Protocol Title: Extended Follow-Up of the Argus™ II Retinal Stimulation System Feasibility Protocol

Protocol Number: CP-003-001-US

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Sponsor: Second Sight Medical Products, Inc.
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Protocol Synopsis

Study Element	Description
Title:	Extended Follow-Up of Argus II Retinal Stimulation System Feasibility Protocol
Protocol Number:	CP-003-001
Device:	Argus II Retinal Stimulation System
Intended Use:	The Argus II Retinal Stimulation System is intended to provide electrical stimulation of the retina to elicit visual perception in blind subjects with severe to profound retinitis pigmentosa.
Diagnosis and Main Criteria for Eligibility:	Retinitis pigmentosa with remaining vision of bare light perception or worse in both eyes.
Study Phases:	This study is being conducted in 2 phases: Investigational phase (i.e. up to 7 years of study participation) and Post-Approval phase (i.e. years 7-10 of study participation). These two study phases are summarized on the following pages.
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Study Element	Description
Investigational Phase:	
Primary Objective:	The objective of this feasibility study is to evaluate the safety and utility of the Argus II Retinal Stimulation System in providing visual function to blind subjects with severe to profound retinitis pigmentosa.
Study Design:	Single-armed feasibility study
Primary Endpoints:	The primary effectiveness endpoint is the subject's visual acuity. The primary safety endpoint is the evaluation of the safety profile in this population.
Secondary Endpoint(s):	Secondary endpoints in this study relate to the subject's ability to perform orientation and mobility tasks, their perceived quality of life and ability to undertake activities of daily living. Secondary safety endpoints are related to the stability of the device and sensitivity of the underlying retinal tissue to electrical stimulation. These will be qualitatively evaluated using optical coherence tomography, fluorescein angiography, retinal photography, CT scan and perceptual thresholds for electrical stimulation over time. The set-up, optimization and functionality of the Argus II System will be evaluated based on the tests performed and the feedback from the investigators and the subjects.

Study Element	Description
Length of Follow-Up:	Subjects initially enrolled in the study for 3 years. Following completion of 3 years follow-up, subjects may consent to extended follow-up for up to an additional 4 years (years 4-7) in the investigational phase and another 3 years in the post-approval phase. This provides for a total duration of follow-up in the study of 10 years per subject. Average length of follow-up in the investigational phase will be 5 years, and will range from approximately 3.5 – 5.5 years per subject depending on when the subject initially enrolled in the study.
Number of Centers:	Up to ten (10) centers within the U.S.
Number of Subjects:	Up to twenty (20) in the U.S.

Study Element	Description
Post-Approval Phase:	
Post-Approval Study Questions:	1. Are there any significant changes in the device-related adverse events in the late follow-up period in subjects implanted with the Argus II device? 2. What is the long-term reliability of the implant?
Study Design:	Extending the Single-armed feasibility study
Study Hypothesis:	There is no study hypothesis
Study Population:	Subjects who have completed participation in the Investigational Phase of this study and who have the Argus II device still implanted are eligible for enrollment in the Post-Approval Phase of this study.

Study Element	Description
Sample Size:	N=29. Fourteen (14) subjects were enrolled in the Investigational Phase of the study. One of these 14 subjects was explanted, which leaves a maximum of 13 subjects in the U.S. eligible for the post-approval phase of this study. An additional 16 subjects were enrolled in a similar study in Europe. All 16 of these subjects are eligible for participation in the post-approval phase of the study.
Study Endpoints:	The primary endpoint of the post-approval phase is safety (i.e. the rates of adverse events). The secondary endpoint of the post-approval phase the long-term reliability of the Argus II implant.
Enrollment Plan and Follow-up Measures:	As with all protocol amendments, IRB approval will be obtained at each site prior to adding the post-approval phase to the protocol. At the completion of the 7 year follow-up visits, all eligible subjects will be offered the option of participating in the post-approval phase of the study. Subjects who consent to the post-approval phase will be enrolled in this extended follow-up portion of the study. During the post-approval phase, subjects will undergo annual eye exams, assessments of medical status and adverse events, and measurement of stimulation thresholds. In addition, at the mutual agreement of the investigator and the subject, subjects will have the option of participating in psychophysical research which could occur as frequently as monthly. Functional tests at 10 years: photographic flash, square localization, direction of motion and grating visual acuity.
Length of Follow-up:	Extend the subjects' overall participation in the study to 10 years post-implant.

Study Element	Description
Frequency of Follow-up Assessments	During year 5 to 7, every six month; from year 8 to 10 annually. Note the examinations are not exactly the same prior to year 7 and thereafter, because the study undergoing was extended to year 7.
Statistical Plan:	Descriptive statistics will be used to report data collected in the Post-Approval Phase of the study. The proportion of subjects experiencing adverse events will be calculated along with the 95% confidence intervals.

This protocol should be read in conjunction with the latest revisions of:

- Clinician's Manual (090201)
- Patient's Manual (090101)
- Procedures and Operations Manual (POM) (CP-003-007)
- Investigator Agreement (CP-003-008)
- Clinical Trial Agreement

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1 Introduction and Rationale

> **"In outer retinal degeneration, such as retinitis pigmentosa (RP), the photoreceptors and their supporting retinal pigment epithelium are impaired. In RP (incidence 1:4000) legal blindness is reached after 25 years. In many RP patients over sixty years of age, elementary vision with only gross movement or bright light perception remains, with little or no appreciable peripheral vision. Eventually, even light perception may recede. Currently, there is no treatment that stops or reverses the loss of photoreceptors in retinitis pigmentosa".[1]**

Traditionally, the approach to vision rehabilitation in subjects with retinitis pigmentosa has been to use the remaining vision with optical aides. If no useful vision is achieved, auditory or tactile information is substituted (e.g. Braille, cane travel, etc.). Attempts to remedy or alleviate vision loss have been made by replacing damaged cells or by electrically stimulating an undamaged proximal level, bypassing impaired cells. Replacement of damaged photoreceptors has been studied in animals through transplantation.[2] Although there are indications that transplanted photoreceptors can make functional connections, many questions remain about the optimal methods to achieve long term graft survival and functionality in a human eye.

More recently, visual prostheses have been developed to address the extreme low vision population with retinal degeneration.[3] Electrical stimulation at the primary visual cortex has been attempted and has the advantage of not requiring a viable optic nerve.[4] However, such cortical stimulation has its own risks, such as exposing the brain to surgical complication and infection.

Stimulation at more distal neuronal locations has received recent attention and may provide an alternative in an outer retinal degenerative disease such as retinitis pigmentosa.[5,6,7,8,9,10,11,12] Electrical stimulation of the optic nerve has been used to elicit a sensation of streaks or dots (phosphenes). Also, electrical stimulation through a contact lens electrode elicits phosphenes in subjects with advanced photoreceptor degeneration. These perceptual responses, and the electrically evoked responses recorded from the scalp in response to such stimuli, have been interpreted as evidence that inner retinal cells in subjects with photoreceptor degeneration retain at least partial function. However, the phosphenes elicited with a contact lens electrode or by electrical stimulation of the optic nerve lack well defined shape or localization.

The production of a small localized visual percept that might allow the generation of a two-dimensional array of phosphenes to provide "pixelized

visual input" has been explored in both acute and chronic studies of blind subjects. Even partial restoration of vision in subjects blind from photoreceptor degeneration has been shown to be important.[13,14,15,16,17,18,19,20,21,22,23,24,25,26] Second Sight has undertaken the development of a Retinal Stimulation System intended for use in subjects with retinitis pigmentosa. The earlier generation device (Argus 16 Retinal Stimulation System) has been implanted in six subjects in an Investigational Study. The Argus 16 Study has demonstrated that subjects have the ability to perceive phosphenes generated by epi-retinal electrical stimuli and perform simple tasks such as:

- Determine the position, orientation and direction of motion of objects,
- Locate doorways

Based on the results of the study, the current system has incorporated several improved features:

- Increased number of electrodes. Up to sixty electrodes will be used to increase visual resolution up to a theoretical limit of 2.1 logMAR based on a 575μm spacing of the electrodes.
- Increased field of view. The electrodes will cover an area of the retina corresponding to a 20 degree diagonal field of view,
- Thin Film Electrode Array and cable. The thin film cable replaces the round cable to reduce the risk of conjunctival erosion by the cable.
- Extra-ocular placement. The Argus II implant electronics are placed on the outer surface of the eye, removing the need for a tunneled cable and the implanting of the case in the skull of the subject. The new implant procedure this affords reduces operative duration significantly and should also reduce post-operative complications.

This feasibility study will utilize an array with up to sixty independently controllable electrodes implanted epiretinally to provide visual input via an external camera system and seeks to evaluate the utility of this system for safety, improvement in visual acuity, orientation and mobility, activities of daily living, and quality of life in subjects with retinitis pigmentosa.

2 System Description

2.1 Introduction

The Argus II Retinal Stimulation System developed by Second Sight is a second generation system following the first generation Argus 16. The main differences are that the Argus II provides more independent channels for stimulation and that the Argus II Implant (including the Internal Coil) is attached to the outside of the eye. Like the Argus 16 System, the Argus II system comprises three sub-system components: the Argus II Implant, the Video Processing Unit (Argus II VPU) and the Argus II Glasses, and the Clinical Fitting System. The principle of operation and a description of each of the Argus II sub-system components (Implant, VPU, and the Clinical Fitting System) are provided below.

2.2 Principle of Operation

The principle of operation of the Argus II System is shown schematically in Figure 2.1.

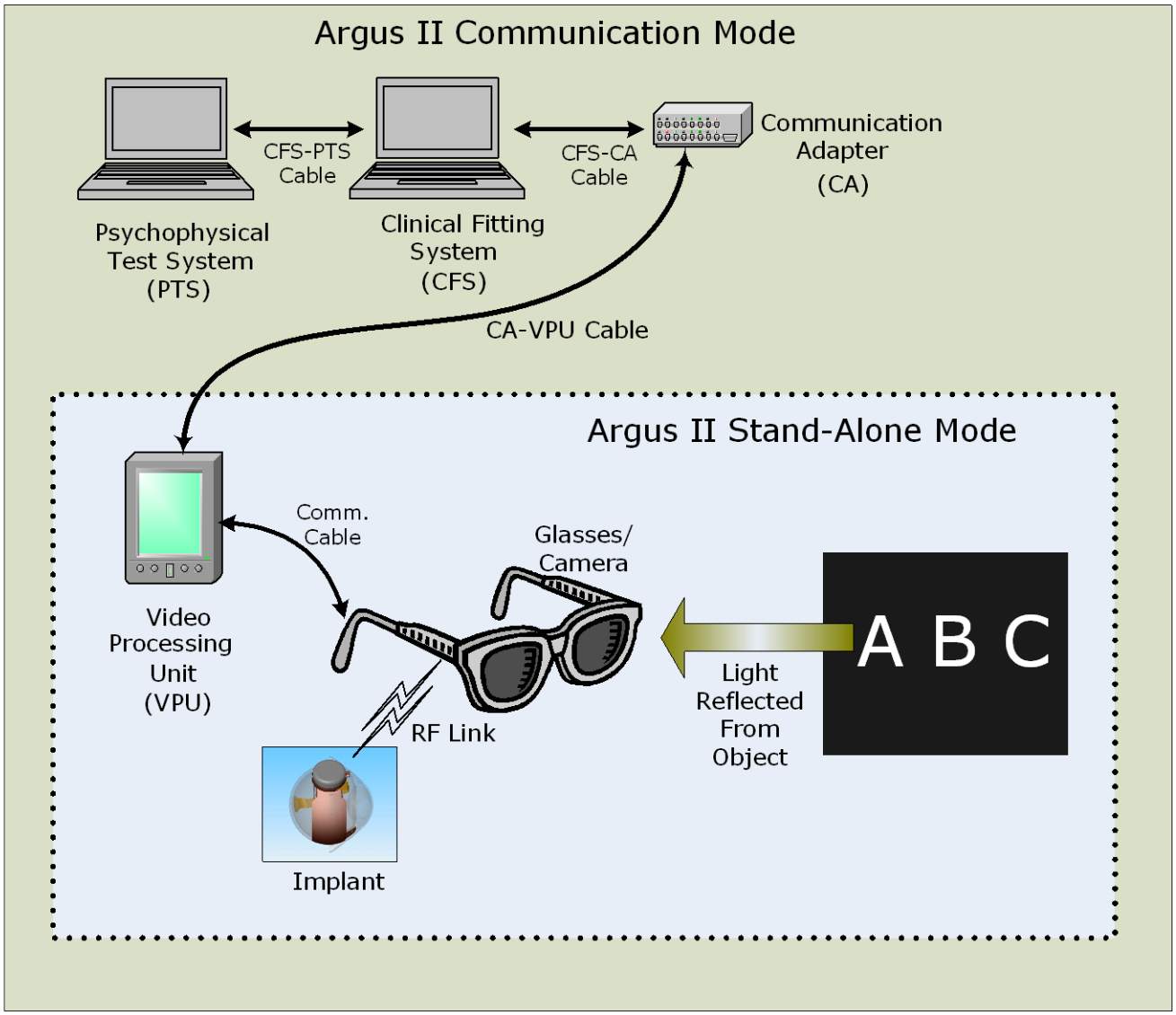
2.2.1 Stand-Alone Mode

In Stand-Alone Mode (inset in Figure 2.1), the camera, which is attached to eye-glasses worn by the subject, captures a video image (Argus II Glasses). The camera signal is sent to the Argus II VPU (powered by a rechargeable battery), which processes the camera image and transforms it into electrical stimulation patterns. The electrical stimulation data are then sent to the eye-glasses mounted coil which sends both data and power via radio-frequency (RF) telemetry to the Argus II Implant. The implant coil receives the radio-frequency commands which control an application-specific integrated circuit which in turn delivers stimulation to the retina via an electrode array.

2.2.2 Communication Mode

When parameters are being adjusted to tailor the system to a subject or to do psychophysical testing with a subject, the Argus II VPU is connected to a dedicated fitting system (Clinical Fitting System), as seen in (Figure 2.1) via a cable between the VPU and the Communications Adapter. In this mode, computer generated stimuli may be presented to the subject and programming parameters may be adjusted. In addition, a second computer (Psychophysical Test System) may be utilized to perform more sophisticated testing and analysis.

Figure 2.1 Schematic Overview of the Argus II System



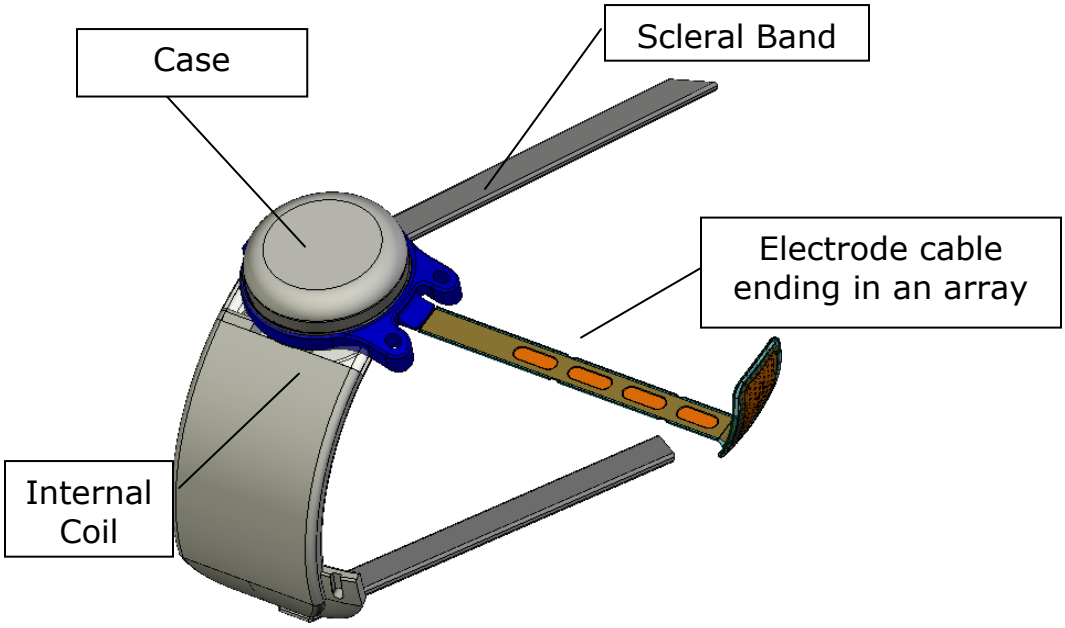
2.3 Argus II Implant

A diagram of the Argus II Implant is provided in Figure 2.2. The implant consists of four components:

1. A small hermetic case that contains the electronics to receive power and communicate with the external system, and to drive the electrical stimulation of the electrodes.
2. An internal coil that receives power and data from the external primary coil.

3. An electrode cable ending in an array that is electrically connected to the case and transmits the stimulation signals to the retina via the exposed electrodes. It is secured to the retina with a retinal tack.
4. A scleral band that allows the implant to be secured to the outside of the eye.

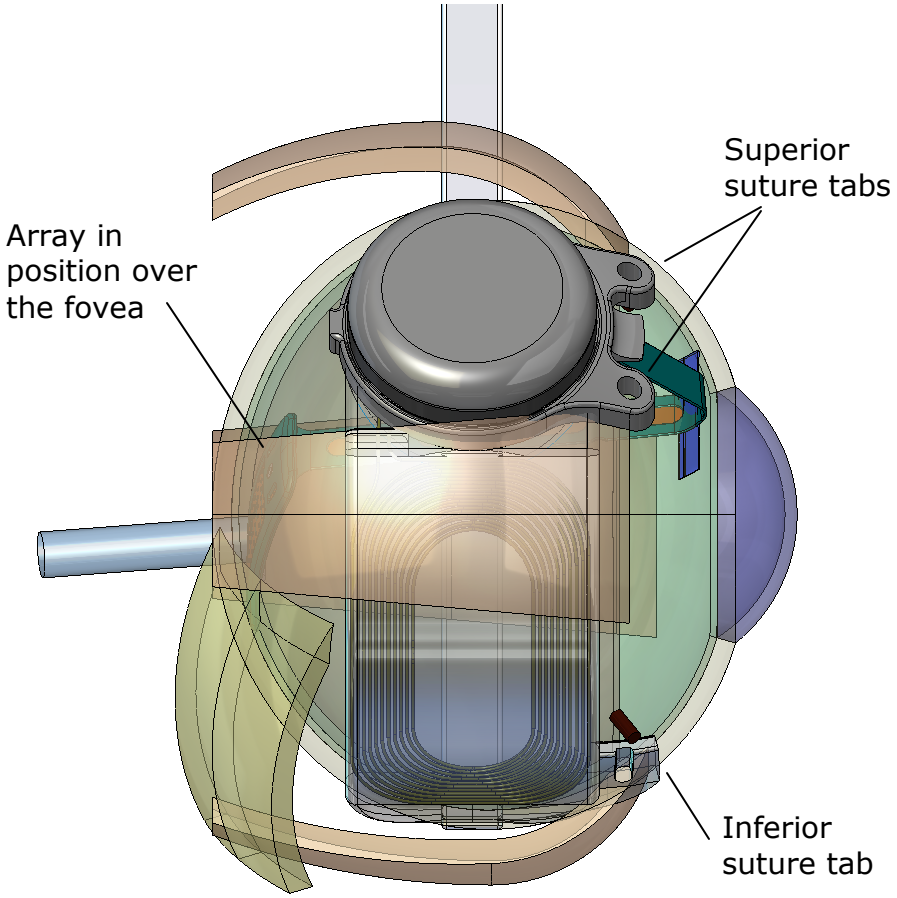
Figure 2.2 Illustration of Argus II Implant



2.3.2 Implant Placement

A conceptual side view illustrations of the Argus II Implant on a right eye is provided in Figure 2.3. The array enters the eye through a pars plana incision and the array is placed on the retina over the macula using a retinal tack. The extra-ocular portion of the Argus II Implant is secured to the eye by means of a scleral band held in place by a Watzke sleeve (typical of scleral buckling procedures), and also by suture tabs. The inferior and superior implant suture tabs can be seen in Figure 2.3. Additionally, the surgeon may elect to place a suture around the scleral band in the inferior medial quadrant. A description of the surgical implantation procedure is provided in Chapter 3 of the Clinician's Manual.

Figure 2.3 Argus II Implant in Position on a Right Eye (Conceptual Temporal Side View)



2.3.3 Packaging and Sterilization of Argus II Implant

The Argus II implant is individually packaged in a sealed tray with two Second Sight retinal tacks and provided sterile. The method of sterilization is ethylene oxide and the process has been validated for ocular use.

2.4 External System

The External System consists of a pair of glasses with a video camera mounted above the nose piece and a RF coil that provides power and sends and receives data from the implant and the Video Processing Unit. The purpose of the Argus II Video Processing Unit is to convert the input video

signal to a pattern of electrical stimulation to be sent to the implant. The VPU also allows the subject to turn the system on and off, and to manually adjust settings within pre-determined safe limits. This section describes the main components of the Argus II External system. A detailed description of these components is provided in Chapter 2 of the Clinician's Manual.

2.4.1 Argus II Video Processing Unit (VPU)

The Argus II VPU comprises a case, buttons, connectors, rechargeable battery and digital circuit boards. The buttons are large and shaped so that they can be easily identified by touch. There is one connector that connects the Argus II VPU to the Argus II Glasses. The Argus II VPU can also be connected to the Argus II Clinical Fitting System during subject testing and fitting using a specialized connector that is covered by a rubber seal when the Argus II VPU is used in stand-alone mode. An illustration of the Argus II VPU is provided in Figure 2.4.

Figure 2.4 Argus II Video Processing Unit (VPU)

The Argus II VPU is in constant communication with the implant. The Argus II VPU transmits null frames (containing no stimulation information) until it synchronizes with the implant. Stimulation can then occur. Any loss of synchronization causes an alarm.

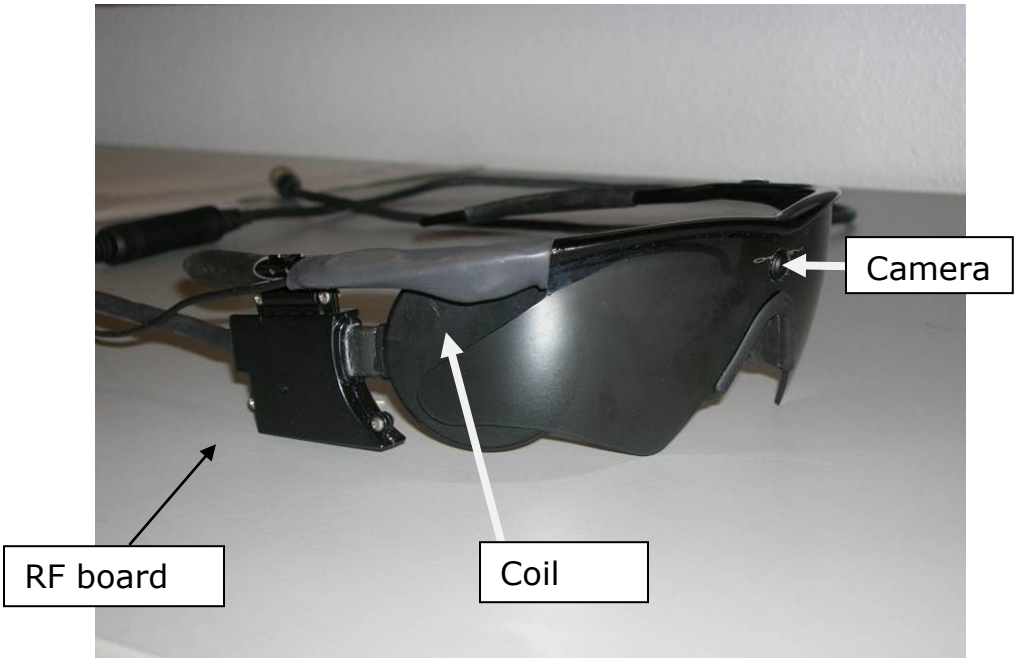
The Argus II VPU acquires video input from the camera and converts it into a digital format. Filters, such as edge detection, may be then applied. The image is then reduced to sixty channel resolution using a downscaling filter. This representation of the image is then mapped to stimulation intensity using customized look-up tables that have been derived from testing of individual subjects. A check is performed to assure that the overall current and the maximum charge per phase are within safety limits. The stimulation parameters are then sent via telemetry to the implant in frames that employ an error detection scheme.

The Argus II VPU is battery powered and has no "mains" connection. As will be discussed below, when the Argus II VPU is connected to the Argus II Clinical Fitting System, it is optically isolated. This removes the risk of electrical shock that can be associated with medical equipment.

2.4.2 Argus II Glasses

The Argus II Glasses provide a convenient and discreet way to house the video camera and radio-frequency system needed to power and communicate with the implant. A photograph of a sample design of the Argus II Glasses is shown in Figure 2.5 below.

Figure 2.5 Argus II Glasses



A small, light-weight color video camera is mounted in the center of the frame above the nose-piece. The telemetry coils and radio-frequency board are mounted on the ear piece. The position of the coil housing is adjustable to provide comfort to the subject and to allow the external coil assembly to be optimally positioned relative to the implant coil to achieve a good communication link for subjects with different facial structure.

2.4.3 Argus II Clinical Fitting System

The Argus II Clinical Fitting System consists of software with a graphical user interface running on a laptop computer. This computer is connected to the Argus II VPU using an optically isolated serial connection (Argus II Communication Adapter). Being optically isolated, the serial connection assures that no electric leakage current can flow from the Argus II Clinical Fitting System to the Argus II VPU in the event of a fault condition.

The Argus II Clinician Fitting System is used to configure the Argus II system stimulation parameters and video processing strategies for each subject. The fitting application, operating system, laptop, isolation unit and Argus II VPU are tested and configuration controlled as a system. The

software provides modules for electrode control, permitting the clinicians to interactively construct test stimuli with control over amplitude, pulse-width, and frequency of the stimulation waveform of each electrode. These parameters are checked to ensure that the maximum charge per phase is not exceeded, the charge in each biphasic pulse is balanced, and power limitations are not surpassed before the test stimuli are presented to the subject. In addition, these parameters are checked a second time by the Argus II VPU firmware. The fitting system also allows the clinician to control the spatial relationship between the video input and the electrodes, and to apply image processing filters to the video input.

The Argus II Clinician Fitting System software provides a psychophysical software module that allows the clinician to quickly administer pre-programmed test protocols. Responses to these test protocols may be verbal or may be recorded by a keypad, or by other computer input devices. Using this module, important perceptual parameters, such as electrical stimulation threshold, can be reliably measured. Based on these perceptual parameters, the fitting software allows the clinician to custom configure the transformation between the video image and electrode stimulation parameters thereby optimizing the effectiveness of the retinal prosthesis for each subject. Multiple transformation strategies may be downloaded to the VPU and stored in non-volatile memory. The software can also load a previously used transformation strategy from the VPU for adjustment.

To enable customized psychophysical testing, an Argus II Psychophysical Test System is connected to the Argus II Clinician Fitting System. This system utilizes MatLAB® to develop, perform and analyze results of subject testing. During such testing, the safety checks for charge balance, current density and total charge in the Argus II Clinician Fitting System and Argus II VPU will continue to operate to protect subject safety.

3 Study Design

3.1 Study Objectives

Investigational Phase of the Study

The objective of this feasibility study is to evaluate the safety and utility of the Argus II Retinal Stimulation System in providing visual function to blind subjects with retinitis pigmentosa.

Post-Approval Phase of the Study

To collect post-approval data in order to monitor the ongoing safety and reliability of the Argus II System

3.2 Study Overview

The Argus II chronic retinal stimulation system is an implantable electronic device designed to provide chronic electrical stimulation of the retina in order to elicit visual percepts in blind subjects with retinitis pigmentosa.

The Argus II Implant has a theoretical equivalent acuity (or Nyquist limit) of approximately 2.1 logMAR.[27,28] To ensure that subjects will enter the study with worse acuity than a conservative estimate of the potential afforded by the Argus II System, we will initially only enroll subjects with bare light perception or worse, in both eyes. These subjects will be at the least visual risk, since they have very progressed disease and almost no usable spatial vision.

Visual acuity will be measured with a test that uses high contrast square wave gratings. High contrast square gratings can be calibrated using a photometer, which can directly compare the luminance of the light and dark areas, whereas sinusoidal gratings require a more complex calibration procedure. Campbell showed that in subjects with low vision square gratings yield similar results to sinusoidal ones, due to the limited visual frequency response of these subjects.[29] The test requires subjects to report the orientation of the grating in each trial (horizontal, vertical, oblique left or oblique right). The visual acuity score is defined as the highest level at which the subject guesses the orientation correctly at a rate that is half way between chance and perfect performance.

To facilitate a more targeted screening population, only adults (twenty-five years of age or older) will be evaluated.

Prior to formal enrollment, subjects will be screened for inclusion by undergoing a series of interviews and tests including a complete ophthalmic examination, a medical history interview, a psychological evaluation and

visual acuity testing. Once enrolled, subjects will undergo additional testing and diagnostic imaging to gather baseline data. It is estimated that screening and baseline testing will each last less than six hours.

This study evaluates the impact of the Argus II system on subjects' quality of life and activities of daily living. Quality of life will be assessed in all subjects using the VisQOL instrument. The VisQOL is a validated instrument for the evaluation of the quality of life in visually impaired subjects.[30] The VisQOL scores will serve as a baseline means of comparison for the implanted population, pre- and post-operatively. The difficulty and importance of daily activities will be assessed using portions of the self-reported questionnaire developed by Massof.[31,32]

To evaluate the utility of the Argus II System for orientation and mobility, each subject will be asked to complete a mobility tasks modeled after that used by Turano but greatly simplified for the extreme low vision population.[33,34] The tasks will use high contrast targets and the subject's accuracy and time taken to complete the tasks will be evaluated.

A functional low-vision observer rated assessment (FLORA) will be performed by a certified low vision therapist to evaluate how the Argus II System affects subjects' everyday lives.

The implant position, proximity to the retina and the retina under and around the array will be evaluated using retinal photography, optical coherence tomography (OCT) and fluorescein angiography. An ultrasound B-scan will be obtained to measure the posterior coats thickness in the region where the array is placed. The extra-ocular placement of the device will be documented by CT scan.

Subjects may be hospitalized for up to one day after surgery as needed. Post-operatively, study subjects will be treated and monitored per routine hospital post-operative procedure for ophthalmic surgery.

Post-operative visits to evaluate and optimize the parameters of the Argus II will occur up to twice weekly and will last up to 4 hours at each visit. As with the model A16 implant, subjects will be allowed to use the system outside the clinic. Home use will only be permitted after system configuration and adequate training.

Subjects will be followed post-operatively for 36 months. Whether the subject completes the study or withdraws from the study, the subject will have the option to either keep the device implanted, or have it surgically removed.

Following completion of 36 months follow-up, subjects may consent to extended follow-up for up to an additional 7 years. Subjects will be asked to

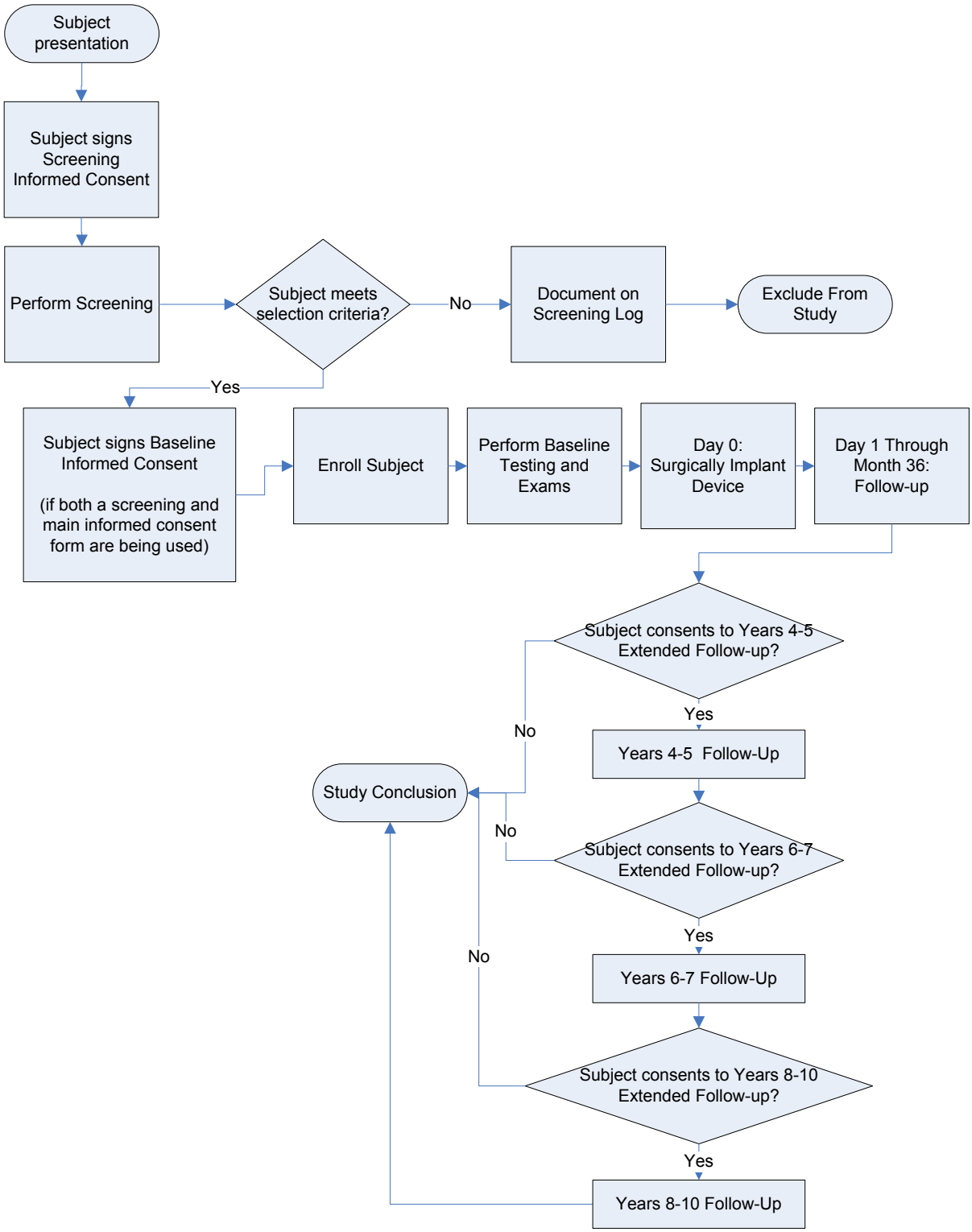
consent for extended follow-up in 3 increments (i.e. years 4-5, then years 6-7, then years 8-10). During this time, subjects will be allowed to continue using their system and they will undergo periodic clinical follow-up and optional testing in the clinic.

The device will be explanted if the subject experiences unresolved intraocular infection, clinically significant retinal detachment, unexplained or known device failure that may pose a risk to the subject, or intractable pain. All surgically removed devices will be returned to Second Sight for examination.

This study is designed to enroll up to twenty (20) subjects in the U.S. and will require approximately 48 months to complete 3 years follow-up on all subjects. If subjects consent to participate in extended follow-up, the study will continue for up to an additional 7 years.

A flow chart of a subject's participation in the study follows in Figure 3.1 below.

Figure 3.1 Study Flow Chart



3.3 Justification for the Study Design

This is a feasibility study to evaluate the safety and utility of the Argus II Retinal Stimulation System and to evaluate the methods used for optimizing programmable parameters. Measurements taken with the device both off and on will serve as internal controls in each subject. The risks involved with the implantation of the Argus II System are justified by the lack of alternate treatments for retinitis pigmentosa.[1] In addition, the subjects for this feasibility study will have only bare light perception, minimizing the risk due to loss of residual vision. Edwards, et.al. and Gartner, et.al. indicate that advanced retinitis pigmentosa provides a protective effect against possible retinal detachment.[35,36] A detailed clinical risk assessment is attached in Appendix B.

This study will not be masked to the subjects or the investigators.

3.4 Study Endpoints

3.4.1 Primary Effectiveness Endpoint

The primary effectiveness endpoint is determined by objective measurement of visual acuity, the finest detail a subject can see. Visual acuity in the treated eye is quantified over a wide range of spatial vision with a high contrast grating acuity test and a full field stimulus threshold test. Subjects' visual acuity will be scored according to Table 3.1.

Effectiveness will be analyzed by comparing the subject's visual acuity score at enrollment and at follow-ups after implant. Control will be established using the subject's fellow eye and the implanted eye with the device OFF.

Methods for performing the visual acuity tests are provided in the Procedures and Operations Manual.

Table 3.1 Visual Acuity Scores

Visual Acuity		
log MAR	**Snellen**	**European**
1.6	20/796	6/239
1.7	20/1002	6/301
1.8	20/1262	6/379
1.9	20/1589	6/477
2.0	20/2000	6/600
2.1	20/2518	6/755
2.2	20/3170	6/951
2.3	20/3991	6/1197
2.4	20/5024	6/1507
2.5	20/6325	6/1898
2.6	20/7962	6/2389
2.7	20/10024	6/3007
2.8	20/12619	6/3786
2.9	20/15887	6/4766
N/A	Bare Light Perception (BLP)	
N/A	No Light Perception (NLP)	

3.4.2 Primary Safety Endpoint

The primary safety endpoint is the evaluation of the safety profile in this population.

3.4.3 Secondary Endpoints

Orientation and Mobility

Geruschat, Turano et al have used a simple mobility task consisting of a corridor with high contrast obstacles to evaluate the orientation and mobility of low vision subjects.[33,34] It was found that the time to traverse the course was correlated with visual acuity and visual field. This study will use a greatly simplified course. Each subject will be asked to walk to a high-contrast target on the wall and in a second test asked to follow a straight line on the floor. The subject's time and accuracy will be measured. This instrument will be given to the subject pre-implant, then at prescribed intervals post-operatively.

Subjects' use of the Argus II System for orientation and mobility in their everyday lives will be assessed by an independent, certified low-vision therapist (e.g. CLVT, OTR/L, COMS, etc.) using commonly accepted techniques for performing such assessments and an instrument (Functional Low-Vision Observer Rated Assessment [FLORA]) designed specifically for this study.

Quality of Life and Activities of Daily Living

These secondary endpoints are the subject's perceived quality of life and ability to undertake activities of daily living. These endpoints will be measured using:

a) the VisQOL survey,
b) the Massof Activity Inventory
c) Functional Low-Vision Observer Rated Assessment [FLORA] (mentioned above)

The VisQOL Health Survey is a health-related quality of life instrument that has been validated and used in low vision subjects.[30] The use of this instrument will provide a baseline for the general quality of life for these subjects and the impact of a retinal implant on their outlook. This instrument will be given to the subject pre-implant, then at prescribed intervals post-operatively.

The Massof Activity Inventory is a series of activity related questionnaires that allow discrimination of both the usefulness and the difficulty of each task.[31,32] Through the evaluation of tasks the subject finds useful or pleasurable, the inventory provides a measure of the "real-world" daily living changes, rather than artificial constructs. This yields a meaningful measure without the risks of the subject "training to the test."

Spatial Vision

Two additional spatial vision tests will be performed to supplement the Grating Visual Acuity test. These tests, Square Localization and Direction of Motion, are designed to provide an objective measure of spatial vision in subjects who cannot reach the lowest level of the Grating Acuity scale (2.9 logMAR). These tests are similar to two of the procedures included in the Basic Light and Motion (BaLM) test developed by Michael Bach (U. of Freiburg, Freiburg, Germany).

Stability of the Implant

The stability of the array will be qualitatively evaluated using electrode impedances, stimulation thresholds, optical coherence tomography (OCT), CT scan and retinal photography.

System Functionality

The set-up, fitting and functionality of the Argus II System will be evaluated via psychophysical testing and feedback from the investigators and the subjects via the customer contact system.

3.4.4 Endpoints for the Post-Approval Phase of the Study

The primary endpoint of the post-approval phase is safety (i.e. the rates of adverse events). The secondary endpoint of the post-approval phase the long-term reliability of the Argus II implant by calculating the rate of implant failure over time.

4 Study Population

All subjects who are referred to the investigator with retinitis pigmentosa with significant visual loss are potential study candidates and may be screened for eligibility. Eligibility of the subject must be established before enrollment. Subjects who do not meet all selection criteria will not be enrolled.

4.1 Inclusion Criteria

Each enrolled subject must:

1. Have a confirmed history of retinitis pigmentosa and have a visual acuity of Bare Light Perception or worse in both eyes (see Table 3.1). NOTE: The implant should be implanted in the worse-seeing eye. If there is no significant difference in vision between the two eyes, then the investigator will ask the subject which eye is his/her worse eye to determine which eye should be implanted.
2. Have functional ganglion cells and optic nerve in the implanted eye as determined by documented light perception or a measurable electrically evoked response.
3. Have a history of useful form vision in the worse-seeing eye.
4. Be twenty-five (25) years or older at the time of enrollment.
5. Reside within two (2) hours distance (by ground transportation) of the investigational site.
6. Be willing and able to comply with the protocol testing and follow-up requirements.

4.2 Exclusion Criteria

Each enrolled subject must NOT have or be:

1. Optic Nerve disease
    a. History of glaucoma
    b. Optic neuropathy or other confirmed damage to optic nerve or visual cortex
2. Diseases or conditions that affect retinal function including but not limited to:
    a. Central retinal artery/vein occlusion (CRAO or CRVO)
    b. End-stage diabetic retinopathy
    c. Retinal detachment or history of retinal detachment
    d. Trauma
    e. Infectious or inflammatory retinal diseases
3. Diseases or conditions that prevent adequate visualization of the retina including, but not limited to cataract or corneal degeneration that cannot be resolved before baseline testing. Cataracts that permit visualization of the retina are NOT exclusive and will be removed at the time of implant surgery.

4. Diseases or conditions of the anterior segment that prevent the ability to adequately perform the physical examination including but not limited to trauma or lid malpositions.
5. Diseases of the ocular surface including but not limited to keratitis sicca and corneal ulcers.
6. An ocular condition that predisposes the subject to eye rubbing.
7. Any disease or condition that prevents understanding or communication of informed consent, study demands, and testing protocols, including:
    a. Cognitive decline including diagnosed forms of dementia and/or progressive neurologic disease
    b. Psychiatric disease including diagnosed forms of depression
    c. Does not speak a principal language associated with the region
    d. Deafness or selective frequency hearing loss that prevents hearing device alarms and alerts
8. Pregnancy.
9. Any metallic or active implantable device (e.g. cochlear implant) in the head.
10. Conjunctival thinning which may predispose the subject to conjunctival erosion in the area where the implant will be installed extra-ocularly (Note: this is generally associated with a history of tobacco use greater than twenty pack-years.[*])
11. Participating in another investigational drug or device study that may conflict with the objectives, follow-up or testing of this study
12. Any health concern that makes general anesthesia inadvisable.
13. Unrealistic expectations of the system.
14. Known allergy or contraindication to anticipated pre-operative, intra-operative and post-operative medications. Refer to Section 7 for a description of these medications.
15. Conditions likely to limit life to less than 1 year from the time of screening.

[*] Pack-years is the number of packs per day times the number of years smoked. For example two packs a day for ten years is 20 pack-years. Also one pack per day for 15 years is 15 pack-years.

16. Diseases or conditions that, in the judgment of the surgeon, impede the ability to implant the device or would prevent the system from functioning for the duration of the study (e.g. strabismus).
17. An axial eye length <21.5 mm or >26.0 mm in the implanted eye as measured by ultrasound.

5 Study Procedures

Table 5.1 Study Event Schedule

Evaluation or Test	Screening (-60 days – BL)	Baseline (BL) (-60 days – day 0)	Implant (Day 0)	1 Day (12-36 hours)	1 Week (5-9 days)	2 Weeks (12 – 16 days)	4 Weeks (24- 32 days)	3 Months (75-105 days)	6 Months (170-200 days)	9 Months (250 – 290 days)	12 Months (330-390 days)	18 Months (525-565 days)	24 Months (700-740 days)	30 Months (890 – 930 days)	36 Months (1065-1125 days)
Informed Consent	x	x													
Medical Evaluation	x[†]	x		x	x	x	x	x	x	x	x	x	x	x	x
Psychological Evaluation	x														
Complete Eye Exam	x			x	x	x	x	x	x	x	x	x	x	x	x
Visual Field		x							x		x		x		x
Retinal Photography		x			x		x	x	x	x	x	x	x	x	x
Fluorescein Angiogram		x			x		x	x	x	x	x	x	x	x	x
Optical Coherence Tomography		x			x		x	x	x	x	x	x	x	x	x
Ultrasound A- and B-scans	x						x (B-only)	If subject was enrolled before March 2010, B-scan should be performed at next available clinic visit.							
CT Scan					x										
Document Fixation Position and Eye Movement Range		x			Performed on an as-needed basis.										
Visual Acuity, including Grating Acuity Full Field Stimulus Threshold (Electrically Evoked Response (EER)[‡]	X[§]							x	x		x	x	x		x
Orientation and Mobility Tasks		x						x	x		x	x	x		x
Massof Activity Inventory		x						x	x		x	x	x		x
VisQOL		x						x	x		x	x	x		x
Functional Low-Vision Observer Rated Assessment (FLORA)											X***				X***
Square Localization & Direction of Motion		x						x	x		x	x	x		x
Perceptual Thresholds for Electrical Stimulation							x	x	x		x	x	x		x
System Fitting and Psychophysical Testing					Ongoing.[**] Typically 1-2 times per week.										
Home Use					Ongoing after subjects meets home use criteria.										

[†] If the subject is female and capable of giving birth, this evaluation must include a pregnancy test
[‡] EER is only performed at screening and only if the subject has no light perception
[§] These tests are to be performed twice, on different days
[**] Testing commences at latter of the following: (a) 1 week post-implant, or (2) when the conjunctiva is sufficiently healed in the opinion of the clinician.
*** For subjects enrolled in the study prior to August 2010, the FLORA should be performed as soon as possible after the subject consents to the test. The assessment will be counted toward the closest follow-up visit (i.e. 1 or 3 years) even if it is performed outside that visit window.

Table 5.2 Post-Explant Schedule

Evaluation or Test	Explant (Day 0)	1 Day (12-36 hours)	1 Week (5-9 days)	4 Weeks (24- 32 days)	3 Months (80-100 days)	6 Months (170-200 days)	12 Months (340-380 days)
Medical Interview, Complete Eye exam and Review for AE		X	X	X	X	X	X
Retinal Photography			X	X	X	X	X
Optical Coherence Tomography			X	X	X	X	X
Fluorescein Angiogram			X	X	X	X	X

The post–explant schedule should be followed ONLY in the event that the device is explanted and the subject consents to post-explant follow-up. Unless otherwise indicated, the device will remain implanted at the conclusion of the study.

Table 5.3 Study Procedures and Tested Eyes

Evaluation or Test	Screening & Baseline	Follow-up	
	Eye Tested	**Eye Tested**	**System ON/OFF**
Complete Eye Exam	Both, separately	Both, separately	OFF
Visual Field	Both, separately	System OFF - Both, separately System ON – Both, together	ON and OFF
Retinal Photography	Both, separately	Both, separately	OFF
Fluorescein Angiogram	Both, together	Both, together	OFF
Optical Coherence Tomography	Both, separately	Both, separately	OFF
Ultrasound A- and B-scans	Both, separately	N/A	N/A
CT Scan	N/A	Implanted only	OFF
Document Fixation Position and Eye Movement Range	Both, together	Both, together	OFF
Visual Acuity Tests			
Grating Acuity	Both, separately	Both, separately	ON and OFF
Full Field Stimulus Threshold	Both, separately	Both, separately	OFF
Electrically Evoked Response	Implanted only	N/A	N/A
Orientation & Mobility Tasks	Both, together	Both, together	ON and OFF
Massof Activity Inventory	N/A	N/A	N/A
VisQOL	N/A	N/A	N/A
Square Localization & Direction of Motion Test	Both, together	Both, together	ON and OFF
Perceptual Thresholds for Electrical Stimulation	N/A	Implanted Only	ON
FLORA	N/A	Both, together	ON and OFF

Table 5.4 Extended Follow-Up Schedule (Years 4-7)

Evaluation or Test	**Enrollment in Years 4-5 Extended Follow-up** (After 36 Month follow-up)	**3.5 Years (40.5 – 43.5 Months)**	**4 Years (46.5 – 49.5 Months)**	**4.5 Years (52.5 – 55.5 Months)**	**5 Years (58.5 – 61.5 Months)**	**Enrollment in Years 6-7 Extended Follow-up** (After 5 Year follow-up)	**5.5 Years (64.5 – 67.5 Months)**	**6 Years (70.5 – 73.5 Months)**	**6.5 Years (76.5 – 79.5 Months)**	**7 Years (82.5 – 85.5 Months)**
Informed Consent	x					x				
Medical Follow-Up, including: Complete Eye Exam Current Medical Status Adverse Events		x	x	x	x		x	x	x	x
Retinal Photography			x		x					
Optical Coherence Tomography			x		x					
Visual Function Full-Field Stimulus Threshold (FST)* Photographic flash test Grating Visual Acuity Square Localization Direction of Motion			x		x					
Orientation and Mobility Tasks			x		x					
Massof Activity Inventory			x		x					
Functional Low-Vision Observer Rate Assessment (FLORA)		If not performed in years 1-3, perform as soon as practical following subject consenting to this additional assessment. This assessment will serve at the 3 year FLORA.								
Perceptual Thresholds for Electrical Stimulation			x		x			X		X
System Fitting and Psychophysical Testing	Optional at the joint discretion of subject and investigator. May occur as frequently as 1x/week, but usually occurs no more than 1x/month.									
Home Use	Optional at the discretion of the subject. Ongoing.									

* FST is only required at those centers that have a Diagnosys Espion System

Table 5.5 Post-Approval Phase Follow-Up Schedule (Years 8-10)

Evaluation or Test	**Enrollment in Years 8-10 Extended Follow-up** (After 7 Year follow-up)	**8 Years (± 1.5 Mo)**	**9 Years (± 1.5 Mo)**	**10 Years (± 1.5 Mo)**
Informed Consent	x			
Medical Follow-Up, including: Complete Eye Exam Current Medical Status Adverse Events		x	x	x
Photographic Flash*				x
Square Localization Test*				x
Direction of Motion Test*				x
Grating Visual Acuity*				x
Perceptual Thresholds for Electrical Stimulation*		x	x	x
Transfer VPU data to sponsor*		x	x	x
System Fitting and Psychophysical Testing*	Optional at the joint discretion of subject and investigator. May occur as frequently as 1x/week, but usually occurs no more than 1x/month.			
Home Use	Optional at the discretion of the subject. Ongoing.			

* These tests are only required for subjects who are using the System at home.

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6 Screening, Baseline and Enrollment Procedures

The schedule of observations and assessments to take place during screening and baseline testing is summarized in Table 5.1.

To determine which eye should be tested during screening and baseline testing, refer to Table 5.3.

Methodologies for all screening and baseline testing procedures are detailed in the Procedures and Operations Manual.

6.1 Screening

6.1.1 Informed Consent

Screening is intended to determine whether a subject meets the selection criteria defined in Section 4 of this protocol. Prior to undergoing any screening procedures, each subject must sign the Screening Informed Consent Form. Since potential subjects are severely visually impaired, the informed consent should be read to the subject in addition to providing them with a printed copy of the document as well as an audio version.

6.1.2 Screening Log

All subjects screened must be recorded on the screening log regardless of whether they are subsequently enrolled or not. Subjects who continue to meet the subject selection criteria after screening will be asked to review and sign a second Informed Consent Document (the Baseline Informed Consent Form) prior to beginning participation in the study.

6.1.3 Screening Tests and Exams

Screening consists of the following tests and exams:

1. Medical Evaluation

   This evaluation is performed to:

   a. Evaluate the subject's expectations of the system
   b. Review the subject's ophthalmic history and records
   c. Review the subject's general medical history
   d. If the subject is female and is capable of becoming pregnant, administer a pregnancy test to ensure the subject is not pregnant. Also, advise the subject of appropriate birth control measures that must be maintained during the course of the study.

e. Review of all the subject's chronic and acute medications

2. Psychological Evaluation

   This evaluation is performed to confirm that the subject:

   a. Seeks participation in the study primarily to contribute to the development of effective retinal prosthesis technology, rather than with the expectation of a substantial improvement in his or her level of vision, and is willing and able to commit to a lengthy rehabilitation process with limited benefits.

   b. Does not have any underlying psychological condition that would impede the study evaluations and follow-up such as:

      i. Cognitive decline including diagnosed forms of dementia and/or progressive neurologic disease

      ii. Psychiatric Disease including diagnosed forms of depression

3. Complete Eye Exam

4. Ultrasound A- and B-Scans

   An ultrasound A-scan is performed to determine the axial length of the eyes. A B-scan is performed to determine the posterior coats thickness (i.e. the retina, sclera, choroid complex) in the region where the array will be implanted.

5. Visual Acuity Testing

   Visual acuity testing will be performed at screening to confirm that the subject meets the first two inclusion criteria:

   1. Have a confirmed history of retinitis pigmentosa with a visual acuity of Bare Light Perception or worse in both eyes.
   2. Have functional ganglion cells and optic nerve in the implanted eye as determined by documented light perception or a measurable electrically evoked response.

   Refer to Figure 6.1 for the visual acuity procedure.

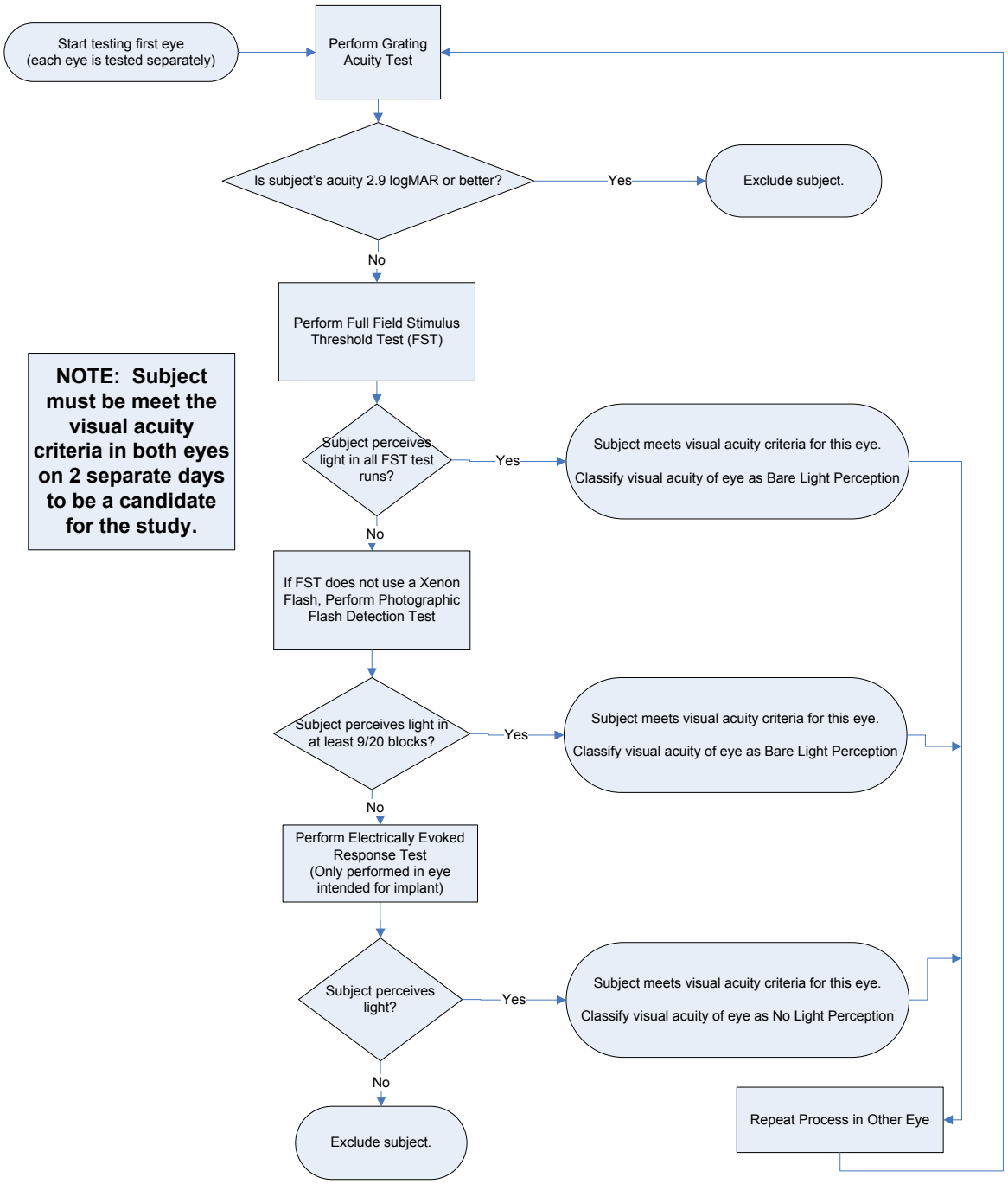
   Visual Acuity must be measured in full, on both eyes, on two separate days. If the subject fails to meet visual acuity criteria on any of the tests in either of the eyes, they may not participate in the study.

   Following completion of each visual acuity screening test, a visual acuity score will be assigned for each eye using Figure 6.1 and

represents the highest acuity a subject attains in a particular session.

In the event that the subject is eligible for inclusion in the study, the highest visual score measured from the two days of screening tests will be used as the baseline value.

Figure 6.1 Visual Acuity Testing at Screening



6.2 Enrolling a Subject

Subjects who meet all the patient selection criteria are eligible for enrollment in the study. Interested subjects must sign the Baseline Informed Consent Form. Once again, the Baseline Informed Consent form should be read to the subject in addition to providing the subject with a printed copy of the document and an audio version of the document.

Subjects meeting all the patient selection criteria and who sign the Baseline Informed Consent form will be considered to be enrolled and will be formally assigned their study number. Subjects will be numbered sequentially within each site upon enrollment. Subject numbers contain the prefix of the site number to allow unique identification.

6.3 Baseline Testing

Baseline testing consists of the following:

1. Medical Evaluation.
2. Visual Field
3. Retinal Photography
4. Fluorescein angiogram (FA)
5. Optical Coherence Tomography (OCT)
6. Documentation of Fixation Position and Eye Movement Range
7. Orientation and mobility tasks
8. Massof Activity Inventory questionnaire
9. VisQOL questionnaire
10. Square Localization and Direction of Motion tests

Baseline testing may reveal that a subject no longer meets the subject selection criteria (e.g. imaging reveals that the subject has a condition that could prevent the system from functioning for the duration of the study). In this situation, the subject would be withdrawn from the study. Refer to Section 10 for instructions on subject withdrawal.

7 Peri-Operative Study Procedures

7.1 Pre-Operative Medication Regimen

Subjects will be treated pre-operatively with Ciprofloxacin (or an equivalent dosage of another quinolone family antibiotic) 500mg BID for 48 hours before implant.

7.2 Argus II Retinal Prosthesis Implantation

Refer to the Clinician's Manual, Chapter 3 (Surgical Procedures) for instructions for how to implant the Argus II Retinal Prosthesis, including intra-operative medications.

If there is a significant difference in vision between the two eyes, the device should be implanted in the worse eye. This decision will be made by the clinician, in consultation with the subject, as necessary.

If the subject is phakic in the eye intended for implant, the lens will removed at the beginning of the implant procedure to either remove an existing cataract or prevent the formation or progression of a cataract during follow-up which could impair the ability to visualize the implant and the retina.

The day of implant is considered Day 0.

7.2.1 Post-Operative Medication Regimen (starting on Day 1)

1. Antibiotics
   - Ciprofloxacin: 500mg BID for 14 days
   - Gatifloxacin (Zymar) eye drops: 1 drop QID for at least 14 days

2. Steroids
   - Prednisolone 60mg daily PO for two weeks, immediately followed by a Methylprednisolone (Medrol) taper pack (8mg), until the pack is completed
     - If Medrol pack is unavailable, reduce Prednisolone by 10mg per day
   - Pred Forte 1% – 1 drop QID for 2 weeks. Continue prn.

   NOTE: If the subject experiences low intraocular pressure (IOP) post-operatively, then the steroid regimen should be as follows:

   - Halve the oral Prednisolone dose if IOP mmHg reaches 5 or less
   - Reduce Pred Forte 1% to 1 drop daily

- Once IOP has reached 10 mmHg or higher, increase the oral Prednisolone dose as clinically indicated
- Continue Pred Forte drops as clinically indicated

3. Mydriatics
   - 1 drop topical Atropine 1% once daily for 2 weeks

NOTE 1: Investigators should direct subjects taking chronic or acute medication to make their primary physician aware of the medications anticipated for pre and post management of the implant and that these may affect their pre-existing medical conditions and/or interact with the medications they are taking.

NOTE 2: Modifications to the medication regime should be made where necessary to optimize subject care.

8 Follow-Up Study Procedures

Postoperative follow-up provides the data necessary to monitor system safety, including medical/surgical risks or complications and adverse events, and to monitor system effectiveness over time. Subjects will be followed post-operatively for 36 months. At the end of 36 months, subjects will be offered the opportunity to extend their follow-up for up to an additional 7 years (Refer to Section 8.8, Extended Follow-Up (Years 4-10)).

The schedule of observations and assessments to take place during follow-up and the appropriate time intervals during which each visit should occur are summarized in Table 5.1. Postoperative evaluations are counted from the date of the surgery, with the day of surgery being Day 0.

To determine which eye should be tested during follow-up, refer to Table 5.3. Methodologies for clinical follow-up, endpoint testing procedures, and certain system fitting and psychophysical testing procedures are detailed in the Procedures and Operations Manual.

8.1 Clinical Follow-Up

Clinical follow-up consists of the following:

1. Medical Evaluation, including a review for adverse events, current medications and other relevant clinical findings
2. Complete eye exam
3. Visual Field
4. Retinal photography
5. Fluorescein angiography
6. Optical coherence tomography (OCT)
7. Ultrasound B-scan – If the subject was enrolled prior to March 2010, this test should be performed at the next available clinic visit.
8. CT-Scan
9. Documentation of Fixation Position and Eye Movement Range – This is only performed on an as-needed basis.

If a portion of the subject's implant array overlaps the optic nerve head, clinicians should carefully monitor the optic nerve head during the follow-up eye exams and review serial photographs from retinal photography, fluorescein angiography and OCT to confirm that the array is a safe distance from the optic nerve head surface and does not appear to be damaging this structure.

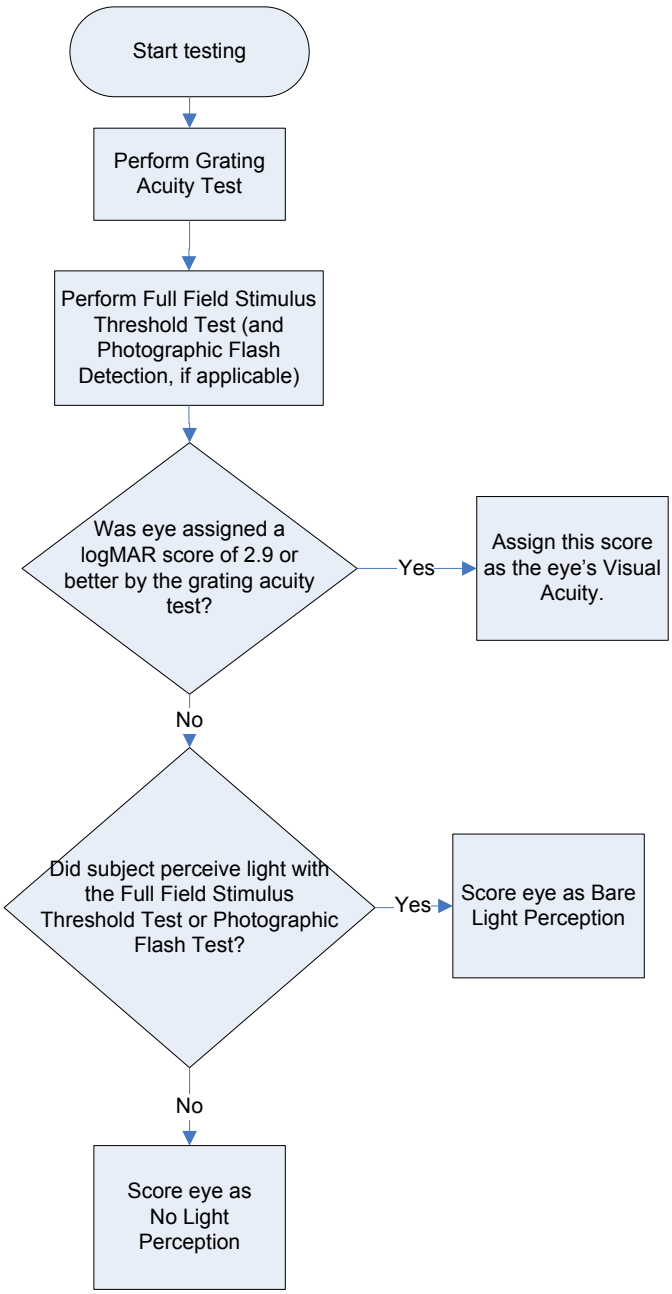
8.2 Endpoint Assessments

8.2.1 Visual Acuity

Follow-up visual acuity testing should be performed and scored according to Figure 8.1.

Figure 8.1 Visual Acuity Testing at Follow-Up

Perform this test in both eyes, separately.
Refer to Table 5.3 for instructions about performing the test with the System ON or OFF.



8.2.2 Orientation and Mobility Task

Once the subject has been successfully fitted with the external system (i.e. the subject's VPU has been loaded with a Video Configuration File), the subject will be asked to perform the orientation and mobility tasks per the schedule in Table 5.1.

8.2.3 Quality of Life and Activities of Daily Living

Commencing at three months post-implant, the VisQOL and Massof Activity Inventory will be administered to each subject.

8.2.4 Functional Low Vision Observer-Rated Assessment (FLORA)

This assessment will be performed at 1 and 3 years post-implant. For subjects enrolled in the study prior to August 2010, who may have already passed one or both of these time points, this assessment will be performed as soon as can be scheduled after the subject has consented to this additional assessment. For these subjects, the assessment will be counted toward the closest required follow-up visit (i.e. 1 or 3 years) even if it is performed outside that test window.

8.2.5 Spatial Vision Tests

Commencing at three months post-implant, the Square Localization and Direction of Motion tests will be administered to each subject per the schedule in Table 5.1.

8.2.6 System Performance

System performance will be evaluated using two measures:

- Electrode impedance will be recorded to ensure continued function of the electrodes in the array. Electrode impedance measurements will be taken at the beginning and, if possible, at the end of each testing session.
- Perceptual Thresholds for Electrical Stimulation will be recorded to document the level at which electrical stimulation produces a phosphene (the perception of a spot of light). Threshold testing will be performed according to the schedule in Table 5.1.

8.3 Argus II System Fitting and Psychophysical Testing

Subjects will be scheduled for fitting and psychophysical testing sessions up to twice weekly, with sessions lasting up to four (4) hours. A Second Sight Field Clinical Engineer may assist the investigator during these test sessions.

8.3.1 Argus II System Fitting

Fitting refers to the procedure for establishing the most effective Visual Processing Unit (VPU) settings for subjects implanted with a retinal prosthesis. Psychophysical testing will be used to establish the electrical pulse parameters for stimulating retinal neurons and to determine the optimal method for transforming the video input signal to a useful pattern of electrical stimulation.

The procedure for converting video camera input to a pattern of electrical stimulation can be broken down into two general parts: the video chain and the Video Configuration File (VCF).

The Video Chain

The image is captured by a video camera mounted on the glasses. This video image is sent to the VPU, where the video input signal is processed by a series of digital filters. The goal of these operations is to construct the inferred "neural image" best suited for presentation to the retinal circuitry through electrical stimulation. The image should consist of intensity values that are scaled to maximize the dynamic range for perceived brightness.

Video Configuration File (VCF)

The Video Configuration File specifies the method for converting the output of the video chain to electrode stimulation values. The perceptual brightness produced by an electrode can be manipulated by changing the electrical pulse parameters, such as the pulse amplitude. The VCF contains a look-up table that specifies the mapping between the video image intensity values and the pulse parameter values. The file also specifies which spatial sections of the video image are sent to each electrode.

Constructing the Video Configuration File

The video configuration file will be constructed based on measurements of the percepts produced by patterned electrical stimulation. The experimental data required to construct a video configuration file may vary from subject to subject, and the design and execution of these experiments is referred to as fitting. During the course of this feasibility study, we will refine and evaluate our fitting procedures to determine the most efficient and effective method of optimizing system parameters.

Video Configuration File Refinement

Based on the subjective feedback from the subject and any subsequent testing, the VCF may be altered to improve the subject's perception. For example, if a subject's performance is hindered by the perception of flicker, the frequency of stimulation may be increased.

8.3.2 Psychophysical Testing

During some fitting and testing sessions, we will conduct various non-invasive objective tests ("psychophysical testing") to monitor the progress of the fitting procedure and to determine the most appropriate testing to optimize system parameters. The specific psychophysical tests to be performed may vary from subject-to-subject and additional tests will be developed as the study progresses. Results will be summarized in the annual report.

8.3.3 Training and Rehabilitation

Throughout the study, subjects will receive training on how to use the Argus II System. This training will typically take place during the weekly System Fitting and Psychophysical Testing Sessions at the clinic. Subjects may also receive some vision rehabilitation to enhance their ability to receive benefit from the Argus II System. Qualified vision rehabilitation specialists (e.g. CLVT, OTR/L, COMS, etc.) may assist with this training and rehabilitation. At the discretion of the investigator and with the agreement of the subject, a certain amount of training and rehabilitation may take place at the subject's home and/or immediate environs or in an environment outside of the clinic.

8.4 Home Use

As soon as possible after implant, subjects will be trained to use the Argus II system at home. After meeting the requirements for home use (see below), they will be allowed to take their system home and will be instructed to use it for approximately 4 hours/day, 28 hours a week.

Subject and caregiver (if applicable) are instructed that the system may not be used as the primary mechanism for mobility.

Subjects will report the details of their home use to the investigator during their fitting and testing sessions.

Criteria for Home Use

Before being allowed to use the Argus II System at home, subjects must demonstrate the ability to set-up and use the system and respond to audible alarm states without trainer intervention. In addition, the subjects and their caregivers (if applicable) will be provided with a Patient's Manual (hard copy and audio version) for information regarding the operation the Argus II

system. Subjects and their caregivers (if applicable) will be specifically trained on the following:

1. **System Set-up and Operation**

   1.1. The Patient Manual will be used to instruct the subject to set-up and operate the system.

   1.2. The Patient Manual will be used to review all safety information related to the system, including the Warnings and Precautions section, the significance of audible alerts and how to respond to them, any Caution statements that are included throughout the manual, and how to troubleshoot problems.

2. **"Real World" Training**

   2.1. Tasks, such as the ones listed below, will be used to familiarize the subject with operation of the system in real world environments.

      a. Identify and localize a combination of fluorescent lights that are switched on and off.

      b. Identify the locations of doors or windows.

      c. Find the position of a dark colored chair against a white background.

      d. Identify whether a person passed by in front of them and the direction of travel.

Equipment for Home Use

Each subject will be furnished with the following:

1. Argus II Video processing unit
2. Argus II Glasses
3. Argus II VPU Pouch to hold the Argus II VPU.
4. Two Argus II VPU Batteries.
5. Argus II VPU Battery Charger.
6. Argus II Traveling Case.
7. Patient User manual (hardcopy and audio version).
8. Tactile targets to practice using the system.

8.5 Explantation of the Implant

The Argus II implant will be explanted at any time during the study (i.e. either during the initial 36 month follow-up period or during extended follow-up in years 4-10) if any of the following conditions occur:

1. Subject requests explant either upon study termination or subject withdrawal.
2. Device becomes compromised in any way that compromises the subject's safety.
3. Unresolved infection.
4. Clinically significant retinal detachment that does not respond to treatment.
5. Unexplained device failure that places the subject at risk.
6. Intractable pain.

All surgically removed devices will be returned to Second Sight for analysis. Second Sight will provide a procedure for treatment and shipping of returned devices.

Subjects will be followed post-explant per the schedule in Table 5.2 unless they have withdrawn from study and refuse further follow-up.

Refer to the Clinician's Manual, Chapter 3 (Surgical Procedures) for instructions for how to surgically remove the Argus II Retinal Prosthesis. The pre-, Intra-Op and Post-Explant medication regimen is provided below (Section 8.7).

8.6 Revision of the Implant

The position of the Argus II implant may be revised during the study to address a variety of situations including, but not limited to:

1. Correct the position of the implant due to movement.
2. Reposition extra-ocular parts of the implant to improve functionality of the system.

The revision may include replacing or adding materials that were used in the original surgery to better secure the implant (i.e. sutures and metal tacks). The decision to revise an implant will be made by the surgeon, in consultation with the Second Sight. The procedure for performing the revision surgery will vary from subject-to-subject. It is recommended that the surgeon consult with Second Sight as to how to perform the revision surgery. The pre-, Intra-Op and Post-revisions surgery medication regimen is provided below (Section 8.7).

The short-term follow-up schedule following revision surgery should be directed by the nature of the surgery and determined by the surgeon. The Revision Surgery Case Report Form provides general guidelines for post-revision surgery follow-up. In general, subjects should resume their normal follow-up schedule after about 1 month post-revision surgery.

8.7 Medication Regime for Explant or Revision Surgery

Pre-Surgical

Two days (48 hours) prior to the planned surgery, start the subject on Ciprofloxacin (or an equivalent dosage of another quinolone antibiotic) 500mg BID.

Intra-Operative

Intra-operative medications should follow the same regime as for the initial surgery.

Post-Operative (starting the day after surgery)

1. Antibiotics
   - Ciprofloxacin: 500mg BID for 14 days
   - Gatifloxacin (Zymar) eye drops: 1 drop QID for at least 14 days

2. Steroids - Steroids should be prescribed according to clinician judgment. Oral steroids are not required for subjects whose device is explanted. Below is a potential regime for consideration.

   - Prednisolone 60mg daily PO for up to two weeks, immediately followed by a Methylprednisolone (Medrol) taper pack (8mg), until the pack is completed.
     - If Medrol pack is unavailable, reduce Prednisolone by 10mg per day

     NOTE: The requirement for and duration of oral steroids should be adjusted based on the duration and nature of the surgery. The full fourteen days of oral steroids should be administered before tapering in cases where the surgery is extensive and/or involves manipulation of the extra-ocular parts of the device.

   - Pred Forte 1% – 1 drop QID for 2 weeks. Continue prn.

   NOTE: If the subject experiences low intraocular pressure (IOP) post-operatively, then the steroid regimen should be as follows:

- Halve the oral Prednisolone dose if IOP mmHg reaches 5 or less
- Reduce Pred Forte 1% to 1 drop daily
- Once IOP has reached 10 mmHg or higher, increase the oral Prednisolone dose as clinically indicated
- Continue Pred Forte drops as clinically indicated

3. Mydriatics
   - 1 drop topical Atropine 1% once daily for 2 weeks

8.8 Extended Follow-Up (Years 4-10)

Following completion of the 36 months follow-up, subjects will be offered the opportunity to extend their participation in the study for up to an additional 7 years, to provide a maximum follow-up duration of 10 years. Subjects still implanted with the Argus II device will be asked to consent for extended follow-up in the following increments:

- Years 4-5
- Years 6-7
- Years 8-10

If subjects consent to extend their follow-up, they may continue to use the Argus II System at home and they will be required to undergo clinical follow-up. During the extended follow-up period, testing in the clinic (i.e. psychophysical testing and system fitting) will be optional and will be scheduled at the joint discretion of the subject and investigator. The schedule for the extended follow-up for years 4-7 is provided in Table 5.4 (page 36). The schedule for the extended follow-up for years 8-10 is provided in Table 5.5 (page 37).

9 Study Completion

Subjects will be considered to have completed the study when they have been followed through 36 months post-implant (if the subject does not consent to extended follow-up), or through 5, 7, or 10 years post-implant (if they consent to extended follow-up), at the time of withdrawal, or 12 months post explant, whichever is the longest. One exception to this is when a subject has an unresolved adverse event at the end of the study. Refer to Section 14.1 for instructions for how to handle this situation.

At the completion of the study, subjects will be allowed to continue use of the system with prior government regulatory and institutional review board/ethics committee approval.

The study will be complete when all subjects have completed the study.

10 Withdrawal and Replacement of Subjects

Subjects are at liberty to withdraw from participation in the study at any time without penalty or prejudice. Any subject who withdraws will be given the option of keeping the Argus II implant or having the device explanted.

If a subject does not return for a scheduled visit, every effort will be made to contact her/him. In any circumstance, every effort must be made to document subject outcome, if possible.

If the subject becomes pregnant, she must be withdrawn from the study. Such subjects may elect to rejoin the study at the completion of pregnancy and lactation if the study is still open.

In all cases, the reasons for withdrawal must be recorded on the case report form and in the subject's medical records. If possible, a complete, final examination should be performed on all subjects who intend to withdraw from the study.

If the Argus II Implant is explanted, the subject will be followed post-surgery for twelve months to allow evaluation of adverse events related to the explant procedure unless they have withdrawn and refuse further follow-up.

Any subject who has been implanted with the study device and withdrawn from the study will not be replaced. Subjects withdrawn prior to implant may be replaced.

11 Statistical Methods

11.1 Sample Size Estimate and Justification

As the objective of the study is to evaluate the safety of the implanted system and the utility of the study measures in this population, a maximum of twenty (20) subjects are to be enrolled in this feasibility study in the U.S.

This number of subjects will allow evaluation of the basic performance of the system, an estimate of the level of vision provided and the safety profile of the system in the specified patient population.

11.2 Eligibility of Subjects, Exclusions, and Missing Data

All subjects enrolled according to the entry criteria in Section 4 will be eligible for evaluation, regardless of the sequence of treatment that ensues.

All subjects enrolled in the study are considered eligible for follow-up and will be required to adhere to the follow-up schedule outlined in Table 5.1 and Table 5.2.

Management of dropouts and missing data will depend on their frequency and the nature of the outcome measure. Adjustments for missing data will be performed only if deemed necessary and will be described completely.

Outlier values will be evaluated for their validity; all data will be included unless judged to be invalid.

11.3 Primary Analysis Population

The primary analysis sample will be based on the principle of intention-to-treat. All subjects who sign the written Informed Consent form, meet the study entry criteria, and are enrolled will be included in the analysis sample, regardless of whether or not the device was implanted.

11.4 Secondary Analysis Population

A secondary analysis will be performed to evaluate the results of device placement and consist of subjects on an "as treated" basis.

11.5 Statistical Analysis

Subject demographics, clinical history, risk factors, preoperative, and procedure data will be summarized using descriptive statistics for continuous variables (e.g. mean, standard deviation) and frequency tables or proportions for discrete variables.

Post-procedure information will be collected at regularly scheduled follow-up examinations according to the clinical study schedule. Estimates of primary and secondary endpoints will be reported along with their 95% confidence intervals. The Kaplan-Meier product limit method will be used to determine rates of events for time-to-event endpoints such as retinal detachment.

Where testing is conducted with the system on and off, comparison will be made between subject performance under both conditions. Where testing is conducted with the implanted and non-implanted eyes separately, comparison will be made between subject performances using each eye.

12 Data Management

12.1 Data Collection

Case Report Forms (CRF) are required and must be completed in black or blue ink for each subject enrolled. The authorized site representative signs and dates the case report forms on the specified pages to assure the accuracy and completeness of the recorded data.

Some data may be collected from the output of the clinical fitting system or ophthalmic diagnostic equipment. In such cases, a signed and dated printout, de-identified images or encrypted electronic media may be used in place of the case report form pages.

Some data may be collected directly onto the case report forms, e.g. subject questionnaires and tests that are not standard for retinitis pigmentosa patients. In such instances, the case report form will constitute source documentation.

12.2 Data Processing

Second Sight Medical Products is the responsible coordinating center for data management.

All case report forms, images and data electronically captured by the Argus II System will be sent to the Second Sight for entry into a database. Visual and computer error checks will be carried out. The Investigator will be queried on discrepancies concerning completeness and consistency.

All above-mentioned tasks will be performed according to relevant Standard Operating Procedures. Audits may be performed for quality assurance of data handling.

13 Monitoring Procedures

Second Sight Medical Products, Inc will be the study monitor.

13.1 Monitoring

Second Sight personnel will monitor all clinical studies in a manner consistent with applicable health authority regulations and the clinical research standards adopted by Second Sight. Site monitoring includes a site qualification visit, initiation/training visit, interim monitoring visits, and a study closure visit. Monitoring visits will occur according to the schedule in table 11.1 at a minimum. Additional interim visits will be conducted according to subject number and site performance in regard to accuracy and completion of data and compliance to the protocol.

Table 11.1 Monitoring Visit Schedule

Monitoring Visit	Number of Visits	Frequency	Timing
Qualification	1	Once	Before IRB submission.
Initiation/Training	1	Once	Before first subject enrollment.

			Training may be repeated.
Interim	Ongoing	At least every six months, and within one month of first implant.	Commencing within one month of first implant.
Closure	1	Once	Within 3 months of study closure at site.

13.1.1 Site Qualification

A site qualification visit will be conducted to determine the adequacy of subject population, clinical facilities/equipment and the adequacy of the investigator and additional staff's credentials, availability and resources to conduct the study.

13.1.2 Site Initiation/Training

A site initiation/training visit will be performed to train the investigational staff on the investigational plan, which includes, but is not limited to, confidentiality, consenting process, enrollment, device accountability, study deviations, subject testing, product training, adverse event reporting, data collection, and study documentation. In addition, the implanting surgeon will receive training in how to implant the Argus II system.

13.1.3 Interim Monitoring

Interim monitoring visits will be conducted to evaluate study progress, continued acceptability of the facility, staff, and equipment, adherence to the protocol, maintenance of records, verification of case report form data to source documentation, verification of adverse event data to source documentation, collection of case report forms, and affirmation of investigational product/device inventory control.

All investigative sites will be monitored for deviations related to protocol test procedures, exams, missed or out of window visits and subject noncompliance with study requirements. If a significant deviation/violation from the protocol is noted such as Inclusion/Exclusion violation, consent violation, or system misuse, the investigator must notify the Sponsor and the IRB immediately so that appropriate action can be taken. If the investigator fails to implement the corrective action, the Sponsor may cease shipment of supplies, discontinue the investigation and/or notify the appropriate agencies.

13.1.4 Site Closure

Site/Study Closure Visit will focus on device inventory/reconciliation, adequacy of space for retention of study records, re-verification that the investigator study file contains all appropriate documentation, and verification that the investigator's final study report is in progress.

13.2 Device Accountability

Device accountability records must be maintained at each study center. The number of devices delivered to and/or returned to SSMP and assigned to individual subjects by the Investigator will be registered. Any accountability discrepancy at the end of the study needs to be explained in writing by the Investigator.

13.3 Protocol Violations and Deviations

All violations and deviations related to study inclusion or exclusion criteria, conduct of the study, subject management, or subject assessment are to be documented on the case report form provided for that purpose.

14 Adverse Events

Adverse Events (AE) are to be monitored from the time of enrollment through the last follow-up visit.

An **adverse event** is defined as any undesirable clinical occurrence in a subject whether it is considered system related or not. This definition includes events occurring during surgery or the follow-up period. Events may be:

1. Observed or volunteered problems
2. Physical signs and symptoms
3. Medical condition(s) which occurs during the study, having been absent at baseline
4. Medical condition(s) present at baseline, which appear to worsen during the study

Excluded from the definition of adverse event are normal post-operative occurrences (e.g. inflammation, pain, etc.) that are routinely observed and managed medically. Post-operative occurrences that are more severe than those normally observed would be considered adverse events.

14.1 Recording Adverse Events

All AEs must be recorded on the case report forms provided. Each event must be on a separate form, regardless of whether one event may be secondary to another.

The following data are required for each AE:

1. Reportable term (name of the AE)
2. Seriousness and reason for being serious.

   Serious Adverse Event Definition – United States

   A **Serious Adverse Event (SAE)** for subjects enrolled in the US is defined as one that causes/is any one of the following:

   - death
   - life threatening
   - permanent impairment of a body function or permanent damage to body structure
   - necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure

   Permanent means irreversible impairment or damage to a body structure or function, excluding trivial impairment or damage.
3. Relatedness to the subject's disease, a procedure or the system. Some adverse events may be unrelated. Relatedness is based on likelihood of the causal relationship
4. Anticipated (anticipated or AEs are listed in section 14.1.1 of the protocol). All others are 'unanticipated'
5. Start and resolution dates
6. Description of the event, commentary on interventions (actions, procedures, medications) and outcomes

AE forms are to be completed at the time of the event regardless of all data being available. In cases where not all data are available, follow-up and final AE forms are to be completed as significant new data become available and when the event resolves.

The need to capture adverse events is not dependent upon whether or not the clinical event is associated with the use of the study product.

All adverse events occurring during the course of the study will be followed through to their resolution, even if this extends the subject's participation

beyond the normal end of the study (i.e. 36 months). If an AE is unresolved at the subject's final study visit, the investigator should continue to follow and treat the adverse event as is clinically indicated, and report the follow-up information on an adverse event form.

14.1.1 Anticipated Adverse Events

1. Infection
   - If an infection is presumed, attempt to confirm with microbiological testing
2. Inflammation is not an AE if it is < Kimura class 2 and lasts for < 1 month unless it raised IOP above 30mmHg.
3. Hypopyon
4. Hyphema is an AE if it:
   - Occurs in the immediate post-operative period and lasts > 1 month post surgery OR
   - Occurs later than one month post surgery , is mild (or worse) and lasts > 1 month OR
   - Is '8-ball hyphema' OR
   - Causes high IOP (>30 mmHg).
5. Vitreous hemorrhage is an AE if it:
   - Occurs in the immediate post operative period and lasts > one month post surgery OR
   - Occurs later than one month post surgery, is mild (or worse) and lasts ≥ 1 month OR
   - Obscures the view of the retinas such that ultrasound is needed to assess OR
   - Leads to IOP >30mmHg
6. Retinal Folds are AEs if the affect the array placement or the tack.
7. Vascular Congestion/Occlusion
8. Cystoid Macular Edema/Choroidal Hemorrhage
9. Conjunctival Erosion is an AE if there is device exposure.
10. Suture irritation is an AE if it requires surgical intervention.
11. Scleral Erosion
12. Choroidal detachment is an AE if –
    - It is ≥to 4 disc diameters OR
    - It displaces the array OR
    - Choroidals are 'kissing' OR

- It lasts for longer than 1 month OR
- It is associated with a flat anterior chamber.

13. Conjunctival congestion is an AE if it:
    - Occurs in the immediate post-operative period (within 1 month post-operative) and lasts > 1 month OR
    - Occurs later than one month post surgery, is mild (or worse) and lasts > 1 month.
14. Scleral Perforation – unintended perforation of the sclera
15. Scar or fibrosis formation, including epiretinal membrane
16. Ocular fibrin (anterior or vitreous) is an AE if it
    - Occurs in the immediate post-operative period and lasts >1month post surgery OR
    - Occurs later than one month post surgery, is mild (or worse) and lasts > 1 month OR
    - Obscures the view of the retina
    - Raises IOP above 30mmHg.
17. Retinal Tear or retinal break is an AE
18. Retinal Detachment should be classified as:
    - Rhegmatogenous (AE) OR
    - Subretinal fluid
        - Subclinical - ≤1 disc diameter and well demarcated is <u>not</u> an AE.
        - Clinical - >1 disc diameter is an AE classified as either rhegmatogenous or tractional
19. Retinal edema
20. Retinal/subretinal hemorrhage is an AE only if it causes dislocation of the array.
21. Cataract
22. Corneal Opacity is an AE if it:
    - Covers the visual axis OR
    - Is infectious in nature.
23. Corneal degeneration
24. Corneal vascularization is an AE if it covers the visual axis.
25. Corneal epithelial defect is an AE if it persists > 2 weeks post-surgery.
26. Iris/Pupil changes are AEs if they
    - Lead to atrophy associated with significant functional or structural defects of the iris OR

- Lead to high IOP.

27. Increased intra-ocular pressure (IOP)
    - Intra-ocular pressure increase more than 10 mmHg above baseline or intraocular pressure greater than 30 mmHg
28. Hypotony (<5mmHg) is an AE if it
    - Persists for > 2weeks OR
    - Is associated with kissing choroidals OR
    - Is associated with a flat anterior chamber.
29. Ptosis
30. Ocular pain or discomfort in the implanted eye
31. Disturbed/difficult eye movement
32. Dry eye
33. Extrusion of band
34. Intrusion of band
35. Dislodgement of human sclera or equivalent allograft
36. Electric Shock
37. Migration of array
38. Loosening/extrusion of device
39. Increase in photophobia
40. Side effects of medications and/or interactions with concurrent mediations and underlying medical conditions
41. Respiratory failure – fail to wean from ventilator post-surgically
42. Blood loss requiring active intervention such as transfusion
43. Allergic reaction to anesthesia
44. Loss of light perception in eyes having pre-operative light perception

The following are not AEs:

- Corneal dryness
- Descemets Folds
- Retinal pigmentary changes

14.1.2 Anticipated General Adverse Events

These are normal events or health issues common to the general population. The following list is provided as general guidance but is not intended to be inclusive.

Neurologic

- Depression
- Degeneration of cognition
- Vertigo

Cardiovascular

- Stroke/Transient Ischemic Attack
- Cardiac arrhythmia
- Cardiac arrest
- Hypertension

Musculo-Skeletal

- Arthritis
- Fracture
- Gout

Gastro-Intestinal

- Ulcer
- Mesenteric ischemia

Endocrine

- Diabetes
- Thyroid disorders
- Hormonal changes

Systemic

- Infection unrelated to the implant site.

Mobility

- Falls
- Bumps
- Minor injury

14.1.3 Unanticipated Adverse Events

An adverse event that occurs which is not listed above will be considered unanticipated.

Both anticipated and unanticipated adverse event information will be collected throughout the study

14.2 Reporting Adverse Events

14.2.1 Unanticipated, Serious, Device Related Adverse Events

Any unanticipated, serious, device related adverse event must be reported to the Sponsor within **24 hours**. This must be done by telephone and by scanning/emailing or faxing the completed Adverse Event Form to the address below. In addition, the Sponsor recommends any such adverse events also be reported to the Institutional Review Board within ten working days of learning of the event or in accordance with the IRB terms of approval.

Second Sight Medical Products

Attn: Clinical Affairs

12744 San Fernando Road, Building 3

Sylmar, CA 91342

eFax: +1-818-698-8168

Scan and email to: safety@2-sight.com

Phone: +1-818-833-5039

The sponsor and investigator shall immediately conduct an evaluation of any unanticipated, serious, system related adverse events. A report of the results of such evaluation shall be submitted to FDA and to all reviewing Institutional Review Boards/Ethics Committees and all participating investigators within 10 working days after the Sponsor first receives notice of the adverse system event.

Reports relating to the subject's subsequent medical course must be submitted to the study Sponsor until the event has subsided or, in case of permanent impairment, until the event stabilizes and the overall clinical outcome has been ascertained.

14.2.2 Serious Adverse Events

Serious Adverse Events should also be reported immediately to the Sponsor and to the IRB in compliance with the terms of study approval, regardless of system relatedness or if they are anticipated.

14.2.3 Other Adverse Events Requiring Immediate Notification

The following events should also be reported immediately to the Sponsor, regardless of their system relatedness or if they are anticipated:

- Endophthalmitis
- Rhegmatogenous retinal detachment requiring laser treatment or surgical intervention to repair
- Hypotony requiring surgical intervention to treat

14.2.4 Other Adverse Events

All other adverse events will be documented in annual reports.

14.3 Independent Medical Safety Monitor

An Independent Medial Safety Monitor (IMSM) has been appointed to oversee this study. The IMSM is independent of the study and has no real or apparent conflict of interest. The IMSM is responsible for:

- Reviewing individual serious adverse events (SAEs) submitted by the Sponsor in real time to ensure good clinical practice and to quickly identify safety concerns
- Suggesting protocol modifications to prevent the occurrence of particular adverse events
- Serving as a resource to the clinical investigators for advice about management of SAEs
- Preparing regular reports concerning AEs. Such reports will be submitted on a regular basis (at least) once per year.

In the event of unanticipated SAEs or an unduly high rate of AEs, the Medical Safety Monitor will promptly contact the Sponsor to consider the concerns and plan appropriate action.

15 Device Failures and Malfunctions

All device failures and malfunctions are reported to the Sponsor via the complaint handling process, and the investigational device is returned to

Sponsor for analysis if necessary. The final report on the study results will include information on device failures and malfunctions. Instructions for returning the investigational device will be provided by Second Sight.

16 Ethical Considerations

16.1 Declaration of Helsinki

The study will be performed in accordance with the relevant parts of the ICH Guidelines for Good Clinical Practices, the Declaration of Helsinki and the United States Code of Federal Regulations.

16.2 Ethics Committee/Institutional Review Board

It is the Investigators' responsibility to obtain and maintain written approval of the final study protocol, including the Informed Consent, from the appropriate Institutional Review Board/Ethics Committee. It is also the Investigators' responsibility to notify that body about any amendments to these documents. A copy of the written approval and the approved versions of the documents and a list of the Institutional Review Board/Ethics Committee members, their titles and occupations must be forwarded to the responsible study personnel at Second Sight Medical Products prior to first device shipment. The written approval must identify the study and document the date of review.

The Investigators must file all correspondence with the Institutional Review Board/Ethics Committee and forward copies of such correspondence to Sponsor.

16.3 Emergency Actions

Second Sight Medical Products accepts the right of the Investigator to deviate from the protocol in an emergency when necessary to safeguard the life or the physical well being of a study subject. The Investigator must give notice of any emergency deviations and justification for the deviation to the study personnel responsible at Sponsor and the Institutional Review Board/Ethics Committee as quickly as possible after the episode, in any event no later than 24 hours after the emergency**.**

16.4 Informed Consent Form

It is the responsibility of the Investigator to give each subject before inclusion in the study, full and adequate verbal and written information about the objectives and the procedures of the study and the possible risks involved. The subjects must be informed about their right to withdraw from the study at any time and for any reason without sanction, penalty, or loss

of benefits to which they are otherwise entitled and that withdrawal from the study will not jeopardize their future medical care. It is the responsibility of the Investigator to obtain a signed Informed Consent form from each subject prior to performing any investigational procedures.

The Informed Consent must be updated or amended whenever new information becomes available that may be relevant to the subject. Modifications to these documents must be approved by Second Sight Medical Products.

16.5 Amending the Protocol

This protocol is to be followed exactly. Only Second Sight Medical Products is permitted to write amendments in order to alter the protocol. All protocol amendments must be approved following applicable FDA and Institutional Review Board/Ethics Committee procedures before implementation. Following approval, the protocol amendment(s) will be distributed to all protocol recipients with instructions to append them to the protocol.

17 Study Administration

17.1 Study Timelines for the Post-Approval Phase of the Study

Expected date of study initiation: The post-approval phase of this study will begin in May 2013, following FDA approval of Second Sight's Humanitarian Device Exemption (HDE) application for the Argus II Retinal Prosthesis System and IRB approval of the protocol at the participating sites.

Expected monthly number of study sites with IRB approvals: Second Sight anticipates that all sites who enrolled subjects in the investigational phase of the study will continue to participate in the post-approval phase of the study.

Expected number of subjects enrolled per month: Enrollment in the study is complete. All subjects have been enrolled in the study during the investigational phase of the study.

Expected date of study follow up completion: Study follow-up will be completed by October 2019 (taking into account the allowable follow-up window).

Expected date for Final Report submission: Assuming all follow-up has been completed by October 2019, the final report will be submitted to the FDA by January 2020.

17.2 Study Reporting Schedule

Data collected in this study prior to Humanitarian Device Exemption (HDE) approval have been reported to the FDA in the HDE application. Data reported after the FDA has approved the HDE application will be reported to the FDA as part of the post-approval reporting process.

In the post-approval phase of the study, the study sponsor will prepare the following reports for the FDA. Copies of the final clinical report will be provided to all principal investigators for submission to their reviewing Institutional Review Boards. Copies of the routine progress reports will be provided to principal investigators upon their request.

- Routine Progress Reports: Progress reports, which report the number of sites participating in the study, the number of subjects still enrolled in the study, and the rates of adverse events will be provided at the following intervals from the date of HDE approval:
    - 6 Months
    - 1 Year
    - 1.5 Years
    - 2 Years
    - Annually thereafter until the study is complete

- Final Clinical Report: A final clinical report, reporting all safety and benefit data, will be prepared once all subjects have completed 10 years follow-up.

17.3 Record Retention

In order to constitute evidence with respect to product safety or regulatory or legal compliance, the Investigator agrees to retain study-related documents in a location that is secure and to which access can be gained if required. The following documents must be archived: the Investigator's File containing all required Good Clinical Practice documents, including signed Informed Consent forms and subject-related materials, Case Report Forms and electronic records.

In general, documents related to the clinical trial must be retained for at least 2 years (USA) after its completion or regulatory approval. Refer to the Clinical Trial Agreement for the record retention period for your site.

17.4 Criteria for Terminating the Entire Study

Sponsor reserves the right to terminate the study but intends only to exercise this right for valid scientific or administrative reasons and reasons

related to protection of subjects. Investigators and associated Institutional Review Boards will be notified in writing in the event of termination.

Possible reasons for study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study.
- A decision on the part of Sponsor to suspend or discontinue development of the device.

17.5 Criteria for Terminating the Study at an Investigational Site

The Sponsor reserves the right to stop the inclusion of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled. In addition, the Sponsor may elect to terminate the study at an investigational site if the site has severe protocol violations without any justification or adequate corrective action or if the center fails to adequately staff the study.

Likewise, a principal investigator may terminate the study at his/her institution. This decision must be followed by written notification to the Sponsor within five working days, stating the reasons for termination.

17.6 Sponsor Responsibilities and Commitments

Second Sight Medical Products is responsible for complying with the Declaration of Helsinki and all applicable health authority regulations governing the conduct of clinical research studies. These responsibilities and commitments are listed in Appendix A.

17.7 Investigator Qualifications/Responsibilities

Each Investigator must be qualified to participate in the study and agree to meet the responsibilities detailed in the Investigator Agreement (CP-003-008).

18 Publication Policy

Refer the Procedures and Operations Manual for the complete publication policy.

Appendix A - Sponsor Responsibilities

1. Protecting the rights, health, safety and welfare of study subjects.
2. Informing the clinical investigators of any new information about the study which may affect the health, safety or welfare of the subjects, or may influence their decision to continue participation in the study.
3. Providing the clinical investigators with the study protocol and a full set of Case Report Forms on which to document the study evaluation variables for each subject entered into the study.
4. Providing the statistical analysis and resources necessary to complete reporting of the study results.
5. Ensuring equity of consideration among all investigators in multi-center studies in all matters of publications, meeting presentations, etc.
6. Certifying that Institutional Review Board/Ethics Committee approval of the protocol and Investigators Agreement will be completed prior to treatment at an investigational site.

Appendix B - Clinical Risk/Benefit Assessment

1. Surgical Risks

The subjects' risks may involve standard surgical risks resulting from the use of general anesthesia, steroids and antibiotics, use of conscious sedation, surgical related equipment and device implant. The common surgical risks for vitreo-retinal procedures have been evaluated and are shown below:[37]

Complication	**Incidence (95% CI)**
Chest Pain	0.48 (0.06 – 1.72)
Urinary Retention	0.96 (0.26 – 2.43)
Myocardial Infarction	0.24 (0.01 – 1.33)
Pulmonary Embolism	0.48 (0.06 – 1.72)
Deep vein Thrombosis	0.48 (0.06 – 1.72)

Other risks associated with general surgery include:

- Respiratory failure
- Blood loss greater than anticipated
- Infection of operative site
- Systemic infection
- Hospitalization longer than seven days
- Allergic reaction to anesthesia

Some subjects may require clear corneal phacoemulsification at the start of the implant procedure to remove the lens. The incidence of adverse events associated with clear corneal phacoemulsification is very low, and a high volume cataract surgeon typically observes a rate of adverse events of approximately 0.1% for this procedure. The adverse events can range from posterior capsular tear to cortical drop in vitreous, or vitreous prolapse. All these adverse events can be successfully managed in the operative setting, since associated vitrectomy is being performed at the same time.

If a subject has a small eye, a canthotomy may be performed to help fit the implant in the orbit. A careful canthotomy, followed by layered suturing usually does not lead to any adverse effects. Possible side effects of canthotomy include improper apposition of the eyelids, tearing, and chronic irritation at the lid margin.

If a subject has an epiretinal membrane present at the time of implant surgery, this membrane may be gently peeled off the surface of the retina, usually with forceps. Possible adverse events associated with this procedure include accidental tearing of the retina, improper removal of the membrane causing re-proliferation of the membrane, and macular hole if the membrane covers the macular area.

During the clinical feasibility study of the Argus 16, there were no surgery-related adverse events in the six subjects implanted.[38] The implantation surgery for the Argus II is anticipated to be approximately three hours (five hours shorter than the Argus 16) and should present a lower risk for the surgical procedure. In addition, the Argus II does not require implantation in the skull, again reducing the risks for the implantation procedure.

2. Study Procedure Risks

2.1. Retinal Photography and Optical Coherence Tomography

Retinal photography and optical coherence tomography (OCT) are standard non-invasive diagnostic tests used routinely. Possible adverse reactions may arise from the pupil dilation and include blood pressure changes and other cardiovascular reactions particularly in elderly subjects.[39,40]

As the subjects enrolled in this study have end-stage retinitis pigmentosa, they will have undergone multiple eye examinations using such pupil dilation and thus the risk of a reaction during the study is remote.

2.2. Electrically Evoked Response

To determine optic nerve function in subjects with no light perception an electrically evoked response will be performed. In this test, a low current stimulus is applied via a standard ERG corneal electrode and the subject is asked if they perceive the stimulus as a light. Additional risks include pain and muscle stimulation. In a study of 17 subjects, Dorfman, et. al. reported no adverse events beyond muscular twitch in the stimulated eye.[41]

2.3. Fluorescein Angiogram

Fluorescein angiography, a routine ophthalmic test, requires the injection of a fluorescent dye into the bloodstream followed by retina photography. Allergic response including nausea and occasional vomiting are the most likely adverse reactions to the dye, occurring in five to ten percent of subjects.[42] In rare cases (<0.1%), anaphylactic shock may occur.[43,44,45]

As the subjects enrolled in this study have retinitis pigmentosa, they will have undergone multiple eye examinations using such dyes and thus the risk of a reaction during the study is remote.

2.4. CT Scan

This will be performed once only to document the surgical placement of the device. No contrast media is required for this scan hence risks associated with allergic responses to such media are not applicable. As the effect of the scan on the functioning of the system is unknown, all CT scans will be performed with the system off.

2.5. Orientation and Mobility Testing

During Orientation and Mobility (O&M) testing, subjects will be asked to walk a simple course without any obstacles in their way while closely supervised. During this testing the subjects may become disoriented with an elevated risk of bumping against walls and falling.

3. Device-Related Risks

Adverse events specifically associated with the use of the Argus II System may occur. These may include transient electric shock, facial nerve stimulation and/or pain. In addition, excessive heating of the external equipment may cause burn to the user.

The Argus II Retinal Implant System may unexpectedly stop functioning. The cause of failure may include electrical shorts, and/or interconnect failure. As a result of such a failure, explant may be required.

3.1. Related to Sterility

The surgical procedure and/or the Argus II implant may introduce sources of infection into the operative region. To minimize the risk of infection, the Argus II implant is sterilized to a sterility assurance level (SAL) of 10^{-6} and the surgical procedure will be performed using sterile technique. In addition, subjects will be provided the standard pre- and post-operative antibiotic regimen of the hospital. Sustained infection may result in explant of the Argus II implant, removal of the eye, sepsis or death.

The Argus II implant is sterilized using ethylene oxide (EtO). High levels of EtO residuals are known to be toxic in the eye. Testing has been performed to demonstrate that the ethylene oxide (EtO) residuals present on the device after sterilization are below acceptable safety limits for this type of device.

3.2. Related to Materials

The Argus II implant is manufactured with known biocompatible materials. A risk remains, however, that a subject may have a foreign body reaction to the implant. If this type of reaction were to occur, it would be treated medically. A sustained reaction may require explant of the Argus II implant.

3.3. Related to Cleanliness

The Argus II implant may carry pyrogens and other contaminants, which may result in fibrin proliferation within the eye, fever and corneal opacity.

The Argus II is periodically tested to assure that bioburden is within required levels.

3.4. Related to Sclerotomy and Vitrectomy

Preparation of the eye to receive the Argus II implant requires multiple sclerotomy sites followed by pars plana vitrectomy. The surgical removal of the vitreous has a risk of retinal detachment of approximately 4%, [46,47,48,49] endophthalmitis of 0.05% and a risk of sympathetic ophthalmia of 0.1%.[50]

In addition, vitrectomy may result in hyphema/vitreous hemorrhage, suprachoroidal hemorrhage, cystoid macular edema, or changes to intraocular pressure.

3.5. Related to the Extra-ocular Case and Scleral Band

Implantation of the Argus II requires the placement of a scleral band upon which the case and internal coil ride. Potential complications following band placement include band infection, endophthalmitis, scleral erosion and band extrusion. In a series of 19 subjects with primary scleral band placement, Arroyo, et al. found no occurrence of band infection, endophthalmitis, scleral erosion or band extrusion.[51]

In two histopathologically examined cases, D'Hermies, et al. found the scleral bands well encapsulated with changes to the scleral curvature and thickness, with implant durations of 60 and 161 months.[52] The changes noted did not result in band infection, endophthalmitis or band extrusion.

Additional potential risks of the scleral band and case are increased intra-ocular pressure, scleral perforation, eye-movement disruption and ptosis, ocular pain and discomfort, conjunctival or scleral erosion, retinal tear and disrupted ocular lubrication resulting in dryness and corneal erosion or vascularization.

3.6. Related to the Retinal Tack

In the Argus II System, the retinal tack fixes the array to the vitreal surface of the retina. Retina tacks of different materials have been used for many years to repair retinal tears and detachments. The tack penetrates the eye wall, thereby holding together the layers of the eye. A dislodged tack may damage intraocular structures. In particular it may cause a retinal break or detachment through contact with the lower retinal surface, through allowing the array edge to contact the retina, or through the extrusion process. A dislodged tack will require the subject to have a procedure to re-tack the implant to the retina.

As with any surgical implant, the retina tack is subject to fibrovascular proliferation and scar formation. The proliferative growth around the tack could cause epiretinal membranes or fibrin strands to grow within the vitreous, potentially leading to proliferative retinopathy (PVR).

Studies as short a two months and as long as 2.5 years have shown this phenomenon, [53,54,55] although Gerding, et.al. [56] showed that for tack implantation post-vitrectomy, no fibrous strand or PVR occurred. Ohira, et al. also studied chronic implantation and found that after 2.5 years of implant, that all tacks were intact and that retinal tissue was normal within one millimeter of the tacks.[57]

In clinical practice, Abrams, et al [58] reported 50/53 (94%) of tacks implanted remained stable over 5 months and in a ten year follow-up of one subject, Puustäjrvi [59] reported that 12/13 (92%) tacks were in place after 120 months.

Based on the above, the risk of tack dislodgement and proliferation leading to detachment is small.

3.7. Electrode Array/Cable/Electronics Package

The electrode array is connected to the extra-ocular case via a polyimide cable, passing through a sclerotomy. The retinal tack holds the array in place.

There is a risk of a comparatively long recovery period from the original sclerotomy procedure and of conjunctival erosion in the area over the electronics package. In the Argus 16 clinical study, only two subjects (2/6, 33%) had conjunctival erosion requiring surgical intervention.[38] The smaller size and increased flexibility of the cable for the Argus II will reduce the risk of conjunctival erosion. However, the presence of the transcleral cable may predispose subjects to a leak at this sclerotomy site which could cause low intraocular pressure.

Placement of the array may result in retinal touching, leading to retinal damage, break, or detachment. In addition, the retinal structure under the array may be damaged during the implant procedure, by long-term pressure exerted by the array on the retina or by migration/twisting of array across the retina. Such damage may result in retinal break and/or detachment. In the Argus 16 clinical study, no subjects have had the implant removed due to movement of the array.

We do not believe that pressure damage associated with the array will prevent the perception of phosphenes based on the reported experience with cochlear implants. Linthicum, et.al. [60] performed a post-mortem histopathological analysis of 22 temporal bones and one brain stem from 13 cochlear implant subjects and reported, "Results of analysis suggested that ganglion cells were the responding elements to this implant and that useful auditory sensation could result from as few as 10 percent of the normal number of ganglion cells."

In addition, the subjects for this feasibility study are the most advanced in the disease. Edwards, et.al. and Gartner, et.al. indicate that advanced retinitis pigmentosa provides a protective effect against possible retinal detachment.[61,62]

3.8. Related to the Heating by the Implant

The Argus II implant is an electronic implant which converts energy from incoming radiofrequency electromagnetic waves to electrical current to stimulate the retina and power the electronics in the case. The process of energy conversion and the operation of the implanted electronics generate heat. This heat is mostly concentrated on and near the extra-ocular case. The most sensitive tissues within the eye are those contained within the retina. These tissues are also the most critical to the continued operation of the Argus II. Excessive heating of biological tissues denatures proteins within the cellular structure and kills living cells. Piyathaisere, et al. showed that no retinal tissue damage occurred when the temperature of the vitreous increased by 5 °C, with 2 °C at the retina, using direct heating with 500mW.[63]

In vitro testing of the Argus II has shown an extra-ocular temperature rise of less than 2 °C. This small temperature increase indicates that heating damage to ocular structures is unlikely to occur with the current design which limits transmitted power to a nominal value of 100mW.

In the unlikely event of heating damage, potential adverse events are cellular death, retinal detachment and loss of ability to elicit percepts.

3.9. Related to the Explant Procedure

The explant procedure has the same risks as the implant procedure, array placement and retinal tacking. In addition, the removal of scleral bands has an 8.3% risk of retinal damage. [64]

3.10. Related to Revision Surgery

Revision surgery is expected to have the same surgical risks as the implant procedure, array placement and retinal tacking. It is possible for the revision surgery to be more extensive than the initial implant if the device requires significant repositioning or replacement. In such cases it is important to evaluate the potential benefits of revision surgery against the risks of prolonged general anesthesia and significant manipulation of the ocular structures. These decisions will be based on clinical grounds on a per subject basis.

It is possible that the revision surgery may not achieve the desired improvement or may worsen the system performance. In addition, it is possible that the implant may become damaged during the revision surgery, requiring further surgical intervention to remove or repair it. Guidance for avoiding damage to the device during revision surgery is provided in the Clinician's Manual.

3.11. Long-Term Radiofrequency Transmission Risks

With radio-frequency transmitter coils, there is a concern about the risk to the subject related to their long-term use. The FDA has approved, as safe and effective, a number of implanted nerve stimulators that are powered by radio-frequency coils. There is a substantial history dating back to the 1960s of using radio-frequency to power various implanted nerve stimulators. Such power transmission obviates the need for implanting bulky batteries (and the need for surgery to replace batteries). The history of these devices in subjects, which includes cochlear implants and a class of spinal cord stimulators, demonstrates uniform safety and reliability of the radio-frequency links.

Furthermore, the radio-frequency transmission in the megahertz frequency range would be too rapid to effect any nerve stimulation; the only established effect would be tissue heating when very high powers are applied. With this in mind, several organizations have established standards for safe levels of energy deposition. The specific absorption rate (SAR) is a measure of the rate of energy absorbed by (dissipated in) an incremental mass contained in a volume element of dielectric materials such as biological tissues. The table below lists several organizations that have established a recommended SAR level for this type of device.

3.11.1. Radiofrequency Transmission Standards

Organization	SAR Level
Federal Communications Commission (FCC) Office of Engineering and Technology (OET) [65]	<8 W/kg (during occupational or controlled partial-body exposure)
Institute of Electrical and Electronics Engineers (IEEE) [66]	<8 W/kg (during occupational or controlled partial-body exposure) <1.6 W/kg (in uncontrolled environments)
International Commission on Non-Ionizing Radiation Protection (ICNIRP) [67]	<10 W/kg (during occupational or controlled localized head or trunk exposure)

Lazzi et.al. have modeled the thermal elevation due to induced electric and magnetic fields and have found that power dissipation under worst case conditions for a retinal implant are 0.6C in the eye and 0.2C in the retina.[68]

The maximum SAR for the radio-frequency coil used in this study has been calculated to be well below each of the levels recommended by the organizations listed above. Based on these data, the radio-frequency energy transmitted by the coil does not pose a risk to the subject.

3.12. Risks of Stimulation

Stimulation of the retina may result in muscle stimulation, pain and disorientation. Stimulation waveforms with anodic and cathodic phases that do not contain the same amount of total charge may result in damage to the retina and the implanted device. Both the implant and VPU have automatic safety checks to ensure that all delivered stimulation is charge balanced.

3.12.1. Risks of High Stimulation

One of the risks of electrical stimulation is that high levels of stimulation for prolonged periods of time can result in damage to the electrodes, to the tissue being stimulated and/or to the retina. To protect against this, the Argus 60 System incorporates a preset limit and other safety checks to limit the maximum stimulation that can be delivered to the subject. The maximum allowable chronic stimulation charge is 350 $\mu C/cm^2$.

The Argus II implant has been tested to demonstrate that the electrodes can withstand this maximum stimulation level for the duration of use anticipated in this study.

McCreery, et al. studied the risk of neural damage related to peripheral neural stimulation.[69] In their study, they found that at lower frequencies

(<50Hz), continuous stimulation at up to 1600 μc/cm^2 induced little or no neural injury using electrodes of a similar size to that of the Argus II. In addition, they concluded that even when nerves must be stimulated at higher frequency it should be possible to safely stimulate the nerve continuously at an amplitude that fully recruits all the motor-neuron axons in the nerve (i.e. it is possible to activate the nerve and reach therapeutic effect before causing damage).

Weiland, et al.[70] showed no histopathological changes with up to 120 days of stimulation in the canine model at current levels of 180 μA and 90 μA and Rizzo, et al.[71] found no clinical or histological damage using charge densities of up to 1000 μC/cm^2 acutely in humans.

In the event that physiologic responses cannot be achieved at 350 μC/cm^2, it may be necessary to temporarily exceed the safe chronic limit (i.e. stimulate up to 1000 μC/cm^2). If it is necessary to exceed the 350 μC/cm^2 limit, this would only occur for brief periods of time (i.e. not more than 4 hours at any one time in the clinic). The risk of increasing the charge density limit is that damage could occur to the electrodes or to the tissue. In physiologic saline, electrolysis of water and bubbling occurs (gassing limit) above 2000 μC/cm^2 with platinum electrodes, therefore stimulation at 1000 μC/cm^2 should be well below the limit for the electrode material. In addition to Rizzo's results, experimental data from acute experiments performed at Johns Hopkins showed acute stimulation in patients with injected charge as high as 4900 μC/cm^2/phase (with platinum electrodes) resulted in no adverse events and no histopathologic abnormalities.

Based on these results, the potential for injury related to the maximum stimulation current allowable by the Argus II is remote.

3.13. Risks of Device Degradation

All implantable devices are susceptible to degradation over time due to the harsh environment of the body. The Argus II implant has been tested to demonstrate that it can survive (i.e. maintain hermeticity and functionality) for the duration of this study. In the remote event that the device did lose hermeticity or functionality, it may require explantation.

3.14. Risks of System Use While Mobile

Subjects are allowed to use the system while mobile as long as they do not use the system as their only mobility aid. When using the system while mobile, they may become disoriented leading to an elevated risk of bumping against walls and falling. A failure of the system while mobile could also cause these events. In addition, subjects may become entangled in the

Glasses cable while walking. The Glasses cable is designed to easily break away from VPU to reduce the likelihood of an injury occurring. By requiring subjects to not use the system as their only mobility aid, the likelihood of these events occurring should be minimal.

4. General Population Risks

This section lists the general life-risks associated with our targeted population. It is not anticipated that the Argus II System will increase the frequency of these risks.

4.1. General Risks

Neurologic

- Depression
- Degeneration or change in cognition
- Vertigo

Cardiovascular

- Stroke/Transient Ischemic Attack
- Cardiac arrhythmia
- Cardiac arrest

Musculo-Skeletal

- Arthritis
- Fracture
- General musculo-skeletal degeneration

Gastro-Intestinal

- Ulcer
- Mesenteric ischemia

Systemic

- Infection unrelated to the implant site.
- Carcinoma

4.2. Depression

Depression is commonly associated with vision loss due to the loss of a sensory organ and the social isolation. [72,73] Functional ability is inversely

correlated with depression [74] and both optical and non-optical interventions has a positive effect on the incidence of depression.[75] In the Argus II Study, subjects will have retinitis pigmentosa and therefore be at the highest risk for depression. Literature would indicate, however, that the provision of percepts may reduce the incidence in this population.

4.3. Falls and Minor Injuries

Falls and minor injuries are a serious concern for aging subjects. Nordell in a retrospective survey found that 30% of subjects over the age of 65 had suffered falls and that a contributor to the risk of falling was visual acuity. [76] The potential for falls increases as the subject's acuity decreases. Tobis et.al. studied non-impaired, blind and deaf subjects for the propensity to fall.[77] They found that the rate of falling in blind subjects (20/200 – no light perception) was twice that of non-impaired subjects (53.4% vs. 26.7%, p = 0.003).

5. Potential Benefits

The potential benefits of the Argus II System are under study in the feasibility human trial stage and as such cannot be numerically evaluated. Evidence from the rate of increasing depression, isolation, falls and minor injuries in blind subjects would suggest that the use of the Argus II System might:

- allow subjects to have an increased interaction with their surroundings,
- reduce the risk of injury by providing visual cues for obstacles, and
- increase the quality of life of subjects

6. Risk/Benefit Analysis

The implantation and use of the Argus II System has a small risk of serious injury and many of the anticipated adverse events can be treated either non-invasively with minimally invasive surgery, although unforeseen risks may be identified during the course of study. In addition, this feasibility study will enroll only subjects with minimal or no vision, reducing the risk to residual vision and the potential for retinal detachment. The potential benefits to the subjects overall life quality, with greater independence and mobility outweigh the relatively minor risks from implantation and use.

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