,039

Abbreviations: UHN, University Health Network.

[a]Cost data were provided in the submission for the review of Argus II (personal communication, Dr. Robert Devenyi, lead investigator of the Argus II study, University Health Network, August 18, 2015, and Dr. Marnie Weber, University Health Network, August 25, 2015).

Appendix 4: Letter of Information/Consent and Release Form

Letter of Information

Project Title: Health Technology Assessment of the Argus II retinal prosthesis system for the treatment of retinitis pigmentosa

Introduction
The Argus II retinal prosthesis system (Argus II) is the first implanted device and the only treatment available to restore partial functional vision in blind patients with severe retinitis pigmentosa and bare to no light perception. Currently, Argus II is uninsured in Ontario. In 2015, the University Health Network requested that Health Quality Ontario (HQO) review evidence on the effectiveness of Argus II for the treatment of retinitis pigmentosa.

Currently, HQO is conducting an evidenced-based review of this technology, based on clinical and economical studies and lived experience. The goal of the project is to provide recommendations to the Ontario Health Technology Assessment Committee, which advises the Ontario Ministry of Health and Long-Term Care on the appropriateness of funding.

What Your Participation Involves
If you agree to enroll, you will be asked to participate in an interview conducted by HQO staff. The interview will likely last 30–60 minutes. The interview will be conducted in a private location and will be audiotaped. The interviewer will ask you questions about your lived condition and your perceptions about the Argus II retinal prosthesis system.

Participation in this review is voluntary. You may refuse to participate, refuse to answer any questions or withdraw before your interview. Withdrawal will in no way affect care you receive.

Confidentiality
All information collected for the review will be kept confidential and privacy will be protected except as required by law. The results of this review will be published; however, no identifying information will be released or published. That said, due to the limited number of participants who have received the Argus II retinal prosthesis system, the potential exists that you may be identifiable. Any records containing information from your interview will be stored securely.

Risks to Participation
There are no known physical risks to participating in this review. Some participants may experience discomfort or anxiety after the interview. If this is the case, please contact any staff.

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Consent and Release Form

This form is to be read and completed in accordance with the following instructions before it can be signed.

1. I, _____ allow Health Quality Ontario (Ontario Health Quality Council) to use to inform the development of an evidence based review:

    Check off all appropriate boxes (a to e).
    a) ___   a recording of my voice
    b) ___   a quotation or summary of my opinion that I expressed during an interview
    c) ___   name

2. Please read the following paragraphs before affixing your signature under section 3.
    a) Personal information collected pursuant to, and on this form, will be used for purposes described on this form and for no other purpose. Health Quality Ontario (Ontario Health Quality Council) acknowledges that you have provided this personal information freely and voluntarily. If you have any questions about this collection of this personal information, contact:
        Suzanne Dugard
        Director, Communications
        Tel: (416) 323-6868, x 223, Email: suzanne.dugard@hqontario.ca
    b) By signing this form as indicated below, you agree to hereby release and forever discharge the Health Quality Ontario (Ontario Health Quality Council), its officers, employees, agents and representatives from any and all claims, demands, expenses, actions, causes of action and for any and all liability howsoever caused, arising out of, or in any way related to the collection, use and disclosure of information, recordings and images authorized to be collected pursuant to, or on this form.
    c) By signing this form as indicated below, you agree to forever waive any and all rights that you may have to the use of information and recordings that are authorized to be collected pursuant to, or on this form; and you acknowledge that all information, recordings and images shall hereafter remain the exclusive property of the Health Quality Ontario (Ontario Health Quality Council).

3. Signature is to be affixed in the appropriate space provided below.

I have read this form after it was completed, I understand and agree to be bound by its contents, and I am eighteen (18) years of age or over.

        Signature _____
        Print name _____
        Date _____

Appendix 5: Interview Guide

- What is the impact of retinitis pigmentosa on your life? For example, how does the condition affect your quality of life? How does the condition affect your loved ones or caregivers?

- What were your experiences of health interventions before Argus II? For example, how well could you manage your condition with available therapies prior to the Argus II technology? Did you have any treatment for retinitis pigmentosa before Argus II implantation? If yes, what kind of health care services you need, and was there any associated cost?

- What was the procedure like to obtain the Argus II technology? Please describe your postoperation rehabilitation and how long after the implant you could start to use the functional vision gained in real life?

- What your experiences with the Argus II technology? For example, what difference does it make to your quality of life? Are there any activities that they used to enjoy but couldn't do before the implant, but could do it now?

- After Argus II implantation, do you need any treatment for retinitis pigmentosa? Are there any maintenance costs associated with the device?

- What are your expectations for Argus II? Are there any drawbacks or limitations?

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About Health Quality Ontario

Health Quality Ontario is the provincial advisor on the quality of health care. We are motivated by a single-minded purpose: **Better health for all Ontarians.**

Who We Are.

We are a scientifically rigorous group with diverse areas of expertise. We strive for complete objectivity, and look at things from a vantage point that allows us to see the forest and the trees. We work in partnership with health care providers and organizations across the system, and engage with patients themselves, to help initiate substantial and sustainable change to the province's complex health system.

What We Do.

We define the meaning of quality as it pertains to health care, and provide strategic advice so all the parts of the system can improve. We also analyze virtually all aspects of Ontario's health care. This includes looking at the overall health of Ontarians, how well different areas of the system are working together, and most importantly, patient experience. We then produce comprehensive, objective reports based on data, facts and the voice of patients, caregivers and those who work each day in the health system. As well, we make recommendations on how to improve care using the best evidence. Finally, we support large scale quality improvements by working with our partners to facilitate ways for health care providers to learn from each other and share innovative approaches.

Why It Matters.

We recognize that, as a system, we have much to be proud of, but also that it often falls short of being the best it can be. Plus certain vulnerable segments of the population are not receiving acceptable levels of attention. Our intent at Health Quality Ontario is to continuously improve the quality of health care in this province regardless of who you are or where you live. We are driven by the desire to make the system better, and by the inarguable fact that better has no limit.

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