**Title:** Comprehensive Visual and Mobility Training after Retinal Prosthesis Surgery
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## BACKGROUND

As of 2010, the estimated number of visually impaired people in the world is 285 million with 39 million considered legally blind and 246 million having low vision.[1] Blindness and visual impairment are associated with higher medical care expenditures, a greater number of informal care days, and a decrease in health utility.[2] In 2006, the annual total financial burden of major adult visual disorders in the United States was estimated to be $35.4 billion ($16.2 billion in direct medical costs, $11.1 billion in other direct costs, and $8 billion in productivity losses).[3]

The advances within the field of ophthalmology have led to novel interventions for patients with profound vision loss who previously had no treatment options. In addition to gene and stem cell therapies, there is a burgeoning field of artificial vision due to such devices as retinal and cortical implants. Presently, the resolution of artificial vision is termed "ultra-low vision" as it allows for crude perceptions of larger, high contrast objects.[4] Despite rapid development of these new technologies, they lack objective and standardized methods of assessing visual function in this patient population.

Retinitis pigmentosa (RP) is a group of hereditary retinal degenerative diseases demonstrating significant genotypic and phenotypic heterogeneity. Typically, patients with RP are born with normal vision; however, rod photoreceptor cell death leads to symptoms of nyctalopia and visual field loss. Over time, the disease progresses affecting the cone photoreceptor cells and patients have diminished color vision and central vision loss. In severe cases the disease renders patients completely blind – unable to detect light. There is currently a dearth of treatment options for these patients, but retinal prosthesis and other potential therapies such as stem cell therapy, gene therapy, and cortical prostheses are in development across Europe and North America. However, the methods of assessment and integration for optimal use have not been developed and represents a major obstacle in the use and development of these technologies.

**The aim of the current project is to fill the unmet clinical needs around the objective assessment of visual function and develop an outcome-oriented visual rehabilitation approach using the computer assisted rehabilitation environment (CAREN) system.** The development of objective outcomes coupled with a rehabilitation protocol will provide a unique clinical-technical platform that will: 1) facilitate Staff within Cole Eye Institute to better compete for NIH funding, 2) result in a scalable outcome assessments conducive to commercialization and 3) create an industry standard in assessment of the ultra-low vision patient. The technology and rehabilitation approach will be developed using a unique group of ultra-low vision patients with a diagnosis of RP who underwent Argus II retinal prosthesis implantation.

*Argus II retinal prosthesis system: A novel device to restore vision:* The Argus II Retinal Prosthesis System

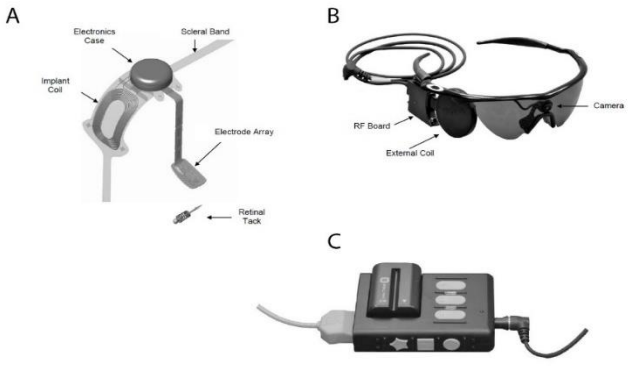


Figure 1: The Argus II Retinal Prosthesis System. (A) Implanted components. The retinal tack secures the electrode array to the surface of the retina. The implant coil and electronics case are secured around the sclera with the scleral band. (B) Glasses worn by the patient contains a camera and an external coil which communicate wirelessly with the implant coil. (C) The VPU is worn by the patient and is connected to the glasses.

(Argus) is the only FDA-approved treatment for patients blind from RP (Second Sight Medical Products; Sylmar, CA). The Cleveland Clinic Argus team, Drs. Aleksandra Rachitskaya and Alex Yuan, within the Cole Eye Institute have performed the greatest number of surgeries post-FDA market approval in the United States and the institute is considered to be an Argus center of excellence by the manufacturer. Between June 2015 and May 2017, a total of 10 implant surgeries have been performed at Cleveland Clinic out of a total of approximately 80 in the U.S. The Argus system was named the 2014 Cleveland Clinic No. 1 Medical Innovation of the Year. In 2015 the work of the Cleveland Clinic Argus Team was recognized as one of the top Clinical Achievements of the Year. Considering the importance, relevance, innovation and commercial and consumer visibility of the Argus system, developing outcomes and a protocol for evaluation of this cutting edge technology will yield multiple scientific publications and commercial attention which will facilitate success of extramural and industry sponsored research.

The Argus system consists of a retinal implant that is surgically implanted into one eye, a pair of glasses with an integrated video camera, and a video processing unit (VPU) (Figure 1). These components work together to provide electrical stimulation to the electrode array, stimulating the patient's remaining inner retinal cells. The electrode array consists of 60 platinum electrodes arranged in a 6 x 10 grid pattern centered over the macula (Figure 2), the part of the retina responsible for central vision. The primary sensory neurons are the photoreceptors which reside in the outer retina. Normally, these cells are responsible for phototransduction and synapse with second order bipolar cells in the inner nuclear layer. The bipolar cells then synapse with the third order neurons, the ganglion cells, which relay visual input to the brain. In RP, there is a drastic reduction in photoreceptor outer segments and abnormal residual rods and cones. The inner retinal neurons, although reduced in number, appear to be preserved.[5,6] The preservation of ganglion cell function is important for the function of the Argus, as the second and third order neurons are stimulated by the Argus electrode array.

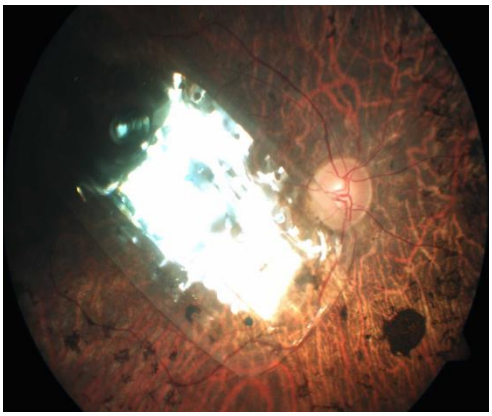

Figure 2: The Argus electrode array is shown centered over the macula next to the optic nerve.

The Argus system works by capturing video through the camera mounted on the glasses worn by the patient. The image is captured as the patient slowly moves his/her head and "scans" the scene. The video is sent to the VPU which encodes brightness via stimulus amplitude and sends the stimulus pattern wirelessly to the implanted device via the implant coil. Stimulation of the electrode array results in the generation of visual percepts or phosphenes (flashes of light or a glow) detected by the patient in a retinotopic manner.[7] Patients who receive the Argus do not have their vision restored. Rather, the device provides them with a new type of artificial vision.

Given that phosphene interpretation is not intuitive, in order for this vision to become meaningful, patients must undergo a post-implantation rehabilitation regimen. The training focuses on learning how to use the device, develop the necessary scanning skills to know how to "scan the scene", and how to interpret the new artificial vision. Currently, there is a fundamental knowledge gap in how to best approach visual rehabilitation of Argus recipients. Patient success with the Argus is largely dependent on the rehabilitation process; however, there are no established guidelines for rehabilitation. Patients who receive the system currently work with low vision therapists and orientation and mobility (O&M) specialists with the goal of increasing safety, mobility, and independence. The number of sessions and the type of training varies from one patient to the next. In addition, the field is lacking standardized outcomes to measure visual functional recovery. Currently, the only objective tests utilized include visual function tests (square localization, direction of motion, and grating visual acuity)

developed by the Argus manufacturer. All the tests are performed with the patient seated in front of a touch screen monitor and the patient responds to images and their direction/orientation on the screen. The current visual function tests are limited as they lack the ability to mimic "real world" situations and thus fail to address if the device is useful to a patient. Moreover, in our experience, they do not always correspond with each patient's functional outcomes, device usage, and overall satisfaction with the device.

*Optimizing utilization of low vision innovations requires a multi-disciplinary approach:* Sensorimotor integration is key during postural control activities. The central nervous system integrates three major systems to maintain posture and balance: visual, vestibular, and somatosensory.[8] Of those three systems, vision is the main sensory system used to maintain standing posture.[9] With vision impairment, individuals experience impaired bilateral coordination,[10] increased postural sway during static standing[11] and increased sway during sit-to-stand transfers.[12] The visual, vestibular, and somatosensory systems are heavily dependent on one another.[8] Just as the onset of visual impairment results in higher fall risk,[13] it is possible that regaining visual function will alter postural control and heighten fall risk.

Given these unique limitations to visual rehabilitation in the Argus population, a collaboration between Drs. Rachitskaya and Yuan and Dr. Alberts' was born to investigate more effective approaches to the evaluation and rehabilitation process. Dr. Alberts' laboratory contains one of the only non-military Computer Assisted Rehabilitation Environment (CAREN) system. The CAREN is a versatile, multi-sensory virtual reality system with a fully integrated Vicon three dimensional (3D) motion capture system, a dual belt instrumented treadmill with a six degree of freedom motion base platform, and a 180° curved projection screen with surround sound audio to immerse an individual into a virtual environment (Figure 3).[14,15] A harness is donned during ambulation and balance activities to ensure patient safety. The programmable software of the CAREN system allows for the creation and modification of a variety of interactive modules. Modules can be as simple as reaching for an objects on a blank screen, and as complex as crossing the street during rush hour, and can be adjusted to increase contrast and complexity as patient's abilities improve. The functionality of CAREN is unlike that of any other rehabilitation assistive tool and is only available at a few facilities in the United States. Collectively, the Cleveland Clinic is uniquely positioned to attract extramural and industry sponsored research, as we are already an established clinical partner for many technology companies. No other center in the United States has the combined clinical, engineering, and commercialization expertise. The proposed project utilizing Argus recipients will serve as a model of study that will be extended to other industry partners and future clinical trials and studies.

CAREN would allow Argus recipients to be trained in a safe, controlled, and standardized environment. Additionally, biomechanical outcomes (gait variables, center of mass and positional sway during balance activities, head position to capture scanning techniques) can be collected during training to measure patient performance. The addition of biomechanical outcomes resulting in

Figure 3: CAREN system. The 180-degree projection screen allows an individual to be immersed in an activity or scene while performing balance or gait activities on the platform.

objective measures of gait, posture, and visual awareness will provide a more complete picture of functional performance.

Recognizing the need and opportunity to develop affordable and objective methods of assessing balance and gait, the Alberts' lab developed a way to use the accelerometer and gyroscope of the iPad to provide biomechanical measures of postural sway during static standing and gait. Biomechanical measurements from the iPad have been validated against traditional biomechanical measures including 3-D motion capture[16] and force platforms,[17] and are able to differentiate between a healthy and diseased population.[18] The biomechanical measures from the iPad will be used to supplement clinical assessments. The inclusion of biomechanically-based methods to augment clinical evaluations is a novel application of technology that will lead to a more complete understanding of the functional rehabilitation of the ultra-low vision patient population.

**SPECIFIC AIMS**

The goal of the current project is to fill the unmet clinical needs around the objective assessment of visual function and develop outcome-oriented visual rehabilitation approach using the computer assisted rehabilitation environment (CAREN) system for Argus recipients.

**Aim 1: Determine feasibility of clinical and biomechanical outcome measures on individuals with ultra-low vision.** To date, there are no valid and reliable functional outcome measures for individuals with ultra-low vision. This study will determine the feasibility of functional and biomechanical outcome measures that have been established as valid and reliable in fully sighted individuals on Argus recipients.

**Aim 2: Develop a comprehensive vision rehabilitation program for Argus recipients using the CAREN system.** The team will consist of ophthalmologists/surgeons, Argus patient coordinator, visual function testing administrator, biomedical engineers, physical therapists and rehabilitation specialists. The collaborative team is well-trained to create a comprehensive rehabilitation program with a focus on functional outcomes. The program will focus on contrast sensitivity training, object identification, visual scanning, and object tracking. Body proprioception in relation to other objects will be a key focus of the rehabilitation, as safety with mobility is paramount. Ultimately an eight session rehabilitation program (2x/week for 4 weeks) will be created.

**Aim 3: Determine the effects of a 4-week visual retraining session on Argus recipients.** The 8 session rehabilitation program (2x/week for 4 weeks) will be implemented in a total of 5 patients implanted with the Argus II device. The patients will be tested at baseline and after the eight session protocol. The primary outcome will be change in the Timed Up and Go and an object navigation course. Standard visual outcomes as well as biomechanical outcomes will also be used.

**APPROACH**

Table 1 displays a timeline of the study design. Approval will be obtained from the Institutional Review Board of the Cleveland Clinic. The multidisciplinary team will collaborate on rehabilitation protocol development and quality assurance of the CAREN technology in Quarter 1. This will take several months due to the high level of collaboration that must occur by the engineers, vision experts, and rehabilitation experts. The visual capabilities status post Argus placement can vary widely, thus tasks must be able to be used on all subjects.

Table 1: Proposed study timeline

| | Year 1 | | | |
|---|---|---|---|---|
| | Q1 | Q2 | Q3 | Q4 |
| Institutional Review Board Approval | ■ | | | |
| Programming of CAREN modules | ■ | | | |
| Quality assurance of CAREN modules | ■ | | | |
| Subject enrollment | | ■ | ■ | |
| Data analysis | | | ■ | ■ |
| Manuscript preparation | | | | ■ |

*Recruitment and Outcomes Testing:*

Once CAREN programing and quality assurance is complete, subjects will be enrolled in Quarters 2-3 to complete the training modules. Subjects will be recruited from the database of patients who have had the Argus device implanted at the Cleveland Clinic Cole Eye Institute. Subjects will be enrolled in this study for a minimum of 6 weeks, as visualized in Figure 4. Study enrollment will begin at the time of informed consent and study participation will end after completion of the EOT day 2 visit.

**Inclusion criteria are as follows**: 1) implanted Argus device, 2) ability to provide informed consent, 3) ability to follow two-step commands, 4) ability to ambulate 300+ feet with or without visual assistance, and 5) able to tolerate Argus device turned on for >20 continuous minutes.

**Participants will be excluded from participation if they have**: 1) dementia, 2) musculoskeletal contraindication to exercise or walking, or 3) cardiopulmonary contraindication exercise (i.e. uncontrolled heart failure, cardiac arrhythmia, or pulmonary disease).

Outcomes will be assessed at baseline and end of treatment (EOT), as visualized in Figure 4. Table 2 describes the outcomes that will be collected: visual function, overground, and CAREN outcomes. Three visual function tests (VFT) will be assessed: square localization, direction of motion and grating visual acuity. The square localization test presents a 2.75" square (250 pixels) at a random location on a black background and the subject is instructed to touch the square. The direction of motion test assesses the patient's ability to determine the direction an object is moving by presenting a white line (1.4'' wide) that moves across the screen in a random series of directions and angles. The grating visual acuity test measures the patient's visual acuity using the principles of acuity charts modified for ultra-low vision subjects. The subject is presented with black and white bars in one of four orientations (horizontal, vertical, diagonal to the left or diagonal to the right), and the subject provides a verbal response as to which orientation they perceived the bars.

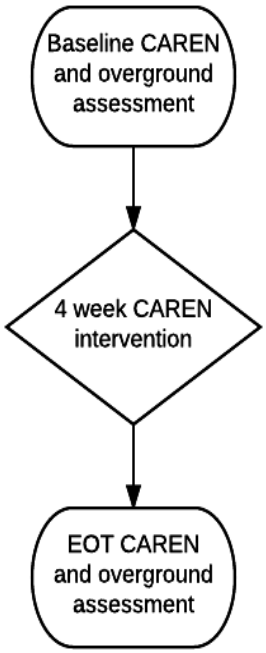


Figure 4: Overview of baseline assessment (week 1), intervention (weeks 2-5), and end of treatment (EOT) assessment protocol (week 6).

To determine functionality, the participant will also complete overground testing. The Timed Up and Go (TUG) test is a test of mobility where the individual is required to stand, ambulate 3 meters, turn, and return to a seated position in the chair.[19] During the TUG the iPad is attached to the patient's waist and the accelerometer and gyroscope collect biomechanical data that allows for analysis of the transfer, ambulation, and turning. The Five Time Sit to Stand requires the subject to stand up and sit down from a standard height chair without the use of their upper extremities.[20] This will be tested with the Argus device on and off to see the effects of vision on transfer ability. Postural sway will be measured during static standing by volumetric sway using the iPad. This test will be performed with the Argus device on and off. The Activities-specific Balance Confidence (ABC) scale has been used in individuals with visual impairments to measure confidence with household and community mobility.[13] Participants will complete an object navigation course modeled after Nau, et al.[21] The object navigation course simulates obstacles that are commonplace in a community setting: ramp, curb, and stepping over and around objects. Time to completion of the obstacle course will be recorded. The CAREN system will be used for baseline and EOT testing to track spatiotemporal gait parameters and visual tracking.

Because of the anticipated length of time and cognitive demand required to complete all outcomes testing, both baseline and EOT testing will occur over a two days during the first and last weeks of study participation. Day one will include standard visual outcomes, ABC Scale administration,

and iPad assessments in the Cole Eye Center. Day two will include the CAREN testing and the object navigation course in the Mellen Center.

| Table 2: Outcome measures | | |
|---|---|---|
| Name of outcome measure | Domain tested | Testing Day |
| Standard Visual Outcomes | | |
| Square localization, direction of motion and grating visual acuity | Ultra-low visual function tests currently used as an outcomes measure for Argus recipients | 1 |
| Overground Outcomes | | |
| Timed Up and Go | Transfer, gait, turning | 1 |
| Five Time Sit to Stand (Argus on, off) | Transfers | 1 |
| Postural sway measured by iPad (Argus on, off) | Static standing balance | 1 |
| Activities-specific Balance Confidence (ABC) Scale | Balance confidence questionnaire about household and community tasks | 1 |
| Object Navigation Course | Real-world object navigation consisting of stepping over and around objects, curb and ramp negotiation | 2 |
| CAREN Outcomes | | |
| Baseline visual assessment | Shapes displayed from large to small to establish baseline visual function | 2 |
| Contrast sensitivity | Lightening black background by 10% until subject no longer able to identify the shape | 2 |
| Accuracy of object localization | Object displayed on CAREN screen; time, biomechanical coordinates of turning head to locate objects | 2 |
| Spatiotemporal gait parameters | Gait variables (i.e. velocity, cadence, step length, etc.) during single and dual task conditions x 2 minutes | 2 |

*Intervention:* Following baseline testing, participants will begin a 2x/week training program using the CAREN system. Training will continue for at least four weeks, or until completion of eight sessions. Interventions will be collaboratively designed between an expert in CAREN system operations and a physical therapist or physical therapist assistant. Because each recipient of the Argus implant has unique challenges and needs, treatment sessions will be tailored on an individual basis, with the over-arching goal of improving functional vision and safety. Participants will engage in static and dynamic activities to simulate the demands of real-life situations, and will be permitted seated or standing rest breaks as needed. It is relevant to note that the testing module will be completely different from the training module to minimize the training effect.

*Feasibility of CAREN system in a single Argus recipient:* Preliminary testing of the CAREN system on a single Argus recipient was performed. The patient was able to get on the treadmill and interface with the CAREN system. The patient was able to identify simpler targets on the screen as well as successfully identify large letters (3 out of 3), while scenes with lower contrast or with increased visual stimuli were more challenging. The patient tolerated testing for over 2 hours. This preliminary session indicates that Argus recipients are able to interface with and perform tasks on the CAREN system and can provide our team with biomechanical data.

*Data Confidentiality:* Study data that will be collected on the CAREN system will be de-identified using only the participant's study number. For purposes of the 3-D motion analysis, participants are

videotaped; however this video will not leave the computer of the CAREN system without further written consent from the participant. The Apple iPad will be used to collect some of the cognitive and biomechanical data necessary for this study. Only a study number will be associated with this iPad data. All data which is captured on the iPad will be securely transmitted to a HIPPA compliant research database. All points of access to the research database will take place over Transport Layer Security/Secure Sockets Layer encrypted connections.

Other outcome measures will be collected on Redcap ®, a secure electronic database that limits access to study personnel. Other electronic data will be labeled with only the subject number. The original signed and dated informed consent document along with any paper that may be used for data collection will be maintained in a study binder in a locked office within Cole Eye Institute. The regulatory binder for this study will be kept in Cole Eye, and only research personnel will have access to this information.

*Potential Risks:* There are potential risks and discomforts to this study. There is a risk of muscle soreness and fatigue that comes along with exercising. There is a risk of cognitive and visual fatigue from the tasks as well. Participants will be permitted to rest as needed. There is a risk of falls in the clinical and VR setting, although in the VR setting participants will wear a harness to prevent falls. With the markers that will be worn for the gait analysis, there is a risk of temporary skin irritation. Although the intensity of exercise will be low, there is a risk of a cardiovascular event. All exercise personnel will be CPR certified and there is a medical emergency team located on site. There may be other risks with this intervention that are not yet known.

*Data Collection and Statistical Analysis:* The 10-camera Vicon system in combination with D-Flow software captures the 3D position of several retro-reflective markers placed on anatomic landmarks of the body. Gait recordings will focus on the lower extremities, while object localization will require markers placed on the glasses worn by the patient. Recordings are completed at 100 Hz and filtered using a 2nd order low-pass Butterworth filter with a 6 Hz cut-off frequency. Data output from the CAREN system will be analyzed using custom Matlab scripts. Spatiotemporal parameters of velocity, step length, step width, and stride time will be calculated from the averaged per gait cycle. This study has a case-series design and statistically will be treated as such. Thus the study team will be looking for minimal clinical importance difference and trends from pre to post testing in the biomechanical and clinical outcomes.

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